Clinical Practice Guideline for Diagnosis, Treatment and Follow-up of Diabetes Mellitus and Its Complications - 2019

English Version of the 12th Edition
CLINICAL PRACTICE GUIDELINE FOR DIAGNOSIS, TREATMENT, AND FOLLOW-UP OF DIABETES MELLITUS AND ITS COMPLICATIONS-2019

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English Version of the 12th Edition
“Major achievements and important undertakings are only possible through collaborations”

“Büyük işler, mühim teşebbüler; ancak, müşterek mesai ile kabil-i temindir.”

MUSTAFA KEMAL ATATÜRK, 1925
Dear colleagues,

The prevalence of diabetes has been increasing tremendously in the last few decades. As a result, medical professionals/specialists from different fields encounter many diabetics in their daily practice. At this point, updated guidelines on diabetes management, which take regional specification into consideration is needed.

“The Clinical Practice Guideline for Diagnosis, Treatment, and Follow-up of Diabetes Mellitus and Its Complications” updated in August 2019 by Diabetes Mellitus Working Group of “the Society of Endocrinology and Metabolism of Turkey” (SEMT) will be a response to this need.

It’s content is enriched with latest literature and SEMT Recommendations. These recommendations make it very practical.

We are grateful to the dedicated group members who put a lot of effort and time in this task.

On behalf of SEMT Executive Committee

Füsun SAYGILI, MD
President
Esteemed colleagues,

We are proud and excited to present you with the English translation of “Clinical Practice Guideline for Diagnosis, Treatment, and Follow-up of Diabetes Mellitus and Its Complications”.

This guideline is regularly prepared under the light of current global guidelines and based on the facts of our country. The journey started in 2006, and to date, our guideline become a reference book for many of our colleagues in Turkey. In previous years, the revision was done annually, with the accelerated accumulation of scientific data, there has been a need to update twice a year since 2018. First English translation was pressed in 2010 as a supplement of Turk-JEM (Turkish Journal of Endocrinology and Metabolism), and as the 2nd one, the current product is the translation of the 12th Turkish version.

The aim of publishing an English translation is to present our point of view as Turkish physicians interested in diabetes and to share the data of our country on the international platform.

We hope that this work will be helpful to all our colleagues interested in diabetology, especially in countries around Turkey, and in the regions where the number of Turkish residents is high.

On behalf of the SEMT Diabetes Guideline-2019 Writing Committee

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CONFLICT OF INTEREST

Authors in the Writing Committee of “SEMT Clinical Practice Guideline for Diagnosis, Treatment, and Follow-up of Diabetes Mellitus and Its Complications-2019” declared no commercial conflict of interest with any company or group during the preparation, writing and printing of the guideline.

Note: “Medical Nutrition Therapy in Diabetes” section has been prepared by “Dietitians Society for Diabetes” and coordinated by Emel OZER.
## TABLE 1: Evidence system used in this guideline

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
</table>
| **A**             | • Definitive evidence obtained from the following randomized controlled trials with sufficiently powerful design, good execution and data that can be generalized.  
  • Multi-center studies  
  • Meta-analyses with quality assessment performed  
  • Inevitable evidence obtained from nonexperimental studies like "all or nothing" rule developed by Oxford University Centre for Evidence-Based Medicine  
  • Supporting evidence obtained from the following randomized controlled trials with sufficiently powerful design and well execution:  
  • Studies carried out in one or more institutions  
  • Meta-analyses with quality assessment performed |
| **B**             | • Supportive evidence obtained from the following well-conducted cohort studies:  
  • Prospective cohort or record studies  
  • Meta-analyses of cohort studies  
  • Supportive evidence obtained from well-conducted case-control studies |
| **C**             | • Supportive evidence obtained from insufficiently controlled or uncontrolled studies  
  • Randomized clinical trials with one or more major or three or more minor faults that may affect the verification of the results  
  • Observational studies with high bias probability (e.g., comparison of case series and historical control cases)  
  • Case series or case reports  
  • Evidence contradicting with the weight of the evidence supporting the hypothesis |
| **D**             | • Evidence based on expert opinion or clinical experience |
| CONTENTS |
|-----------------|-------|
| PREFACE         | 5     |
| INTRODUCTION    | 7     |
| WRITING COMMITTEE | 8     |
| ENGLISH VERSION | 9     |
| COLLEAGUES CONTRIBUTED TO THE PREPARATION OF PREVIOUS EDITIONS | 9 |
| CLASSIFICATION OF EVIDENCE-BASED MEDICAL INFORMATION | 10 |
| **01 DIAGNOSIS, CLASSIFICATION AND SCREENING IN GLYCEMIC DISORDERS** | 15 |
| 1.1. | DEFINITION | 15 |
| 1.2. | DIAGNOSTIC CRITERIA AND CLASSIFICATION | 15 |
| 1.3. | TYPE 1 DIABETES MELLITUS | 22 |
| 1.4. | TYPE 2 DIABETES MELLITUS | 23 |
| 1.5. | GESTATIONAL DIABETES MELLITUS | 25 |
| 1.6. | SPECIFIC TYPES OF DIABETES | 25 |
| 1.7. | SCREENING AND DIAGNOSTIC TESTS | 26 |
| **02 STANDARDS OF CARE FOR PATIENTS WITH DIABETES** | 33 |
| 2.1. | ANAMNESIS | 34 |
| 2.2. | PHYSICAL EXAMINATION | 34 |
| 2.3. | CONSULTATIONS | 35 |
| 2.4. | LABORATORY EXAMINATIONS AND ROUTINE FOLLOW-UP | 35 |
| 2.5. | COMPLICATIONS | 38 |
| 2.6. | EDUCATION | 40 |
| 2.7. | ROUTINE PARAMETERS OF DIABETES MONITORING | 41 |
| **03 PRINCIPLES OF HOSPITALIZATION IN PATIENTS WITH DIABETES** | 43 |
| 3.1. | ACUTE METABOLIC COMPLICATIONS | 43 |
| 3.2. | UNCONTROLLED DIABETES | 43 |
| **04 GLYCEMIC CONTROL TARGETS IN PATIENTS WITH DIABETES MELLITUS** | 45 |
| 4.1. | GLYCEMIC TARGETS | 45 |
| 4.2. | SELF-MONITORING OF BLOOD GLUCOSE | 50 |
| **05 MEDICAL NUTRITION THERAPY IN DIABETES** | 53 |
| 5.1. | GENERAL PRINCIPLES OF MEDICAL NUTRITION THERAPY | 53 |
| 5.2. | CARBOHYDRATE COUNTING METHOD | 64 |
| **06 EXERCISE AND PHYSICAL ACTIVITY IN DIABETES** | 69 |
| 6.1. | GENERAL PRINCIPLES | 69 |
| 6.2. | EXERCISE-RELATED PROBLEMS | 71 |
07 PRINCIPLES OF USE FOR NON-INSULIN ANTIHYPERGLYCEMIC (ORAL ANTIDIABETIC AND INSULIN-MIMETIC) DRUGS 75
7.1 | BIGUANIDES 75
7.2 | INSULIN SECRETAGOGUES 77
7.3 | THIAZOLIDINEDIONES 78
7.4 | ALPHA-GLUCOSIDASE INHIBITORS 79
7.5 | INCRETIN-BASED DRUGS 80
7.6 | SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS 82
7.7 | USE OF ANTIDIABETIC DRUGS IN CHRONIC KIDNEY DISEASE 83
7.8 | EFFECTIVENESS OF ANTIHYPERGLYCEMIC DRUGS USED IN MONOTHERAPY 85
7.9 | PRE-MIXED ANTI-HYPERGLYCEMIC DRUG COMBINATIONS 86

08 PRINCIPLES OF INSULIN THERAPY 87
8.1 | GENERAL PRINCIPLES 87
8.2 | MANAGEMENT OF INSULIN THERAPY 90

09 CURRENT APPROACH IN DIABETES TREATMENT 95
9.1 | CURRENT TREATMENT IN TYPE 1 DIABETES 95
9.2 | CURRENT TREATMENT IN TYPE 2 DIABETES 97

10 PRINCIPLES OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION THERAPY 113
10.1 | PRINCIPLES OF INSULIN INFUSION (INSULIN PUMP) 113
10.2 | CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING SYSTEMS (GLUCOSE SENSORS) 118
10.3 | NEW TECHNOLOGIES 120

11 PANCREAS AND ISLET TRANSPLANTATION 123

12 ACUTE COMPLICATIONS OF DIABETES 125
12.1 | DIABETIC KETOACIDOSIS 126
12.2 | HYPEROSMOLAR HYPERGLYCEMIC STATE 132
12.3 | LACTIC ACIDOSIS 135
12.4 | HYPOGLYCEMIA 137

13 CHRONIC COMPLICATIONS OF DIABETES 141
13.1 | MACROVASCULAR DISEASE 141
13.2 | MICROVASCULAR COMPLICATIONS 147

14 DIABETIC FOOT PROBLEMS 161
14.1 | ETIOPATHOGENESIS OF DIABETIC FOOT ULCER 161
14.2 | CLASSIFICATION 163
14.3 | CLINICAL EVALUATION 164
14.4 | TREATMENT 167
14.5 | PREVENTION OF RECURRENTURE 169
1.1. DEFINITION

Diabetes mellitus is a life-long, chronic, metabolic disease of multiple etiologies. Although it is characterized by hyperglycemia, it affects carbohydrate (CH), fat and protein metabolisms resulting from insulin deficiency and/or defects in insulin action. Consistent education of both healthcare professionals and patients is essential to reduce the risk of acute complications of the disease and to avoid the development of chronic (e.g. retinal, renal, neural, cardiac, and macrovascular) complications. Diabetes requires steady care and creates a huge burden on the public health system mainly resulting from costly treatment of devastating complications in the long-term.

This guide has been prepared in the light of current evidence-based information, and international consensus, while the special conditions of the country are also considered. Recommendations presented here aim to reduce the health problems and improve the quality of life of patients with diabetes.

1.2. DIAGNOSTIC CRITERIA AND CLASSIFICATION

Since the last two decades, important changes have been made in the diagnosis and classification of diabetes and other disorders of glucose metabolism. First, in 1997, the American Diabetes Association (ADA) published new diagnosis and classification criteria, and following this, the World Health Organization (WHO) accepted these criteria with minor revisions in 1999.

In 2003, the ADA revised the cut-point for impaired fasting glucose (IFG) to 100 mg/dL. This was based on ROC (receiver operating characteristics) curve analysis of data from population-based studies (Pima Indian, Mauritius, San Antonio, and Hoorn study) which identified the most appropriate baseline FPG cut-point with reasonable sensitivity and specificity to predict diabetes over a 5-yr period. However, WHO and International Diabetes Federation (IDF) opted for the continuation of 1997 criteria in the report published in 2006.

1.2.1. DIAGNOSTIC CRITERIA

A. Diabetes mellitus

Current diagnosis criteria of diabetes and other disorders of glucose metabolism are presented in Table 1.1.
**TABLE 1.1: Diagnostic criteria of diabetes and other disorders of glucose metabolism**

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>Overt DM</th>
<th>Isolated IFG</th>
<th>Isolated IGT</th>
<th>IFG + IGT</th>
<th>High Risk Group for DM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FPG (≥8 hr fasting)</strong></td>
<td>≥126 mg/dL</td>
<td>100-125 mg/dL</td>
<td>&lt;100 mg/dL</td>
<td>100-125 mg/dL</td>
<td>-</td>
</tr>
<tr>
<td><strong>OGTT 2-hr PG (75 g glucose)</strong></td>
<td>≥200 mg/dL</td>
<td>&lt;140 mg/dL</td>
<td>140-199 mg/dL</td>
<td>140-199 mg/dL</td>
<td>-</td>
</tr>
<tr>
<td><strong>Random PG</strong></td>
<td>≥200 mg/dL + Diabetes symptoms</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>A1C</strong></td>
<td>≥6.5% (≥48 mmol/mol)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.7-6.4% (39-47 mmol/mol)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; FPG, fasting plasma glucose; 2 hr PG, 2 hour plasma glucose; OGTT, oral glucose tolerance test; A1C, glycated hemoglobin A1c; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; WHO, World Health Organization; IDF, International Diabetes Federation.

*Glycemia measured in venous plasma using glucose oxidase method, and quantified as “mg/dL”. Either one of four diagnostic criteria is sufficient for “Overt DM” diagnosis, whereas, both criteria are required for “Isolated IFG”, “Isolated IGT”, and “IFG+IGT”.

**Must be measured with a standardized method.

Accordingly, diabetes diagnosis can be made by either one of the four methods. Except for the cases presented with severe diabetes symptoms, the diagnosis must be confirmed on another day, preferably using the same (or different) method. If two different tests were performed initially at the same time, and test results were contradictory, the test that was over the threshold level should be repeated and diabetes diagnosis should be made if the result remained within diagnostic range again.

A standard OGTT with 75 g glucose is more sensitive and specific than the diagnostic method based on fasting plasma glucose (FPG) levels measured in the morning after at least 8 hours fast, however, its day-to-day variability in the same person, intense labor required, and high costs makes it difficult to use regularly. On the other hand, easier use and low costs associated with FPG increases its use in clinical practice. However, OGTT has an important role both in the diagnosis and screening of diabetes and prediabetes. Although OGTT is less reproducible than FPG levels, it is more sensitive for the detection of prediabetes and diabetes.

Most of the time OGTT is not required for diagnosis of type 1 diabetes due to its overt clinical onset.

Diagnostic criteria are based on glucose measurement in venous plasma using glucose oxidase method. Whole blood, capillary blood and serum glucose values used in the clinic or by patients at home for monitoring (self-monitoring of blood glucose: SMBG) are slightly lower than venous PG values as shown by the formula below*. Based on these formulae, in recent years, it has been adopted to use calibrated devices (glucometers). In this case, the device measures glucose levels in capillary whole blood but the results are automatically calibrated to PG levels. According to WHO, fasting glucose levels in whole blood samples are considered equal to that of venous PG levels. However, postprandial glucose levels in capillary blood samples are accepted as approximately 11% lower than that of plasma. This difference varies depending on the hematocrit (Hct) values; the difference increases by 15% for an individual with a 55% Hct, and decreases by 8% if Hct is 30%.

* Plasma glucose (mg/dL) = 0.558 + (20.254 x whole blood glucose [mg/dL]/18)
  Plasma glucose (mg/dL) = 0.102 + (19.295 x capillary blood glucose [mg/dL]/18)
  Plasma glucose (mg/dL) = -0.137 + (18.951 x serum glucose [mg/dL]/18)

Accordingly, 126 mg/dL glucose level in venous plasma is measured ~11% (112 mg/dL) lower in whole blood, ~7% (118 mg/dL) lower in capillary blood, and ~5% (120 mg/dL) lower in serum.
In daily practice, in some persons despite fasting and/or 2 hour PG levels have not been found within diagnostic range for diabetes (e.g., found within normal or IFG or impaired glucose tolerance [IGT] ranges) a PG level can be found over 200 mg/dL at any time point prior to the 2nd hour. Some authors describe this clinical presentation as “Dysglycemia” and it is a widely recognized approach to follow-up these cases as in overt diabetes.

**Hemoglobin A1c (HbA1c: A1C) as a diagnostic test**

For many years, the use of glycated hemoglobin A1c (HbA1c: A1C) as a diagnostic tool for diabetes had not been recommended due to the issues involved in its standardization and uncertainty with its diagnostic threshold. As a result of the global standardization efforts and increased evidence with regards to its prognostic importance, A1C has also been accepted as a diagnostic test for diabetes since 2008. In the United States, all laboratories are required to have their A1C measurement methods certified by National Glycohemoglobin Standardization Program (NGSP) and calibrate their results based on High-Performance Liquid Chromatography (HPLC) method, which is used in Diabetes Control and Complications Trial (DCCT) and regarded as gold standard.

A1C cut-off point for diabetes diagnosis is determined as 6.5% (48 mmol/mol) by the International Expert Committee on Diabetes, a committee consisted of members appointed by International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), ADA, European Association for the Study of Diabetes (EASD) and IDF.

WHO, in 2011 Consultation Report recommended the use of A1C as a diagnostic test, if provided that a reliable method is used and regularly standardized based on international reference values.

In some A1C measurement methods, A1C and PG results may be discordant due to hemoglobin variants (hemoglobinopathies). In such case, a non-interfering A1C measurement method should be used for diabetes diagnosis or FPG diagnostic criteria should be considered. Additionally, in the presence of conditions such as sickle cell anemia that accelerates the turnover rate of red blood cells, pregnancy (especially in second and third trimesters), hemodialysis, recent history of hemorrhage or blood transfusion, or erythropoietin therapy, diabetes diagnosis must be based solely on PG glucose levels.

National (The Turkish Epidemiology Survey of Diabetes, Hypertension, Obesity and Endocrine Disease-II [TURDEP-II]) and international population-based studies demonstrated that patients diagnosed with diabetes based on A1C have a more advanced metabolic condition in terms of weight, waist circumference, lipids and blood pressure (BP) in comparison to those who are diagnosed as per FPG or OGTT. In TURDEP-II survey, metabolic risk profile of the group defined as “High Risk Group” (HRG: 5.7-6.4%; 39-47 mmol/mol) based on A1C was found be impaired to a similar extent with the risk profile of the group with “Combined Glucose Intolerance” (CGI = IFG + IGT) measurement. In consideration of this case, it is apparent that the diagnostic use of the test would provide benefits for the identification and treatment of individuals who are more prone to complications, and also for preventing or delaying the complications. Therefore, standardization studies of A1C should be accelerated with the regulations to be made by the Ministry of Health.

**B. Gestational diabetes**

Conventionally, a two-step diagnostic approach is used for the investigation of gestational diabetes (GDM; pregnancy diabetes). Today, in addition to the “two-step” diagnostic approach, the “one-step” diagnostic approach is also becoming more common. Interpretation of diagnostic tests detailed below are summarized in Table 1.2.
TABLE 1.2: Gestational diabetes diagnostic criteria*

<table>
<thead>
<tr>
<th>Approach</th>
<th>Test</th>
<th>FPG</th>
<th>1 hr PG</th>
<th>2 hr PG</th>
<th>3 hr PG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-step test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First step</td>
<td>Screening with 50 g glucose</td>
<td></td>
<td>≥140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second step</td>
<td>OGTT with 100 g glucose (at least 2 pathological values required for diagnosis)</td>
<td>≥95</td>
<td>≥180</td>
<td>≥155</td>
<td>≥140</td>
</tr>
<tr>
<td>One-step test</td>
<td>IADPSG criteria OGTT with 75 g glucose (at least 1 pathological value required for diagnosis)</td>
<td>≥92</td>
<td>≥180</td>
<td>≥153</td>
<td></td>
</tr>
</tbody>
</table>

IADPSG, International Association of Diabetes in Pregnancy Study Group; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; 1 hr PG, 2 hr PG, and 3 hr PG, 1, 2, and 3 hr plasma glucose; IGT, impaired glucose tolerance.

*Glucose levels were measured in venous plasma samples using glucose oxidase method, and quantified as “mg/dL”.

a. Two-step diagnostic approach

1) Screening test with 50 g glucose: At a random time between 24-28th gestational weeks, PG value ≥140 mg/dL determined 1 hour after a liquid 50 g glucose load identifies pregnant women suspected for diabetes, and a more advanced test (100 g or 75 g glucose OGTT) is required. In the screening test, after 50 g glucose load, 1 hr PG cut-off level of 140 mg/dL capable to diagnose 80% of women with GDM; on the other hand, a cut-off level of 130 mg/dL can diagnose 90% of women with GDM. In general, if 1 hr PG value is >180 mg/dL after 50 g glucose, then OGTT is not considered as necessary, and these cases are recommended to be followed and treated as GDM.

2) OGTT: For definitive diagnosis in pregnant women with a positive 50 g glucose screening test, 3-hour 100 g OGTT should be performed. Although it has been suggested that diagnostic OGTT could be performed as 2-hour with 75 g as an alternative, this approach was not supported. In both tests, at least two values exceeding the normal limit allow for GDM diagnosis.

b. Single-step diagnostic approach

OGTT with 75 g glucose: The results of Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO), a multi-center and prospective trial, were published in 2008 and revealed that maternal hyperglycemia has a significant correlation with fetal macrosomia, hyperinsulinemia, neonatal hypoglycemia, and cesarean section. Based on finding of the HAPO study the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended GDM screening with one-step OGTT with 75 g glucose on 24-28th gestational week.

Today, there is yet to be a consensus about the use of one-step diagnostic approach instead of a two-step test in the diagnosis of GDM.

In our country, authorities opt to maintain the two-step (50 g screening test and then 100 g glucose OGTT) diagnostic approach by highlighting that the number of pregnant women diagnosed with GDM based on IADPSG criteria would drastically increase, leading to economic and emotional problems.

Therefore, until we have sufficient evidence in terms of long-term outcomes of mother with GDM diagnosed based on IADPSG criteria, and along with outcomes of their babies, the Working Group for the Study and Education of Diabetes Mellitus in The Society of Endocrinology and Metabolism of Turkey (SEMT), recommends the continuation of the two-
step diagnostic approach, which is adopted by the gynecology community as well. However, we also suggest that 75 g glucose OGTT can be used in GDM diagnosis since it is easily applicable, provides standardization for GDM diagnosis and has glucose cut-off points directly based on fetal complications.

### SEMT RECOMMENDATIONS

1. **In the diagnosis of diabetes, all four different diagnostic methods (FPG, OGTT, 2 hr PG, A1C, random PG accompanied with diabetes symptoms) can be used with equal value (D).**

2. **If A1C method will be used for diagnosis, it is strongly recommended the test should be performed using a standard method at laboratories with an up-to-date proficiency certificate issued by an international quality control organization (B).**

3. **A1C should not be used as a diagnostic test in cases involving hemoglobinopathy or conditions that accelerate the turnover of red blood cells (pregnancy, recent history of hemorrhage or blood transfusion, hemodialysis, erythropoietin therapy etc.) (B).**

4. **For GDM diagnosis, two-step (100 g glucose 3 hr OGTT following a screening test with 50 g glucose) or one-step (75 g glucose OGTT) diagnostic methods can be used (A).**

### REFERENCES


### C. Prediabetes

Plasma glucose levels that are higher than normal but do not meet the diagnostic criteria for diabetes are called "Prediabetes". Accordingly, IGT and IFG which were previously known as "Latent Diabetes" or "Borderline Diabetes" are now considered as "Prediabetes". Both IGT and IFG are important risk factors for diabetes and cardiovascular disease (CVD).

As shown in Table 1.1, the requirements of FPG 100-125 mg/dL and 2 hr PG <140 mg/dL for "Isolated IFG", and 2 hr PG 140-199 mg/dL and FPG <100 mg/dL for "Isolated IGT" are widely accepted. In contrast, cases with "Combined Glucose Intolerance (CGI = IFG+IGT)", FPG is between 100-125 mg/dL and 2 hr PG is between 140-199 mg/dL. This category represents a more advanced stage of glucose dysregulation.

In 2006 consensus report of WHO and IDF, it was stated that the upper limit for normal FPG should be less than 110 mg/dL and the definition of IFG was opted to be maintained at 110-125 mg/dL.

International Expert Committee on Diabetes reported that patients with A1C between 5.7% and 6.4% (39-47 mmol/mol) are at high risk in terms of diabetes, and they called them "High-Risk Group: HRG)". These people should be placed on diabetes prevention programs in priority.
Studies performed in various populations and Turkish population as well (e.g. TURDEP-II survey) revealed that in patients who are determined to be in HRG category based on A1C, glucose metabolism impairment is actually more severe than isolated IFG and isolated IGT, and closer to CGI (IFG+IGT) in severity. Patients, who are determined to be in HRG category based on A1C performed with a standard method, are more prone to overt diabetes development and therefore their placement in diabetes prevention studies must be prioritized.

Risk surveys that are validated based on population characteristics (e.g. FINDRISC or ADA Risk Survey) can be used for simple, practical and low-cost determination of the individuals who are at risk of prediabetes and diabetes. It is also recommended to strive by using technology to raise public awareness on healthy lifestyle modifications as diabetes is an increasingly prevalent global health problem.

1.2.2. | SYMPTOMS OF DIABETES

Common (classic) symptoms
- Polyuria
- Polydipsia
- Polyphagia or loss of appetite
- Fatigue, malaise
- Dry mouth
- Nocturia

Less common symptoms
- Blurred vision
- Unexplained weight loss
- Persistent infections
- Repeated fungal infections
- Pruritus

**SEMT RECOMMENDATIONS**

1. For prediabetes diagnosis, FPG (IFG: FPG 100-125 mg/dL), and 75 g glucose OGGT (IGT: 2 hr PG 140-199 mg/dL) or A1C (provided that a standardized method is used; HRG: A1C 5.7-6.4%; 39-47 mmol/mol) tests can be used (B).

2. Especially patients fit in HRG (A1C 5.7-6.4%; 39-47 mmol/mol)’ or with CGI (IFG+IGT) are at a higher risk for diabetes and CVD. Therefore, their inclusion in diabetes prevention programs should be prioritized and they should be closely followed up (A).

**REFERENCES**


1.2.3. | CLASSIFICATION

These four clinical types included in the diabetes classification is summarized in Table 1.3. Three of these (type 1 diabetes, type 2 diabetes, and GDM) are known as primary and the other one [specific diabetes types] is known as secondary diabetes forms.
### TABLE 1.3: Etiological classification of diabetes mellitus

<table>
<thead>
<tr>
<th>I. Type 1 diabetes</th>
<th>involves β cell destruction that generally leads to absolute insulin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Type 2 diabetes</td>
<td>characterized by insulin secretion defect which is progressive based on insulin resistance</td>
</tr>
<tr>
<td>III. Gestational diabetes mellitus</td>
<td>GDM: A form of diabetes that first occurs during pregnancy and generally resolves after delivery</td>
</tr>
<tr>
<td>IV. Other specific types of diabetes</td>
<td></td>
</tr>
<tr>
<td>A. Genetic defects of β-cell function (monogenic forms of diabetes)</td>
<td></td>
</tr>
<tr>
<td>1. Chromosome, HNF-4α (MODY1)</td>
<td></td>
</tr>
<tr>
<td>2. Chromosome, GLUCokinase (MODY2)</td>
<td></td>
</tr>
<tr>
<td>3. Chromosome, HNF-1α (MODY3)</td>
<td></td>
</tr>
<tr>
<td>4. Chromosome, IPF-1 (MODY4)</td>
<td></td>
</tr>
<tr>
<td>5. Chromosome, HNF-1β (MODY5)</td>
<td></td>
</tr>
<tr>
<td>6. Chromosome, NeuroD1 (MODY6)</td>
<td></td>
</tr>
<tr>
<td>7. Chromosome, KLF11 (MODY7)</td>
<td></td>
</tr>
<tr>
<td>8. Chromosome, CEL (MODY8)</td>
<td></td>
</tr>
<tr>
<td>9. Chromosome, APPL1 (MODY9)</td>
<td></td>
</tr>
<tr>
<td>10. Chromosome, INS (MODY10)</td>
<td></td>
</tr>
<tr>
<td>11. Chromosome, BLK (MODY11)</td>
<td></td>
</tr>
<tr>
<td>12. Chromosome, mitochondrial DNA</td>
<td></td>
</tr>
<tr>
<td>14. Chromosome, KJN11 (MODY13)</td>
<td></td>
</tr>
<tr>
<td>15. Chromosome, PAX4 (MODY14)</td>
<td></td>
</tr>
<tr>
<td>B. Genetic defects of insulin action</td>
<td></td>
</tr>
<tr>
<td>1. Leprechaunism</td>
<td></td>
</tr>
<tr>
<td>2. Lipotrophic diabetes</td>
<td></td>
</tr>
<tr>
<td>3. Rabson-Mendenhall syndrome</td>
<td></td>
</tr>
<tr>
<td>4. Type A insulin resistance</td>
<td></td>
</tr>
<tr>
<td>5. Others</td>
<td></td>
</tr>
<tr>
<td>C. Diseases of exocrine pancreas</td>
<td></td>
</tr>
<tr>
<td>1. Fibrocalculous pancreatopathy</td>
<td></td>
</tr>
<tr>
<td>2. Hemochromatosis</td>
<td></td>
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<tr>
<td>3. Cystic fibrosis</td>
<td></td>
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<tr>
<td>4. Neoplasia</td>
<td></td>
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<tr>
<td>5. Pancreatitis</td>
<td></td>
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<tr>
<td>6. Trauma/pancreatectomy</td>
<td></td>
</tr>
<tr>
<td>7. Others</td>
<td></td>
</tr>
<tr>
<td>D. Endocrinopathies</td>
<td></td>
</tr>
<tr>
<td>1. Acromegaly</td>
<td></td>
</tr>
<tr>
<td>2. Aldosteronoma</td>
<td></td>
</tr>
<tr>
<td>3. Cushing syndrome</td>
<td></td>
</tr>
<tr>
<td>4. Pheochromocytoma</td>
<td></td>
</tr>
<tr>
<td>5. Glucagonoma</td>
<td></td>
</tr>
<tr>
<td>6. Hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td>7. Somatostatinoma</td>
<td></td>
</tr>
<tr>
<td>8. Others</td>
<td></td>
</tr>
<tr>
<td>E. Medications or chemical agents</td>
<td></td>
</tr>
<tr>
<td>1. Atypical antipsychotics</td>
<td></td>
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<tr>
<td>2. Anti-viral drugs</td>
<td></td>
</tr>
<tr>
<td>3. β-adrenergic agonists</td>
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<tr>
<td>4. Diazoxide</td>
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<tr>
<td>5. Phenyltoin</td>
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<tr>
<td>6. Glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>7. α-Interferon</td>
<td></td>
</tr>
<tr>
<td>8. Nicotinic acid</td>
<td></td>
</tr>
<tr>
<td>9. Pentamidine</td>
<td></td>
</tr>
<tr>
<td>10. Protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>11. Thiazide diuretics</td>
<td></td>
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<tr>
<td>12. Thyroid hormone</td>
<td></td>
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<tr>
<td>13. Vancer</td>
<td></td>
</tr>
<tr>
<td>14. Statins</td>
<td></td>
</tr>
<tr>
<td>15. Others (drugs used to prevent transplant rejection)</td>
<td></td>
</tr>
<tr>
<td>F. Immune-mediated rare forms of diabetes</td>
<td></td>
</tr>
<tr>
<td>1. Anti insulin-receptor antibodies</td>
<td></td>
</tr>
<tr>
<td>2. Stiff-man syndrome</td>
<td></td>
</tr>
<tr>
<td>3. Others</td>
<td></td>
</tr>
<tr>
<td>G. Diabetes associated with genetic syndromes</td>
<td></td>
</tr>
<tr>
<td>1. Alström syndrome</td>
<td></td>
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<tr>
<td>2. Down syndrome</td>
<td></td>
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<tr>
<td>3. Friedreich type ataxia</td>
<td></td>
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<tr>
<td>4. Huntington chorea</td>
<td></td>
</tr>
<tr>
<td>5. Klinefelter syndrome</td>
<td></td>
</tr>
<tr>
<td>6. Laurence-Moon-Biedl syndrome</td>
<td></td>
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<tr>
<td>7. Myotonic dystrophy</td>
<td></td>
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<tr>
<td>8. Porphyria</td>
<td></td>
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<tr>
<td>9. Prader-Willi syndrome</td>
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<tr>
<td>10. Turner syndrome</td>
<td></td>
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<tr>
<td>11. Wolfram (DIDMOAD) syndrome</td>
<td></td>
</tr>
<tr>
<td>12. Others</td>
<td></td>
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<tr>
<td>H. Infections</td>
<td></td>
</tr>
<tr>
<td>1. Congenital rubella</td>
<td></td>
</tr>
<tr>
<td>2. Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>3. Coxsackie B virus</td>
<td></td>
</tr>
<tr>
<td>4. Others (adenoviruses, mumps)</td>
<td></td>
</tr>
</tbody>
</table>

HNF-1α, hepatocyte nuclear factor-1α; MODY1-11, maturity onset diabetes of the young 1-11; HNF-4α, hepatocyte nuclear factor-4α; HNF-1α, hepatocyte nuclear factor-1α; IPF-1, insulin promoter factor-1; HNF-1; hepatocyte nuclear factor-1β; NeuroD1, neurogenic differentiation 1; BLK, beta lymphocyte-specific kinase; DNA, deoxyribonucleic acid; HIV, human immune deficiency virus; DIDMOAD syndrome, syndrome characterized by diabetes insipidus, diabetes mellitus, optic atrophy and deafness (Wolfram syndrome); KLF11, Kruppel like factor 11; CEL, carboxyl ester lipase (bile salt-dependent lipase); PAX4, paired box4; ABCC8, ATP-binding cassette C8; KCNJ11, potassium inwardly-rectifying channel J11; INS, insulin.

Type 1 and type 2 diabetes are heterogeneous diseases due to their clinical onset form and progression processes. Conventionally, type 1 diabetes is considered to acute onset with hyperglycemia or diabetic ketoacidosis (DKA) in children and young peoples, and type 2 diabetes onset is assumed to be insidious, mild and relatively slow-progressing in adults, however, some cases do not fit in this differentiation during diagnosis, therefore exact classification can be difficult initially. In October 2015, a symposium was gathered...
to discuss this uncertainty with the participation of experts from ADA, Juvenile Diabetes Research Foundation (JDRF), EASD, American Association of Clinical Endocrinologists (AACE). The symposium focused mainly on the differentiation of diabetes cases based on its pathophysiology, natural course, and prognosis characteristics. In the symposium, discussion topics included genetic and environmental determinants of the risk and progression of type 1 and type 2 diabetes, determination of diabetes risk and progression based on pathophysiology and stage of the disease, and personalized treatment approach. According to the experts, various genetic and environmental factors in both type 1 and type 2 diabetes reduce β-cell mass and function. The pathophysiology of type 1 diabetes has been studied better than type 2 diabetes. It has been well-known that constantly positive results obtained for two or more islet autoantibodies in cohort studies, where first degree relatives of type 1 diabetes patients are prospectively followed up, strongly predicts clinical hyperglycemia and diabetes development. The rate of progression to clinical diabetes depends on the number of autoantibodies, the age when antibody is first detected in the blood, specificity, and titer of the autoantibody. It is emphasized that the increases in glucose and A1C levels are always occur before DKA development. It has been determined that the development of autoimmune type 1 diabetes is usually completed in three stages (Table 1.4).

1.3. | TYPE 1 DIABETES MELLITUS

1.3.1. | PATHOPHYSIOLOGY / ETIOLOGY

There is an absolute insulin deficiency in type 1 diabetes. About 90% of patients have autoimmune, 10% have non-autoimmune beta-cell destruction.

In patients with genetic predisposition (at-risk HLA groups), autoimmunity is activated with environmental triggering factors [viruses, toxins, emotional stress, etc.] and progressive beta-cell destruction starts. Clinical diabetes symptoms occur when beta-cell reserve is reduced by 80-90%. In the above mentioned early stages of type 1A diabetes, islet autoantibodies are found positive in the blood and usually remain positive until the onset of stage 3. These antibodies disappear from the blood generally at the end of the first year of clinical diagnosis. Clinical stages of autoimmune type 1 diabetes are summarized in Table 1.4.

TABLE 1.4: Stages of type 1 diabetes

<table>
<thead>
<tr>
<th>Phenotypical characteristics</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmunity</td>
<td>Autoimmunity</td>
<td>Newly onset hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>Dysglycemia</td>
<td>Symptomatic</td>
<td></td>
</tr>
<tr>
<td>Presymptomatic</td>
<td>Presymptomatic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple autoantibodies</td>
<td>Multiple autoantibodies</td>
<td>Clinical symptoms</td>
<td></td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>Dysglycemia: (IFG/IGT/HRG/ increased A1C (≥10%))</td>
<td>Diabetes diagnosed with standard criteria</td>
<td></td>
</tr>
</tbody>
</table>

IFG, FPG 100-125 mg/dL; IGT, OGTT 2 hr PG 140-199 mg/dL; HRG, A1C 5.7-6.4%, IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HRG, high risk group; FPG, fasting plasma glucose; OGTT 2 hr PG, 2 hr plasma glucose in oral glucose tolerance test).

A1C level may not be high at the time of diagnosis since type 1 diabetes has an acute clinical onset. Therefore, instead of A1C, FPG elevation should be considered for the diagnosis of type 1 diabetes.
1.3.2. | CHARACTERISTICS

- Generally onsets before the age of 30. Three peaks are observed: pre-school (around 6 years), puberty (around 13 years) and late adolescence (around 20 years of age). However, it has been reported that the incidence of “Latent autoimmune diabetes in adults” (LADA) form, which can occur at more advanced ages, is getting closer to childhood (<15 years of age) type 1 diabetes in the last two decades.
- Symptoms and signs related to hyperglycemia (dry mouth, polydipsia, hunger, polyuria, weight loss, fatigue, etc.) occur acutely.
- Patients generally underweight or normal weight. However, in recent years, a specific form of type 1 diabetes, which is phenotypically similar to predominantly insulin resistant type 2 diabetes has been described in overweight/obese individuals, and this named as “Double diabetes”, “Hybrid diabetes”, “Dual diabetes” or “Type 3 diabetes”.
- Predisposed to diabetic ketoacidosis.

1.3.3. | TREATMENT

- Insulin injections (can be applied with injector, pen or pump) (see Chapter 8 and 10)
- Medical nutrition therapy (MNT; see Chapter 5)
- Physical activity (see Chapter 6)
- Education (see Chapter 2)
- Self-monitoring of blood glucose (SMBG) and ketone monitoring (see Chapter 4) / Continuous glucose monitoring: CGM (see Chapter 9)

1.4. | TYPE 2 DIABETES MELLITUS

1.4.1. | PATHOPHYSIOLOGY / ETIOLOGY

A. Insulin resistance

The cells are unable to uptake glucose and use it for energy (there is intracellular hypoglycemia) due to the problems related to defective cell-receptor interactions (at the post-receptor level) occurring in the utilization of insulin produced by pancreatic β-cells. The effects of insulin are insufficient in peripheral tissues (especially in muscle and adipose tissue). Glucose uptake is decreased in muscle and adipose cells.

B. Decreased insulin secretion

The pancreas is unable to secrete sufficient amount insulin in response to increased blood glucose levels. Glucose production in the liver is significantly increased. Insulin secretion defect and counter-regulatory system hormones (cortisol, growth hormone, and adrenaline; Dawn phenomenon) that are more active towards morning are responsible for increased hepatic glucose production.

Generally, insulin resistance is predominant for long years starting before type 2 diabetes, and a significant decrease in insulin secretion becomes more predominant in the later stages of diabetes or during intercurrent illnesses.
1.4.2. **CHARACTERISTICS**

- Mostly occurs after 30 years of age, however, there are increasingly more type 2 diabetes cases occurring at childhood or adolescence in the last 10-15 years.
- There is a strong genetic predisposition. As the gene density in the family increases, the diabetes risk also increases in the next generations and the disease onsets at earlier ages.
- Patients are frequently obese or overweight (body mass index [BMI] > 25 kg/m²).
- The disease generally has an insidious onset. Many patients have any symptoms initially.
- Some patients may present with blurred vision, numbness and tingling in the hands and feet, foot pain, repeated fungal infections, or delayed wound healing.
- No DKA predisposition initially. However, DKA may occur during the long-term hyperglycemic course or in advanced stages where β-cell reserve is decreased.
- In recent years, it has been reported that type 2 diabetes cases that onset with DKA at a young-adult age is increasing in some ethnic groups (African-American and Hispanic in USA, and India). This atypical form of diabetes, which is called “ketosis-prone diabetes (KPD),” is highly heterogeneous form and is more commonly seen in overweight or obese men with clinical insulin resistance findings. A/b classification system is recommended for the determination of treatment response and prognosis in these cases. According to this classification, which is based on β-cell reserve (β) as practically determined by C-peptide measurement and islet-cell autoimmunity (A) determined by islet-cell autoantibodies, KPD has four different variants identified:
  - In Type 1A (A+/β-) form, there are islet-cell autoimmunity markers and permanent β-cell deficiency. Requires lifelong insulin therapy.
  - In Type 2A (A+/β+) form, β-cell functions are preserved, however, there are islet-cell autoimmunity markers present. In these cases, exogenous insulin can be terminated by clinically restoring β-cell function, or lifelong insulin therapy may be required in case of progressive β-cell destruction.
  - In Type 1B (A-/β-) there is also permanent β-cell deficiency, however, there is no islet-cell autoimmunity. Requires lifelong insulin therapy.
  - In Type 2B (A-/β+) β-cell reserve is preserved and there is no islet-cell autoimmunity. This subtype of KPD has the highest possibility of achieving remission close to normoglycemia and stopping insulin therapy.

1.4.3. **TREATMENT**

- Medical nutrition therapy (MNT, diet) and weight control (see Chapter 5)
- Education (see Chapter 2)
- Physical activity (see Chapter 6)
- Oral antidiabetic drugs (OAD), peptide and/or insulin therapy as needed (see Chapters 7 and 8)
- SMGB by the patient, and CGM in special circumstances (see Chapter 4 and Chapter 9)
- Treatment of the accompanying diseases (hypertension [HT], dyslipidemia, etc.) and anti-platelet treatment (see Chapters 16 and 17).
1.5. | GESTATIONAL DIABETES MELLITUS

1.5.1. | PATHOPHYSIOLOGY / ETIOLOGY

- Pregnancy-related insulin resistance
- Genetic predisposition

1.5.2. | CHARACTERISTICS

- GDM or gestational glucose intolerance must be investigated at first prenatal visit for women at risk.
- Generally asymptomatic
- Usually recovers after delivery, however, tends to repeat in future pregnancies.
- An important risk factor for type 2 diabetes.

1.5.3. | TREATMENT

- In cases where glycemic control cannot be achieved with MNT (diet) and exercise, insulin must be initiated, and the treatment should be arranged based on patient’s SMBG and ketone monitoring (see Chapter 15.3).

REFERENCES


1.6. | SPECIFIC TYPES OF DIABETES

In this section, brief information has been provided on several diabetes forms that linked to specific causes.

1.6.1. | MATURITY ONSET DIABETES OF THE YOUNG (MODY)

The patients who have suspected monogenic diabetes (maturity-onset diabetes of the young; MODY) are generally young [age at diabetes onset is <25 years]. They have diabetes history in two or more generations of their families (autosomal dominant inheritance), have normal weight and good pancreas reserve, and no insulin resistance. The primary defect is in the insulin secretion mechanism. Islet autoantibodies are negative in these patients. Insulin therapy is not required for blood glucose regulation. However, some patients may require insulin but glycemic control can be achieved with low-dose insulin.

MODY cases can be confused with type 1 diabetes that is diagnosed after adolescence or type 2 diabetes that occurs in young ages. In the case of suspected type 1 diabetes. Differential diagnosis requires measuring C-peptide levels, and testing for islet autoantibodies.

MODY should be considered in cases with early-onset diabetes, without insulin resistance and who respond well to sulphonylureas (SU).
Genetic screening tests should be performed in families with confirmed or highly suspected MODY cases. However, the number of centers that can perform these expensive tests are limited. In this case, some biomarkers may be used. For example MODY3 is a common type of MODY and occurs due to HNF-1α mutation. High sensitive C-reactive protein (hsCRP) levels in MODY3 patients are lower in comparison to type 1 diabetes, type 2 diabetes, and other MODY types (<0.3 mg/L). In centers where genetic tests are not readily available, demonstration of low hsCRP levels in serum suggests the diagnosis of MODY3.

If genetic screening opportunities are available for patients with suspected MODY, it is convenient to test for MODY3, MODY2, and MODY1, which are relatively more common types.

1.6.2. CYSTIC FIBROSIS RELATED DIABETES

Although not common in Turkey, diabetes screening with FPG or OGTT should be performed beginning from 10 years of age in children diagnosed with cystic fibrosis. There is no clear evidence about the use of A1C as a diagnostic tool in patients with cystic fibrosis. Insulin is recommended to treat diabetes in patients with cystic fibrosis. Insulin regimens should be arranged based on patient-specific glycemic control targets.

The patients diagnosed with cystic fibrosis-related diabetes have a high risk of diabetes complications. Screening for complications should be initiated five years after the diagnosis in these patients.

1.6.3. POST-TRANSPLANTATION DIABETES

Patients who underwent to solid organ (i.e. kidney, liver) transplantation are prone to develop diabetes due to various reasons (such as immunosuppressive medications, and other risk factors). Therefore, transplanted patients should be screened for hyperglycemia after the transition to a stable immunosuppressive treatment and in the absence of acute infection. OGTT is the preferred diagnostic test. In the selection of immunosuppressive drugs, potential benefits for the patient should be considered rather than the risk of diabetes.

1.7. SCREENING AND DIAGNOSTIC TESTS

1.7.1. TYPE 1 DIABETES SCREENING

- There is no indication for routine screening. However, general population or family screening tests (autoantibody screening in first degree relatives of type 1 diabetes patients) are conducted for research purposes in various populations.
- In the presence of typical diabetes symptoms and signs (polyuria, polydipsia, mouth dryness, polyphagia, weight loss, blurred vision, etc.), blood glucose measurements should be performed for diagnosis.
- Even if in adulthood, patients should be investigated for type 1 diabetes in case of acute onset diabetes, sudden weight loss, low body weight, and type 1 diabetes history in the family.
- In a nondiabetic individual with first-degree relative type 1 diabetes, if two or more autoantibodies are positive, the risk of developing type 1 diabetes is high. Such individuals may be directed to type 1 diabetes prevention studies.
1.7.2. | **TYPE 2 DIABETES SCREENING**

All adults should be evaluated for type 2 diabetes risk factors in accordance with their demographic and clinical features. Individuals with high diabetes risk are presented below:

<table>
<thead>
<tr>
<th><strong>Individuals with high diabetes risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Because the prevalence of diabetes exceeds 10% in the population over 40 years, diabetes screening should be performed every three years, starting from 40 years of age regardless of weight. FPG test is the preferred method.</td>
</tr>
<tr>
<td>2. Asymptomatic individuals with BMI ≥ 25 kg/m² and belong to any of the following risk groups should be screened for diabetes more frequently (for example, annually), and starting from earlier ages.</td>
</tr>
<tr>
<td>• Individuals who have first and second-degree relatives with diabetes</td>
</tr>
<tr>
<td>• Individuals belong to ethnic groups with high diabetes prevalence</td>
</tr>
<tr>
<td>• Women who gave birth to macrosomic (birth weight of 4.5 kg or more) baby or who have previous diagnosis of GDM</td>
</tr>
<tr>
<td>• Hypertensive individuals (BP ≥ 140/90 mmHg)</td>
</tr>
<tr>
<td>• Individuals with dyslipidemia (HDL-cholesterol &lt;35 mg/dL or triglycerides ≥ 250 mg/dL)</td>
</tr>
<tr>
<td>• Women with polycystic ovarian syndrome (PCOS)</td>
</tr>
<tr>
<td>• Individuals with clinical conditions or findings (e.g. acanthosis nigricans) related to insulin resistance</td>
</tr>
<tr>
<td>• Those with coronary, peripheral or cerebral vascular disease</td>
</tr>
<tr>
<td>• Individuals born with low birth weight</td>
</tr>
<tr>
<td>• Individuals with sedentary life style or low physical activity</td>
</tr>
<tr>
<td>• Nutritional habits rich in saturated fat and low in fibers</td>
</tr>
<tr>
<td>• Patients with schizophrenia and those on atypical antipsychotic medication</td>
</tr>
<tr>
<td>• Solid organ (especially renal) transplantation patients</td>
</tr>
<tr>
<td>• Patients with long-term corticosteroid or antiretroviral drug use</td>
</tr>
</tbody>
</table>

3. Annual diabetes screening should be performed in individuals with prediabetes (IFG, IGT, or HRG).

4. Diabetes screening should be performed every three years in women with previous GDM diagnosis.

AFPG, fasting plasma glucose; BMI, body mass index; GDM, gestational diabetes mellitus; BP, blood pressure; HDL-cholesterol, high density lipoprotein cholesterol; PCOS, polycystic ovarian syndrome; IFG, impaired fasting glucose (FPG: 100-125 mg/dL); IGT, impaired glucose tolerance (OGTT 2-hr PG: 140-199 mg/dL; HRG, high risk group [A1C: 5.7-6.4%; 39-47 mmol/mol].

Children and adolescents with high type 2 diabetes risk (especially obese or overweight and have additional risk factors) should have diabetes screening every two years starting from 10 years of age.

The following scheme shows the diabetes screening and diagnosis algorithm (Figure 1.1).
SEMT RECOMMENDATIONS

1. All adults should be evaluated for type 2 diabetes risk factors in accordance with their demographic and clinical features (D).

2. FPG levels should be measured in all individuals starting from 40 years of age (A), and from earlier ages if they have diabetes risk factors and BMI ≥25 kg/m² (D).

3. Individuals with additional risk factors should be evaluated with FPG from an early age, and more frequently; individuals with prediabetes or previous history of GDM should be evaluated with OGTT (D).

4. 75 g glucose standard OGTT should be performed for individuals with FPG 100-125 mg/dL and should be assessed based on 2-hr PG levels (D).

5. In a nondiabetic individual with first-degree relative type 1 diabetes, if two or more autoantibodies are positive, the risk of developing type 1 diabetes is high. Such individuals may be directed to type 1 diabetes prevention studies (B).

REFERENCES


1.7.3. **SEMT GESTATIONAL DIABETES MELLITUS SCREENING**

In all asymptomatic pregnant women without known diabetes, risk evaluation and FPG measurements should be performed at the first antenatal visit. If FPG ≥126 mg/dL, the test should be repeated on the following day or the diagnosis should be confirmed with A1C or OGTT. Should the diagnosis is confirmed with FPG or OGTT 2-hr PG or A1C, then it should be considered and treated as previously undiagnosed diabetes (pregestational diabetes).

If FPG is found in prediabetes range (FPG 100-125 mg/dL) at the beginning of pregnancy, preferably OGTT (or A1C) should be performed and interpreted as in nonpregnant women. Should 2-hr PG is ≥200 mg/dL during OGTT (or A1C ≥6.5%), then “pregestational diabetes” diagnosis is made. If 2-hr PG is 140-199 mg/dL during OGTT (or A1C 5.7-6.4%), then it should be considered as “pregestational prediabetes” and such individuals should be monitored same as pregnant women with diabetes. In case of negative OGTT or A1C tests, then the tests should be repeated in the subsequent trimesters.

**GDM risk factors**
- Obesity
- Previous GDM history
- Maternal age over 40
- Glycosuria
- Previous history of hyperglycemia (prediabetes)
- Diabetes in first degree relatives
- Giving birth to macrosomic (birth weight of 4.5 kg or more) infant
- PCOS
- Corticosteroid or antipsychotic drug use

In a pregnant woman with osmotic symptoms (polyuria, polydipsia etc.) that suggest diabetes at the beginning of pregnancy, if a random blood glucose (measured at any time of the day) is ≥200 mg/dL, then this should be considered as “pregestational diabetes” and the treatment should be initiated.

To reduce macrosomia and related risks in the fetus, to protect maternal health, and to monitor women at risk of future development of type 2 diabetes or insulin resistance in the Turkish population; GDM screening is recommended in all pregnant women at the 24th-28th gestational weeks. The SEMT criteria to be used for the screening and diagnosis of GDM are detailed in the “Diagnostic criteria” section above (Section 1.2.1) and summarized in Figure 1.2. As seen in the figure, GDM investigation can be performed with two- or one-step approach.

**In two-step approach**, a screening test with 50 g glucose is performed first.

- In women with 1 hr PG 140-179 mg/dL after 50 g glucose load, a 3-hour 100 g glucose OGTT test is performed for definitive diagnosis of GDM. OGTT is not required if 1-hr PG is ≥180 mg/dL in 50 g glucose screening test. These cases should be considered as GDM and treatment must be started.
- The diagnosis of GDM is made if at least two out of four cut-off points in 3-hour 100 g glucose OGTT are exceeded. Cases with only 1 value over the cut-off are considered as “Gestational Glucose Intolerance” and should be closely monitored as in GDM.
In one-step approach, 75 g glucose OGTT is directly performed before any pre-screening test. In this test GDM diagnosis is made if either one of FPG, 1-hr PG or 2-hr PG cut-off points is exceeded.

Post-pregnancy screening: In women diagnosed with GDM, a standard 2-hour OGTT with 75 g of glucose should be performed 4-12 weeks after delivery and interpreted based on standard diabetes criteria. Women with a history of GDM should be screened for diabetes every 3 years for lifelong.

The risk of permanent type 2 diabetes is high in women with a history of GDM. Lifelong healthy lifestyle interventions should be applied and if necessary, metformin should be prescribed.

**SEMT RECOMMENDATIONS**

1. All pregnant women without known diabetes should be screened for diabetes at first antenatal visit and interpreted as in non-pregnant women (B).
2. To reduce fetal morbidity, and to predict future development of type 2 diabetes and insulin resistance in mother (C), regardless of the presence of any risk factors, GDM should be screened at 24-28 gestational weeks with OGTT in all pregnant women (D).
3. There is not any confirmed diagnostic method other than OGTT for the diagnosis of GDM for today (A).

4. Two different approaches, two-step and one-step, can be used for GDM screening (D).

5. In two-step approach, PG is measured 1 hour after a 50 g glucose loading at any time of the day (D). If 1-hr PG 140-179 mg/dL, then an OGTT with 100 g glucose is performed for definitive diagnosis of GDM. The diagnosis of GDM is made if at least two of the four (i.e. fasting, 1-hr, 2-hr, and 3-hr) PG levels are over the normal limit in OGTT (A).

6. OGTT is not required if 1-hr PG is ≥180 mg/dL after 50 g glucose load. These cases should be closely monitored as in GDM (A).

7. In one-step approach, 75 g glucose OGTT is directly performed (D). GDM diagnosis is made if at least one of the three (i.e. fasting, 1-hr, and 2-hr) PG levels are over the normal limit (A).

8. Women with a history of GDM should be screened for diabetes with standard OGTT 4-12 weeks after delivery, and screening should be repeated every three years with any method (D).

REFERENCES

1.7.4. | PREPARATION AND PERFORMANCE OF ORAL GLUCOSE TOLERANCE TEST

The rules required to be considered during OGTT are specified below:

- Before the test, a sufficient amount of CH (≥150 g/day) should be consumed for at least 3 days and routine physical activity should be maintained.
- The test is performed after at least 8 hours of fasting and in the morning.
- It is recommended to consume a meal containing 30-50 g of CH in the evening before the test.
- Water is allowed before and during the test; however, beverages like tea/coffee and smoking are prohibited.
- The person should be at rest during the test.
- OGTT should not be performed if drugs that impair CH tolerance are used, there is inactivity or acute/chronic infection.
- A fasting blood sample is collected, then 75 g of anhydrous glucose or 82.5 g of glucose monohydrate is dissolved in 250-300 ml of water and the patient is asked to drink the mixture within 5 minutes.
- The moment when the patient starts drinking the glucose liquid is accepted as the starting time of the test. A blood sample is collected 2 hours after the starting time.
- Glucose amount to be given in children is 1.75 g/kg (maximum 75 g).
If the glucose cannot be measured immediately, serum that is collected to tubes containing sodium fluoride, can be centrifuged and the plasma can be refrigerated until glucose can be measured.

1.7.5. **OTHER DIAGNOSTIC TESTS**

**C-peptide level**

C-peptide levels reflect the pancreatic β-cell (endogenous insulin) reserve. Routine measurement is not required in type 1 diabetes. Fasting and stimulated C-peptide levels can be measured for the differentiation of autoimmune forms of diabetes (e.g., LADA) from type 2 diabetes and for the determination of type 2 diabetes cases for whom insulin therapy will be initiated. However, in cases with extreme hyperglycemia, C-peptide levels may not reflect the actual endogenous insulin reserve due to glucose toxicity on the pancreatic β-cells.

**Islet autoantibodies**

These are anti-glutamic asid decarboxylase (Anti-GAD), islet-cell cytoplasmic antibody (ICA), insulin autoantibody (IAA) anti-tyrosine phosphatase, anti-phogrin antibodies (IA2 and IA2-β) and zinc transporter-8 antibody (anti-ZnT8). Routine measurement of autoantibodies is not required in type 1 diabetes. However, it may be useful for suspected MODY or for the determination of autoimmune forms of diabetes (i.e. LADA).

**SEMT RECOMMENDATIONS**

1. Except for high suspicion of diabetes due to symptoms and high-risk individuals, FPG should be preferred for diabetes screening and diagnosis in children and non-pregnant adults (D).

2. In case of high suspicion of diabetes and high-risk individuals, OGTT should be performed for diagnosis even if FPG levels are within normal range (D).

3. An A1C test performed with a certified and standardized method can also be used for diabetes screening and diagnosis (D).

**REFERENCES**

Standards of care for patients with diabetes are summarized in this section. Important issues to be asked in anamnesis are individually specified. Considerations to be noted during physical examination are discussed, laboratory tests and their repetition frequencies are explained briefly. Preferred drug choices for treatment, especially for HT and lipid disorders, are presented according to the evidence-based information. In the “Complications” section, atherosclerosis is addressed in particular and prevention, monitoring, the importance of quitting smoking and the role of education are highlighted.

Figure 2.1 shows the standard diabetes care algorithm in adults with type 1 diabetes.

**FIGURE 2.1:** Diabetes care for adults with type 1 diabetes

- **First evaluation**
  - Diagnosis and evaluation (acute care if needed)
  - Initial education and skill acquisition
- **Annual follow-up**
  - Annual evaluation of education and skills
  - Closing gaps in education (skill building and encouragement, avoiding prejudice)
  - Follow-up of CV risk factors
  - Follow-up of complications
- **Regular follow-up (every 3-6 months)**
  - Regulation and dose adjustment of insulin therapy
  - Structured recommendations of education, lifestyle and nutrition
  - Treatment of CV risk factors
  - Treatment specific to complications, referral to other disciplines

**CV, Cardiovascular**
2.1. ANAMNESIS

- Symptoms, physical examination findings and laboratory results related to diabetes diagnosis
- Previous A1C
- Eating habits, nutritional condition, weight history, growth and development in children and adolescents
- Details of previous treatment programs (nutrition, self-monitoring of blood glucose [SMBG], habits and beliefs on health)
- Ongoing diabetes treatment (drugs, meal plan, SMBG results)
- Other drugs that may influence glucose level
- Details of physical activity program
- Frequency, severity and causes of acute complications (DKA, hypoglycemia)
- Previous or current infections (skin, foot, tooth, genitourinary)
- Symptoms and treatment details related to chronic complications (eye, kidney, nerve, genitourinary, gastrointestinal, heart, vascular disease, diabetic foot, cerebrovascular event)
- Risk factors for atherosclerosis (smoking, HT, obesity, dyslipidemia, family history)
- Other diseases related to endocrine system and eating habits
- Factors (lifestyle, cultural, psychosocial, educational and economic) that may affect diabetes monitoring and treatment
- Smoking and alcohol use, substance abuse
- Contraception, reproductive life, sexual anamnesis
- Diabetes and other diseases (chronic diseases, endocrinopathies and autoimmune diseases) in the family should be inquired.

2.2. PHYSICAL EXAMINATION

- Height, weight measurements (comparison with standard growth [weight and height] curves in children and adolescents)
- Waist circumference measurement (for all adult with diabetes)
- Stage of puberty, sexual development degree
- Blood pressure (orthostatic measurement if necessary, comparison with normal values based on age)
- Fundoscopic examination
- Oral examination
- Thyroid palpation
- Cardiac examination
- Abdominal examination (liver palpation)
- Pulse examination (palpation and auscultation)
- Hand/finger examination (for sclerodactyly and Dupuytren contracture)
- Foot examination (for diabetic foot risk)
- Skin examination (acanthosis nigricans, insulin injection sites)
- Neurological examination
- Signs related to diseases/conditions (hemochromatosis, pancreatic diseases, endocrinopathies, genetic syndromes) that may cause secondary diabetes
2.3. | CONSULTATIONS

- Referral to diettian for medical nutrition therapy
- Diabetes educator (if there is no diabetes educator, physician should provide the education)
- Fundoscopy examination
- Family planning for women at reproductive age
- Psychologist (if behavioral therapy is needed)
- Foot examination (as there are very few podiatrists in our country, assistance should be sought from diabetes nurse, dermatologist or physiotherapist)
- Other departments (eye diseases, neurology, nephrology, cardiology, gynecology, dentistry etc.) should be consulted when needed.

2.4. | LABORATORY EXAMINATIONS AND ROUTINE FOLLOW-UP

Routine laboratory tests that should be requested from diabetes patients and follow-up periods are shown below:

- **A1C:** Every 3-6 months.
- **Fasting lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides):** Annually
- **Albuminuria [albumin/creatinin ratio (ACR) or urinary albumin excretion (UAE)]:** On puberty or 5 years after the diagnosis in type 1 diabetes; at the time of diagnosis in type 2 diabetes and then annually. ACR in first-morning (or spot) urine should be preferred. UAE is interpreted based on the principles shown in Table 2.1, however, in recent years, the quantitative change of UAE over time is taken into consideration instead of progression to microalbuminuria or macroalbuminuria.
- **Serum creatinin and eGFR:** Annually in adults (in children if there is proteinuria) and estimated glomerular filtration rate (eGFR) should be calculated.
- **Liver enzymes:** Annually.
- **TSH (in all type 1 diabetes patients and, if needed, in type 2 diabetes patients):** If TSH is not normal, free-T4 should be tested. Anti-thyroid peroxidase (Anti-TPO) and anti-thyroglobulin (Anti-Tg) antibodies should be screened for autoimmune thyroiditis at first diagnosis in type 1 diabetes. Moreover, TSH should be controlled after metabolic control is achieved. TSH test should be repeated once in every 1-2 years or when thyroid disease-related symptoms occur if the initial check was normal
- **ECG:** Annually in adults
- **Urinary analysis (ketone, protein, sedimentation):** At each visit.
- **In children and adolescents with type 1 diabetes, antibodies related to gluten enteropathy [antibodies to tissue transglutaminase and anti-endomysium-IgA, provided that serum IgA level is normal] should be analyzed, and symptomatic cases or patients with positive antibody should be referred to gastroenterologist for endoscopy to provide definitive diagnosis.
- **Vitamin B12 level should** be measured especially in adults using metformin and in individuals with suspected pernicious anemia.
• Serum potassium level: Annually especially in patients using angiotensin converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), mineralocorticoid antagonist or diuretic.

**TABLE 2.1: Assessment of albuminuria**

<table>
<thead>
<tr>
<th></th>
<th>First-morning void</th>
<th>24-hr urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UACR (mg/g)</td>
<td>UAE (mg/day)</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
<td>&lt;30</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Microalbuminuria*</td>
<td>30-300</td>
<td>30-300</td>
</tr>
<tr>
<td>Macroalbuminuria (Clinical albuminuria)</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
</tbody>
</table>

UAE, urinary albumin excretion; UACR, urine albumin-to-creatinine ratio
*Microalbuminuria is accepted if at least two of the three measurements taken in the last 3-6 months are higher than normal. UAE may be high if intense physical exercise performed in the last 24 hours or presence of infection, fever, congestive heart failure, severe hyperglycemia, and hypertension.

**Glomerular filtration rate (GFR)**

It is measured with creatinine clearance. Estimated GFR (eGFR) can be calculated by using one of the following formulas.

**Cockcroft-Gault formula**

\[
eGFR = \left(\frac{140 - \text{Age}}{\text{Weight (kg)}}\right) \times \left(\frac{\text{Serum Creatinine (mg/dL)}}{88.4}\right)\
\]

*Multiplied by 0.85 in women.
Some references recommend Cockcroft formula as

\[
GFR = \left(\frac{140 - \text{Age}}{\text{Weight (kg)}}\right) \times \left(\frac{\text{Serum Creatinine (mg/dL)}}{72}\right)
\]

**MDRD formula**

Alternatively, eGFR can be calculated by using the MDRD formula obtained in the Modification of Diet and Renal Disease (MDRD) study. MDRD formula has been claimed to provide more accurate results than the Cockcroft formula, especially in elderly patients with diabetes.

Estimated GFR calculation with shortened MDRD equation:

\[
eGFR = 186 \times \left(\frac{\text{Serum Creatinine (mg/dL)}}{88.4}\right)^{1.154}\times \left(\text{Age}\right)^{-0.203}\times (0.742 \text{ if woman})
\]

**CKD-EPI formula**

\[
eGFR = 141 - \text{Min(Serum Creatinine/κ, 1)}^{1.209}\times \text{Max(Creatinine/κ, 1)}^{0.993} \times 0.993^{85} \times 1.018 \text{ if female}
\]

**For serum creatinine (mg/dL) values are 0.7 for female, 0.9 for; a values are -0.329 for female, -0.411 for male. Min: Minimum, Max: Maximum.**

The following web site can be used to calculate eGFR by using one of these three formulae:

[www.kidney.org/professionals/KDOQ/gfr_calculator - Calculators for Health Care Professionals - National Kidney Foundation]
2.4.1. | GLYCEMIC CONTROL

Self-monitoring of blood glucose (SMBG)

- Measurement frequencies of blood glucose should be determined according to the patients’ need (3-4 times or more in a day for type 1 diabetes patients under basal-bolus insulin therapy, pregnant women, and patients using insulin pump; 3-4 times a week for patients with uncontrolled type 2 diabetes).

- Postprandial glycemia (PPG): It should be measured in patients whose A1C is not achieved to target despite the acceptable fasting and pre-prandial glucose levels, and in patients with diabetes whose therapy is directed to postprandial glycemic regulation. In general, PPG is measured 2 hours after the first bite of a main meal. In pregnant women, the measurement must be performed 1 hour later.

- Patients should be trained about MNT and insulin/drug dose adjustments based on SMBG results.

- SMBG technique should be checked regularly, and patients should be reminded that they should store their glucose test strips in closed vials and keep away from heat as per instructions.

Continuous glucose monitoring systems (glucose sensors)

In recent years, the use of these systems has become more common. It has been shown to facilitate patient education and providing better glycemic control, especially for patients with type 1 and pre-gestational diabetes.

Long-term glucose control (A1C)

- A1C should be measured once in every three months for type 1 diabetes patients and type 2 diabetes patients that use insulin or lack glycemic control, and in every six months for type 2 patients who are under control.

- A1C result should be evaluated together with SMBG.

This subject is described in Section 4.1 and 4.2 in detail.

2.4.2. | BLOOD PRESSURE CONTROL

Target blood pressure

- Blood pressure (BP) target is <140/90 mmHg. Self-BP monitoring should be recommended to hypertensive patients with appropriate conditions.

- Cardiovascular (CV) risk factors also should be considered with BP. In young cases without severe hypotension risk, lower BP targets which the patients can tolerate should be aimed (<130/80 mmHg).

This subject is described in Section 16.1 and 16.2 in detail.

2.4.3. | LIPID PROFILE

The recent international lipid guidelines recommend the evaluation of atherosclerotic CV disease (ASCVD) risk in addition to lipid levels.
Based on these guidelines, diabetic individuals with a previous history of atherosclerotic coronary artery disease (CAD) or those with 10-year CAD risk >7.5%, and LDL-cholesterol level 70-189 mg/dL are considered at risk, and statin initiation is recommended. The following lipid levels are the targets for the treatment.

**Target lipid levels**
- LDL-cholesterol <100 mg/dL (<70 mg/dL in patients with diabetes with history of primary CV event)
- Triglyceride <150 mg/dL
- HDL-cholesterol for men >40 mg/dL, for women >50 mg/dL
- Non-HDL-cholesterol <130 mg/dL (for low risk), <100 mg/dL (for high risk).

However, in recent years, it is preferred to consider the 10-year CV risk level and to plan lipid treatment accordingly rather than focused just LDL-cholesterol and HDL-cholesterol targets.

**Frequency of measurement**
- Annually (may vary depending on the patient needs)
- This subject is described in Section 17 in detail.

### 2.5. COMPLICATIONS

#### 2.5.1. PREVENTION OF CORONARY ARTERY DISEASE

Risk, poor prognosis, and mortality of CAD has increased notably in patients with type 2 diabetes. Considerations to prevent CAD are summarized below:

**Anti-thrombocyte (antiaggregant) treatment**
- In all adults with diabetes and macrovascular disease, acetylsalicylic acid (ASA) should be considered 80-150 mg/day as a secondary protection.
- ASA (80-150 mg/dL) should be used as primary protection in diabetic patients with high 10-year CV risk (>10%). Individuals who are older than 50 years of age and have at least one additional risk factor (CVD history in the family, HT, dyslipidemia or microalbuminuria and smoking in the patients) are at high risk for CV disease (see Section 13.1).
- No ASA should be administered for diabetes patients younger than 21 years of age according to the risk of Reye syndrome risk.
- The protective role of ASA hasn’t been studied in patients younger than 30 years of age.

**Smoking Cessation**
- Epidemiological case-controlled studies have clearly demonstrated a causal relationship between smoking and health risks. Statistics in developed countries reveal that one in every five deaths is related to smoking.
- Smoking is the most important and changeable CV risk factor.
- In people with diabetes, smoking more significantly increases CVD morbidity and early mortality risk than the general population.
- Moreover, smoking is associated with earlier development and progression of microvascular complications.
• Some prospective studies have shown that smoking can increase type 2 diabetes development risk. However, sometimes individuals that quit smoking consume uncontrolled amounts of snack food to fight the physical mouth habit of smoking, and this can lead to weight gain and diabetes. Therefore, the necessity of increased physical activity and healthy nutrition must be emphasized in the program of smoking cessation and nutritional support should be provided for the patients.

• All members of the diabetes team (physician, nurse, dietician and psychologist) should encourage patients with diabetes to quit smoking,

• The amount of cigarette consumption and how long it has been used should be recorded,

• Support should be provided to patients who have at risk of smoking again,

• Routine diabetes care/education programs should include smoking cessation methods that are proven to be effective.

• Tobacco products with lowered health risks [electronic cigarette, heated tobacco products, nicotine bands, etc.] are not recommended as they are harmful as well.

In conclusion, smoking cessation is an efficient and cost-effective approach for the mitigation of described risks.

**Screening**

1. Exercise stress test should be performed for symptomatic patients with high CVD risk.
2. Patients should be referred to the cardiologist when necessary.

This subject is described in Section 13.1 in detail.

2.5.2. | **DIABETIC RETINOPATHY**

**General recommendation**

• Optimal glycemic and BP control must be achieved.

**Screening and follow-up**

• Fundus examination should perform five years after the diagnosis or during puberty in type 1 diabetes, and at the time of diagnosis in type 2 diabetes. If examination findings are normal, it should be repeated one year later. If it is normal again, follow-up intervals can be increased to two years.

• Fundus examination can be done by indirect ophthalmoscopy that will be performed by a physician preferably by dilating the pupils, or through retinal images from standard angles to be acquired by a diabetes nurse. If an abnormality is detected, the patient must be referred to an ophthalmologist. In places that are absent from such opportunities, patients should be referred to an ophthalmologist.

• The patients with persistent microalbuminuria have a higher risk of retinopathy; therefore, fundus examinations must be more frequent in those.

• In women with diabetes who are planning for pregnancy, fundus exam should be performed before pregnancy. Monitoring should be done in the first trimester and necessary intervals afterward.

• An ophthalmologist should monitor patients with macular edema, advanced non-proliferative retinopathy, or proliferative retinopathy.

This subject is described in Section 13.2.1 in detail.
2.5.3. **DIABETIC NEPHROPATHY**

**General recommendation**
- Glycemic and BP control must be achieved.

**Screening**
1. Albuminuria (UACR or UAE): Should be annually measured;
   - In type 1 patients with diabetes duration ≥ 5 years,
   - In all type 2 patients, since diagnosis of diabetes.
2. eGFR should be calculated with annual serum creatinine measurements.
This subject is described in Section 13.2.2 in detail.

2.5.4. **DIABETIC FOOT PROBLEMS**

**General recommendation**
- A multidisciplinary approach is essential. Detailed examination of feet and vascular evaluation must be performed, patients should be trained about foot care and avoiding diabetic foot.

**Patients with the following conditions have high amputation risk**
- Peripheral sensory neuropathy,
- Deteriorated foot biomechanics,
- Increased pressure findings (erythema under the callus, bleeding),
- Bone deformity,
- Peripheral artery disease (weak or disappeared pulse),
- Ulcer or amputation history,
- Severe nail pathology.
This subject is described in Section 14 in detail.

2.6. **EDUCATION**

Education is the basis of both type 1 and type 2 diabetes treatments. When urgent problems are solved, newly diagnosed patients should be referred to a diabetes center for education programs given by the physician, nurse, and dietitian. The education should repeat regularly.

The program should provide the following skills to people with diabetes.

**Patients with type 1 diabetes should know;**
- When to eat and what?
- What to do during and after exercise?
- Performing SMBG 4-8 times a day,
- Insulin injection 2-5 times a day,
- Symptoms and treatment of hypoglycemia,
- Glucagon injection when needed,
- Managing anxiety due to the fear of hypoglycemia and/or hyperglycemia,
- Managing anxiety due to the fear of microvascular complication risk,
- Avoiding microvascular complications,
- Foot care,
- How to regulate diabetes in case of acute diseases and exceptional condition, and when to contact the healthcare team,
- Contraceptive methods for women in reproductive age, and the importance of glycemic control in pregnancy.

**Patients with type 2 diabetes should know;**

- The importance of a healthy diet for weight loss,
- How to increase physical activity,
- Number and timing of SMBG based on treatment,
- When to use the prescribed antidiabetic drugs,
- The possible need of insulin during the natural course of the disease,
- Those accompanying other problems may affect their diabetes,
- Insulin injection if needed,
- Symptoms and treatment of hypoglycemia,
- Prevention the micro- and macrovascular complications,
- Foot care,
- How to regulate diabetes in case of acute diseases and exceptional condition, and when to contact the healthcare team,
- Contraceptive methods for women in reproductive age, and the importance of glycemic control in pregnancy.

All type 1 and type 2 diabetes patients must be informed about dental and gingival diseases, and annual dental examination should be recommended. Also, all patients with diabetes should be informed about vaccination practices and their timing (see Section 15.8).

**SEMT RECOMMENDATIONS**

1. **Patients with diabetes and their family members should be provided with diabetes education to increase their information and skills in self-management of diabetes (A).**
2. **All people with diabetes their family members must be taught SMBG, and education should be provided to enable them to make treatment adjustments as per the PG results (A).**

**REFERENCES**


**2.7. ROUTINE PARAMETERS OF DIABETES MONITORING**

Table 2.2 summarizes the parameters which should be asked in anamnesis at the diagnosis and during follow-up.

Table 2.3 summarizes which physical examinations and consultations will be performed at the beginning and during the follow-up, and information about the required laboratory tests.
### TABLE 2.2. Anamnesis parameters required during diagnosis and follow-up of patients with diabetes*

<table>
<thead>
<tr>
<th>Life Style and Habits</th>
<th>At Diagnosis</th>
<th>At each follow-up (once in every 3–6 months)</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Nutritional habits</td>
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<td></td>
</tr>
<tr>
<td>Sleep</td>
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<tr>
<td>Tobacco use</td>
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<tr>
<td>Alcohol use</td>
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<td></td>
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<tr>
<td><strong>Background Information</strong></td>
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<td>Onset form of diabetes</td>
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<td>Previous diabetes treatments</td>
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<td>Hospitalizations due to diabetes</td>
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<td>Depression disorder</td>
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<td>Other accompanying diseases</td>
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<tr>
<td>Surgeries</td>
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</tr>
<tr>
<td>Reproductive life of women**</td>
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<tr>
<td><strong>Vaccination History</strong></td>
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<td>Seasonal flu</td>
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<td>Pneumonia</td>
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<tr>
<td>Hepatitis B</td>
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</tr>
<tr>
<td>Other</td>
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<td><strong>Family History</strong></td>
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<td>Diabetes in the family</td>
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<td>Hypertension in the family</td>
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<td>Early ASCVD in the family</td>
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<tr>
<td>Autoimmune diseases in the family</td>
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<td></td>
</tr>
</tbody>
</table>

ASCVD: Atherosclerotic cardiovascular disease  
**Refer to related sections for a description**

**Reproductive life: Menstrual cycle, menopause, polycystic ovarian syndrome, gestational diabetes, obstetric history, etc.

### TABLE 2.3. Physical examination, consultation and laboratory parameters*

<table>
<thead>
<tr>
<th>Physical Examination and Consultations</th>
<th>At Diagnosis</th>
<th>At each follow-up (once in every 3–6 months)</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height/Weight/BMI</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Waist circumference</td>
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<td></td>
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</tr>
<tr>
<td>Blood pressure</td>
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<td></td>
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</tr>
<tr>
<td>Systemic examination</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fundus oculi examination</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Foot/pulse examination</td>
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<td></td>
</tr>
<tr>
<td>Nervous system examination</td>
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</tr>
<tr>
<td>Thyroid examination</td>
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</tr>
<tr>
<td>Dental examination</td>
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<td></td>
</tr>
<tr>
<td>Nutritional evaluations</td>
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<tr>
<td><strong>Laboratory Examination</strong></td>
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<td></td>
</tr>
<tr>
<td>FPG/random glucose</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>SMBG</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATC</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine/eGFR</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid panel</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K+</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete urinary assay</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Albuminuria [spot UACR]</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>TSH</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-TPO</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D (25OHD)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; FPG, fasting plasma glucose; SMBG, self-monitoring of blood glucose; eGFR, estimated glomerular filtration rate; ALT, alanine amino transferase; K+, potassium; UACR, albumin-to-creatinine ratio in spot urine; TSH, thyroid-stimulating hormone; Anti-TPO, anti-thyroid peroxidase antibody.  
*Refer to related sections for description*
PRINCIPLES OF HOSPITALIZATION IN PATIENTS WITH DIABETES

3.1. | ACUTE METABOLIC COMPLICATIONS

In the following cases, patient must be hospitalized and monitored.

**Diabetic ketoacidosis (DKA)**
- Plasma glucose >250 mg/dL, arterial pH <7.30, serum bicarbonate <15 mEq/L, and moderate/severe ketonuria and ketonemia is present.

**Hyperosmolar hyperglycemic state (HHS)**
- Impaired mental state, severe hyperglycemia (PG >600 mg/dL) and increased serum osmolality (>320 mOsm/kg) is present.

**Severe hypoglycemia and neuroglycopenia**
- PG <50 mg/dL, mental state not recovering despite the hypoglycemia treatment or coma due to identified or suspected hypoglycemia, convulsion, behavioral disorder (disorientation, ataxia, unstable motor coordination, dysphagia, etc.) is present.

3.2. | UNCONTROLLED DIABETES

In the presence any of the following causes in diabetic patients, hospitalization should be considered to investigate the reasons and provide treatment.

- Hyperglycemia accompanying fluid loss
- Constant and resistant hyperglycemia related to metabolic deterioration
- Recurrent and ambulatory treatment-resistant fasting hyperglycemia (>300 mg/dL) or A1C measurement that is more than two times higher than the “normal upper limit” (A1C >11%)
- Recurrent severe hypoglycemia (<50 mg/dL) episodes despite the treatment
- Metabolic imbalance: Frequently repeating hypoglycemia (<50 mg/dL) and fasting hyperglycemia (>300 mg/dL) episodes
- Recurrent DKA episodes without any precipitating cause like infection or trauma
- Interruption of the school or work life due to severe psychosocial problems that disrupt metabolic control and cannot be controlled in ambulatory conditions.

In additions, hospitalization can be required for the following as well.

- At the onset of diabetes-related retinal, renal and neurological complications and in acute CV events
- In cases where diabetes increases the other existing health problems
- In cases that require rapid metabolic control like in pregnancy
- In uncontrolled metabolic conditions related to primary health problems or their treatments (e.g. high-dose glucocorticoid use).
GLYCEMIC CONTROL TARGETS IN PATIENTS WITH DIABETES MELLITUS

4.1. | GLYCEMIC TARGETS

The glycemic control targets for diabetic adults and pregnant women based on widely recognized recommendations are summarized in Table 4.1.

Glycemic targets must be personalized. Goals should be determined based on the conditions of patients such as limited life expectancy, long diabetes duration, increased hypoglycemia risk, having micro and macrovascular complications, and other accompanying diseases. If necessary, more flexible glycemic control should be targeted, as A1C 8.5% (69 mmol/mol).

### TABLE 4.1: Glycemic control targets

<table>
<thead>
<tr>
<th></th>
<th>Target*</th>
<th>In pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C</strong></td>
<td>≤7% (53 mmol/mol)</td>
<td>6-6.5% (42-48 mmol/mol)</td>
</tr>
<tr>
<td><strong>FPG and pre-prandial PG</strong></td>
<td>80-130 mg/dL</td>
<td>&lt;95 mg/dL</td>
</tr>
<tr>
<td><strong>Postprandial 1-hr PPG</strong></td>
<td>-</td>
<td>&lt;140 mg/dL** (preferably &lt;120 mg/dL)</td>
</tr>
<tr>
<td><strong>Postprandial 2-hr PPG</strong></td>
<td>&lt;160 mg/dL</td>
<td>&lt;120 mg/dL</td>
</tr>
</tbody>
</table>

A1C, HbA1c; FPG, fasting plasma glucose; 1-hr PPG and 2-hr PPG, 1-hr and 2-hr postprandial plasma glucose

*Glycemic targets must be personalized (see text).

**In pregnant women, postprandial monitoring should be performed with 1 hour PG.

4.1.1. | GLYCEMIC CONTROL TARGETS IN SPECIFIC GROUPS

**Children and adolescents**

- In children and adolescents with type 1 diabetes, A1C target should be <7.5% (58 mmol/mol). Glycemic targets must be personalized based on the requirements and ability of the patients and their families.
Elderly or patients with short life expectancy

- Strict metabolic control is not recommended for diabetic patients with advanced age, less than 10 years of life expectancy, long-duration diabetes, long-term uncontrolled glycemia, diabetes-related advanced complications, and accompanying diseases. In ACCORD and VA-DT studies, published in 2007 and 2008 respectively, strict metabolic control has been shown to increase CV event risk and that such increase is associated with hypoglycemia in patient groups with elderly and more than 10 years of diabetes.
- In addition to the chronological age of the patient, their life expectancy should also be taken into consideration in the determination of glycemic control targets.
  - If life expectancy >15 years and no major comorbidity, A1C should be <7% (53 mmol/mol).
  - If life expectancy is 5-15 years and there is moderate comorbidity, A1C should be 7.5-8% (58-64 mmol/mol).
  - If life expectancy <5 years and there is major comorbidity, A1C should be 8-8.5% (64-69 mmol/mol)
- For elderly patients with diabetes, when complications, comorbid diseases, and other risks are considered, A1C target value for robust patients with low hypoglycemia risk is recommended to be between 7-7.5% (53-558 mmol/mol). For patients requiring care and with high hypoglycemia and other risks, the A1C target value is recommended to be between 8-8.5% (64-69 mmol/mol).

Women planning pregnancy

- Target A1C should not exceed a maximum of two standard deviations above the upper limit of normal in the pre-conception period, and set at 6.0-6.5% (42-48 mmol/mol).

4.1.2. | A1C MEASUREMENT

A1C test reflects the average glycemic control over the past three months before the measurement. The test can be performed at any hour of the day, and the patients are not required to be fasting.

The normal range is 4.0-6.0% [20-42 mmol/mol] based on the “high-performance liquid chromatography” (HPLC). This method is standardized according to the DCCT study, and the non-diabetic upper limit of A1C [mean 5.9% + 2 standard deviation] should not exceed 6.0% [42 mmol/mol].

Based on this study, it was assumed that mean blood glucose level in a normal person is 100 mg/dl and that this corresponds to an A1C value around 5% [31 mmol/mol] on average, and it was calculated that every 1% increment in A1C above 5% would elevate mean glucose by 35 mg/dl (approximately 2 mol/L). Therefore, estimated mean glucose level for the last three months of a patient with 10% A1C [86 mmol/mol] would be “100 + (5 x 35) = 275 mg/dL”. The mean glucose assumed in the DCCT study is believed to reflect the mean value slightly higher than it should be. “A1C-Derived Average Glucose” (ADAG) study has been conducted to determine the average glucose for the last three months closer to the actual value. The results of this study were published in 2008 and estimated mean glucose levels corresponding to A1C in measurements that are standardized based on this study can be calculated by using the following regression formula.

‘ADAG mean glucose = 28.7 x A1C - 46.7’
Mean glucose levels can be calculated from the related website [http://professional.diabetes.org/eAG].

However, IFCC experts recommend representing A1C in “mmol/mol” unit globally instead of NGSP (%). Some countries, such as the United Kingdom have introduced this practice. Others have started to provide both units together in laboratory reports and decided to convert to only “mmol/mol” unit within the next few years.

The regression formula developed for the conversion of A1C unit from “%” to “mmol/mol” is given below:

\[ \text{IFCC-A1C (mmol/mol) = [(DCCT-A1C (%)] - 2.15) \times 10.929} \]

The following web site can be used for conversion of A1C to “mmol/mol”.

https://www.diabetes.co.uk/hba1c-units-converter.html

According to this conversion, the A1c range determined as 4-6% in non-diabetics is 20-42 mmol/mol, and the glycemic control target determined as 7% in patients with diabetes is 53 mmol/mol.

### TABLE 4.2: The relationship between A1c* and average glycemia

<table>
<thead>
<tr>
<th>NGSP - A1C (%)</th>
<th>DCCT average glucose (mg/dL)</th>
<th>ADAG** average glucose (mg/dL)</th>
<th>IFCC - A1C*** (mmol/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>100</td>
<td>97</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>135</td>
<td>126</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>170</td>
<td>154</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>205</td>
<td>183</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>240</td>
<td>212</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>275</td>
<td>240</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>310</td>
<td>269</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>345</td>
<td>298</td>
<td>108</td>
</tr>
</tbody>
</table>

NGSP, national glucose standardization program; A1C, glycated HbA1c; DCCT, Diabetes Control and Complications Trial; ADAG, A1C- derived average glucose; IFCC, international federation of clinical chemistry and laboratory medicine.

*A1C values are given as both ‘%’ and ‘mmol/mol’

**ADAG average glucose = 28.7xA1C - 46.7

***A1C (mmol/mol) = (A1C [%] - 2.15) \times 10.929


Table 4.2 shows the estimated average 3-month glucose levels corresponding to A1C in DCCT and ADAG studies, and also the equivalent levels of A1C expressed in “%” by NGSP and “mmol/mol” by IFCC.

- 50% of A1C reflects glycemic changes in the last one month, 30% in the second month before the measurement and the remaining 20% in the third month before the analysis.
- As A1C increases, the contribution of fasting glycemia increases further. However, if A1C is close to normal, then the contribution of postprandial glycemia is more prominent.
- A1C does not reflect glycemic variability and hypoglycemia.
- The studies conducted with type 1 and type 2 diabetes patients revealed a close association between the glycemic control degree and the risk of microvascular complications in particular (Table 4.3).
• A1c It should be measured every three months until the glycemic control targets are achieved and every six months in stable patients.

• In cases involving hemolytic and other anemia that affect the lifespan of erythrocytes, glucose-6 phosphate dehydrogenase (G6PD) deficiency, recent blood transfusion, medication that affects erythropoiesis, end-stage renal failure and pregnancy, the actual glucose average and A1C result may be incompatible.

<table>
<thead>
<tr>
<th>TABLE 4.3: The reduction rate in complication and mortality risk achieved with a 1% decrease in A1C.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetes (DCCT)</strong></td>
</tr>
<tr>
<td>Retinopathy risk 35%</td>
</tr>
<tr>
<td>Nephropathy 24-44%</td>
</tr>
<tr>
<td>Neuropathy risk 30%</td>
</tr>
<tr>
<td>-</td>
</tr>
</tbody>
</table>


4.1.3. | FRUCTOSAMINE

Fructosamine shows the glycated proteins (90% glycated albumin) in the plasma. The result reflects the glycemic control over the past 1-3 weeks before the measurement. However, its standardization is inadequate.

• Fructosamine can be used for the evaluation of short-term glucose control in pregnancy or for some hemoglobinopathies.

4.1.4. | KETONE TESTING

**Ketone bodies**

• β-hydroxybutyric acid, acetoacetic acid, and acetone

• They are by-products of fat metabolism. The presence of ketone bodies suggests an inability to properly metabolize food due to insulin deficiency or insufficient CH intake (mild ketone can be seen in fasting).

• Excess amounts of ketone in urine/blood may indicate DKA or may be a predictor for DKA.

• Ketone bodies should be followed in type 1 diabetes, pregestational diabetes, and GDM.

**Method**

• β-hydroxybutyric acid can be measured qualitatively by dipping the strips (sticks) into urine or dropping blood on a strip.

• Ketone measurement in blood is more useful for earlier detection of ketone bodies and to follow treatment response.

**When to measure?**

• When PG is >300 mg/dL (PG >200 mg/dL in pregnancy)

• In cases of acute disease, trauma, and surgeries that cause stress for the organism

• When hyperglycemia symptoms are accompanied by nausea, vomiting, abdominal pain, and fever; and when acetone odor is felt in breath.
# SEMT RECOMMENDATIONS

1. **A1C level should be measured every three months in type 1 diabetes and uncontrolled type 2 diabetes patients, or when treatment adjustments are made (D).** A1C can be measured more frequently (e.g., in pregnancy) when needed (D).

2. **A1C measurement interval can be six months in adult patients with sufficient glycemic control, stable lifestyle, and suitable treatment (D).**

3. **In type 1 and type 2 diabetes patients, glycemic targets for long-term complication risk reduction should be determined on a personal basis according to characteristics and clinical status of each patient (D).**

4. **If there are no special conditions that increase hypoglycemia risk in type 1 and type 2 diabetes patients and the life expectancy is long enough, then A1C target should be <7% (53 mmol/mol) to reduce microvascular complications (A).** For young patients with low hypoglycemia risk, pregnant women or those planning to get pregnant, A1C target can be <6.5% (48 mmol/mol) (C).

5. **A1C reduction should be targeted to reduce macrovascular complications in type 1 diabetes patients (C).**

6. **In patients with CVD risk, the benefit from maintaining a low level of A1C must not increase hypoglycemia and mortality risks (for hypoglycemia: [A]; for mortality in patients with high CV risk: [A]).**

7. **To achieve A1C ≤7% (53 mmol/mol) target in patients with diabetes:**
   - FPG and preprandial PG levels should be 80-130 mg/dL (for type 1 diabetes: [B]; for type 2 diabetes: [B]).
   - 2-hr PG levels should be <160 mg/dL (for type 1 diabetes: [D]; for type 2 diabetes: [D]).

8. **In children and adolescents with type 1 diabetes, A1C target should be <7.5% (58 mmol/mol).** Glycemic targets must be personalized based on the requirements and conditions of the patients and their families (E).

9. **For elderly diabetes patients with normal functional capacity and no other health problems, A1C target should be 7-7.5% (53-58 mmol/mol).** In patients with accompanying diseases, deteriorated neurocognitive functions or limited functional capacity, A1C target should be 8.0-8.5% (64-69 mmol/mol) (C).

10. **Ketone in blood or urine should be tested when PG >250 mg/dl in case of acute disease in type 1 diabetes patients and when PG >200 mg/dl in pregnant women (D).**

11. **Ketone measurement in blood should be preferred under appropriate conditions for earlier detection of ketone bodies and following the treatment response (B).**
REFERENCES


4.2. SELF-MONITORING OF BLOOD GLUCOSE

- Self-monitoring of blood glucose (SMBG) in type 1 diabetes should be performed as an integral part of the treatment.
- SMBG should be performed 3-4 times a day in multi-dose insulin therapy.
- Patients who use an insulin pump should perform SMBG at least before each meal (preferably before snacks as well), before bedtime, before exercise, and if necessary in postprandial period and in the early morning hours.
- Blood glucose level should be measured for all patients with diabetes in the presence of suspected hypoglycemia, especially for those who use insulin, and blood glucose levels should be monitored until safe normoglycemic values are achieved following the hypoglycemia treatment.
- In cases of significant treatment adjustments and intercurrent diseases, SMBG should be performed more frequently.
- Women with diabetes who are pregnant or planning for pregnancy should perform SMBG more frequently. Fasting glycemia and postprandial glycemia 1 hour after the meals should be monitored in pregnant women.
- SMBG is useful for reaching glycemic targets in patients with diabetes who use 1-2 doses of insulin or OAD or those who are followed with MNT (diet). There is no consensus on SMBG frequency and timing in type 2 diabetes patients.
- SMBG can be used to achieve postprandial glycemic targets.
- Patients should be trained on SMBG, and SMBG technique, and they should be checked for the ability to reflect the measurement results through the treatment.
- Continuous subcutaneous glucose monitoring (CGM): CGM can provide additional benefits over SMBG in young patients and those who are familiar with technology. Use of CGM especially for individuals with hypoglycemia unawareness or those with severe or nocturnal hypoglycemia episodes can be useful for the reduction of hypoglycemia (see Chapter 10).
SEMT RECOMMENDATIONS

1. SMBG is an essential component of self-management of diabetes in patients who use insulin (for patients with type 1 diabetes: [A]; for patients with type 2 diabetes [C]).

2. Glucose measurement devices that are approved by international authorities (e.g., IFCC or NGSP) and calibrated based on PG levels should be used, and concurrent fasting venous plasma measurement should be performed at least once a year or in suspected cases to ensure the accuracy of the device (D).

3. Type 1 diabetes patients, pregnant women with diabetes (GDM or pregestational) and type 2 diabetes patients using basal-bolus insulin therapy should perform measurement 3-4 times a day before meals, after meals if required based on personal condition, also once a week at night, at bedtime, and between 02:00-04:00 in the morning once a month (for type 1 diabetes: [A]; for type 2 diabetes [C]; for diabetic pregnancy: [D]).

4. In type 2 diabetes patients who only use OAD with basal insulin, SMBG should be performed at least once a day and at varying times (D).

5. Based on glycemic control level, treatment method and personal characteristics, 3-4 times a week SMBG is recommended for type 2 diabetes patients who are monitored with MNT and OAD.

6. Fasting and 1-hr postprandial PG measurements should be preferred for pregnant women.

7. SMBG should be performed more frequently during treatment adjustment periods, in cases with acute disease and exceptional conditions, as well as in insulin pump users (D).

8. CGM can be useful for patients with repeating severe hypoglycemia, insulin pump users, and women with pregestational diabetes (D).

REFERENCES

5.1. GENERAL PRINCIPLES OF MEDICAL NUTRITION THERAPY

Nutrition treatment is an essential component for the prevention and treatment of prediabetes, diabetes, and related complications. The American Dietetic Association and The American Diabetes Association (ADA) recommends patients with type 1 and type 2 diabetes be referred to a dietitian (if possible, to a dietitian who is in a diabetes team) within the month following diagnosis. Gestational Diabetes Mellitus (GDM) cases should be referred within the first week. Medical nutrition therapy (MNT) training initially completes within 3-6 months and includes 3-4 visits that last 45-90 minutes, and then continues with at least one visit a year to support lifestyle modifications and for the evaluation of the treatment.

MNT consists of four essential implementation steps:

1. General evaluation

For the first recommendations to be given for patients with diabetes; parameters such as the type of diabetes, presence of complications, status of blood glucose control, anthropometric measurements, laboratory findings, administered medical treatment, 24-h or 3-day food consumption, nutritional habits, physical activity level, presence and treatment of other diseases, readiness to any potential modification to dietary habit, and motivation are evaluated on a personal basis and documented.

2. Nutritional diagnosis and target determination

Nutritional diagnosis is determined at evaluation, and current problems associated with dietary habits are identified. Nutritional diagnosis is established, such as unsuitable carbohydrate (CH) intake, fat intake more than required, variable amounts of CH intake on meals, frequent consumption of food with a high glycemic index.

The treatment target should be individualized. It may be to maintain blood glucose control, to achieve acceptable lipid profile, lose weight, etc. Achievable and viable targets and specific behaviors oriented at nutritional diagnosis and individual treatment targets are determined together by the dietitian and the patient with diabetes.

3. Nutritional intervention, self-management training

Nutritional intervention, the essential part of the treatment, focuses on enabling the patient to modify their dietary habits. A meal planning method (food pyramid, plate model, substitution lists, CH counting) suitable for the patient is determined. Recommendations
must be fit for personal requirements, nutritional habits, lifestyle. The patients’ ability and willingness to make necessary modifications should be into account.

The content of nutritional self-management training must make it easier to achieve the determined goal, support to use a meal planning method, to gain acknowledgement and practical skills about diabetes and nutrition treatment.

4. Evaluation of the treatment

It is needed to evaluate practices, compliance, and clinical results and to detect the current problems and treat them. In this step, pre- and post-prandial blood glucose monitoring results and food consumption are evaluated together. Meal time and content can be re-scheduled based on the changes in medical treatment.

Nutritional diagnosis and treatment target can change during follow-up. Self-management of nutrition is provided and the progress towards the target is monitored.

MNT evaluation criteria and timing of the evaluations are presented in Table-5.1.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checking the compliance with meal timing</td>
<td>At every visit</td>
</tr>
<tr>
<td>Combined evaluation of self-monitoring blood glucose [SMBG] and food consumption</td>
<td>At every visit</td>
</tr>
<tr>
<td>Checking the behavioral change</td>
<td>At every visit</td>
</tr>
<tr>
<td>Checking the exercise compliance</td>
<td>At every visit</td>
</tr>
<tr>
<td>Weight and height measurement</td>
<td>Weight at every visit, height once in a year</td>
</tr>
<tr>
<td>FPG and PPG records (together with 3-day food consumption)</td>
<td>At every visit</td>
</tr>
<tr>
<td>A1C</td>
<td>Every 3-6 months</td>
</tr>
<tr>
<td>Fasting lipid profile [LDL-chol., HDL-chol., and TG]</td>
<td>At week 1, 3-6 months later if high, then annually</td>
</tr>
</tbody>
</table>

MNT, medical nutrition therapy; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; A1C, HbA1c; LDL-chol., low-density lipoprotein cholesterol; HDL-chol., high-density lipoprotein cholesterol; TG, triglyceride.

5.1.1 | PURPOSES OF MEDICAL NUTRITION TREATMENT IN THE PREVENTION AND TREATMENT OF DIABETES

1. By building nutritional habits and supporting practices that will improve overall health; To ensure and maintain personalized targets in • Blood glucose levels, • Lipid profile that will reduce CVD risk, • BP and • Body weight.

2. To prevent chronic complications of diabetes by modifying nutrient intake in compliance with lifestyle,

3. To determine the nutritional requirements of the patients’ by considering their personal and cultural preferences and willingness to change,
4. Not to ignore eating pleasure while making scientifically evidenced restrictions in food selection,
5. To meet food requirements in different periods of life in young patients with type 1 and type 2 diabetes, pregnant or breastfeeding women and adults with diabetes,
6. To provide self-management training for diabetes treatment, management of hypoglycemia, and exercise during acute diseases in patients using insulin or insulin secretagogues.

5.1.2. | EFFICACY OF MEDICAL NUTRITION TREATMENT

- Personalized MNT should be used for patients with prediabetes or diabetes. This treatment can be best provided by a qualified dietitian.
- Nutrition training must be responsive to the personal needs, ability to make necessary changes, and willingness to change of the patients with prediabetes or diabetes.

Similar to most of the agents used for the regulation of A1C levels, medical nutrition treatment can provide approximately 1% (0.3-1%) A1C reduction in patients with type 1 diabetes and 0.5-2% (0.5-2.6%) A1C reduction in patients with type 2 diabetes. MNT provides 5-8% reduction in fat intake, 2-4% reduction in saturated fat intake, and 232-710 kcal energy intake in patients with hyperlipidemia; moreover, triglyceride levels a decrease by 11-31%, LDL cholesterol by 7-22% and total cholesterol by 7-21%. In prediabetic patients, mild weight loss and reduction of diabetic risk score and A1C levels have been shown at the end of 12 weeks of MNT.

5.1.3. | EVIDENCE-BASED MEDICAL NUTRITION TREATMENT RECOMMENDATIONS

Evidence-based MNT recommendations have been published by American Dietetic Association, ADA, British Diabetic Association, and Canada Diabetes Association. In light of current evidence and guidelines, evidence-based MNT recommendations prepared by Diabetes Dietary Association are summarized below.

A. Recommendations for energy balance, excess weight, and obesity

- Even a weight loss of 5% in overweight and insulin-resistant obese individuals reduces insulin resistance. Therefore, weight loss is recommended for overweight or obese individuals with diabetes risk.
- The patient’s initial weight can be reduced by 5-7% with structured programs that are focused on lifestyle changes, including less than 30% of energy from fat, regular physical activity, and regular monitoring. Reducing daily energy intake by 500-750 kcal allows 2-3 kg weight loss in a month.
- For the calculation of resting metabolic rate (RMR) of overweight or obese individuals, “Mifflin-St. Jeor Equation” based on current body weight should be used.
  
  RMR (Male): 10 x Weight (kg) + 6.25 x Height (cm) - 5 x Age + 5  
  RMR (Female): 10 x Weight (kg) + 6.25 x Height (cm) - 5 x Age - 161

- Energy Requirement = RMR x Physical Activity Factor (PAF) formula is used for energy requirement calculation. PAF is 1-1.4 for sedentary individuals, 1.4-1.6 for individuals with low activity, 1.6-1.9 for active individuals, and 1.9-2.5 for highly active individuals. Energy requirements calculated with the formula maintains current body weight. Calculated requirement should be reduced by 500-750 kcal to enable weight loss.
• Low CH diets that maintain a daily CH intake of less than 130 g are not recommended. Low CH diets provide similar weight loss with low-fat diets; however, it increases LDL cholesterol levels. Short-term positive effects of low CH diets cannot be maintained in the long term.

• Lipid profile, kidney functions, and protein intake (especially for individuals with nephropathy) should be monitored, and hypoglycemia risk should be evaluated with low CH, low-fat, and energy-restricted diets.

• Individuals who are targeted to achieve > 5% weight loss in a short period (3 months) with very-low-calorie diets (<800 kcal/day) should be carefully identified. Close clinical monitoring should be applied.

• Mediterranean Diet, Dietary Approach Stop Hypertension (DASH), and vegetable-based diets are examples for healthy nutrition models. Their positive effects have been demonstrated in studies. However, personal preferences, needs, and targets should be the focus rather than pre-defined nutrition models.

• In attempts to reduce body weight, it should be noted that sarcopenia is a critical health problem in the geriatric population. Considering that muscle mass begins to decline in the 50s, recommendations should be made to provide adequate protein and energy requirements in overweight or obese people over 65 years of age.

• Fiber intake should be >14 g/day for each 1000 kcal energy intake.

• Physical activity and behavioral changes are essential components of a weight loss program and also help to achieve weight control. Approximately 5-10% weight loss can be achieved with the combination of medication, lifestyle modifications, and physical activity.

Bariatric surgery Surgical intervention can be considered for patients with type 2 diabetes with BMI >35 kg/m². Studies on the risk and long-term benefits of bariatric surgery in prediabetes and diabetes are ongoing.

Bariatric surgery must be performed in well-equipped centers with experienced surgeons. Before the surgery, patients should undergo an extensive and multi-disciplinary examination in terms of previous diet attempts, secondary causes, and risks related to obesity. For the metabolic and nutritional requirements, they should be under life-long follow up starting from the peri-operative period.

B. Recommendations for diabetes prevention

• For individuals with a high risk of type 2 diabetes, structured programs aimed at lifestyle changes are effective. That would provide 7-10% weight loss in 6 months, at least 150 minutes of physical activity per week to maintain weight loss and reduce fat and energy intake.

• The quality of overall food consumption (whole grain, legume, fatty seeds, fruits, vegetables, less processed food) as evaluated by the Alternate Healthy Eating Index is important.

• Individuals with a high risk of type 2 diabetes should be encouraged to ensure 14 g dietary fiber consumption per 1000 kcal and use whole grain for half of their grain intake.

• They should be trained to restrict sugar-flavored beverage consumption.

• Mediterranean nutrition model, low calorie, and low-fat nutrition plan can be useful for prediabetic individuals. There is inadequate evidence for the recommendation of low CH (especially <35% CH) nutritional model. There is limited evidence to suggest that diets with low glycemic load reduce diabetes risk. However, consumption of food with a low
glycemic index and high in fiber and other essential nutrients can be recommended.

- Fatty seeds, soft fruits like strawberry, yogurt, coffee, and tea consumption are associated with decreased diabetes risk. Unlike red meat and sugar-flavored beverages are associated with increased diabetes risk.
- Some observational studies report that a slight amount of alcohol consumption can lower the risk of type 2 diabetes. But, clinical data do not support recommending alcohol consumption for individuals with diabetes risk.
- There is no nutritional recommendation for the prevention of type 1 diabetes. Cohort studies showed that breastfed children have a lower incidence of type 1 diabetes.
- Despite the absence of any specific recommendation associated with the prevention of type 2 diabetes in young individuals, nutritional recommendations that would enable and maintain healthy growth and development and approaches shown to be effective in adults can be applied.

C. Recommendations for diabetes treatment

Macronutrients in diabetes treatment

- The portion of energy to be generated from CH, protein, and fat may vary depending on the nutritional habits, metabolic targets, and personal preferences of diabetes patients. It is not accurate to make recommendations based on a standard distribution. 45–60% of the energy requirement can be met from CH, 10–20% from protein, and 20–35% from fat. Meeting <30% of energy requirement through fat and <7% saturated fat and keeping trans-fat intake <1% is effective for the prevention of cardiovascular diseases.
- Diets that are very low in CH are not recommended as they restrict the consumption of many nutrients that are sources of vitamin, mineral, fiber, and energy

Carbohydrates

- The nutritional model necessary to maintain overall health should include CH foods such as whole grains, fruits, vegetables and low-fat milk.
- In diabetes treatment, low CH diets that maintain a daily CH intake of less than 130 g are not recommended. CH intake should be minimum 175 g/day in pregnant women, and 210 g/day in breastfeeding women.
- In order to achieve glycemic control and reduce the risk of hypoglycemia in individuals receiving, applying or using MNT with OAD or mixed insulin, the time and recommended amount of CH should be determined, daily CH intake should not vary significantly from day to day, and should be consumed in similar amounts every day.
- Monitoring the CH intake through CH count, substitution lists, or experience-based calculations is the key to achieve glycemic control.
- Patients with type 1 and type 2 diabetes who self-regulate the mealtime insulin dose or use insulin pump should adjust the insulin dose based on their CH intake (carbohydrate/insulin: CH/I ratio). Therefore, individuals should be given a detailed nutrition training for CH counting, calculation of CH/I ratio and insulin sensitivity factor (ISF), practices should be frequently checked, and the impact of CH on blood glucose levels should be identified by associating personal blood glucose results and food consumption records. It should be emphasized that the CH counting method does not give the individual with diabetes the liberty to consume CH-containing foods as much as they want to.
• Individuals who practice CH counting as a meal planning method should be warned that increased energy intake would cause weight gain and that protein and fat intake should not exceed prescribed amounts as well.

• In addition to daily total CH intake, taking glycemic index and glycemic load of CH into consideration can provide additional benefit for glycemic control.

• Sucrose intake is not recommended. If consumed, it should not exceed 10% of daily energy intake. Sucrose-containing nutrients can be used as a substitute for another nutrient with equivalent CH amount in the meal plan. To control glycemia, and to prevent fatty liver, and cardiovascular disease (CVD), sugar-flavored beverages intake should be restricted, and excessive energy intake should be avoided.

• Fructose, a natural component in fruits, cause a relatively slow increase in postprandial glucose (PPG) levels in comparison to sucrose or starch consumption with an equivalent energy content. Fructose consumption has no negative impact on triglyceride levels if the amount does not exceed 12% of the daily energy intake. Fruit juice consumption should be avoided, and daily 200 g of fruit should be used instead.

• Fiber consumption should be encouraged; however, it is not necessary to recommend more fiber intake for diabetic individuals than the general population (14 g/1000 kcal/day, 7-13 g soluble fiber).

**Fat and cholesterol in diabetes treatment**

• Saturated fat consumption should be limited to 7-8% of the daily energy intake.

• Due to its LDL cholesterol-increasing and HDL cholesterol-decreasing effect, “trans-fat” consumption must be significantly reduced (<1% of the daily energy intake).

• Daily cholesterol intake should be less than 300 mg in diabetic individuals. Although the last version of “Nutrition Therapy Recommendations for Diabetic Individuals” published by ADA recommends daily cholesterol intake similar to the non-diabetic population for people with diabetes, it seems reasonable to restrict the daily cholesterol intake considering the nutritional habits of Turkish population and the high CV risk of patients with diabetes.

• Two or more portions of fish a week provides omega-3 (n-3) multiple unsaturated fatty acids and should be recommended at this amount.

**Protein in diabetes treatment**

• In the general population, it is recommended that 15-20% (0.8-1 g/kg/day) of daily energy be supplied from proteins. If the renal functions are normal, there is no need to modify this recommendation specifically for diabetic individuals.

• Protein digestion can increase insulin response without increasing the blood glucose concentration in individuals with type 2 diabetes. Proteins should not be used for the treatment of acute or nocturnal hypoglycemia.

• High-protein diets are not recommended for weight loss. The effect of protein intake of more than 20% of energy on the treatment and complications of diabetes is unknown. These types of diets may provide weight loss and improve glycemia in the short term. However, it is not determined that these benefits are maintained in the long term. Besides, increased protein intake also increases saturated fat intake.

**Micro nutrients in diabetes treatment**

• The dietitian should ensure that the recommended vitamins and minerals are met with the meal plan.
• Unless there are any signs of deficiency, as in the general population, there is no obvious evidence that requires vitamin and mineral supplementation or herb and spice recommendation for patients with diabetes.

• As there is limited evidence related to the reliability and efficacy of long-term use, routine supplement of antioxidants like vitamin E, C and carotene is not recommended.

• The benefits of chromium supplement in diabetic or obese individuals have not been clearly demonstrated, and therefore not recommended.

• Evidence that supports the use of cinnamon and other herbal supplements in diabetes treatment is inadequate.

Artificial sweeteners in diabetes treatment

1. Sweeteners with nutritional sustenance: Sorbitol, mannitol, xylitol, erythritol, D-tagatose, isomalt, lactitol, maltitol, and hydrogenated starch hydrolysates are sweeteners that provide energy between 0.2-3.0 kcal/g.

2. Non-nutritive sweeteners: Saccharin, aspartame, acesulfame K, neotame, luo han guo, stevia, and sucralose are energy-free [no nutritional value] sweeteners approved by the FDA. Acceptable daily intake for these sweeteners is shown in Table 5.2.

TABLE 5.2: Acceptable daily intake for energy-free sweeteners

<table>
<thead>
<tr>
<th>Sweetener</th>
<th>Saccharin/Cyclamate</th>
<th>Aspartame</th>
<th>Acesulfame K</th>
<th>Neotam</th>
<th>Stevia</th>
<th>Sucralose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable daily intake (mg/kg)</td>
<td>15</td>
<td>50</td>
<td>15</td>
<td>0.3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Recommendations for artificial sweetener use

1. Foods that contain sweeteners with reduced calorie should be ensured to have their calorie values clearly stated on the product labels. Patients should be trained to build the habit of reading product information.

2. Reduced-calorie or calorie-free sweeteners have no indication as to provide weight loss or prevent diabetes in obese or overweight individuals.

3. The overuse of fructose-containing sweeteners can cause hypertriglyceridemia.

4. Sweeteners such as mannitol and sorbitol can cause diarrhea, especially in children.

5. Aspartame derivatives may exacerbate the disease in children with phenylketonuria.

6. Sugar alcohols and non-nutritive sweeteners are safe to consume within limits approved by the FDA.

Diabetes and alcohol

• Alcohol is not preferred for patients with diabetes. Alcohol consumption can cause various health problems (severe hypoglycemia, ketosis, acute CV events, pancreatitis, fatty liver etc.) in patients with diabetes with poor glycemic control, high hypoglycemia risk, or uncontrolled hyperlipidemia.

• If a diabetic adult without high risks prefers to consume alcohol, recommended daily intake is one unit for women and two units for men, provided that the alcohol use does not exceed two days a week.

• Individuals using insulin or insulin secretagogues should have alcohol together with food to reduce the risk of nocturnal hypoglycemia.
A low level of alcohol consumption solely has no effect on glucose and insulin concentrations in individuals with diabetes. However, alcoholic beverages containing CH can increase blood glucose.

D. Nutrition for specific populations

**Nutrition in patients with type 1 diabetes**

- In type 1 diabetes, insulin therapy should be integrated into the nutrition and physical activity habits of the individual.
- Individuals using rapid-acting (analogous) insulin with injection or pump should adjust their insulin dose to be taken at meal and snack time based on the CH content of the meal and snack.
- CH intake of individuals using mixed insulin should be consistent in between days in terms of time and amount.
- Matching the insulin dose and the amount CH intake in patients with intensive insulin therapy is very important to provide flexibility to CH intake and meal timing as well as regulating the meal timing and to ensure glycemic response that is suitable for a specific meal plan.
- Protein and fat content of the meal can influence postprandial glycemia. The patients may need to adjust their mealtime insulin dose to prevent delayed postprandial hyperglycemia after meals rich in protein and fat intake.
- Patients who inject multiple doses of insulin or use an insulin pump should administer insulin before the meal. If an exercise session is planned within the first two hours after the insulin injection, reducing the insulin dose decreases the risk of hypoglycemia.
- Those who use mixed insulin therapy should maintain similar insulin injection time and meal time every day, identical if possible. Skipping meals is not recommended to prevent hypoglycemia. Patients should keep CH-containing food (table sugar, fiber-free fruit juice) to reduce hypoglycemia risk that may develop due to exercise.
- In addition to the dietitian, all other members of the diabetes team should give consistent and clear messages about food, nutrition, and meal timing behavior.

**Nutrition in patients with type 2 diabetes**

- In order to improve glycemia, dyslipidemia and BP values in patients with type 2 diabetes interventions aimed at reducing the intake of energy, saturated and trans fats, cholesterol, and sodium and increasing physical activity should be encouraged.
- Plasma glucose monitorization can be used to evaluate whether adjustments made in foods and meals are sufficient to ensure target blood glucose levels or whether it is necessary to combine drug therapy with MNT.
- In patients using mixed insulin, the time and amount of CH intake should be consistent between days in order to reduce the risk of hypoglycemia, and to improve glycemic control.
- Sugar-sweetened [sucrose, glucose, high-fructose corn syrup (HFCS)] beverage consumption should be restricted or not recommended in order to prevent weight gain, CV risk, and non-alcoholic steatohepatitis risk.
- Patients who use insulin secretagogue pills should not change CH intake in meal and snacks, make sure to have CH-containing food with meals to reduce hypoglycemia risk, not skip meals, and keep CH-containing food (table sugar, fiber-free fruit juice) with them to reduce hypoglycemia risk that may develop due to exercise.
Nutrition for pregnant or breastfeeding mothers with diabetes

- Proper weight gain in pregnant women is determined based on the BMI values before pregnancy. If pre-pregnancy BMI 18.6-24.9 kg/m², 11.5-16 kg of weight gain, 7-11.5 kg with BMI 25-29.9 kg/m², and 5.5-10 kg of weight gain is recommended throughout of pregnancy with pre-pregnancy BMI ≥30 kg/m².
- In second trimester 340 kcal/day, and in breastfeeding period 450 kcal/day additional energy intake is recommended.
- The energy intake in pregnancy must be sufficient to provide proper weight gain during pregnancy. Weight loss diets are not recommended for pregnant women; however, mild-moderate energy and CH restriction may be suitable for overweight or obese women with GDM.
- Carbohydrate intake in pregnancy should be >175 g/day in pregnant women, and >210 g/day in breastfeeding women.
- As glucose tolerance is decreased in the morning, ≤45 g CH is recommended for breakfast.
- DKA-related ketonemia or fasting ketosis should be avoided.
- MNT in GDM is focused on nutrition selection aimed at proper weight gain, normoglycemia, and absence of ketones in the urine.
- As GDM is a risk factor for future type 2 diabetes risk, lifestyle modifications that target weight loss and increased physical activity are recommended after delivery.

Nutrition for elderly patients with diabetes

- Elderly patients with diabetes can benefit from mild energy restriction and increased physical activity. The energy requirement of the elderly can be lower than younger individuals with the same body weight.
- Daily multivitamin supplements can be suitable for older people with low energy intake in particular.
- Muscle mass loss is faster in elderly individuals with diabetes compared to their non-diabetic counterparts. In attempts to reduce body weight, it should be noted that sarcopenia is an critical health problem in the geriatric population. Considering that muscle mass begins to decline in the 50s, recommendations should be made to provide adequate protein and energy requirements in overweight or obese people over 65 years of age.

E. Nutritional recommendations for the treatment and control of diabetes complications

Microvascular complications

- In the early periods of diabetes and chronic kidney disease, protein intake is reduced to 0.8-1.0 g/kg body weight. In the late stages of chronic kidney disease 0.8 g/kg protein intake may improve renal functions (UAER and GFR).
- Recommended protein intake is 0.8 g/kg/day for non-dialysis diabetic patients with kidney disease. Protein intake is increased depending on the type of dialysis in dialysis patients to preserve muscle mass and function.
- MNT has positive effects on CVD risk factors, and it can be also helpful for microvascular complications such as retinopathy and nephropathy.
- In the 3rd-5th stages of the chronic kidney disease, hypoalbuminemia and energy intake should be monitored, and potential malnutrition risk should be prevented.
Treatment and management of cardiovascular disease risk

- A1C values that are as close to normal as possible should be the target on the condition that such values do not cause any significant hypoglycemia.
- In individuals with diabetes, a diet rich in vegetables and fruit, whole grains and nuts can reduce CVD risk.
- Restricting the daily sodium intake below 2000 mg can decrease symptoms in patients with diabetes and symptomatic heart failure.
- In normotensive and hypertensive patients, reducing the sodium intake (<2300 mg/day) through a diet rich in fruits, vegetables, and low-fat dairy products decreases BP values.
- Slight weight loss helps to decrease BP levels in many people.
- To improve blood lipid levels in diabetic patients with dyslipidemia, lifestyle modifications that would enable body weight loss when needed; reduce saturated fat, cholesterol and trans-fat intake, and increase fruit and vegetable consumption (≥5 servings/day), n-3 fatty acids, soluble fibers and plant stanol/sterol intake as well as physical activity should be recommended.
- Macronutrient intake recommendation to decrease LDL-cholesterol should include ~2 g/day plant stanol or sterol together with 10-25 g/day soluble fiber.

Hypoglycemia

- For hypoglycemia, 15-20 g glucose intake is the preferred treatment method. Any CH source that contains glucose can be used.
- The response to hypoglycemia treatment should be observed within 10-20 minutes. Blood glucose level should be measured again 1 hour after hypoglycemic episode, and additional treatment should be administered if needed.
- The time between treatment of hypoglycemia and the next mealtime should be considered to reduce the risk of recurrent hypoglycemia. If the next meal is 30 or more minutes away, then a snack with 15-20 g CH may be required. Mealtime can be earlier if there is less than 30 minutes from the next meal.

Acute diseases

- Insulin and oral drugs should be continued during acute diseases.
- It is essential to perform blood glucose and ketone tests, drink adequate fluid, and consume CH during acute diseases.

Acute healthcare practices

- Assigning an interdisciplinary team, prescribing MNT, planning an education course during and after hospitalization that is specific to diabetes improves the care of the diabetic patients.
- For hospitalized patients with diabetes, a diabetes meal planning system should be implemented to provide appropriate CH content in meals.
**Long-term healthcare practices**

- A regular menu with proper CH amount and timing should be prepared and served for individuals with diabetes.
- An interdisciplinary approach is required to integrate MNT into medical treatment in patients with diabetes.
- No evidence supports prescription diets containing recommendations for patients with diabetes to avoid concentrated sugar and not to add sugar to their meals.
- Iatrogenic malnutrition risk should not be overlooked. Instead of extreme food restriction, drug treatment should be adjusted to achieve glucose, lipid, and BP control.

**Methods for meal planning**

- Patients with diabetes are trained in meal planning during nutrition education. Dietitians can use different meal planning methods and educational tools like plate model, substitution list, food pyramid, 1st level of CH counting by considering the patient’s lifestyle, education level, and practical skills.
- The number of meals to determine in meal planning varies based on the diabetes type, medical treatment (insulin type), physical activity level, current blood glucose level and, most importantly the lifestyle of the patient.
- The plate model is a visual method that aims to provide information quickly for the explanation of healthy nutrition principles and restriction of CH intake. This model can be preferred for patients with diabetes who frequently eat outside the house, who have difficulty in applying other methods, who are undereducated, determined to have high protein and CH intake or patients who are recently diagnosed (Figure 5.1).
- Food pyramid is a visual tool that identifies food groups.

![Plate model in nutrition for diabetes](image)
Food substitution groups

- In the substitution lists, foods are collected in 8 main groups: bread (flour and bakery products), legumes, milk, meat, vegetables, fruits, fat, and sugar. The names, practical serving amounts and gram information of the foods with approximately the same energy and macronutrient values that can be used as a substitute are identified for each group.

- For example; instead of 1 thin slice of bread (25 g), 3 spoons of pilaf (40-45 g) or 1 scoop of soup (150 g) can be used as an alternative to bread since they are in the same group. Each food in this group provides 15 g of CH, 2 g of protein and 68 kcal of energy intake.

- Meat substitution includes 30 g of meat, 30 g of cheese, and 1 egg, which provides 6 g of protein, 5 g of fat, and 69 kcal energy.

- Fruits in the fruit substitution provides 15 g of CH and 60 kcal of energy.

Substitution lists offer various options for diabetic patients and allow them to plan their meal based on their personal preferences, provided that energy and macronutrient intake is the same. Substitution is performed by choosing a different food from the same group.

5.2 | CARBOHYDRATE COUNTING METHOD

Carbohydrate counting is a meal planning method that provides better glycemic control by allowing adjustment of the CH amount to be consumed in a meal, regulation of the insulin dose appropriate to the amount of HR to be consumed according to the preprandial blood glucose levels. Patients with diabetes can easily learn the effect of consumed CH amount or amount of CH-containing food intake on their blood glucose levels and build the skills to plan their meals according to the daily changes in their lives. Using the CH counting method allows patients with diabetes to learn the association between their food intake, physical activities, and glucose measurement results, enabling them to perform proper adjustments in their diabetes treatment.

- CH counting method has three levels: simple, moderate and advanced, and dietitians (diabetes dietitians, preferably) should meet their patients with diabetes 1 to 3 times to teach each level of the CH counting. The first level can be taught in 30-90 minutes with 1-4 weeks interval; each one of 2nd and 3rd levels can be taught in 30-60 minutes with 1-2 weeks interval.

- The CH counting method can be used by patients with type 1 and type 2 diabetes, women diagnosed with GDM, people who are at risk for diabetes, and even those with reactive hypoglycemia.

- As the patient with diabetes who will employ CH counting meal planning method is required to be literate, come to visits frequently, practice for food amounts with a kitchen scale, write a food consumption list, measure blood glucose at specified times, record measurement results, read food labels and perform mathematical calculations necessary for the method, the patient selection should be very careful.

- CH requirement of the patients with diabetes is determined in the first level of CH counting. The amount of CH is determined according to the number of meals, and snacks, which are based on the individual’s living conditions, preferences and medical treatment, and then distributed. Patients with diabetes are told how to achieve CH intake. Patients are taught foods that have 15 g of CH and the amount of CH they contain based
on portion sizes/amounts of foods they eat. It is essential for the diabetic individual, who is being trained on this level, to be willing to learn. Servings of some foods that contain 15 g CH are shown in the following table (Table 5.3).

**TABLE 5.3: Serving measures and amount of various foods/drinks that contain 15 g of carbohydrate**

<table>
<thead>
<tr>
<th>Food</th>
<th>1 serving</th>
<th>Amount (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White bread</td>
<td>1 slice</td>
<td>25</td>
</tr>
<tr>
<td>Rye bread</td>
<td>1 slice</td>
<td>25</td>
</tr>
<tr>
<td>Hamburger bread</td>
<td>1/2 pcs</td>
<td>25</td>
</tr>
<tr>
<td>Wholemeal bread</td>
<td>1 slice</td>
<td>25</td>
</tr>
<tr>
<td>Dried bread</td>
<td>2-3 pcs</td>
<td>20</td>
</tr>
<tr>
<td>Cracked wheat pilaf</td>
<td>1/3 water glass</td>
<td>40-50</td>
</tr>
<tr>
<td>Tomato soup</td>
<td>1 soup bowl</td>
<td>130-150</td>
</tr>
<tr>
<td>Lentil soup</td>
<td>1 soup bowl</td>
<td>150</td>
</tr>
<tr>
<td>Pasta (spaghetti, cooked)</td>
<td>1/2 water glass</td>
<td>45</td>
</tr>
<tr>
<td>Rice pilaf</td>
<td>1/3 water glass</td>
<td>40-50</td>
</tr>
<tr>
<td>Bun (plain)</td>
<td>1/2 pcs</td>
<td>30</td>
</tr>
<tr>
<td>Shell beans (boiled)</td>
<td>1/2 water glass</td>
<td>100</td>
</tr>
<tr>
<td>Chickpea (raw)</td>
<td>1/4 water glass</td>
<td>25-30</td>
</tr>
<tr>
<td>Muesli</td>
<td>1 tea glass</td>
<td>25</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>3/4 tea glass</td>
<td>25</td>
</tr>
<tr>
<td>Potato (boiled, peeled)</td>
<td>1 medium size</td>
<td>90</td>
</tr>
<tr>
<td>Apple (not peeled)</td>
<td>1 small size</td>
<td>100</td>
</tr>
<tr>
<td>Watermelon (peeled)</td>
<td>1 slice [1/10 medium size]</td>
<td>200</td>
</tr>
<tr>
<td>Apricot</td>
<td>4 pcs-with seeds</td>
<td>160</td>
</tr>
<tr>
<td>Mandarin</td>
<td>2 small size</td>
<td>140</td>
</tr>
<tr>
<td>Peach</td>
<td>1 small size</td>
<td>130</td>
</tr>
<tr>
<td>Grape</td>
<td>1 water glass/17 pcs</td>
<td>75</td>
</tr>
<tr>
<td>Milk</td>
<td>1 medium sized water glass</td>
<td>240</td>
</tr>
<tr>
<td>Yogurt</td>
<td>1 medium sized water glass</td>
<td>240</td>
</tr>
<tr>
<td>Orange juice (freshly squeezed)</td>
<td>1.5 pcs orange</td>
<td>120</td>
</tr>
<tr>
<td>Coke</td>
<td>1/2 water glass</td>
<td>130</td>
</tr>
<tr>
<td>Honey</td>
<td>2.5 brim dessert spoon</td>
<td>19</td>
</tr>
<tr>
<td>Cube sugar (white)</td>
<td>5-6 pcs</td>
<td>15</td>
</tr>
<tr>
<td>Cube sugar (brown)</td>
<td>5-6 pcs</td>
<td>15</td>
</tr>
</tbody>
</table>

- Patients who use rapid-acting insulin analogs, and particularly those using an insulin pump, should be provided with level 3 training to ensure that insulin is matched with CH intake. Advanced CH counting training is not recommended for patients who use mixed insulins.
- Glycemic control must be achieved and basal insulin dose must be well-adjusted in order for a patients with diabetes to start advanced level CH counting training. At this level, the calculation of CH/I ratio and the situations in which it should be used are explained to the patient with diabetes who uses an insulin pumps or multi-dose insulin therapy. The method should not give the perception of “I can eat as much CH-containing food as I like and adjust my insulin dose accordingly” to the patients. Practical applications should
be evaluated frequently for food consumption records, blood glucose measurement results, hypoglycemia incidence, and body weight change.

- After the application accuracy of the patients with diabetes, for whom the CH/I ratio is determined, is confirmed, then the patients should be taught the calculation of “Insulin Sensitivity Factor” (ISF).

- In cases where it is not possible for the patient to receive training from a dietitian, brief and simple information can be provided about CH counting by explaining foods that are equivalent to 15 g CH (e.g., 25 g 1 slice of bread, 3 spoons of pilaf, 3 spoons of pasta, 300 ml of yogurt, 300 ml of milk, 1 medium-sized fruit etc.).

- Individuals with diabetes who are taught CH counting should also be told about the importance of protein and fat consumption. Otherwise, a nutrition habit that solely depends on CH consumption may develop.

5.2.1. CARBOHYDRATE/INSULIN RATIO (CH/I)

- CH/I = amount of CH consumption (g) in the meal or number of CH servings/short- or rapid-acting insulin dose (IU) or conventional ‘CH/I = 500/TID’ formula can be used (TID: Daily total insulin dose).

- Pre- and postprandial blood glucose of the patients with diabetes must be at the targeted levels in order to determine the CH/I and to adjust the insulin dose appropriate to the amount of CH to be consumed with the meal. CH/I should not be calculated in patients with diabetes where blood glucose control is not achieved, and CH intake varies from meal to meal or day to day.

- In patients whose CH/I ratio is yet to be determined based on nutrition, the recommendation was a rough calculation with CH/I = 500/TID formula. However, this formula may not be suitable for all patients with diabetes. In the “Insulin Pump Application Guide” updated by American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) in 2014, CH/I ratio is recommended to be calculated with “CH/I = 300/TID” formula in obese or insulin-resistant patients and with “CH/I = 450/TID” in underweight or insulin-sensitive patients. Alternatively, CH/I ratio can be calculated by using CH/I = 5.7 x Weight (kg)/TID formula. “CH/I = 300-400/TID” formula is known to be more valid in type 1 diabetes patients who use insulin pumps.

5.2.2. INSULIN SENSITIVITY FACTOR

Insulin Sensitivity Factor (ISF) is defined as the amount of blood glucose (mg/dL) decreased by 1 IU rapid or short-acting insulin. ISF is also known as “correction factor”, “correction bolus” or “addition factor”. In addition to determining CH/I, this stage of CH counting also enables the calculation of insulin amount that would bring blood glucose levels within targeted limits. For the determination of ISF, 1500 (for individuals who use short-acting insulin or those with insulin resistance) or 1800 (for individuals who use rapid-acting insulin analog or those with insulin sensitivity), rules are used.

- ISF = 1500/TID or ISF = 1800/TID formula is used for calculation. “Insulin Pump Application Guidelines” 2014 AACE/ACE recommends the use of “ISF=1700/TID”.

- Alternatively, CH/I = ISF/3 and ISF = 4.44 x CH/I formula can be used.
As a result of ISF calculation with CH/I:

- The insulin dose or amount of CH to be consumed with the meal is increased or decreased based on pre-prandial blood glucose levels.
- The insulin dose is adjusted based on the amount of CH to be consumed with the meal.

**SEMT RECOMMENDATIONS**

1. **MNT should be prescribed to decrease A1C in patients with diabetes. Nutrition treatment must be provided by an expert dietitian experienced in diabetes nutrition; for type 1 diabetes (A); for type 2 diabetes (A), for gestational diabetes (A).**

2. **Overweight and obese patients with diabetes should reduce their daily energy intake and build healthy nutritional habits in order to reach and maintain a healthy body weight (A).**

3. **Patients with type 1 diabetes should be taught how to count CH and calculate CH/I (B) or if this is not possible, they should be recommended to consume fixed amounts of CH with meals (B). In cases where it is not possible for the patient to receive training from an experienced dietitian, brief and simple information can be provided about CH counting by explaining foods that are equivalent (B).**

4. **In order to achieve optimal glycemic control, individuals with type 2 diabetes should be recommended to eat regularly with the proper meal timing (B).**

5. **Patients with type 1 and type 2 diabetes whose glycemic control is inadequate should be recommended to prefer foods with a low glycemic index instead of those with a high glycemic index (D).**

6. **Consumption of sucrose or sucrose-containing foods not exceed 10% of the daily total energy intake will not deteriorate glucose and lipid levels in patients with diabetes with adequate glycemic control (B).**

7. **Saturated fat intake of adult patients with diabetes should not exceed 7% of the daily total energy intake (C), and trans fatty acid intake should be limited (D).**

8. **Type 1 diabetes patients should be informed that alcohol consumption increases late time hypoglycemia risk (C). In order to reduce alcohol-induced hypoglycemia risk, measures such as limiting alcohol intake, additional CH intake, lowering insulin dose, and more frequent SMBG should be taken (D).**

**REFERENCES**


6.1. | GENERAL PRINCIPLES

6.1.1. | TARGETS OF EXERCISE

- Regular physical activity planned and modified to existing complications is recommended for all patients with diabetes.
- Regular physical activity reduces insulin resistance and prevents type 2 diabetes in high-risk individuals.
- Exercise/physical activity in diabetes has positive effects on blood glucose regulation, blood pressure control, dyslipidemia, and weight loss. It helps to maintain the lost weight and increases the quality of life.
- Type 2 diabetes is a strong risk factor for muscle loss in adults. Resistance exercises provide essential benefits for patients with diabetes.

In order to reduce the risks involved in the exercise, safety principles should be observed before, during, and after exercise.

6.1.2. | PRE-EXERCISE EVALUATION

The presence of chronic complications is investigated regardless of the patient’s age. Examinations to be performed within this scope are summarized below:

- Glycemic control level and A1C are determined.
- CV system examination is performed. Exercise test should be done for patients with diabetes in the following groups:
  - All patients with diabetes older than 35 years
  - Individuals older than 25 years and type 1 or type 2 diabetes duration of more than 10 years
  - Patients with diabetes with risk factors for coronary artery disease
  - Individuals with peripheral vascular disease, microvascular disease or autonomous neuropathy
  - Neurological and musculoskeletal system examination, foot examination must be performed.
  - Fundus must be examined.

6.1.3. | CONFIGURATION OF EXERCISE PROGRAM

In patients with diabetes, mostly aerobic exercises (high tempo walking, running, swimming) and resistance exercises are recommended to increase muscle strength. Aerobic exercises are repetitive and long term exercises that involve large muscle groups. Resistance exercises are muscle strengthening movements that are performed against a load or with
a specified weight. High-intensity interval training is an alternative to continuous aerobic exercise. These exercises improve glycemic control in type 2 diabetes, and they have been shown to have no negative effect on glycemic control in type 1 diabetes.

Sports like deep diving and high altitude paragliding are not recommended.

In type 1 diabetes, blood glucose response to exercise is highly variable. This response is very personal due to factors like activity type, time, and duration. For example, if the usual insulin dose is administered before the meal, postprandial aerobic exercise generally lowers blood glucose levels. More severe reduction can occur if the exercise duration extended. Pre-prandial exercise may cause milder increases or decreases in blood glucose levels. In type 1 diabetes, performing resistance training first, then aerobic exercise at the same session decreases exercise-related hypoglycemia.

Table 6.1 shows examples of activities that a 70 kg adult should do to burn 150 kcal energy.

### TABLE 6.1: Physical activity examples that would provide 150 kcal energy consumption in adults

<table>
<thead>
<tr>
<th>Exercise type</th>
<th>Amount</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td>5 km</td>
<td>40 min</td>
</tr>
<tr>
<td>Cycling</td>
<td>8 km</td>
<td>30 min</td>
</tr>
<tr>
<td>Dancing or table tennis</td>
<td>-</td>
<td>30 min</td>
</tr>
<tr>
<td>Swimming and basketball</td>
<td>-</td>
<td>20 min</td>
</tr>
<tr>
<td>Cycling</td>
<td>6 km</td>
<td>15 min</td>
</tr>
<tr>
<td>Jumping rope</td>
<td>-</td>
<td>15 min</td>
</tr>
<tr>
<td>Running</td>
<td>2.5 km</td>
<td>15 min</td>
</tr>
<tr>
<td>Climbing stairs</td>
<td>-</td>
<td>15 min</td>
</tr>
</tbody>
</table>

Exercising on an empty stomach or right after a meal should be avoided. There is no consensus on the most convenient time of the day for exercise. Although patient’s conditions are the determinant factors in this regard, it may be recommended to exercise 1-3 hours after the main meal. Adequate hydration must be provided before and during exercise.

6.1.4. | **EXERCISE RECOMMENDATIONS FOR DIABETIC INDIVIDUALS**

- Adults with diabetes should be ensured to perform moderate intensity (60-75% of maximum heart rate, for elders 50-70%) exercise for at least three days a week and total of 150 minutes with no more than 48 hours of interval between the sessions (Maximal heart rate = 220 - Age).
- Exercise should start with a mild intensity and gradually increased up to moderate intensity.
- If there is no contraindication, diabetes patients should be ensured to do resistance exercises 2-3 days a week.
- Flexibility and balance exercises increase joint mobility in patients with diabetes, especially in elderly patients. These exercises are recommended to be performed 2-3 days a week to increase flexibility, strength, and balance (provided that aerobic and resistance exercises are not hindered).
- Individuals with diabetes or prediabetes should not sit still for more than 30 minutes during the day; they should stand up or walk for a short time.
6.2. | EXERCISE-RELATED PROBLEMS

- Patients that exercise should be ensured to have an accessory (bracelet, necklace, etc.) stating that they are diabetic or an identification card that is readily visible.
- Frequent glucose monitoring (SMBG) is performed to observe the glycemia change with exercise. PG monitoring allows necessary precautions to be taken to avoid hypoglycemia in patients with diabetes who use insulin or insulin secretagogue drugs.
- Elderly patients with diabetes with autonomic neuropathy, cardiovascular disease, or pulmonary disease are not recommended to exercise outside in very hot or humid weather.
- Exercise must be stopped in case of extreme fatigue or the presence of the following findings:
  - Dizziness and stumbling
  - Discomfort, pressure, or pain in the chest
  - Unexpected and severe shortness of breath
  - Nausea

6.2.1. | POTENTIAL RISKS AND COMPLICATIONS IN EXERCISE

**Hypoglycemia**

- Hypoglycemia may occur due to increased insulin sensitivity in muscles and increased glucose use during exercise. It is particularly important for patients using insulin or insulin secretagogue drugs. Increased body activity and temperature also increases the effect of insulin.
- Ideal blood glucose levels before exercise should be 90-250 mg/dL. If PG is <90 mg/dL, 15-30 g CH (e.g., one portion of fruit, one slice of bread) should be taken before exercise.
- However, it must be noted that hypoglycemia possibility occurs despite these recommendations, and the patients must be warned in this regard.
- If the patient doesn’t have CH sources that can quickly increase blood glucose (such as glucose tablet, glucose gel, table sugar, fruit juice), exercise should be avoided. That is critical, particularly in case of the insulin effect is at its peak.
- To prevent hypoglycemia in cases with more than 30 minutes of exercise, additional CH intake or decreased insulin dose before the exercise may be required.
- If hypoglycemia symptoms develop during exercise, capillary blood glucose should be immediately measured if possible, and CH-containing drink or food should be consumed. Against the risk of hypoglycemia, diabetes patients should be recommended to avoid exercise on an empty stomach, avoid exercising alone, measure their blood glucose levels before, during, and after the exercise, and decrease the insulin dose before and after exercise if necessary.
- Exercise may lower blood glucose levels for up to 24 hours.

**Hyperglycemia**

- Blood glucose level may increase with intense exercise.
- If PG >250 mg/dL and ketone [+], then exercise should be avoided until ketones are cleared.
- If PG >250 mg/dL and ketone [-], the patient feels good and adequate hydration is provided, then mild intensity exercise can be performed without additional CH intake.
Cardiovascular risks
- The need of coronary artery perfusion increases with exercise, and this may increase ischemia in the presence of CAD.
- Potentially accompanying CV risk factors should be evaluated in people with diabetes before exercise.

Retinopathy
- Exercise can be performed in the presence of controlled non-proliferative diabetic retinopathy or macular edema.
- In severe non-proliferative or proliferative diabetic retinopathy, strenuous activities that increase intraocular pressure and lead to vitreous bleeding and retinal detachment risk should be avoided. Exercise should be avoided if there is vitreous bleeding.

Nephropathy
- There is no evidence that exercise in the presence of diabetic nephropathy causes renal disease to progress.
- As albuminuria and proteinuria can increase CVD risk, cardiac evaluation must be more detailed in these patients.

Peripheral neuropathy
- In patients with peripheral neuropathy feet should be examined for trauma, infection and ulcers before exercise.
- Exercise can be performed with proper foot care in patients with mild and moderate severe neuropathy.
- In patients with severe peripheral neuropathy, exercises that may lay the ground for diabetic foot (thread-mill, long term walk, mild running and step exercises etc.) due to sensory loss and increased infection risk should be avoided. Other exercises that do not increase load in feet (swimming, cycling and arm training) are recommended.

Autonomic neuropathy
- Cardiac evaluation should be performed in patients with cardiac autonomic neuropathy due to tachycardia, orthostatic hypotension, risk of hypertensive or hypotensive response to exercise.
- Exercises that involve sudden postural or directional changes should be avoided in the presence of orthostatic hypotension.

Other risks and problems
- Aerobic exercise can accelerate basal insulin absorption from subcutaneous tissue in cases that use continuous subcutaneous insulin infusion (CSII) or multiple insulin injections. Skin irritation, aesthetic concerns related to the appearance of the pump may occur.
- It has been reported that there may be measurement errors, calibration problems, breaking of the sensor filament or sensor performance differences during exercise in patients using continuous glucose monitoring (CGM). Therefore, sensor measurements are recommended to be supported with capillary glucose measurements.
6.2.2. **CONTRAINDICATIONS OF EXERCISE**

Exercise may be harmful in the following cases:

- Unadjusted PG levels
- Severe neuropathy that causes sensory loss
- Active CVD
- Proliferative retinopathy (strenuous exercises are contraindicated)
- Vitreous bleeding
- Hypoglycemia unawareness

### SEMT RECOMMENDATIONS

1. **Increasing the physical activity of the people with diabetes makes it easier to control PG and lipid levels and BP (D).**

2. **Before starting an exercise program aiming to increase physical activity, individuals with diabetes must be examined in terms of potential side effects and contraindications of the exercise. Exercise ECG must be performed for patients with high CVD risk and sedentary lifestyle before starting exercise (D).**

3. **Exercise should be personalized based on personal requirements, limitations, and performance (D).**

4. **In addition to calorie limitation for weight loss in patients with prediabetes and diabetes (type 2 in particular), at least 150 minutes a week of moderate-intensity aerobic physical activity should be performed (e.g., high tempo walking) (A).**

5. **Exercise programs must be at least three times a week. Intervals between exercises should not be more than two days (for type 1 diabetes: C; for type 2 diabetes: B).**

6. **If there is no contraindication, patients with diabetes should also perform mild resistance exercises for two days a week(B).**

7. **If possible, the exercise program should be arranged by an exercise specialist based on the individual and initially conducted under the supervision of an expert (D).**

8. **During exercise, the patient is recommended to monitor their heart rate and adjust it to around 60-75% of the maximal heart rate (maximal heart rate = 220 - age). Exercise heart rate can be personally adjusted according to resting heart rate (D).**

9. **Warm-up and cool off exercises should not be skipped before and after the exercise sessions (D).**

10. **Blood glucose should be monitored before, during, and after the exercise. Special attention must be paid for hypoglycemia, especially for patients who use insulin or insulin secretagogue drugs (A).**
REFERENCES


The main antihyperglycemic drugs available in Turkey include insulin secretagogues, thiazolidinediones, insulin-mimetics (incretin-based drugs), alpha-glucosidase inhibitors, and sodium-glucose co-transporter 2 inhibitors (glucoretics, gliflosins).

Pramlintide (an insulin-mimetic amylin analog), rapid-acting bromocriptine (a dopamine-2 agonist), and colesevelam (a bile acid sequestrant) are other drugs used in type 2 diabetes treatment. However, they are not approved for the treatment of diabetes in Turkey.

Oral antidiabetics (OAD) and non-insulin injectable diabetes medications are not used in pregnancy, because most of them have inadequate data about use in pregnancy or are contraindicated. Although there are studies on the use of metformin and some sulphonylurea (SU) group drugs in pregnancy, there are no antidiabetic drugs (except for some insulins) approved by FDA, European Medicines Agency (EMA) and Turkey Pharmaceuticals and Medical Devices Agency (TITCK) for use in pregnancy.

### 7.1 BIGUANIDES

This group includes synthetic guanidine derivatives metformin and phenformin. Phenformin was prohibited in 1970s due to causing lactic acidosis. Metformin is the only drug used in the biguanide group, and it has been used for the treatment of type 2 diabetes for over 60 years. However, its action mechanism is yet to be fully understood. Metformin acts by indirectly activating the 5′ adenosine monophosphate-activated protein kinase (AMPK) enzyme at a cellular level and by partially inhibiting mitochondrial glyceraldehyde dehydrogenase (mGDP) enzyme. In type 2 diabetes, metformin inhibits increased gluconeogenesis in the liver and has a suppressing effect on lipid and cholesterol biosynthesis via temporary inhibition of mitochondrial respiratory chain complex I. However, the classical information stating that it slightly increases muscle glucose uptake and fatty acid oxidation, therefore decreases the insulin resistance, is controversial. Moreover, metformin decreases intestinal glucose absorption and partially suppresses appetite (possibly due to its side effects on the digestive system and maybe for its GLP-1 increasing effects). In recent years, it has been shown to have positive impacts on microbiota. There is a wide clinical experience with metformin as it has been available for a long time and its low cost. It also has advantages as it has a low risk of hypoglycemia, is neutral in terms of weight gain or has slight weight-loss impact. Metformin has also been shown to decrease cardiovascular (CV) event risk (UKPDS).

Information about the clinical use of metformin is shown in Table 7.1.
TABLE 7.1: Characteristics of biguanides (metformin)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Biguanides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>500, 850, 1000 mg tb</td>
<td>500-2500 mg</td>
<td>bid or tid, before, during or after meal (initially starts at 1 dose of 500 mg a day and gradually increased)*</td>
</tr>
<tr>
<td>Extended-release metformin</td>
<td>500, 1000 mg tb</td>
<td>500-2000 mg</td>
<td>qd or bid before, during or after meal, preferably in the evening*</td>
</tr>
</tbody>
</table>

qd, once a day; bid, twice a day; tid, three times a day
*Bioavailability of metformin is higher when taken before meals, however, its gastrointestinal side effects are milder if taken with or after meal.

7.1.1. SIDE EFFECTS OF METFORMIN

- Gastrointestinal irritation (side effects like gas and bloating are generally temporary)
- Abdominal cramp
- Diarrhea
- Metallic taste in mouth
- Vitamin B-12 deficiency (seen in 16%). It is recommended to measure vitamin B-12 levels periodically. Vitamin B-12 replacement is required for cases with low levels, and particularly the ones with neuropathy development.
- Lactic acidosis (incidence <10/100,000 patient-year)
- Warning! For patients with diabetes who will undergo an angiographic examination with a high amount of iodinated contrast agents, metformin should be stopped 24 hours before the procedure, patients should be hydrated, serum creatinine level should be measured 24 hours later, and then metformin should be restarted if there is no problem.

7.1.2. CONTRAINDICATIONS OF METFORMIN

- Metformin is contraindicated in the presence of advanced renal failure (if eGFR <30 ml/min). If eGFR is 30-45 ml/min, metformin should not be started and if eGFR decreases to this range in patients currently using metformin, the dose should be decreased (e.g., halved).
- Liver failure
- Lactic acidosis history
- Severe hypoxia, dehydration
- Chronic alcoholism
- CV collapse, acute myocardial infarction (MI)
- Ketonemia and ketonuria
- Resistance to treatment (class 4) congestive heart failure
- Chronic pulmonary disease (chronic obstructive pulmonary disease)
- Peripheral vascular disease
- Major surgical intervention
- Pregnancy and breastfeeding period (although the number of studies on metformin use in pregnancy is increasing, metformin is absorbed through the placenta, and there is limited long-term data on children whose mothers were using metformin. Breastfeeding is not recommended for 3-4 hours after metformin intake during lactation period)
- Advanced age (>80 years according to some authors)
7.2 | INSULIN SECRETAGOGUES

This group includes subgroups of SU, which increases insulin secretion from pancreas β-cells, and glinide (GLN; meglitinide), which has a shorter but similar action mechanism (Table 7.2).

### TABLE 7.2: Characteristics of insulin secretagogue drugs

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Sulphonylurea group (second-generation SU group drugs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>5 mg tb</td>
<td>2.5-10 mg</td>
<td>bid, at breakfast or dinner</td>
</tr>
<tr>
<td>Glipizide with controlled release</td>
<td>2.5, 5, 10 mg tb</td>
<td>5-10 mg</td>
<td>qd, before or with breakfast</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>80 mg tb</td>
<td>80-240 mg</td>
<td>qd or bid, at breakfast (or at dinner if necessary)</td>
</tr>
<tr>
<td>Gliclazide with modified release form</td>
<td>30, 60 mg tb</td>
<td>30-120 mg</td>
<td>qd, before or with breakfast</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>2.5, 3.5, 5 mg tb</td>
<td>2.5-10 mg</td>
<td>qd or bid, at breakfast (or at dinner if necessary)</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1, 2, 3, 4, 6, 8 mg tb</td>
<td>1-8 mg</td>
<td>qd or bid, at breakfast (or at dinner if necessary)</td>
</tr>
<tr>
<td>Glibornuride</td>
<td>25 mg tb</td>
<td>12.5-75 mg</td>
<td>qd or bid, at breakfast (or at dinner if necessary)</td>
</tr>
<tr>
<td>Gliquidone</td>
<td>30 mg tb</td>
<td>15-120 mg</td>
<td>qd or bid, at breakfast (or at dinner if necessary)</td>
</tr>
<tr>
<td><strong>B. Glinide group (Meglitinides, GLN, short-acting secretagogues)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5, 1, 2 mg tb</td>
<td>1.5-6 mg</td>
<td>tid, right before meals</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>60, 120, 180 mg tb</td>
<td>180-360 mg</td>
<td>tid, right before meals</td>
</tr>
</tbody>
</table>

qd, once a day; bid, twice a day; tid, three times a day

Both of them increase insulin secretion by blocking the KATP channels on the β-cell, for short and long duration respectively, independently from glucose.

There is a wide clinical experience with SU as they have been available for a long time and have low cost. SU group drugs have been shown to decrease microvascular complication risk (UKPDS and ADVANCE studies). Although it has been claimed that these drugs disrupt the myocardial ischemic preconditioning mechanism of myocardial cells, the clinical reflections of these concerns haven’t been demonstrated in studies, especially the ones conducted with gliclazide. The effects of SU group drugs that are currently in use are shorter and more stable than those produced first. However, their efficacy is not very long.

GLN group drugs have short effects. They have weak effects of FPG but more effective in decreasing PPG. This group of drugs provides flexibility as they are used before each main meal and have low cost.

### 7.2.1 | SIDE EFFECTS OF INSULIN SECRETAGOGUE DRUGS

- Hypoglycemia
- Weight gain
- Allergy
- Skin rashes
- Alcohol flushing (seen with chlorpropamide in particular, which is no longer commonly used)
- Hepatotoxicity
- Hematologic toxicity (agranulocytosis, bone marrow aplasia)
7.2.2. **CONTRAINDICATIONS OF INSULIN SECRETAGOGUE DRUGS**

- Type 1 diabetes mellitus (differential diagnosis with LADA is particularly important)
- Secondary diabetes (causes like pancreas diseases etc.)
- Hyperglycemic emergencies (DKA, HHD)
- Pregnancy
- Trauma, stress, surgical intervention
- Severe infection
- Allergy to SU group drugs
- Predisposition to severe hypoglycemia
- Decompansated liver and end-stage renal insufficiency

7.2.3. **DRUGS INTERACTING WITH SULPHONYLUREA**

Many drugs used in patients with diabetes can alter the effect of SU through various mechanisms. Dose adjustment may be required for SU when these drugs (shown in Table 7.3) will be used.

**TABLE 7.3: Interactions of sulphonylurea and other drugs**

<table>
<thead>
<tr>
<th>Causing hypoglycemia</th>
<th>Causing hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding to albumin:</td>
<td>Increasing SU metabolism:</td>
</tr>
<tr>
<td>Aspirin, Fibrate, Trimethoprim</td>
<td>Barbiturates, Rifampin</td>
</tr>
<tr>
<td>Competitive metabolic inhibitors:</td>
<td>Antagonizing the SU effect:</td>
</tr>
<tr>
<td>Alcohol, H-2 receptor blockers, Anticoagulants</td>
<td>β-blockers</td>
</tr>
<tr>
<td>Inhibiting the clearance from kidneys:</td>
<td>Blocking insulin secretion/Effect:</td>
</tr>
<tr>
<td>Probenecid, Allopurinol</td>
<td>Diuretics, β-blockers, Corticosteroids, Estrogen, Phenytoin</td>
</tr>
<tr>
<td>Counterregulatory antagonists:</td>
<td>-</td>
</tr>
<tr>
<td>β-blockers, Sympatholytics</td>
<td></td>
</tr>
</tbody>
</table>

7.3 **THIAZOLIDINEDIONES (TZD, GLITAZONES)**

This group of drugs increases the glucose output in peripheral tissues by increasing the insulin effect and slightly decreases hepatic glucose production. They act by activating the nuclear transcription factor PPAR-γ [peroxisome proliferator-activated receptor-γ] (PPAR-γ agonist) at a cellular level. Thus, they decrease insulin resistance in peripheral tissues (muscle, liver and fat tissue), and partially increase the insulin sensitivity. They also act by increasing adipocyte differentiation in the adipose tissue. Their A1C-decreasing effect is high. In addition, some studies showed that they allow BP reduction for mmHg. Their long term efficacy has been proved (ADOPT study).

Among the TZD group drugs, only pioglitazone (PIO) is available in Turkey. They have advantages like not causing hypoglycemia, increasing HDL-cholesterol and lower triglyceride levels. PIO has been shown to decrease secondary CV event and stroke risk (PROactive study). However, caution must be exercised for the following side effect risks mentioned below.

Information related to clinical use of thiazolidinedione group drugs is given in Table 7.4.

**TABLE 7.4: Characteristics of thiazolidinedione (glitazone) group drugs**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>15, 30, 45 mg tb</td>
<td>15-45 mg</td>
<td>qd, independently from meal</td>
</tr>
<tr>
<td>Rosiglitazone*</td>
<td>4, 8 mg tb</td>
<td>2-8 mg</td>
<td>qd, independently from meal</td>
</tr>
</tbody>
</table>

qd, once a day.

*No longer available in Turkey.
7.3.1. **SIDE EFFECTS OF THIAZOLIDINEDIONES**

- Edema
- Anemia
- Congestive heart failure (particularly when used in combination with intensive insulin treatment)
- Fluid retention
- Weight gain
- LDL cholesterol increase (more with rosiglitazone)
- Increase in transaminases
- These group of drugs are still questioned in terms of increased CV event (fatal or nonfatal MI) risk. In some meta-analyses, rosiglitazone has been determined to increase MI risk. Rosiglitazone was discontinued in 2010 in European countries and in Turkey due to these concerns and suspicions. In the United States and some other countries, the controlled use of rosiglitazone continues in selected cases.
- TZD drugs may exacerbate the ophthalmopathy in patients with Graves ophthalmopathy.
- It has been reported that they cause increased risk of fracture and decreased bone mass postmenopausal women and older men.
- Although some observational studies claimed that PIO causes a minimal increase in bladder cancer risk in men, later studies have mostly eliminated these concerns. Even so, it is recommended to avoid PIO in patients with active bladder cancer, and to decide PIO use based on risk-benefit ratio or avoid in patients with bladder cancer history or chronic hematuria.

7.3.2. **CONTRAINDICATIONS OF THIAZOLIDINEDIONES**

- Cases with elevated alanine aminotransferase (ALT >2.5 x normal upper limit)
- Cases with class I-IV in terms of congestive heart failure based on the criteria of New York Heart Association
- They are not contraindicated in chronic advanced kidney failure; however, should not be preferred due to their edema risk.
- Pregnancy
- Type 1 diabetes patients
- Patient with risk of macular edema
- Adolescents and children

### 7.4  **ALPHA-GLUCOSIDASE INHIBITORS (AGI)**

Alpha-glucosidase inhibitors (AGI) slow down the digestion of carbohydrates and delay their absorption by decreasing the enzymatic degradation of polysaccharides through the competitive inhibition of intestinal \(\alpha\)-glucosidase. Main advantages: decreases postprandial blood glucose, has low hypoglycemia risk, neutral in terms of body weight and has no systemic effects. Among AGI group drugs, only acarbose is available in Turkey. Acarbose has been shown to decrease CV event risk (STOP-NIDDM study). The absence of systemic effects in an advantage of acarbose, however, its long-term use is difficult as it is required to be taken three times a day before main meals, has moderate efficacy in decreasing glycemia and gastrointestinal side effect and thus has low patient compliance (Table 7.5).
TABLE 7.5: Characteristics of alpha-glucosidase inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>50, 100 mg tb</td>
<td>150-300 mg</td>
<td>tid, at the start of meal</td>
</tr>
<tr>
<td>Miglitol</td>
<td>25, 50, 100 mg tb</td>
<td>150-300 mg</td>
<td>tid, at the start of meal</td>
</tr>
</tbody>
</table>

tid, three times a day

7.4.1. SIDE EFFECTS OF ALPHA-GLUCOSIDASE INHIBITORS
- Bloating, indigestion, diarrhea
- Reversible increase in liver enzymes
- Rarely, iron deficiency anemia

7.4.2. CONTRAINDICATIONS OF ALPHA-GLUCOSIDASE INHIBITORS
- Inflammatory bowel disease
- Chronic ulceration
- Malabsorption
- Partial bowel obstruction
- Cirrhosis
- Pregnancy
- Lactation
- Diabetics under 18 years of age

7.5. INCRETIN-BASED DRUGS

One of the major defects in type 2 diabetes is the decrease in the level and/or effect of incretin hormones (GLP-1 and GIP) and the inability to inhibit glucagon secretion. Incretin-mimetic glucagon-like peptide-1 receptor agonists (GLP-1A) mimics incretin hormones, and dipeptidyl peptidase-4 inhibitors (DPP4-I), which increase the incretin effect, inhibit the incretin degradation. As this effect is glucose-dependent, they do not cause hypoglycemia in monotherapy. However, hypoglycemia may occur when they are used in addition to secretagogues (SU/GLN) or insulin. Therefore, the dose of the first drug should be decreased in combination therapy. Clinical use characteristics of these drugs are shown in Table 7.6.

7.5.1. GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1RA, GLP-1 ANALOGS; GLP-1A)

These drugs increase the glucose sensitivity of the pancreas β-cell by activating the GLP-1 receptors, suppress glucagon secretion from α-cells, delay gastric discharge and increase the sense of fullness. The hypoglycemia risk is low as they increase insulin secretion independently from glucose. In addition, these drugs have an area of use despite being injectable (s.c. injection) due to their ability to decrease systolic BP for several mmHg and allow slight weight loss (2-4 kg on average). Short-acting ones, like exenatide and lixisenatide, are more effective on PPG and require two doses a day; drugs that are administered once a day (liraglutide) or once a week (exenatide XR, dulaglutide, semaglutide) are stronger in terms of efficacy. They are preferred in second and third-line treatment, especially for obese (BMI ≥30 kg/m²) type 2 diabetes patients. There is inadequate experience with this group of drugs in obese type 2 diabetic patients younger than 18 years of age. In general, they are expensive and this leads to reimbursement problems.
The results of the studies where exenatide, liraglutide and lixisenatide is used in combination with basal insulin in obese patients demonstrate that glycemic control is achieved at lower insulin doses and there is no or minimal insulin-related weight gain.

**a) Side effects of GLP-1A group drugs**
- Nausea, vomiting (generally alleviates over time)
- Diarrhea
- Less common: constipation, abdominal pain
- Minimal increase in heart rate
- Pancreatitis, pancreas malignancy, and gallstone formation: Pancreatitis and pancreas neoplasia cases, and gallstone disease with acute complications in liraglutide have been reported during the use of these drugs. Although this subject is yet to clear since these diseases are already increased in patients with diabetes, GLP-1A group of drugs are subject to additional monitoring in terms of pancreatitis. In case of severe abdominal pain, nausea-vomiting, amylase/lipase elevation, and radiological findings indicating suspected acute pancreatitis, the drug should be terminated immediately.
- C-cell hyperplasia of the thyroid gland has been detected in experimental studies conducted with liraglutide. Despite the presence of evidence suggesting that this is specific to rodents, GLP-1A drugs have been subjected to additional monitoring for medullary thyroid cancer. It is recommended to test calcitonin and perform advanced examinations as needed in suspected patients.
- Worsening of diabetic retinopathy has been reported with semaglutide.

**b) Contraindications of GLP-1A group of drugs**
- Pancreatitis history
- Overt gastrointestinal disease (gastroparesis, recent cholelithiasis or bile tract disease or advanced gastroesophageal reflux disease etc.)
- History of medullary thyroid cancer or type 2 multiple endocrine neoplasia (MEN type 2) syndrome in the patient or his/her family.
- Family history of pancreas cancer
- Pregnancy and lactation

7.5.2. **DIPEPTIDYL PEPTIDASE-4 INHIBITORS (DPP4-I, GLIPTINS)**

Incretin-increasing drugs elevate the endogenous GLP-1 and GIP levels by delaying postprandial catabolism of endogenous incretins via the inhibition of DPP-4. They increase glucose-dependent insulin secretion, moderately decrease postprandial glucose level after the administration, and suppress glucagon secretion. DPP4-I group drugs (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) have been developed for oral administration. DPP4-I group drugs can be used in second and third line for patients with type 2 diabetes for whom an adequate glycemic response cannot be achieved by using metformin, SU, PIO or insulin. Generally, they are used once a day (vildagliptin bid); neutral effect on weight gain and no hypoglycemia induction are their major advantages. They are more expensive than conventional OADs (SU, metformin).

**a) Side effects of DPP-4 inhibitors**
- Complaints similar to upper respiratory tract infection, nasal congestion, throat pain
- Joint pain
- Headache
• Rarely: pancreatitis, bullous pemphigoid, cutaneous vasculitis, interstitial lung disease
• If severe abdominal pain, nausea-vomiting, amylase/lipase elevation, and radiological findings suggesting acute pancreatitis are detected, the drug should be terminated immediately.

b) Contraindications of DPP-4 inhibitors
• Liver failure
• Severe kidney failure
• Pregnancy and lactation
• Cardiac failure (for saxagliptin and alogliptin in particular)

### TABLE 7.6: Characteristics of incretin-based (GLP1A and DPP-4 inhibitor) drugs

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incretin mimetic (GLP-1A)</td>
<td>Exenatide</td>
<td>5, 10 μg cartridge</td>
<td>Initial dose: 10 μg Maintenance: 20 μg</td>
<td>bid, 0-60 minutes before meal in the morning and evening, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Exenatide XR*</td>
<td>2 mg vial, cartridge</td>
<td>2 mg</td>
<td>Once a week, independently from meal, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>6 mg/mL cartridge</td>
<td>Initial dose: 0.6 mg Maintenance: 1.2-1.8 mg</td>
<td>qd, independently from meal, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>150 μg/3 mL ready pen</td>
<td>10-20 μg</td>
<td>qd, 1 hour before meal in the morning or evening, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Albiglutide</td>
<td>50-50 mg cartridge</td>
<td>30-50 mg</td>
<td>Once a week, at any time, independently from meal, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>0.75 mg/0.5 mL, 1.5 mg/0.5 mL single dose ready pen</td>
<td>0.75-1.5 mg</td>
<td>Once a week, s.c. injection</td>
</tr>
<tr>
<td></td>
<td>Semaglutide*</td>
<td>1.34 mg/mL, 0.25-0.5 mg and 1 mg-dose pen</td>
<td>Initial dose: 0.25 mg Maintenance: 0.5-1 mg</td>
<td>Once a week, s.c. injection</td>
</tr>
<tr>
<td>Incretin increasing (DPP4-I)</td>
<td>Sitagliptin</td>
<td>25, 50, 100 mg tb</td>
<td>100 mg</td>
<td>qd, independently from meal</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td>50 mg tb</td>
<td>100 mg</td>
<td>qd or bid, independently from meal</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>2.5, 5 mg tb</td>
<td>5 mg</td>
<td>qd, independently from meal</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>5 mg tb</td>
<td>5 mg</td>
<td>qd, independently from meal</td>
</tr>
<tr>
<td></td>
<td>Alogliptin**</td>
<td>6.25, 12.5, 25 mg tb</td>
<td>25 mg</td>
<td>qd, independently from meal</td>
</tr>
</tbody>
</table>

GLP-1A, glucagon-like peptide-1 agonists; DPP4-I, dipeptidyl peptidase-4 inhibitors; Exenatide XR, extended-release exenatide; qd, once a day; bid, twice a day.
*Not licensed in Turkey. **Certain forms are not available in Turkey.

7.6 | SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS (GLUCORETICS; GLIFLOZINS)

Sodium-glucose co-transporter 2 inhibitors (SGLT2-I), also called "glucoretics" or "glifosins", decrease glucose reabsorption in the kidney by causing SGLT2 inhibition in renal proximal tubulus and increase glucose discharge via urine. As they act independently from insulin, they can be used as an add on to after metformin in any stage of diabetes. Characteristics of use for SGLT2-I group of drugs are presented in Table 7.7.

Main advantages: slight weight loss (2 kg on average), low hypoglycemia risk, decreasing blood pressure (2-4 mmHg), serum uric acid level and albuminuria. They are more expensive than conventional OADs.
Canagliflozin, dapagliflozin and empagliflozin has similar efficacy in decreasing A1C. SGLT2-I group of drugs have been reported to have lower risk of hospitalization due to heart failure and progression to renal failure in comparison to placebo.

7.6.1. SIDE EFFECTS OF SGLT2 INHIBITORS

- Polyuria
- Fluid loss
- Hypotension
- Dizziness
- Slight increase in LDL cholesterol and serum creatinine (initially, temporarily)
- Fractures and lower extremity amputation cases have been reported with canagliflozin.
- Genitourinary infections: Attention should be exercised for genital infections, especially in women, and urosepsis and pyelonephritis in risky cases.
- Fournier gangrene cases have been reported.
- Euglycemic ketoacidosis: It is known that atypical (euglycemic or mildly-moderately hyperglycemic) DKA can develop in relation to fluid loss. In patients using insulin, although blood glucose levels come close to normal when SGLT2-I are added to the treatment, insulin should not be discontinued completely and ketoacidosis should be examined in suspected cases.
- Attention should be paid for dehydration in elderly and the ones using loop diuretics.
- These drugs are recommended to be terminated in cases of major surgery, severe disease or infection.

7.6.2. CONTRAINDICATIONS OF SGLT2 INHIBITORS

- Empagliflozin and canagliflozin are not recommended to be used in patients with type 2 diabetes with eGFR <45 ml/min. Dapagliflozin is not recommended in patients with eGFR <60 ml/min in Turkey.
- Type 1 diabetes (no indication yet, although studies are ongoing).
- Pregnancy and lactation

**TABLE 7.7 Sodium-glucose co-transporter 2 inhibitors (SGLT2-I)**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin*</td>
<td>100-300 mg tb</td>
<td>100-300 mg</td>
<td>qd, preferably before breakfast</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>10 mg tb</td>
<td>5-10 mg</td>
<td>qd at any time, independently from meal</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>10-25 mg tb</td>
<td>10-25 mg</td>
<td>qd at any time, independently from meal</td>
</tr>
</tbody>
</table>

qd, once a day.
*Not licensed in Turkey

7.7 USE OF ANTIDIABETIC DRUGS IN CHRONIC KIDNEY DISEASE

Antihyperglycemic drugs should be used with caution in chronic kidney disease. The dose of some drugs should be decreased and some should not be used. The recently published results of long-term CV safety studies revealed that some drugs with proved CV safety also enable renal protection. Therefore, the use of SGLT2-I group (empagliflozin, canagliflozin) or GLP-1A group (liraglutide, semaglutide) drugs are being considered (provided that GFR is suitable) for patients with chronic kidney disease (CKD). SEMT recommends the preference of insulin in patients with end-stage kidney disease and with or without renal replacement therapy. Based on the studies, the GFR ranges that antihyperglycemic drugs can be used.
are summarized below (recommended eGFR values are given for mL/min/1.73 m² body surface area):

- **Gliclazide/Glipizide**: Preferably should not be used if eGFR <30 mL/min. The dose should be decreased by 50% for 30-60 mL/min eGFR.
- **Glimepiride**: Should not be used if eGFR <30 mL/min.
- **Glibenclamide**: Contraindicated if eGFR <30 mL/min, should not be used if possible for 30-60 mL/min eGFR; if needed to be used then the dose should be decreased by 50%.
- **Repaglinide**: Preferably should not be used if eGFR <30 mL/min. Clinical studies have reported that dose adjustment is not required.
- **Nateglinide**: Contraindicated if eGFR <15 mL/min, the dose should be decreased by 50% for 15-30 mL/min eGFR. Clinical studies have reported that dose adjustment is not required for 15-30 mL/min eGFR.
- **Metformin**: According to FDA and EMA, metformin is contraindicated if eGFR <30 mL/min; it should not be started for patients with 30-45 mL/min eGFR, and should be decreased by 50% for patients who currently use. Caution should be exercised for cases with 45-60 mL/min eGFR while using metformin.
- **Piroglitazone**: If eGFR <30 mL/min, it is recommended to be used with caution and by decreasing the dose when needed as it can cause fluid retention. Clinical studies have reported that dose adjustment is not required.
- **Acarbose**: Contraindicated if eGFR <25 mL/min.
- **Sitagliptin**: Should not be used with eGFR <30 mL/min if possible. According to clinical studies, it can be administered by decreasing the dose by 75% [25 mg/day] when eGFR <30 mL/min; dose should be decreased by 50% [50 mg/day] for 30-50 mL/min eGFR.
- **Vildagliptin**: Preferably should not be used if eGFR <15 mL/min. According to clinical studies, it can be administered by decreasing the dose by 50% [50 mg/day] when eGFR <30 mL/min.
- **Saxagliptin**: Contraindicated if eGFR <15 mL/min, the dose should be decreased by 50% [2.5 mg/day] for 15-30 mL/min eGFR.
- **Linagliptin**: According to studies, it can be used for all patients, including dialysis patients, without requiring dose adjustment.
- **Alogliptin**: It can be administered by decreasing the dose by 50% [12.5 mg/day] for 30-60 mL/min eGFR, and by 75% [6.25 mg/day] for 15-30 mL/min. Alogliptin should not be used for cases with eGFR <15 mL/min.
- **Exenatide**: Contraindicated if eGFR <30 mL/min, the dose should be decreased by 50% for 30-50 mL/min eGFR.
- **Lixisenatide**: Contraindicated if eGFR <20 mL/min.
- **Liraglutide**: Contraindicated if eGFR <15 mL/min.
- **Dulaglutide**: Preferably should not be used if eGFR <15 mL/min, the dose should be decreased when needed.
- **Albiglutide**: Dose adjustment is not recommended in mild or moderate kidney failure. Albiglutide should not be used if eGFR <15 mL/min.
- **Dapagliflozin**: It is not recommended (because it will be ineffective over glycemic control) for cases with 45 mL/min eGFR. In Turkey, dapagliflozin is not recommended in cases with eGFR <60 mL/min.
- **Canagliflozin**: It is not recommended if eGFR <45 mL/min since it will not be effective over glycemic control. It can be used by decreasing the dose [100 mg/day] for renal protection if eGFR is between 45-60 mL/min.
- **Empagliflozin**: It is not recommended if eGFR <45 mL/min as it will not be effective over glycemic control. However, for the purposes of CV or renal protection, it can be used with caution without decreasing the dose for 45-60 mL/min eGFR.
- **Insulin**: If eGFR < 30 mL/min, insulin dose should be decreased due to increased hypoglycemia risk.
### SEMT RECOMMENDATIONS

1. **SEMT does not recommend the use any antihyperglycemic drug other than insulin in patients with advanced kidney disease (eGFR <30 mL/min) or in dialysis patients (D).**

2. **Metformin is contraindicated in stage 5 or end stage kidney disease (eGFR <30 mL/min). In stage 4 kidney disease (eGFR 30-45 ml/min) metformin should not be started if possible, and the dose should be halved in patients who currently use it. Metformin should be used with caution in patients with eGFR 45-60 mL/min (D).**

3. **If an angiographic examination with highly iodinated contrast agent will be performed, metformin should be stopped 24 hours before the procedure, patients should be hydrated and then metformin should be restarted 24 hours later (D).**

4. **Vitamin B-12 level should be periodically measured in patients using metformin and replacement should be administered if needed (B).**

5. **In patients with history of CV event, the use of SGLT2-inhibitors (empagliflozin, canagliflozin) or GLP-1 receptor agonists (liraglutide, semaglutide), with proven data on CV safety should be preferred (A).**

6. **In patients with chronic kidney disease (CKD), the use of SGLT2-I group (empagliflozin, canagliflozin, dapagliflozin) drug (A) or GLP-1A group (liraglutide, semaglutide) drugs (B) provides renal protection (on the condition that GFR is suitable for use).**

7. **SGLT2-I group (empagliflozin, canagliflozin and dapagliflozin) drugs decrease the risk of hospitalization due to heart failure (A).**

### REFERENCES


### 7.8 | EFFECTIVENESS OF ANTIHYPERGLYCEMIC DRUGS USED IN MONOTHERAPY

The effects of various drug groups on glycemia and A1C when used as monotherapy in type 2 diabetes patients are shown in Table 7.8. The initial good responses tend to decrease as the diabetes progresses, in that case combinations should be considered. The response to TZD group of drugs starts in 10-12 days and continues for 2-3 weeks after discontinuation of the drug.

The characteristics of the drugs used in diabetes treatment in terms of metabolic effects, cost, efficacy, their use in different clinical conditions including advanced age, uncontrolled diabetes, CV problems, non-alcoholic fatty liver, chronic kidney disease, congestive heart failure, and side effects such as gastrointestinal complaints, fracture risk and edema are summarized in Table 9.1 of Chapter 9.
### TABLE 7.8: Response to anti-hyperglycemic drugs in monotherapy

<table>
<thead>
<tr>
<th>Lifestyle modification</th>
<th>Decrease in FPG</th>
<th>Decrease in A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle modification</td>
<td>40-60 mg/dL</td>
<td>1.0-2.0%</td>
</tr>
<tr>
<td>Metformin</td>
<td>50 mg/dL</td>
<td>1.5%</td>
</tr>
<tr>
<td>Insulins</td>
<td>50-80 mg/dL</td>
<td>1.5-2.5%</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>40-60 mg/dL</td>
<td>1.0-2.0%</td>
</tr>
<tr>
<td>Glinides</td>
<td>30 mg/dL</td>
<td>1.0-1.5%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>25-55 mg/dL</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>Alpha glucosidase inhibitors</td>
<td>20-30 mg/dL</td>
<td>0.5-0.7%</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>20-30 mg/dL</td>
<td>1.0-1.5%</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>20-30 mg/dL</td>
<td>0.5-1.0%</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>20-30 mg/dL</td>
<td>0.5-1.0%</td>
</tr>
</tbody>
</table>

OAD, oral antidiabetic; FPG, fasting plasma glucose; A1C: Hemoglobin A1C; GLP-1, glucagon-like peptide-1; DPP4, dipeptidyl peptidase-4; SGLT2, sodium glucose co-transporter 2


### 7.9 | PRE-MIXED ANTI-HYPERGLYCEMIC DRUG COMBINATIONS

In type 2 diabetes, with the progression of the disease, monotherapies are replaced with combination therapies. In accordance with the pathophysiologic basis of the disease, insulin sensitizing and insulin secretagogue drugs are combined. Combinations with metformin should be preferred most, considering the cost and the long duration of experience. Generally, based on the characteristics of the patient, metformin can be combined with SU, GLN, DPP4-I, PIO or SGLT2. Similarly, pre-mixed combinations of GLP-1A group drugs with basal insulins are available. Pre-mixed combinations of different anti-glycemic group drugs are produced to increase patients’ compliance with the treatment (Table 7.9).

### TABLE 7.9: Pre-mixed anti-hyperglycemic combined medications

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial form</th>
<th>Daily dose</th>
<th>Administration time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral combinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide/Metformin*</td>
<td>1.25/250, 2.5/500, 2.5/500 mg, 2.5/1000 mg tb</td>
<td>2.5/500 - 10/2000 mg</td>
<td>qd or bid, with meal</td>
</tr>
<tr>
<td>Glipizide/Metformin**</td>
<td>2.5/250, 5/250, 5/500 mg tb</td>
<td>2.5/250 - 10/2000 mg</td>
<td>qd or bid, with meal</td>
</tr>
<tr>
<td>Pioglitazone/Metformin</td>
<td>15/500 mg, 15/850 mg, 15/1000 mg tb; 15/1000 mg XR tb</td>
<td>15/500 - 30/2000 mg</td>
<td>qd or bid, with meal</td>
</tr>
<tr>
<td>Pioglitazone/Glimepiride</td>
<td>30/2, 30/4 mg tb</td>
<td>15/2 - 30/4 mg tb</td>
<td>qd or bid, with meal</td>
</tr>
<tr>
<td>Repaglinide/Metformin</td>
<td>1/500, 2/500, 1/1000, 2/1000 mg tb</td>
<td>2/1000 - 6/2000 mg</td>
<td>bid or tid, before or with meal</td>
</tr>
<tr>
<td>Sitagliptin/Metformin</td>
<td>50/500, 50/850, 50/1000 mg tb</td>
<td>100/1000 - 100/2000 mg</td>
<td>bid, with meal</td>
</tr>
<tr>
<td>Vildagliptin/Metformin*</td>
<td>50/500, 50/850, 50/1000 mg tb</td>
<td>100/1000 - 100/2000 mg</td>
<td>bid, with meal or right after the meal</td>
</tr>
<tr>
<td>Saxagliptin/Metformin*</td>
<td>2.5/500, 2.5/850, 2.5/1000 mg tb; 2.5/1500, 5/1000 mg XR tb</td>
<td>2.5/1000 - 5/2000 mg</td>
<td>bid, independently from meal [metformin XR form is qd]</td>
</tr>
<tr>
<td>Linagliptin/Metformin*</td>
<td>2.5/500, 2.5/850, 2.5/1000 mg tb; 2.5/1500, 5/1000 mg XR tb</td>
<td>5/1000 - 5/2000 mg</td>
<td>bid, independently from meal [metformin XR form is 1 a day]</td>
</tr>
<tr>
<td>Dapagliflozin/Metformin*</td>
<td>5/850, 5/1000, 10/1000 mg tb; 5/500, 10/500, 2.5/1000, 5/1000, 10/1000 mg XR tb</td>
<td>5/1000 - 10/2000 mg</td>
<td>bid, with meal [metformin XR form is 1 time a day]</td>
</tr>
<tr>
<td>Empagliflozin/Metformin*</td>
<td>5/850, 5/1000, 12.5/1000 mg; 5/1000, 10/1000, 12.5/1000 mg, 12.5/1000, 25/1000 mg XR tb</td>
<td>10/1000 - 25/2000 mg</td>
<td>bid, with meal [metformin XR form is 1 a day]</td>
</tr>
<tr>
<td>Empagliflozin/Linagliptin**</td>
<td>10/5, 25/5 mg tb</td>
<td>10/5 - 25/5 mg</td>
<td>qd, independently from meal</td>
</tr>
</tbody>
</table>

**Injectable combinations**

| Insulin glargine/lixisenalide      | 100 U/mL + 33 mcg/mL / 100 U/mL + 55 mcg/mL | Variable based on the patient’s needs | qd, within 1 hour before the meal s.c. |
| Insulin degludec/iraglutide*      | 100 U/mL + 3.6 mg/mL | Variable based on the patient’s needs | qd, s.c. |

qd, once a day; bid, twice a day; tid, three times a day

*Some forms are not available in Turkey. **Not licensed in Turkey.
Discovery of insulin in 1922 and use of it in the treatment shortly thereafter, significantly increased the life expectancy and quality of life of patients with diabetes, particularly those with type 1 diabetes.

Insulin therapy maintains its importance as a major area of R&D since the discovery of insulin allowing the development of different insulin types and new methods of insulin treatment that are increasingly approaching physiologic insulin secretion dynamics.

### 8.1.1. **INDICATIONS OF INSULIN**

- Patients with classical type 1 diabetes mellitus, and latent autoimmune diabetes in adult (LADA)
- It is recommended to switch to insulin therapy in patients diagnosed with type 2 diabetes mellitus in the following conditions:
  - Inability to achieve targeted glycemic control with non-insulin anti-hyperglycemic drugs and those with A1C ≥10% [86 mmol/mol] and/or glycemia ≥300 mg/dL
  - Cases with suspected insulin deficiency (excessive weight loss, overt hypertriglyceridemia and ketosis)
  - Severe hyperglycemic symptoms (polyuria, polydipsia)
  - Hyperglycemic emergencies (diabetic ketoacidosis: DKA, and hyperosmolar hyperglycemic state: HHS)
  - Acute myocardial infarction [MI]
  - Acute, febrile illness
  - Major surgical operations
  - Pregnancy and lactation
  - Severe liver and kidney failure
  - Allergy and severe side effects to non-insulin anti-hyperglycemic drugs
  - Clinically severe insulin resistance
  - Long-term high-dose corticosteroid use
- GDM uncontrolled with diet

### 8.1.2. **ACTION MECHANISM OF INSULIN**

Insulin is used as an insulin replacement therapy in type 1 diabetes, whereas, in type 2 diabetes, insulin is required to improve impaired insulin secretion, elimination of glucotoxicity and achieve optimal glucose control.
• Allows glucose to be absorbed into the cell
• Increases glycogen storage
• Suppresses hepatic glucose output
• Increases peripheral and hepatic insulin sensitivity
• Inhibits fat and protein catabolism.

8.1.3. **INSULIN SOURCES**

• Recombinant DNA technique (human insulin, insulin analogs)
• Bovine and porcine insulin and semi-synthetic insulin derived from porcine (not used in Turkey)

8.1.4. **INSULIN ABSORPTION**

Insulins are generally used via subcutaneous (s.c.) injection. Insulin absorption may vary from patient to patient for the reasons listed below:

• Insulin source: Duration of action of human insulin is shorter than animal insulins.
• There are differences between insulins due to manufacturer reasons.
• Injection site: From fastest to slowest effect: s.c. Injection to abdomen, arm, thigh and hip.
• Ambient temperature: Insulin absorption is faster in hot environments and slower in cold temperatures.
• Exercise, systemic fever or massaging the injection site increases the absorption rate of insulin.

8.1.5. **INSULIN PREPARATIONS**

**Effectiveness of insulin**

Generally, U-100 (100 IU available in 1 mL) insulins are used around the world. In addition, concentrated forms of insulin (U-200, U-300 and U-500) have been developed for insulin resistant patients with high insulin requirement.

**Type and effect profile of insulin**

Insulins are classified in three groups based on their effect profiles: short/fast/faster-acting or inhaler, intermediate-acting and long/longer-acting. Insulin therapy is planned to meet prandial and/or basal insulin requirement. Short/fast/faster-acting or inhaler insulins meet prandial need, while intermediate/long/longer-acting insulins meet basal need. Various combinations of short/fast-acting insulins and intermediate/long-acting insulins have been developed to facilitate insulin therapy in diabetic patients whose condition cannot be controlled only with basal insulin and where it is also difficult to apply basal-bolus therapy (especially in type 2 diabetes). Currently used insulin preparations and s.c. effect profiles are given in Table 8.1. Although insulins do not cross the placental barrier, the data on the use of new insulins during pregnancy, except for human insulin and some analog insulins (lispro, aspart and insulin detemir) is minimal. Biosimilar analog insulins, which have been developed in recent years to lower the increasing insulin prices, have similar effect profiles with original insulin.
### TABLE 8.1: Insulin types and effect profiles*

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Effect onset</th>
<th>Peak effect</th>
<th>Effect duration</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHORT/FAST-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular U100</td>
<td>30 - 60 min</td>
<td>2 - 4 hr</td>
<td>5 - 8 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Lispro U100 &amp; U200</td>
<td>&lt;15 min</td>
<td>30 - 90 min</td>
<td>3 - 5 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Lispro U200**</td>
<td>&lt;15 min</td>
<td>30 - 90 min</td>
<td>3 - 5 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Biosimilar Insulin Lispro U100**</td>
<td>&lt;15 min</td>
<td>30 - 90 min</td>
<td>3 - 5 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Aspart</td>
<td>&lt;15 min</td>
<td>1 - 3 hr</td>
<td>3 - 5 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Glulisine</td>
<td>15 - 30 min</td>
<td>30 - 60 min</td>
<td>4 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Regular Inhaler**</td>
<td>&lt;5 min</td>
<td>20 - 40 min</td>
<td>3 hr</td>
<td>Powder</td>
</tr>
<tr>
<td>Fahrer-acting Aspart**</td>
<td>4 min</td>
<td>30 - 90 min</td>
<td>3 - 5 hr</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>INTERMEDIATE-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular U500**</td>
<td>30 min</td>
<td>2 - 4 hr</td>
<td>&lt;24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>1 - 2 hr</td>
<td>4 - 10 hr</td>
<td>&gt;14 hr</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>LONG-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>3 - 4 hr</td>
<td>6 - 8 hr [≠No peak]</td>
<td>20 - 24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>90 min</td>
<td>No peak</td>
<td>24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Biosimilar Insulin Glargine U100</td>
<td>90 min</td>
<td>No peak</td>
<td>24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Glargine U300</td>
<td>90 min</td>
<td>No peak</td>
<td>24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Degludec U100 &amp; U200</td>
<td>30 - 60 min</td>
<td>No peak</td>
<td>&gt;30 hr</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>PRE-MIXED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH/Reg 70/30</td>
<td>30 min</td>
<td>2 - 4 hr</td>
<td>14 - 24 hr</td>
<td>Blurry</td>
</tr>
<tr>
<td>NPA/Asp 70/30</td>
<td>6 - 12 min</td>
<td>1 - 4 hr</td>
<td>18 - 24 hr</td>
<td>Blurry</td>
</tr>
<tr>
<td>NPL/Lis 75/25</td>
<td>15 - 30 min</td>
<td>30 - 150 min</td>
<td>14 - 24 hr</td>
<td>Blurry</td>
</tr>
<tr>
<td>NPL/Lis 50/50, NPA/Asp 50/50</td>
<td>15 - 30 min</td>
<td>30 - 180 min</td>
<td>14 - 24 hr</td>
<td>Blurry</td>
</tr>
<tr>
<td>NPA/Asp 30/70</td>
<td>10 - 20 min</td>
<td>1.6 - 3.2 hr</td>
<td>14 - 24 hr</td>
<td>Blurry</td>
</tr>
<tr>
<td>Deg/Asp 70/30</td>
<td>14 - 72 min</td>
<td>2 - 3 hr</td>
<td>&gt;24 hr</td>
<td>Clear</td>
</tr>
</tbody>
</table>

NPH, neutral protamine Hagedorn; Reg, regular; NPA, neutral protamine aspart; Asp, aspart; NPL, neutral protamine lispro; Lis, lispro; Deg, degludec.

*Effect onset, peak effect and effect duration may vary due to patient-specific reasons. Peak effect and effect duration are dose-dependent. Effect duration increases at high doses.

**Not licensed in Turkey

8.1.6. **INSULIN ADMINISTRATION ROUTES**

- Insulins are subcutaneously injected in general use. Inhaler insulins are also developed for the inhalation route.
- Fast/short-acting insulins can be administered via intramuscular and intravenous infusion in emergency cases. IV use of intermediate/long-acting insulins is contraindicated.

8.1.7. **AIMS OF INSULIN THERAPY**

Two aims are considered when starting an insulin therapy:

1. **Insulin replacement**: Designed to mimic the normal basal-bolus insulin secretion (insulin replacement) of the body in type 1 diabetes.

2. **Basal insulin supplement**: In type 2 diabetes, treatment generally starts with basal insulin supplement, some cases may require (basal) insulin supplement, and insulin replacement may be needed in time.
8.1.8. **COMPLICATIONS OF INSULIN THERAPY**

- **Hypoglycemia:** The most important and frequent complication of the insulin therapy. Related to strict glycemic control and long diabetes duration. More frequent in patients with type 1 diabetes who receive basal-bolus insulin therapy. In DCCT study, the incidence of hypoglycemia was found to be 3 times higher in the intensive insulin treatment group than the conventional therapy group. Hypoglycemia risk is relatively lower with insulin analogs in comparison to human insulins.

- **Weight gain:** Weight gain is expected at the beginning of insulin treatment due to recovery of lost muscle and adipose tissue, water and salt retention and reduced glycosuria. Afterwards, the fear of hypoglycemia, and unbalanced nutrition may lead to continued weight gain.

- **Massive hepatomegaly:** Related to the filled glycogen stores; it is rare today.

- **Edema:** Edema can occur at the beginning due to decreased osmotic diuresis and Na+ uptake.

- **Immunogenicity:** With the use of human insulin and analog insulin, immunogenicity problems such as the development of insulin antibodies and allergies are now rarely seen.

- **Lipohypertrophy-atrophy:** These problems and lipohypertrophy, which had been encountered before the development of human insulins, are rarely seen now. It may develop as a result of frequent injection to the same site and treated by changing the injection site.

- **Bleeding, leaking and pain:** Bleeding is prevented by injecting to a region where capillary vessels are not visible. Keeping the needle under the skin for 5-10 seconds after the injection is completed or using a long needle can reduce insulin leakage. A mild pain may be felt during injection especially with acid insulin (e.g. glargine), it is insignificant.

- **Hyperinsulinemia, atherosclerosis and cancer risk:** Although experimental studies suggest an association between hyperinsulinemia and atherosclerosis, clinical evidence on the subject is limited. Increased malignancy risk with glargine insulin use has been reported but not proved.

Insulin is an anabolic hormone. The structures of insulin receptors are similar to insulin-like growth factors (e.g., IGF-1). The effect strength of insulin is parallel to its affinity with the receptor. Some strong insulins have high affinity for insulin and IGF-1 receptors. Therefore, it has been thought that there could be an association between long-term insulin use and cancer risk. The subject is still debatable due to contradictory data based on sectional or limited-duration studies. However, there is no long-term (>5 years) randomized clinical study on insulin use.

### 8.2 | INSULIN THERAPY MANAGEMENT

#### 8.2.1. **INSULIN THERAPY PROTOCOLS**

**Insulin supplement therapy**
Basal or biphasic insulins are used in this therapy mode.

**Basal insulin supplement**
It is used as a medium or long-acting basal insulin supplement once or twice a day in patients with type 2 diabetes and in some GDM cases.

**Biphasic mixed insulin therapy**
Twice a day intermediate/long-acting + fast/short-acting mixed insulin: Pre-mixed insulin preparations can be used. Alternatively, two separate insulins can be injected to the patient.
It can be used in type 2 diabetes patients for whom basal insulin supplement is inadequate to control diabetes, patients with type 1 diabetes who are unable to administer (e.g., elderly) basal-bolus insulin therapy, and in mild GDM cases that cannot be controlled with diet.

**Basal-bolus insulin replacement**

It should be used in patients with type 1 diabetes, uncontrolled gestational diabetes, and patients with type 2 diabetes whose endogenous insulin reserves are reduced. The following administration methods can be used:

**Multiple dose insulin injections**
- 3 times a day pre-prandial fast/short-acting (bolus) insulin + once a day intermediate/long-acting (basal) insulin
- 3 times a day pre-prandial fast/short-acting (bolus) insulin + twice a day intermediate/long-acting (basal) insulin
- For some patients with diabetes (especially the ones with type 2 diabetes) who have difficulty in applying basal-bolus insulin therapy with different insulin preparations, the option of analog mixed insulin administration 3 times a day can be considered.
- In patients with type 2 diabetes, for whom the basal insulin therapy is insufficient, treatment can be gradually switched to basal-bolus insulin therapy. In that case, initially, one dose (before the largest meal) of bolus insulin can be added per day. Second and third bolus insulin doses can be added when the initial treatment is no longer sufficient. (see Chapter 9, Figure 9.2).

**Continuous subcutaneous insulin infusion**
- Continuous subcutaneous insulin infusion (CSII) is performed via an insulin pump. The calculation of basal, bolus and adjustment doses with insulin pump is explained in Chapter 10.

### 8.2.2. Calculation and adjustment of the insulin dose

Initially, the daily insulin requirement is calculated based on body weight per kilogram. In addition, the patient’s phenotype and physical activity level, diabetes complications and the presence of prior insulin use should be taken into consideration. Examples for the calculation of the insulin dose are given in Table 8.2. Generally, maintenance of insulin doses for patients with type 1 and type 2 diabetes are as follows:
- 0.4-1.0 IU/kg/day in type 1 diabetes
- 0.3-1.2 IU/kg/day in type 2 diabetes
- In basal-bolus insulin regimens, approximately half of the daily requirements (40-60%) is calculated as basal and the remaining half (40-60%) as bolus.
- In patients who have no prior insulin use, basal insulin supplement can be initiated at 0.1-0.2 IU/kg/day dose.

**Insulin injection time**

Injection time varies according to the insulin type.
- Fast-acting insulins should be administered 5-15 minutes before the meal, whereas, short-acting ones should be administered 30 minutes prior to the meal. The recently introduced ultrafast acting insulin has been developed to be used at the beginning of or with the meal.
- Insulin injection time may also vary depending on the blood glucose levels. For example, if the pre-prandial PG is higher than the targeted level, then the mealtime can be slightly delayed.
• Insulin injection may be delayed until after meals to avoid hypoglycemia in diabetic individuals with prolonged gastric emptying time.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Insulin dose (IU/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal body weight</strong></td>
<td></td>
</tr>
<tr>
<td>High physical activity</td>
<td>0.3</td>
</tr>
<tr>
<td>Moderate physical activity</td>
<td>0.4</td>
</tr>
<tr>
<td>Mild physical activity</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
</tr>
<tr>
<td>High physical activity</td>
<td>0.5</td>
</tr>
<tr>
<td>Moderate physical activity</td>
<td>0.6</td>
</tr>
<tr>
<td>Mild physical activity</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Kidney failure</strong></td>
<td>-0.2</td>
</tr>
<tr>
<td><strong>Factors increasing the risk of hypoglycemia</strong></td>
<td>-0.2</td>
</tr>
<tr>
<td><strong>Overeating</strong></td>
<td>+0.1</td>
</tr>
<tr>
<td><strong>Newly onset type 1 diabetes (&lt;30 years of age)</strong></td>
<td>0.3</td>
</tr>
</tbody>
</table>

### 8.2.3. INSULIN ADMINISTRATION METHODS

**Pen**

Pen provides practical, safe and accurate insulin administration, therefore it is highly preferred. Insulin pens can be disposable or have changeable cartridges and they generally contain 3 ml insulin at 100 IU/mL concentration. U300 glargine is available in ready to-use pen or cartridges that contain 1.5 mL of volume at 300 IU/mL concentration. Pens are set to 1 IU intervals, and pens with 0.5 IU interval are available for children. Insulin pen needles are 4 mm, 5 mm, 6 mm, 8 mm or 12.7 mm. The studies showed that 4-5 mm needles have similar performance with 8 mm needles in obese patients and that 8 mm or longer needles pose intramuscular injection risk (especially when applied vertically) for under or normal weight (BMI < 25 kg/m²) patients, thus may potentially cause hypoglycemia.

In general use, 4-6 mm needles are preferred. 8 mm needles may be required for obese patients.

**Injector**

The use of this method is gradually becoming less common. Injectors generally have 1 IU intervals but 0.3, 0.5 and 1 ml injectors are also available. Injectors set at 0.5 IU can be preferred for children and insulin-sensitive individuals. In general, injectors with 8 mm needle are used, however, injectors with 4, 5, 6 and 12 mm needles are also available. For injectors, 10 ml vials (containing 1000 IU insulin) are used.

**Pump**

Continuous subcutaneous insulin infusion pumps are used. This subject is comprehensively explained in further sections (see Chapter 10 CSII Principles).

**Inhaler insulin**

Inhaler insulin has been developed to meet the prandial insulin requirement, particularly in type 1 diabetes patients. However, currently, it has limited use and is unavailable in Turkey. They cause less hypoglycemia than fast-acting insulins. However, it is less effective due to its low bioavailability. Current cartridge forms do not offer dose flexibility, and the long-term effects (especially on the lungs) are unknown. Inhaler insulin is contraindicated for patients with chronic obstructive pulmonary disease (asthma, bronchitis), smokers, and those who have recently stopped smoking.
8.2.4. STORAGE CONDITIONS FOR INSULIN

- Unopened insulin vials and cartridges can be stored in the fridge at 2-8 oC until the expiration date.
- Opened cartridges and vials can be used up to 30 days at room temperature without exposure to hot temperatures. However, it is safer to store at +4 oC considering the weather conditions, the possibility of violation of the cold chain, and the intellectual level of the patients in our country.
- Intermediate/long-acting or mixed insulin preparations begin to lose their biological activity slightly after 15 days of opening. This factor should be considered if glycemic control begins to deteriorate even if the patient and disease-related conditions remain unchanged.

8.2.5. MIXING OF INSULIN

- Short-acting and NPH insulins must be used immediately after being mixed.
- Glargine and detemir insulins should not be mixed with other insulins.

8.2.6. DRUGS WITH THE POTENTIAL TO CHANGE INSULIN EFFECT

Some of the drugs presented in Table 8.3 can cause hypoglycemia by increasing the insulin effect and other can cause hyperglycemia by decreasing the insulin effect (and others by creating insulin resistance), therefore insulin dose adjustment is required.

### TABLE 8.3: Drugs that change the effect of insulin

<table>
<thead>
<tr>
<th>A. Drugs that increase hypoglycemic effect and decrease glycemia</th>
<th>B. Drugs that decrease hypoglycemic effect and increase glycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Antivirals used in AIDS etc.</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Albuterol</td>
</tr>
<tr>
<td>β-blockers*</td>
<td>Asparaginase</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Danazol</td>
</tr>
<tr>
<td>Phenyl butazone</td>
<td>Dextrothyroxine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Calcium</td>
<td>Diuretics (especially the Thiazide group)</td>
</tr>
<tr>
<td>Clotibrate</td>
<td>Dobutamine</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Etacrylic acid</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Monoamine oksidase inhibitors</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>Calciton</td>
</tr>
<tr>
<td>OAD</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Pentamidine**</td>
<td>Lithium carbonate</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Morphine sulphate</td>
</tr>
<tr>
<td>Propoxyphen</td>
<td>Niacin</td>
</tr>
<tr>
<td>Salicylate</td>
<td>Nicotine</td>
</tr>
<tr>
<td>Somatostatin analog [Octreotide]</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Sulfonyamide</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Somatropine</td>
</tr>
<tr>
<td></td>
<td>Terbutaline</td>
</tr>
<tr>
<td></td>
<td>Thyroid hormones</td>
</tr>
</tbody>
</table>

*May delay the recovery of hypoglycemia. **Sometimes hyperglycemia occurs following hypoglycemia.
SEMT APPROACH and RECOMMENDATIONS

1. Basal-bolus (intense) insulin therapy should be preferred to achieve glycemic control in adults with type 1 diabetes and type 2 diabetics with diminished beta cell reserve (for type 1 diabetes: A, for type 2 diabetes: D).

2. Insulin analogs have no superiorit over human insulin in terms of glycemic control (A1C) (A).

3. Fast-acting insulin analogs (aspart, glulisine, lispro) can be used with an adequate amount of basal insulin to reduce hypoglycemia risk and achieve PPG control while reducing A1C (B).

4. Long-acting insulin analogs (glargine and detemir) can be used as an alternative to NPH insulin for basal insulin supplement (B).

5. Clinical studies have shown that risks of severe hypoglycemia and nocturnal hypoglycemia are relatively lower with basal insulin analogs in comparison to NPH insulin (B).

6. All patients with type 1 diabetes should be evaluated for the risk of hypoglycemia, informed to avoid insulin-induced hypoglycemia and the risk factors that may cause severe hypoglycemia should be identified and treated (D).

7. To achieve improvement in patients with hypoglycemia unawareness:
   - SMBG frequency should be increased and glucose should be measured periodically at night as well (D).
   - In these patients, glycemic control should be loosened (higher glycemic and A1C levels should be targeted) and strict glycemic control should be restored after the patient’s recovery (C).

REFERENCES

9.1 CURRENT TREATMENT IN TYPE 1 DIABETES

Due to autoimmune β-cell destruction in type 1 diabetes, endogenous insulin production decreases from clinical onset, and pancreas almost completely loses its ability to produce insulin in a short period of time. If these cases cannot be treated with exogenous insulin injections, due to the natural course of the disease, severe hyperglycemia (polyuria, polydipsia, weight loss, etc.) occurs first, then weight loss, hypertriglyceridemia, ketosis, and acidosis develops, putting patients’ lives at risk.

Treatment of type 1 diabetes is outlined below:

**Glycemic control targets:** In adults with type 1 diabetes, A1C goal should be <7% (58 mmol/mol), fasting, and pre-prandial plasma glucose [PG] should be 80-130 mg/dl, and postprandial 2-hr PG should be <160 mg/dL.

Young individuals with shorter diabetes duration and no complication, women planning for pregnancy or currently pregnant should have more strict glycemic targets (e.g. A1C 6-6.5%; 42-48 mmol/mol), on the other hand, in elderly patients with high risk of hypoglycemia, complications and comorbidites, glycemic targets should be more flexible (e.g. A1C 7.5-8.5%; 58-69 mmol/mol). A1C should be tested every three months in patients with type 1 diabetes.

**Treatment method:** As both first and second phase insulin secretion is lacking in type 1 diabetes, normal physiological insulin secretion needs to be mimicked with basal and bolus (prandial) insulin injections.

Most patients require intensive insulin therapy with basal-bolus (multiple doses) insulin injections or continuous subcutaneous insulin infusion (CSII via insulin pump) (see Chapter 8 and Chapter 10).

Meta-analyses have demonstrated a minimal difference in favor of the pump in terms of glycemic control and severe hypoglycemia incidents between multiple dose insulin injections and insulin pump therapy with subcutaneous insulin infusion. It has been shown that the incidence of nocturnal hypoglycemia has decreased in patients with type 1 diabetes without A1C increase with the recently developed sensor-augmented insulin pumps that have the ability to stop infusion at a low glycemic threshold.

In adults with slowly progressive type 1 diabetes or latent autoimmune diabetes (LADA) as initially there is some endogenous insulin reserve, glycemic control may be achieved with two or three doses of daily biphasic insulin therapy.

**Insulin dose:** Generally, the insulin requirement in type 1 diabetes ranges 0.4-1.0 IU/kg/day. The average insulin dose is around 0.5 IU/kg/day.

**Basal insulin:** Compared to NPH insulin, long-acting insulin analogs [glargine U100, and detemir] should be preferred as basal insulin as their day-to-day absorption variability is less, and have no peak. In randomized-controlled trials of these insulins, the incidence of nocturnal hypoglycemia decreased even though there was no significant difference in glycemic control (in A1C levels).

In other randomized-controlled trials used novel long-acting insulin analogs [degludec U100 or U200, and glargine U300], which have been developed to provide a longer and peakless basal insulin effect, less symptomatic and nocturnal hypoglycemic events have been reported in comparison to glargine U100 or detemir.
Bolus (prandial) insulin: In patients with type 1 diabetes who have been properly trained and especially the ones who learned carbohydrate (CH) counting, rapid-acting insulin analogs have been shown to cause slightly less hypoglycemia events.

Carbohydrate counting and insulin sensitivity (correction) factor: Bolus insulin doses should be adjusted based on the amount of CH in the meal and physical activity. Blood glucose level at the time of bolus administration should also be taken into consideration for the adjustment of the bolus component of the insulin therapy, and the dose should be corrected by calculating the insulin sensitivity factor (ISF). Detailed information about CH counting and ISF is given in ‘Medical Nutrition Therapy in Diabetes’ chapter [see Chapter 5].

In recent years, it is recommended that the amount of fat and protein contained in the meal should be taken into consideration in the calculation of bolus doses. Fat and protein counting may be taught to suitable patients.

Education: Self-monitoring of blood glucose (SMBG) training should be provided for all type 1 diabetes patients, and continuous glucose monitoring (CGM) training for the cases with suitable conditions [see Chapter 10]. In addition, patients should be taught how to apply and monitor the insulin therapy.

Patients with type 1 diabetes and their relatives should be trained about the symptoms and treatment of hypoglycemia and glucagon injection should also be taught.

Ideally, all patients with type 1 diabetes should receive CH counting training, and should also be taught how to calculate ISF.

Diabetes identification cards should be handed to all type 1 diabetes patients and they should be advised to keep this card with them at all times.

Non-insulin therapies: Studies are ongoing for the use of antihyperglycemic drugs, such as metformin, acarbose, pramlintide, glucagon-like peptide-1 receptor analogs (GLP-1A), dipeptidyl peptidase-4 inhibitor (DPP4-I), pioglitazone (PIO) or sodium-glucose co-transporter 2 inhibitor (SGLT2-I), in addition to insulin to reduce insulin requirement and improve glycemic control in patients with type 1 diabetes.

Except for acarbose, none of these drugs have been approved for use in type 1 diabetes cases in our country.

In randomized-controlled trials and especially with the off-label use of SGLT2-I drugs in patients with type 1 diabetes, few cases developed diabetic ketoacidosis (DKA) have been reported. It should be noted that hyperglycemia may not be severe in these cases.

SEMT RECOMMENDATIONS

1. All patients with type 1 diabetes should receive basal-bolus insulin therapy (A).
2. Insulin analogs should be preferred as they cause less hypoglycemic events in comparison to human insulins (B).
3. CH counting training should be provided to all patients with type 1 diabetes (B).
4. Sensor-augmented insulin pump (CSII) therapy offers less hypoglycemia and more flexibility in daily life for selected patients with type 1 diabetes; these cases should be followed up in the experienced centers (B).
5. In patients with history of repeated nocturnal hypoglycemia, using sensor-augmented pumps with automated insulin suspension feature at low glucose threshold can help reduce nocturnal severe hypoglycemia (B).
REFERENCES


9.2 | CURRENT TREATMENT IN TYPE 2 DIABETES

In recent years, the treatment approach in type 2 diabetes has changed significantly. Therefore, international authorities frequently update guidelines and develop new treatment algorithms on this topic.

In the algorithms, recommendations are given based on the results of the randomized-controlled trials (and sometimes observational studies). As underlined in current guidelines, the results of these trials involving patients with specific characteristics that may not apply to the entire population of patients. Algorithms published in previous years emphasized decreasing the glycemic control targets, whereas, current algorithms recommend the individualized glycemic control targets based on the patients’ characteristics and adopt a patient-centric treatment approach (taking patient characteristics into consideration for treatment selection). Contrary to the traditional step-wise approach; recent guidelines recommend that combination therapies be initiated from the early stage of clinical diabetes.

Today, all guidelines including those published by American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD), International Diabetes Federation (IDF), American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), Scottish Intercollegiate Guidelines Network (SIGN), Joslin Diabetes Center, Canada Diabetes Association, Association of American Physicians, National Institute for Health and Care Excellence (NICE), International Diabetes Center, German Diabetes Association, Finnish Diabetes Association, Italian Diabetes Federation and Australian Diabetes Society recommend planning the diabetes treatment in compliance with patient’s characteristics (lifestyle, habits, the duration of diabetes, the degree of glycemic control previously, the risk of hypoglycemia, the presence of diabetes complications, treatment cost, and comorbid diseases; such as atherosclerotic cardiovascular disease [ASCVD] and chronic kidney disease [CKD], non-alcoholic steatohepatitis [NASH] and fibrosis). The guidelines also recommend that the patient’s preferences be considered when planning the best treatment.

In this section of the guideline, first the results of phase 3 and phase 4 clinical trials of the new drugs developed for use in patients with type 2 diabetes; especially those of cardiovascular outcome trials (CVOTs) and meta-analyses have been reviewed by the Society of Endocrinology and Metabolism of Turkey (SEMT) Diabetes Mellitus Study Group. Then, in the light of the internationally accepted current trends, and taking into consideration of the realities of our country, “The SEMT Approach in the Treatment of Type 2 Diabetes” has been prepared. The SEMT approach is outlined below.

In this context, the results of the above-mentioned CVOTs have been reviewed to make recommendations on rational use of the drugs in second and third-line treatment of patients with type 2 diabetes, especially the ones with macro and microvascular complications;
moreover, surgical treatment of obesity, which has become an option at least for some obese patients with type 2 diabetes is summarized.

In treatment selection, as stated in Table 9.1, the action of the drugs in special patient groups and those with comorbidities should be taken in consideration. “SEMT-2019 Treatment Algorithm in Type 2 Diabetes” is summarized below (Figure 9.1).

9.2.1 | GLYCEMIC TARGETS

- In 2 diabetes patients, glycemic targets should be determined on an individual basis according to the characteristics and clinical condition of the patient.

- Generally, if there is no special condition that increase hypoglycemia risk in patients with type 2 diabetes and the life expectancy is long enough, then A1C target should be ≤7% (53 mmol/mol) to reduce microvascular complications. However, in some patients with special conditions (e.g., pregnant women, insulin treated young patients, and those without serious microvascular complication), as long as there is no risk of hypoglycemic attack, A1C target can be set at 6-6.5% (42-48 mmol/mol).

- The benefit of maintaining a low level of A1C should not exceed the risks of hypoglycemia and mortality, especially in patients with high CVD risk. If the patient’s life expectancy is short and hypoglycemia risk is high, then more flexible glycemic control targets should be adopted. In older patients (≥65 years), A1C target can be set between 7.5-8.5% (58-69 mmol/mol) based on the diabetes-specific conditions, concomitant health problems and functional capacity of the patient.

- Patient’s preferences should also be considered (provided that the patient is well informed) during the treatment selection. Besides, the duration of prior poor glycemic control is also crucial. For example, in a patient with uncontrolled diabetes for more than 10 years, rapid reduction of A1C with an aggressive treatment can lead to severe hypoglycemia and additional CV risks. If A1C >7% (53 mmol/mol) or patient-specific glycemic targets cannot be met, the lifestyle should be evaluated firstly. If A1C remains >7% (53 mmol/mol) despite the lifestyle modifications, then new adjustments are required.

- A1C should be measured every three months until the target is achieved and once in six months after that.

- Glycemic targets that are as close to normal values as possible should be achieved and maintained.

- First, target should be fasting and pre-prandial PG levels should be controlled; the target for pre-prandial and FPG levels should be 80-130 mg/dL.

- If fasting and pre-prandial PG levels cannot be maintained or A1C remains >7% (53 mmol/mol) despite achieving the targets, then postprandial PG control is required. Postprandial PG should be measured at 2nd hour (in pregnant women at 1st hour) from the beginning of the meal. Postprandial 2-hr PG target should be <160 mg/dL. Different timing may be required for postprandial PG measurement in patients who apply CH counting and those on insulin pump therapy.

- In addition, patients with type 2 diabetes should be receive diabetes education by a multidisciplinary team. The main goals of the education are to inform and encourage the patients about the self-management of diabetes, building glucose monitoring skills and ensuring responsibility-sharing between patients and members of the diabetes team.
9.2.2 | TREATMENT SELECTION

Lifestyle modifications (healthy nutrition, proper physical activity, losing excess weight, cessation of smoking, reducing alcohol, avoiding stress and adequate sleep, etc.) are the cornerstone of the treatment of type 2 diabetes and should be applied at all stages of the disease [See Chapter 5 and Chapter 6].

In antihyperglycemic treatment selection, as summarized in Table 9.1, glucose-lowering effects as well as side-effect profile, preference in specific patient groups, safety, tolerability and cost issues should be considered (see Section 7 - Table 7.8 and Section 8 - Table 8.1).

Timely treatment modification and necessary dose adjustments should not be neglected in order to achieve the patient-specific A1C target within 3-6 months.

Generally, modifications should be made to intensify the treatment (i.e., dose increase or addition of new medications), but in some cases treatment may need to be alleviated. For example, in a patient who initially presented with severe hyperglycemia, failure to change treatment even though glucose toxicity was broken with basal-bolus insulin therapy may cause frequent hypoglycemia and excessive weight gain.

a) Treatment of newly diagnosed type 2 diabetes patient without any atherosclerotic cardiovascular disease or chronic kidney disease

- In patients newly diagnosed with type 2 diabetes and with initial A1C of <8.5% (<69 mmol/mol) metformin (if there are no contraindications or severe intolerance; a low-cost drug with long clinical experience, proven efficacy, minimal hypoglycemia and neutral effect on weight) should be started simultaneously with lifestyle modifications.
  - Initial metformin dose should be 500 mg twice daily or, in patients with gastrointestinal sensitivity, 500 mg once daily, and it should be increased up to an effective dose (i.e., 1000 mg twice daily) via a 500 mg increment every 1-2 weeks. The bioavailability of metformin is higher when taken within the first 10 minutes of meal, in comparison to when taken on a full stomach.
  - Vitamin B-12 levels should be checked during metformin therapy and replacement be administered as needed. Vitamin B-12 levels require regular monitoring, especially in patients with anemia or neuropathy.
  - In cases where metformin is contraindicated or cannot be tolerated, in underweight patients or cases that especially require fast response, treatment can be initiated with any other antihyperglycemic drug group. If an insulin secretagogue is administered instead of insulin, a relatively long-acting sulphonylurea [SU] like glibenclamide should not be used; instead, an extended-release SU such as gliclazide or glimepiride or a short-acting glinide [GLN] such as repaglinide or nateglinide be preferred. Initially, FPG should be measured at least three times weekly, then self-monitoring of blood glucose (SMBG) should be applied according to the selected drug. SMBG frequency should be increased when treatment modification was done, at insulin initiation, and during dose titration. Nutritional and physical activity recommendations for weight loss should be emphasized in overweight or obese patients; however, these interventions may become inadequate in the long term. In addition, the drug effects on weight should be taken into consideration while selecting the drugs for hyperglycemia and the concomitant diseases in overweight or obese type 2 diabetes patients.
  - Weight loss targets must be achieved (at least 4 kg or 5% of the body weight) for a positive effect on concomitant diseases such as CV events, HT, and dyslipidemia.
<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>MET</th>
<th>SU/GLN</th>
<th>PIO</th>
<th>DPP4-I</th>
<th>GLP-1RA</th>
<th>SGLT2-I</th>
<th>AGI</th>
<th>INS</th>
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</thead>
<tbody>
<tr>
<td>Effectiveness (glucose-lowering effect)</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑</td>
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<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cost</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑↑↑</td>
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<tr>
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<td>↑↑</td>
<td>↑</td>
<td>↔</td>
<td>↓↓</td>
<td>↓</td>
<td>↔</td>
<td>↑↑</td>
</tr>
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<td>Hypoglycemia risk</td>
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<td>↑↑</td>
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<td>↔</td>
<td>↔</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Edema risk</td>
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<td>↔</td>
<td>↑↑</td>
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<td>↔</td>
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<tr>
<td>Fracture risk</td>
<td>↔</td>
<td>↔!..</td>
<td>↑</td>
<td>↔</td>
<td>↔!..</td>
<td>↔!..</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Preference in special patients groups</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes duration &gt;15 years</td>
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<td>!..</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
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<td>✓✓</td>
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<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Advanced age (&gt;75 years)</td>
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<td>✓GLN</td>
<td>!..</td>
<td>✓✓</td>
<td>!..</td>
<td>!..</td>
<td>!..</td>
<td>Bazal</td>
</tr>
<tr>
<td>Established CVD/high CV risk</td>
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<td>!..</td>
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<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
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<td>Heart failure</td>
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<td>!..</td>
<td>X</td>
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<td>✓!../X</td>
<td>✓!../X</td>
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</tr>
<tr>
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<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
</tr>
<tr>
<td>Advanced DM complications</td>
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<td>!..</td>
<td>!..</td>
<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
</tr>
<tr>
<td>Fatty liver disease</td>
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<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Progression to chronic kidney disease</td>
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<td>!../X</td>
<td>✓!/X</td>
<td>!../X</td>
<td>✓!/X</td>
<td>✓!/X</td>
<td>✓!/X</td>
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<tr>
<td>Neurocognitive dysfunction</td>
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<td>✓!..</td>
<td>!../?</td>
<td>!../?</td>
<td>✓?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Life expectancy &lt;5 years</td>
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<td>✓!..</td>
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<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
<td>✓!..</td>
</tr>
<tr>
<td>Acute disease/Accompanying severe systemic disease.</td>
<td>✓!/X</td>
<td>!../X</td>
<td>✓!/X</td>
<td>✓!..</td>
<td>✓!..</td>
<td>X</td>
<td>✓!..</td>
<td>✓!..</td>
</tr>
</tbody>
</table>

MET, metformin; SU, sulphonylurea group drugs; GLN, glinide group drugs; PIO, pioglitazone; DPP4-I, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 analogues; SGLT2-I, sodium-glucose co-transporter 2 inhibitors; AGI, alpha glucosidase inhibitors; INS, insulins; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus.

↑, Increases; ↓, Decreases; ↔, Neutral; ✓, Can be preferred; !.., use with caution; X, contraindicated; ?, Unknown; !../X, Although generally contraindicated, it can be used with caution in some conditions; should be evaluated case-by-case.

The colors used in this table are based on the colors of traffic lights. Green color means that the drug can be used; yellow and orange indicate use with caution, and red means that the drug should not be used.
Life style modification (healthy diet, physical activity and weight control) is essential in every stage of the therapy.

A1C < 8.5%

MONOTHERAPY

A1C > Target

MET

A1C > Target

DOUBLE COMBINATION

SGLT-2I
GLP-1 A
DPP4-I
INS
TZD
SU/GLN
AGI

A1C > Target

TRIPLE COMBINATION

SGLT-2I
GLP-1 A
DPP4-I
INS
TZD
SU/GLN
AGI

A1C > Target

TREATMENT WITH INSULIN

MET + INS

OAD + BASAL INS

BASAL INS + GLP-1 A

BASAL INS + BOLUS INS

PREMIXED INSULIN

INSULIN PUMP

FIGURE 9.1: SEMT TYPE 2 DIABETES TREATMENT ALGORITHM

1 If A1C is > 7% or above the individual target, then the treatment should be changed. 2 MET is the preferred monotherapy drug. If MET is contraindicated or there is intolerance for MET, treatment with another drug can be initiated.

A1C, glycated HbA1c; MET, metformin; SGLT2-I, sodium glucose co-transporter 2 inhibitor; GLP-1A, glucagon-like peptide-1 receptor agonist; DPP4-I, Dipeptidyl peptidase-4 inhibitor; INS, insulin; TZD, thiazolidinedione; SU, sulphphonylurea; GLN, glinide; AGI, alpha-glucosidase inhibitor; CV, cardiovascular.
• In patients with \textit{A1C} 8.5-10\% (69-86 mmol/mol) at the diabetes onset, the treatment is recommended to be initiated with a second non-insulin anti-hyperglycemic drug or basal insulin combination with metformin. Both patient-specific and disease-specific factors should be taken into consideration for the selection of the second drug to be used in combination with metformin. In patients without severe hyperglycemic symptoms, a DPP4-I with neutral effect on weight and low risk of hypoglycemia, or a SGLT2-I due to low hypoglycemia risk and weight loss up to 2-3 kg, can be selected. For patients with overt insulin resistance, PIO due to low hypoglycemia risk can be preferred. In overweight/obese patients, a GLP-1A drug with low hypoglycemia risk and weight-loss effect can be used. However, in addition to these advantages, the disadvantages of each of these drugs that are explained in detailed in Chapter 7 and summarized in Table 9.1 should also be taken into consideration. Especially in cases involving insulin combinations or metformin and secretagogue (SU/GLN) combinations, patients should be closely monitored and the doses should be decreased once the glucose levels are reduced. This can prevent the patient from experiencing hypoglycemia, and gaining excess weight.

• The treatment should be started with insulin in patients whose initial \textit{A1C} is $\geq$10\% (86 mmol/mol), or FPG $>$ 250 mg/dL or random PG $>$ 300 mg/dL or those with polyuria, polydipsia and nocturia symptoms, patients with weight loss or with catastrophic clinical presentation (hypertriglyceridemia, DKA, hyperosmolar hyperglycemic state [HHS]). It is likely that some of these patients with such conditions may be undiagnosed type 1 diabetes cases. Moreover, some of them are type 2 diabetes cases with severe insulin deficiency. In these patients, insulin therapy should preferably be performed with basal-bolus (or mix) insulin and, if possible metformin should be continued along with insulin. Except for catastrophic cases, what determines the insulin therapy plan is the characteristics of the patient and the experience of the physician.

\textbf{b) Treatment of known type 2 diabetes patient whom A1C target cannot be achieved and without any atherosclerotic cardiovascular disease or chronic kidney disease}

In a previously diagnosed type 2 diabetes patient, if A1C target cannot be achieved or glycemic targets cannot be maintained, the drug doses should be increased in a short period of time (3 months) or a new treatment regimen should be started. If A1C is 7-7.5\% [53-58 mmol/mol] three months after lifestyle modifications and 2000 mg/day metformin, then the lifestyle should be re-evaluated, if A1C is $>$7.5\% [58 mmol/mol] or personal glycemic targets cannot be achieved, then a second drug should be added to the treatment.

• Second drug selection should be based on the individual characteristics of the patient and cost should also be considered in addition to efficacy and safety. Metformin treatment should be continued with the selected second drug if there are no contraindications.

• In cases where metformin is failed to achieve glycemic control, the addition of any other non-insulin anti-hyperglycemic drug provides lower benefit than their efficacy in monotherapy, usually lowering A1C by 0.8-1\%.

• In type 2 diabetes patients with metabolic decompensation (i.e., overt hyperglycemia, hypertriglyceridemia, ketosis or involuntary weight loss), insulin is the most effective medication to control glucose. Especially if A1C $\geq$ 8.5\% [69 mmol/mol], preferably basal insulin (a long-acting analogue or NPH insulin) should be started. In suitable cases, a premixed (biphasic) insulin may also be effective. The risk of hypoglycemia, weight gain and patient’s skills should also be considered if insulin treatment was selected.

• If A1C is between 7.1 and 8.5\% [54-69 mmol/mol] one of the antihyperglycemic drugs [SU, GLN, DPP4-I, AGI, GLP-1A, PIO, or SGLT2-I] should be added to the treatment, depending on the patient’s condition.

• In case of, particularly postprandial glycemic control is desired, one of the GLN, DPP4-I, AGI or GLP-1A groups can be selected. Alternatively, a short/fast-acting or a premixed
insulin addition can be considered. However, cost, hypoglycemia and weight gain are common in insulin treatment; in addition, gastrointestinal side effects in AGI or GLP-1A groups are important issues to be taken into account. DPP4-I and AGI groups are neutral on weight.

- The DPP4-I group, which are incretin-based drugs, has lower hypoglycemia risk compared to insulin or SU; however, they are less powered in reducing A1C. Drugs belonged to the DPP4-I group may be beneficial due to their weight-neutral effect and no major side effects.
- Especially in patients who are thought that weight loss is beneficial, a GLP-1A or a SGLT2-I can be used. Due to insufficient experience, GLP-1A drugs should not be used in obese, young children with type 2 diabetes. If a GLP-1A (i.e., exenatide) is being used, then the patients should be monitored for the risk of pancreatitis and pancreatic cancer. If SGLT2-I is preferred, caution should be taken since there is increased risk of genitourinary (especially mycotic) infections and rarely urosepsis, pyelonephritis, and euglycemic DKA.
- PIO is the only thiazolidinedione (TZD) group drug available in our country and it has lower hypoglycemia risk and more sustained efficacy compared to SU. However, considering the concerns about TZD drugs which increase the risk of edema, congestive heart failure, and fracture, the patients should be carefully monitored in terms of dose and side effects if it is added to metformin as a second-line drug.
- SU/GLN group is the cheapest option. Although its more effective in decreasing A1C than many other anti-hyperglycemic drug groups, the sustainability of its effect is shorter than metformin and PIO. Hypoglycemia and weight gain risks should be considered.
- Non-alcoholic fatty liver, which frequently accompanies type 2 diabetes, should also be considered while choosing the treatment options. As short-term randomized-controlled studies showed that PIO improves non-alcoholic steatohepatitis (NASH) and fibrosis, American and European Liver Disease guidelines state that PIO can be used in NASH cases proved with biopsy. In the preliminary studies, GLP-1A and SGLT2-I group drugs were also showed to provide some improvement in NASH accompanying type 2 diabetes, and randomized-controlled trials have been initiated for this purpose.
- As dehydration and DKA risk increases during acute diseases and before a major surgery, metformin and SGLT2-I recommended be temporarily discontinued.
- If A1C is >8.5% (69 mmol/mol) three months after the second OAD is added to metformin or if the patient-specific glycemic targets cannot achieved, and the patient is overweight or obese, choosing a GLP-1A can effectively lower A1C without increasing the risk of hypoglycemia and providing 3-5 kilograms of weight loss. However, their long-term use is limited due to gastrointestinal side effects, requiring injections and high cost.
- In patients with hyperglycemic symptoms, underweight patients, or those unable to tolerate GLP-1A, the treatment must be switched to insulin therapy without any delay.
  - In patients who did not use insulin previously, basal insulin (alternatively a premixed insulin) should be added to the treatment.
  - It may be suitable to add basal insulin to the treatment in obese patients who use DPP4-I, SGLT2-I, or GLP-1A in combination with metformin.
  - Insulin therapy should be intensified in patients who have used biphasic insulin previously.
  - When PIO is used with insulin, patients should be closely monitored for the risks of edema and congestive heart failure.
  - Metformin should be continued in patients who use insulin.
- In patients who use controlled release SU or GLN with metformin, adding basal insulin would be a more effective treatment modality.
- If A1C remains between 7.1 and 8.5% (54 - 69 mmol/mol) despite the addition of a second drug to metformin; then a third OAD may be added to the treatment. However,
this approach will increase the cost and the effectiveness of the treatment will be lower than insulin. In general, adding a third OAD can reduce A1C by only 0.3-0.5%. Therefore, treatment may become insufficient in a short period of time.

c) Treatment of type 2 diabetes patients with known macro and microvascular complications

The long-term safety of conventional and novel drugs used in the treatment of type 2 diabetes has been investigated in randomized-controlled clinical trials.

Previous studies: The CV and microvascular (particularly renal) safety of conventional diabetes drugs has been investigated in numerous studies.

In the intensive intervention arm of the ADVANCE study, extended release gliclazide, a drug from the SU group was used. In this study, the rate of progression of nephropathy has been slowed down with intensive therapy, nevertheless more hypoglycemia has been reported.

In the intensive glycemic intervention group of the ACCORD study, reduction in risk and/or progression of retinopathy, nephropathy and neuropathy were reported; however, there was an increase in mortality, probably related to cardiovascular autonomic neuropathy and hypoglycemia.

In the intensive intervention arm of the VADT study, ASCVD endpoints, CV death and all-cause death rates were not different than the standard intervention arm; however, lower CV event incidence was reported in the intensive intervention group after a 10-year follow-up period.

In the PROACTIVE study, it has been demonstrated that PIO is safe in terms of CV end points, and especially it was associated with decreased stroke risk.

In clinical studies involving patients with prediabetes (STOP-NIDDM study) and type 2 diabetes, acarbose has been reported to be beneficial in terms of CVD outcomes.

In the meta-analyses, CV safety of metformin was better than SU.

New CVOTs: Based on long-term randomized-controlled trials, CV and renal safety characteristics of the drugs that have been used in type 2 diabetes treatment for the past 10 years are summarized in Table 9.2. Certainly, it should be considered that these studies do not have standard design in terms of both included patient groups (patients with established CVD and/or patients at high risk for CVD) and primary and secondary endpoints (CV, renal and other). In light of these studies, the following conclusions can be drawn:

- Any drug group has not been shown to reduce primary CVD risk in patients with type 2 diabetes who have not previously had ASCVD.
- DPP4-I group is generally neutral (safe) in terms of CV endpoints, however, it has no superiority over the standard treatment in relation to CV risk. Of this group, saxagliptin (and possibly alogliptin) increases the risk of heart failure.
- According to the CV outcome trials of GLP-1A group drugs; liraglutide, semaglutide, extended release exenatide, and albiglutide have been shown to reduce the risk of triple combined major CV events (MACE: nonfatal MI, nonfatal stroke and CV death). When major CV events were examined individually; it was found that liraglutide reduced the risk of CV death, semaglutide reduced stroke risk, and albiglutide reduced the risk of nonfatal MI. Moreover, liraglutide and extended release exenatide reduced the risk of all-cause mortality. To some extent, these drugs have been shown to slow the progression of nephropathy (possibly through alleviating albuminuria).
### TABLE 9.2: Cardiovascular and renal endpoints of novel anti-hyperglycemic drugs used in type 2 diabetes treatment

<table>
<thead>
<tr>
<th>Study, Drug</th>
<th>3-point MACE</th>
<th>MI</th>
<th>Stroke</th>
<th>CV death</th>
<th>CHF hospitalization</th>
<th>All-cause mortality</th>
<th>Progression to CKD</th>
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<tbody>
<tr>
<td><strong>DPP4-I</strong></td>
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<td></td>
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<td>SAVOR-TIMI 53, Saxagliptin</td>
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<td>0.95 [0.80-1.12]</td>
<td>1.11 [0.88-1.39]</td>
<td>1.03 [0.87-1.22]</td>
<td>1.27 [1.07-1.51]</td>
<td>1.11 [0.96-1.27]</td>
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<td>EXAMINE, Alogliptin</td>
<td>0.96 [≤1.16]</td>
<td>1.08 [0.88-1.33]</td>
<td>0.91 [0.55-1.50]</td>
<td>0.79 [0.60-1.04]</td>
<td>1.07 [0.79-1.46]</td>
<td>0.88 [0.71-1.09]</td>
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<td>TECOS, Sitagliptin</td>
<td>0.99 [0.89-1.10]</td>
<td>0.95 [0.81-1.11]</td>
<td>0.97 [0.79-1.19]</td>
<td>1.03 [0.89-1.19]</td>
<td>1.00 [0.83-1.20]</td>
<td>1.01 [0.90-1.14]</td>
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<td>1.12 [0.90-1.40]</td>
<td>0.91 [0.67-1.23]</td>
<td>0.96 [0.81-1.14]</td>
<td>0.90 [0.74-1.08]</td>
<td>0.98 [0.84-1.13]</td>
<td>1.04 [0.89-1.22]</td>
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<td>1.03 [0.87-1.22]</td>
<td>1.12 [0.79-1.58]</td>
<td>0.98 [0.78-1.22]</td>
<td>0.96 [0.75-1.23]</td>
<td>0.94 [0.78-1.13]</td>
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<td>LEADER, Liraglutide</td>
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<td>0.88 [0.75-1.03]</td>
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<td>0.78 [0.66-0.93]</td>
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<td>0.74 [0.51-1.08]</td>
<td>0.61 [0.38-0.99]</td>
<td>0.98 [0.65-1.48]</td>
<td>1.11 [0.77-1.61]</td>
<td>1.05 [0.74-1.50]</td>
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<td>0.85 [0.70-1.03]</td>
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<td>0.75 [0.61-0.90]</td>
<td>0.86 [0.66-1.14]</td>
<td>0.93 [0.73-1.19]</td>
<td>-</td>
<td>0.95 [0.79-1.16]</td>
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<td><strong>SGLT2 I</strong></td>
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<td>EMPA-REG OUTCOME, Empagliflozin</td>
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<td>0.87 [0.70-1.09]</td>
<td>1.18 [0.89-1.56]</td>
<td>0.62 [0.49-0.77]</td>
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<td>0.68 [0.57-0.82]</td>
<td>0.54 [0.40-0.75]</td>
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<td>CANVAS Program, Canagliflozin</td>
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<td>0.85 [0.69-1.05]</td>
<td>0.90 [0.71-1.15]</td>
<td>0.90 [0.71-1.15]</td>
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<td>0.87 [0.74-1.01]</td>
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<td>0.89 [0.77-1.01]</td>
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<td>0.98 [0.82-1.17]</td>
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<td>0.93 [0.82-1.04]</td>
<td>0.53 [0.43-0.66]</td>
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MACE, major adverse cardiovascular events (nonfatal myocardial infarction + nonfatal stroke + cardiovascular death); MI, myocardial infarction; CHF, congestive heart failure; cs., causes; CKD, chronic kidney disease; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP-1RA, Glucagon-like peptide 1 receptor analog; SkrX2: Doubled basal serum creatinine level, N-MA: Newly onset macroalbuminuria, SGLT2-I, sodium glucose co-transporter 2 inhibitor; s.c., subcutaneous injection form; wk, Weekly administrated form; HR, Hazard ratio; CI, Confidence interval.

*Trials do not have standard design in terms of included patient groups (patients with established CVD and/or high CVD risk), and CV and renal endpoints.
• Based on the CV outcome trials of SGLT2-I group drugs; empagliflozin and canagliflozin have been shown to reduce the risk of triple combined MACE (nonfatal MI, nonfatal stroke and CV death). When CV events were examined individually; empagliflozin reduced the risk of CV death; furthermore, empagliflozin, canagliflozin, and dapagliflozin reduced the risk of hospitalization due to heart failure and slowed the progression of mild to moderate nephropathy (through eGFR); In addition, it has been reported that empagliflozin reduced the risk of all-cause mortality.

Based on the conclusions of the above mentioned trials:
• In type 2 diabetes patients with established CVD and insufficient glycemic control with metformin alone, the addition of a GLP-1A (primarily) or a SGLT2-I, which has a proven CV safety, should be preferred.
• In type 2 diabetes patients with mild to moderately decreased eGFR and insufficient glycemic control with metformin alone, the addition of a SGLT2-I to the treatment can slow the progression of nephropathy. However, SGLT2-I group drugs cannot be used in patients with eGFR <45 mL/min/1.73 m²
• In type 2 diabetes patients with known heart failure or those at high risk of heart failure and insufficient glycemic control with metformin alone, the addition of a SGLT2-I to the treatment can reduce the risk of hospitalization due to heart failure.
• PIO can be added to the treatment of patients with severe insulin resistance.
• In patients who use SU/GLN or basal insulin in combination with metformin, the addition of a DPP4-I, or SGLT2-I or GLP-1A to the treatment may be beneficial to achieve glycemic control. However, caution should be paid to the risk of hypoglycemia. In this case, it is recommended to reduce the dose of SU, or GLN or basal insulin.

d) Surgical treatment of obese patient with type 2 diabetes (bariatric surgery)

Today, obesity surgery called “bariatric surgery”, is becoming more commonly used in the treatment of obesity. In recent years, strong evidence has been emerged suggesting that bariatric surgery may be beneficial for the prevention and treatment of obese individuals with type 2 diabetes. Adjustable gastric band, sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion ± duodenal switch (BPD-DS) has been recognized by many current guidelines as the standard bariatric surgery method. Apart from the adjustable gastric band method, which is not commonly preferred today; however, other three methods are thought to provide reliefment in glycemic control through additional mechanisms together with the metabolic improvement associated with weight loss. Some guidelines refer these operations as “metabolic surgery” due to their rapid and strong effects on glucose metabolism.

Gastrointestinal tract has important effects on the normal glucose metabolism and the changes caused by the modified anatomy of gastrointestinal tractus with these operations are claimed to provide additional metabolic benefits, independent from weight loss. Many potential mechanisms that have been highlighted for these good metabolic effects include: increase in intestinal peptide hormones such as GLP-1, avoidance of factors with potential anti-incretin effects in relation to the by-passed proximal small intestine, decrease in ghrelin secretion, and changes in food-sensitive mechanisms that regulate insulin sensitivity, as well as bile acid metabolism and microbiota.

The results of randomized-controlled studies have led to the consideration that bariatric surgery is a more effective method compared to conventional (medical) treatments in the regulation of glycemia and CV risk factors in the treatment of coexistence of obesity and
Additional non-randomized observational studies suggest that bariatric surgery reduces microvascular complications, CVD, and cancer development. The use of laparoscopic techniques and surgical experience has reduced the early morbidity and mortality rates of these operations. However, nutritional deficiencies, osteoporosis, anemia, dumping syndrome, gastrointestinal complaints like diarrhea and constipation, hypoglycemia, alcohol and substance abuse, depression, anxiety, and various other complications may be seen in relation to these operations.

Despite the presence of short and middle-term results that evaluate the effect of bariatric surgery on type 2 diabetes treatment, long-term outcomes of these operations are still debatable and yet to be clear. In addition to the potential benefits, there are many risks associated with bariatric surgery in the long-term. Mortality and morbidity can be higher than expected in unexperienced centers. Therefore, a meticulous evaluation must be performed with a multidisciplinary approach when deciding for bariatric surgery.

**Indications of bariatric surgery**

In the absence of contraindications, the operation indications that are generally accepted for patients with type 2 diabetes and obesity are shown below:

- Regardless of the level of glycemic control and current anti-hyperglycemic treatment they use, type 2 diabetes patients with BMI $\geq 40$ kg/m$^2$
- Type 2 diabetes patients with BMI $\geq 35$ kg/m$^2$ whose optimal glycemic control cannot be achieved despite the suitable antihyperglycemic treatment

Aside from the above indications, diabetes remission or glycemic control improvement after surgery has been reported in type 2 diabetes patients with BMI 30.0-34.9 kg/m$^2$; however, bariatric surgery is controversial for these patients due to limited evidence and lack of long-term data that suggest clear benefit.

In obese patients with type 1 diabetes, surgery is not recommended due to limited number and quality of evidence that suggest improvement in metabolic parameters after surgery.

**Contraindications of bariatric surgery**

- Patients <18 or >65 years of age (relative contraindication)
- Untreated endocrine disease that causes obesity (Cushing’s syndrome, hypothyroidism, insulinoma, etc.)
- Untreated eating disorders (bulimia nervosa etc.)
- Untreated major depression or psychosis
- Severe coagulopathy
- Severe cardiac disease that makes anesthesia difficult
- Alcohol or drug abuse
- Inability to comply with nutritional recommendations like lifelong vitamin replacement or calorie-restricted diet
- Being pregnant or planning for pregnancy in the following 12-18 months
- Active cancer disease
- Severe gastroesophageal reflux disease (relative contraindication especially for SG)
- Portal hypertension
- Crohn’s disease (gastric by-pass is contraindicated)

RYGB has the highest benefit/risk ratio in diabetes treatment through surgery. Although BPD-DS is more effective in diabetes control, postoperative nutritional deficiencies are more severe and there are more complications. While the outcomes of SG are similar to RYGB in terms of early diabetes control, the recurrence of diabetes is more likely after
SG. In randomized-controlled studies, it has been shown that diabetes remission was achieved in 30-63% of patients during the 1-5 years of follow-up period after the RYGB. However, long-term follow-up of these patients reported diabetes recurrence in 30-50% of them. Young age, short duration of diabetes (<8 years), non-insulin therapy, maintenance of weight loss and good glycemic control at the time of surgery are factors that increase the possibility of diabetes remission.

Multidisciplinary team approach, proper patient selection, adequate preoperative evaluation, and proper postoperative follow-up are crucial for the success of bariatric surgery with acceptable morbidity and mortality rates in patients with diabetes (detailed information is available in SEMT Bariatric Surgery Guide 2018 in Turkish version).

9.2.3 | TREATMENT WITH INJECTABLE DRUGS (INSULIN AND GLP-1A) IN TYPE 2 DIABETES

Although there are many non-insulin oral antihyperglycemic (OAD) drugs available, considering that second OAD used in addition to metformin can decrease A1C by 0.8-1%, and the third OAD can decrease A1C by 0.3-0.5%, it is rational to avoid using combination of multiple drugs, and prefer one of the injection therapies (insulin or GLP-1A) in cases where A1C is more than 1.5% above the determined target. In that case, if needed, insulin therapy should not be delayed.

1) GLP-1A treatment

In obese/overweight patients inadequately controlled with metformin and A1C value >1.5% of the target, a GLP-1A should be preferred due to its low hypoglycemia risk, its efficacy and weight loss effect. However, gastrointestinal side effects and cost issues may limit the wider use of this group of drugs. In order to reduce gastrointestinal side effects, the drug should be started at a low dose and increased gradually.

2) Insulin therapy

Insulin therapy may be required at any time during the course of type 2 diabetes. The physician should not present the insulin therapy as a threat or punishment to the patient. How to initiate and intensify insulin therapy in patients with type 2 diabetes is summarized below.

In patients with type 2 diabetes during other intercurrent diseases that increase insulin requirements, severe insulin resistance, acute metabolic decompensation (DKA, HHS), surgery, pregnancy or progression of diabetes complications basal-bolus insulin therapy should be initiated immediately.

Basal insulin therapy: Except for the above specified acute conditions, basal insulin once daily is preferred when initiating insulin therapy in type 2 diabetes.

In some patients with high insulin requirement, a second dose of basal insulin (or two doses of pre-mixed human or analog biphasic insulin) may be required. Degludec (U100 and U200) and glargine U300, which are recently developed ultra-long-acting or concentrated insulin analogues are generally sufficient as one dose a day.

Generally a long-acting analog insulin (glargine or detemir) is started at 0.2 [in obese patients 0.3-0.4] IU/kg at night, or evening or morning time as basal insulin. In cases who have difficulties in accessing to basal insulins, a single dose of NPH insulin 0.1-0.2 IU/kg/day can be administered at night. Since the risk of symptomatic hypoglycemia and nocturnal hypoglycemia is relatively lower, long-acting insulin analogues (glargine, detemir) should be preferred instead of NPH in patients with a high risk of hypoglycemia.
Basal insulin is increased by 2 IU in every three days until FPG is ≤120 mg/dL (increase by 4 IU if FPG >180 mg/dL).

If hypoglycemia occurs or FPG is <80 mg/dL at night in patients using insulin, insulin dose is decreased by 4 IU (and should be decreased by 10% if insulin dose is higher than 60 IU). Moreover, in patients with coronary heart disease, dementia or in geriatric patients, night or evening insulin doses should be decreased if FPG is below 100 mg/dL.

**Intensifying the treatment:** Insulin therapy should be intensified in patients who have high basal insulin requirement (>0.5 IU/kg). In order to intensify the treatment, basal plus, biphasic insulin therapy, or GLP-1A, if not previously used, may be considered. In patients with hyperglycemia symptoms, it is recommended to switch to a basal-bolus regimen.

When basal insulin is insufficient, glycemic control can be achieved by gradually increasing rapid-acting analog or short-acting human insulins starting from the meal with the highest postprandial blood glucose level. Alternatively, a single dose of pre-mixed insulin Asp/Deg 30/70 may be started before the largest meal.

The addition of GLP-1A should be preferred when basal insulin is insufficient, especially in patients who are susceptible to weight gain. Pre-mixed basal insulin plus GLP-1A combinations (insulin degludec plus liraglutide or glargine plus lixisenatide) may be used.

Alternatively, the addition of SGLT2-I to basal insulin may improve glycemic control. However, when used in combination with insulin, it is recommended to stop SGLT2-I, 24-48 hours prior to elective surgery or intense physical activity, avoid diets with restricted CH and excessive alcohol consumption; As these patients may develop DKA, and they should to be followed closely.

Despite basal insulin therapy, if postprandial glycemia (2-hr PPG) targets cannot be met or if A1C is >7.5% (58 mmol/mol), then starting from the largest meal, one dose of prandial insulin (4 IU rapid/short-acting insulin) should be initiated, and increased by 2 IU every three days until PPG ≤160 mg/dL.

If A1C >7.5% (58 mmol/mol) or individual targets are not met despite the addition of one dose of prandial insulin to basal insulin, then a second dose of prandial insulin can be added. Thus, basal-bolus insulin therapy can be intensified by increasing the number of rapid/short-acting (aspart, glulisine, lispro or regular) insulin injections gradually based on 2-hr PPG levels.
If A1C value is more than 1.5% above the target or in the presence of severe hyperglycemic symptoms, it should be directly switched to basal-bolus insulin therapy. In such cases, 50% of the total daily insulin requirement should be used as prandial insulin three times a day.

Alternatively, a biphasic insulin can be administered three times a day especially in patients who would have difficulty in the administration of basal-bolus insulin therapy. Insulin secretagogues (SU or GLN) should be discontinued when prandial (rapid/short-acting) insulins are used. If possible, metformin should be continued together with insulin therapy. The use of PIO with intensive insulin therapy increases the risk of edema and congestive heart failure. However, in insulin resistant patients who require high doses of insulin, a low dose PIO (<30 mg/day) can be added to the treatment for a short period (6-12 months) until the insulin resistance is alleviated. Close monitoring of this patients is necessary.

When GLN, PIO, DPP4-I, SGLT2-I or GLP-1A is added to insulin therapy, insulin doses should be reduced against the risk of hypoglycemia.

Subcutaneous insulin infusion (CSII) therapy may be used in type 2 diabetes patients whose glycemic control cannot be achieved with basal-bolus insulin, who have a flexible lifestyle, and are willing to use insulin pump.

SEMT RECOMMENDATIONS

1. In patients with type 2 diabetes, pharmaceutical treatment selection should be personalized for each patient based on the degree of hyperglycemia, duration of diabetes, drug characteristics (efficacy, power, side effects, CV safety, contraindications, hypoglycemia risk and cost), current diabetes complications, comorbid diseases, life expectancy and patient’s own preferences (D).

2. In patients with newly diagnosed type 2 diabetes, if there are no contraindications, metformin should be started simultaneously with the lifestyle modifications (for obese patients: A, non-obese patients: D).

3. In patients who have hyperglycemic symptoms and/or A1C >10% (>86 mmol/mol) at the time of diagnosis, insulin therapy should be preferred primarily together with lifestyle modifications (D).

4. Glycemic control targets should be determined on an individual basis and without putting the patient at risk for hypoglycemia (D).
   - The optimal target for A1C is ≤7% (53 mmol/mol), and it should be applied for the majority of the patients (A).
   - If A1C is 7-7.5% (53-58 mmol/mol) despite metformin, then the lifestyle modifications should be reviewed.
   - When adequate glycemic control cannot be achieved in 3 months despite the lifestyle modifications and metformin; if A1C is 7.5-8.5% (58-69 mmol/mol), an antihyperglycemic drug from a different group should be added; while if A1C is >1.5% above the target (e.g. >8.5; 69 mmol/mol) GLP-1A or basal insulin should be added to the treatment (D).

5. In patients with established CV event history, GLP-1A (liraglutide: A, semaglutide: A) and SGLT2-I (empagliflozin: A, canagliflozin: C) group drugs should be preferred as they decrease the risk of major CV events and CV death.

6. SGLT2-I should be used to slow the progression of chronic kidney disease in diabetic patients with eGFR >45 mL/min (A).

7. SGLT2-I drugs reduce the risk of hospitalization due to heart failure in patients with or at high risk for heart failure (A).
8. In type 2 diabetes patients with BMI $\geq 40$ kg/m$^2$, bariatric surgery is a treatment option regardless of the glycemic control and the anti-hyperglycemic treatment (A).

9. Bariatric surgery is a treatment option for type 2 diabetes patients with BMI $\geq 35$ kg/m$^2$ and optimal glycemic control cannot be achieved despite the adequate medical treatment (A).

10. For the success of bariatric surgery (with acceptable morbidity and mortality rates) in patients with type 2 diabetes a multidisciplinary team approach, proper patient selection, detailed preoperative evaluation (especially psychiatric evaluation in terms of drug abuse) and appropriate postoperative follow-up are crucial (C).

11. In patients with A1C $>1.5\%$ above the target despite the use of two different types of OAD in addition to metformin, starting a GLP-1A drug improves glycemic control, reduces the risk of hypoglycemia and prevents weight gain (D).

12. All patients with diabetes who use insulin or insulin secretagogues should be educated on the prevention, recognition and treatment of hypoglycemia (D).

13. In patients with type 2 diabetes who have intercurrent illnesses that increase the insulin requirement (infection, disease, severe insulin resistance, DKA, HHNT, surgery, pregnancy, or the progression of diabetes complications etc.), basal-bolus insulin therapy should be initiated immediately (D).

14. Except for above specified conditions, basal insulin (long-acting analog/NPH) should be primarily preferred when initiating insulin therapy in type 2 diabetes. In some patients with high insulin requirements, but unable to administer basal-bolus insulin therapy, 1-3 doses (generally 2 doses) of pre-mixed insulin can also be used (D).

15. Since the risk of symptomatic hypoglycemia and nocturnal hypoglycemia is relatively lower in patients using basal insulin, long-acting insulin analogues (glargine, detemir, degludec) may be preferred to NPH in patients at high risk of hypoglycemia (A).

16. The following drugs can be used to achieve postprandial blood glucose (PPG) control*: Rapid-acting insulin analogues (B), short-acting insulins (B), pre-mixed biphasic insulin analogues (B), pre-mixed biphasic human insulins (B), short-acting GLP-1A (A), GLN (B), AGI (B) or DPP4-I (B).

17. Type 2 diabetes patients using insulin or insulin secretagogues should be evaluated for the risk of hypoglycemia, and the risk factors that may cause hypoglycemia should be identified and treated. These patients should be informed about other drug-induced hypoglycemias (D).

18. In obese patients on OAD combinations with poor glycemic control and have no catastrophic condition, the combination of "metformin + basal insulin + GLP-1A or SGLT2-I" may provide clinical benefit (A).

19. During acute diseases and before major surgery, metformin and SGLT2-I should be discontinued temporarily as the risk of dehydration and DKA will increase (D).

*Drugs are generally effective at the meal that follows the time of administration.
REFERENCES


10.1 | PRINCIPLES OF INSULIN INFUSION (INSULIN PUMP)

Internationally recognized medical approaches about the continuous subcutaneous insulin infusion (CSII) treatment, also called insulin pump, are summarized below.

Pump therapy can help to achieve diabetes treatment goals which are;

- To reach near-normal glycemic targets
- Not to cause hypoglycemia that would require the assistance or intervention of third parties during the treatment
- To reduce chronic complications of diabetes mellitus
- To improve the quality of life and extend life expectancy

10.1.1 | INDICATIONS OF CSII

Main indications of insulin pump treatment for type 1 diabetes patients are summarized below:

1. Recurrent hypoglycemia episodes history that requires the assistance
2. Inability to achieve strict glycemic control (A1C ≤6.5%; 48 mmol/mol) despite the administration of multi-dose (basal-bolus) insulin injection regimens and more than four self-monitoring of blood glucose (SMBG) measurements a day
3. Patients experiencing the Dawn phenomenon (morning fasting plasma glucose [FPG] levels 140-160 mg/dL)
4. Cases with significant day-to-day variability in blood glucose levels (Brittle diabetes, recurrent severe hypoglycemia)
5. Pregnant women or those planning pregnancy (it is mandatory to achieve strict glycemic control before conception for the prevention of fetal abnormalities and spontaneous abortus. Therefore, it is recommended to start CSII several months before pregnancy)
6. Patients who require flexibility in their daily lives (shift workers, frequent travelers or those working in places with high safety requirements)
7. Low insulin requirement (daily insulin requirement less than 20 IU)

Type 1 diabetes patients with one of these conditions, and some type 2 patients (those with conditions matching 2nd-6th items or the ones with more than 500 IU daily insulin requirement due to severe insulin resistance) are eligible candidates for pump therapy.
10.1.2 | CONTRAINDICATIONS OF CSII

Main contraindications of insulin pump are summarized below:

1. Pumps should not be used in patients who are not ready to perform glycemia measurement 4–6 times a day, not trained about SMBG, who do not know carbohydrate (CH) counting technique, or who are not willing to use these methods.
2. Patients with inadequate compliance with multi-dose insulin injection treatment
3. Inability to closely monitor the patient (patients who are not willing to be regularly monitored by the diabetes team consisting of physician, diabetes nurse and dietitian)
4. Patients who lack of environmental support
5. Patients with low socioeconomic background
6. Patients with lower education level and low motivation
7. Patients with inadequate intellectual capacity
8. Patients with psychosis and severe depression
9. Patients who have serious concerns that pump use will adversely affect their lifestyle (athletes in contact sports, divers, those who think pump will have a negative effect on their sexual life)
10. Patients with physical or emotional discomfort with regards to insulin pump use
11. Patients with unrealistic expectations from insulin pump treatment (for example, those who believe they will be free from their responsibilities associated with the disease when they have a pump).

10.1.3 | MANAGEMENT OF CSII THERAPY

Preliminary requirements

The patient must be trained on SMBG, learned CH counting technique, and be willing to utilize these methods.

Insulins used in CSII

Monomeric insulins (crystallized; regular insulin, insulin lispro, insulin aspart, and insulin glulisine) can be used in CSII. Fast-acting insulin analogs have superior aspects over crystallized insulin (more stable maintenance of the glycemia level and ability to administer bolus doses right before the meal). Therefore, although its use is technically possible, regular insulin is not preferred because of its insufficiency in providing the expected benefits from CSII. Some of the insulin analogs can cause precipitation in the catheter; the patient must be well trained about catheter control as this condition can disrupt insulin flow.

Initial insulin dose

The calculation of basal and bolus doses when starting an insulin pump treatment is shown in Table 10.1. Total insulin dose (TID) for CSII can be calculated by decreasing the current total insulin dose by 25% or based on 50% of the patient’s body weight.

The average of doses calculated by two methods can be used to alleviate the clinical concerns:
Lower initial dose can be used for patients with high hypoglycemia risk,
Higher initial dose can be used for patients with hyperglycemia, high A1C level or for pregnant patients.

If a daily TID is calculated by this method, its 50% is administered as basal and the other 50% as bolus. Based on the patient’s condition (pregnancy, young children and adolescents, etc.) these rates can range as 40-50% basal and 50-60% bolus.

1. Calculation of basal infusion doses

- The hourly insulin infusion rate is calculated by dividing the total basal dose by 24. No snack is prescribed until the basal dose adjustment is achieved.
- Treatment starts with the single basal rate, and dose is adjusted every 2-3 days based on glucose level. The target is to ensure stable fasting (between meal and during sleep) glucose level. Different basal doses are added based on daily glucose variability.
- The adequacy of basal and bolus doses are evaluated based on the glycemia level measured before meal, 2-hr after meal, at 00:00 and 03:00 at night.
- The target is to achieve <35 mg/dL difference between basal levels (increase and decrease in glycemia levels before the meals and at night and towards morning) and postprandial 2-hr glycemia level of <180 mg/dL (preferably <140 mg/dL).
- Changes in basal insulin infusion rates of 0.05-0.10 IU/hr are made to keep fluctuations in basal glycemia below 35 mg/dL.
• If the difference between morning PG (FPG) and PG measured at 03:00 is greater than 35 mg/dL, the basal infusion is planned at a rate of 1.5 times the infusion rate at 24:00. This infusion is started 2-3 hours before breakfast.

Meal skipping method: Meal skipping method can also be used to evaluate whether the basal infusion rate is suitable. According to this method:
• During the pre- and post-prandial PG monitoring, no food is taken at the meal where the suitability of basal infusion rate is to be evaluated.
• PG levels are evaluated before the meal, 2-hr after the skipped meal and before the next meal. The difference between these measurements is expected to be <35 mg/dL. If the differences are higher, the basal insulin infusion rate before that meal is re-adjusted.
• One meal is skipped every day, and PG control is maintained before and after the skipped meal (bolus is not administered for that meal as there is no food is taken).
• To evaluate the suitability of basal insulin doses, after food intake, waiting at least four hours is necessary.

2. Calculation of bolus insulin doses
Carbohydrate/insulin ratio (CH/I) and insulin sensitivity factor (ISF) should be known in order to calculate bolus insulin doses.

Carbohydrate/Insulin ratio
Carbohydrate counting: CH counting technique, which has been previously described in Medical Nutrition Therapy (MNT) subject, should be taught to all CSII patients. The CH/I ratio (CH: g, insulin: IU) indicates the amount of insulin required for the CH intake of the patient.
• CH/I ratio can vary 5/1 - 25/1; changes from meal to meal.
• It is influenced by patient’s body weight, physical activity level and insulin resistance, as well as the other conditions and existing diabetes complications.

Practical calculation of CH/I:
I. Method: In obese patients or those with insulin resistance, “300/TID” is used, whereas “450/TID” is used for patients with insulin sensitivity or underweight patients.

II. Method: CH/I ratio can be calculated by using the “5.7 x Weight (kg)/TID” equation
• CH/I ratio is first adjusted according to a low-fat meal with known CH content. 2-hr PPG increase should be approximately 60 mg/dL relative to the pre-prandial measurement. CH/I ratio is increased by 10-20% based on PPG measurement.

A constant meal bolus method may be used as an alternative in patients who require CSII therapy but unable to learn the carbohydrate counting method. Fixed bolus doses are administered before the meals with stable CH content.

“Constant Meal Bolus = [TIDx0.5]/3”

Insulin sensitivity factor
Also known as “insulin correction factor”. “ISF = 1700/TID” or “4.44 x CH/I” equations are used for its calculation. ISF = 1500/TID and 1800/TID formulas are also acceptable for users of short-acting insulin and rapid-acting analog insulin, respectively.
• PG level 2 hours after the correction dose should be ±30 mg/dL different than the target PG level.
If the PG level after the correction dose is constantly higher or lower, then the ICF is increased or decreased by 10-20%.

10.1.4 | CSII THERAPY IN PREGNANCY

Pregnancy is a state of accelerated ketosis. If insulin supply is interrupted due to technical faults in the pump or application errors, this can cause severe hyperglycemia, ketosis or diabetic ketoacidosis (DKA), potentially leading to intrauterine death. Therefore, it is mandatory to provide an intense training to pregnant women who will receive CSII therapy, and they should be closely monitored. Some authors recommend the injection of 0.1 IU/kg NPH before going to bed starting from the second trimester, and to increase the infusion rate of the pump towards the morning to protect against risks such as the potential inefficacy of the pump at night.

CSII protocol in pregnant women is summarized in Table 10.1.

<table>
<thead>
<tr>
<th>TABLE 10.1: CSII treatment protocol in pregnant women with type 1 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy period</td>
</tr>
<tr>
<td>Before pregnancy</td>
</tr>
<tr>
<td>First trimester</td>
</tr>
<tr>
<td>Second trimester</td>
</tr>
<tr>
<td>Third trimester</td>
</tr>
<tr>
<td>Towards delivery (&gt;38 weeks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time period during the day</th>
</tr>
</thead>
<tbody>
<tr>
<td>hr. 00-04</td>
</tr>
<tr>
<td>hr. 04-10</td>
</tr>
<tr>
<td>hr. 10-18</td>
</tr>
<tr>
<td>hr. 18-00</td>
</tr>
</tbody>
</table>

CSII, continuous subcutaneous insulin infusion.

*If there is suspected insulin precipitation in the night infusion set, s.c. 0.1 IU/kg NPH can be administered before going to bed during the second trimester. In that case, the basal infusion rate should be decreased towards morning.

10.1.5 | COMPLICATIONS OF CSII THERAPY

Hypoglycemia

Although hypoglycemia can be seen during CSII, its incidence is lower than the multiple-dose insulin therapy. The possible leading causes are; better insulin pharmacokinetics, achievement acceptable glycemic level in patients with hypoglycemia, and reduced insulin requirement than the multiple-dose insulin therapy.
**Ketoacidosis**

When the insulin flow is interrupted for any reason, DKA develops rapidly due to a lack of subcutaneous repository insulin in patients receiving CSII therapy. The interruption can be caused by patients stopping the infusion, pump and/or battery fault, decreased insulin amount, and catheter occlusion or displacement. However, in many cases, this has been determined to be due to the patient’s lack of training. For well-trained patients, no difference has been found between CSII and multi-dose insulin therapies in terms of DKA incidence.

**Infection at infusion site**

More frequent than the multi-dose insulin therapy. It has been reported to be 7.3-11.3 in one hundred patient-years. The most common infection factors are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Mycobacterium fortuitum*. Sometimes infection can progress to cellulitis and abscess that require surgical treatment. Precautions like changing the infusion set in every 2-3 days, not re-using the set, washing the hands before placing the needle or the catheter, and putting a sterile plaster patch onto the needle can reduce application site infections.

**Technical problems related to the pump and sets**

Pump malfunction is a common problem despite the technological advancement. In a study, it has been shown that 25% of the patients switching to the pump had encountered technical issues within the first year.

45-65% of pump users complaint about problems like twisting, bending, occluding, or leaking of the infusion set and state that they encounter hyperglycemic complications as a result.

To overcome technical problems, the establishment of a good service network and provide adequate training to patients. Pump users should keep an insulin pen and needles to be used when needed.

### 10.2 | CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING SYSTEMS (GLUCOSE SENSORS)

#### 10.2.1 | TYPES OF CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING SYSTEMS

The continuous glucose monitoring technology, developed after the capillary self-monitoring blood glucose (SMBG) that has been used in glucose monitoring for years, has opened a new era in diabetes management. These systems, also called “glucose sensors”, perform continuous glucose measurement from the interstitial fluid in the subcutaneous tissue throughout the day. The system is comprised of a measuring sensor, data transferring transmitter and a reader. It provides continuous glucose monitoring by performing 288-720 measurements a day.
Previous systems allowed necessary changes to be made in the treatment through the professional evaluation of the collected retrospective data; however, they are now being replaced with systems that show instant glucose changes. There are two types of continuous glucose monitoring (CGM) systems:

1. **Real-time continuous glucose monitoring system (Real-time CGM):** These systems perform real-time and instant glucose measurement and continuously display the result on the reader, and provides instant automatic alarms in cases of hypoglycemia and hyperglycemia. The models available in Turkey should be calibrated two times a day with capillary blood glucose.

2. **Intermittent glucose monitoring system (flash, intermittently viewed GM).** These systems display the glucose measurements from the previous 8-hour window starting from the moment when the reader is scanned by approaching it over the device [sensor] and require no calibration. However, the device available in Turkey lacks the automatic alarm function that provides instant notifications when hypo and hyperglycemia thresholds are exceeded.

### 10.2.2 INDICATIONS OF USE FOR CGM SYSTEMS

- Patients who receive intense insulin therapy
- Have frequent hypoglycemia attacks
- Have significant glucose variability
- Have variable/intense daily activity that influence glucose levels
- Target better glycemic control
- For education purposes (e.g. to learn behaviors that affect glucose control)
- Willing to use CGM systems.

Although it is yet to be approved for use in pregnant women with diabetes or those planning for pregnancy, studies suggest that CGM systems can provide benefits for glucose control.

### 10.2.3 NEW CONCEPTS IN GLUCOSE MONITORING

**Time in range:** The time that the individual remains within the target glucose range (generally 70-180 mg/dL) during a day.

**Hypoglycemia ratio:** The ratio of the time when the individual remains at a glucose level lower than the target range; it is evaluated in two levels.

- **Level 1:** Ratio of the time spent at a level <70-54 mg/dL
- **Level 2:** Ratio of the time spent at a level <54 mg/dL

**Hyperglycemia ratio:** The ratio of the time when the individual remains at a glucose level higher than the target range [generally >180 mg/dL]

These subcutaneous glucose monitoring systems that can be used continuously or intermittently (CGM, flash glucose sensor) are applied for a few days to review the suitability basal and bolus doses, and proper dose adjustments can be easily made when needed.
When evaluating the measurement data obtained with CGM system, the priority should be correcting hypoglycemia; first, the night time, then morning fasting and before meals, and lastly, the postprandial period should be evaluated.

**Glycemic variability:** This is determined by the increases and decreases in the blood glucose levels during the day, and the frequency and duration of these changes. Recent studies indicate that glycemic variability is an independent risk factor for the development of diabetes complications. In addition to A1C measurements, the glycemic variability provides extra information for the evaluation of glycemic control. The goal of a good glycemic control is to keep deviations in the blood glucose levels of diabetic patients closer to the course of healthy individuals. Continuous glucose measurements allow for the calculation of parameters related to glycemic variability, which are more detailed and also reflect the dynamic course. These are standard deviation, coefficient of variations and the average magnitude of glucose increases-decreases. The coefficient of variations in stable glucose course is <36%.

The recently developed real-time glucose sensors and sensor-augmented pumps can warn the patient by displaying the increase or decrease trend of the blood glucose on the screen and thus allowing the patient to protect themselves against hypoglycemia and severe hyperglycemia by taking necessary precautions.

### 10.3 | NEW TECHNOLOGIES

**No calibration needed CGM:** The measurements of new CGM sensors, which require no user (diabetic individual) calibration, are much improved, and delay times are significantly reduced.

**Long-term implantable CGM:** These systems are expected to ease the lives of primarily type 1 diabetes patients. These devices, which can perform continuous glucose monitoring for 90 and 180 days, have been approved by FDA and EU, respectively.

**Pumps that stop at low glucose threshold:** Some sensor-augmented new pump models are much more improved, in particular, the hypoglycemia prevention system. In this way, if hypoglycemia is predicted to develop within 30 minutes and the glucose level drops to 20 mg/dl to the determined threshold for hypoglycemia, the pump will stop delivering basal insulin for 30 minutes. If the increase in glucose level does not occur, the system will not start delivering insulin for another 30 minutes. This prevention will continue for 2 hours unless the user intervenes. It has been shown that the risk of hypoglycemia is reduced in users of these systems.

**Patch pumps:** In effective basal insulin replacement for patients with type 1 diabetes, insulin pump therapy options include the systems that deliver subcutaneous insulin through a wireless controller and a cell phone-like device that is directly placed onto the skin as a plaster. In addition, the experience with much simpler, easy to use, and disposable pumps with limited features developed to be used in patients with type 1 and type 2 diabetes is increasing.
**Hybrid pumps:** In renewed versions of these pumps, hyperglycemia can be prevented by increasing the basal insulin rate delivered by the pump when the glucose values start increasing. Patients with diabetes only need to calculate the CH intake of their meal and enter the value to the pump; then, the pre-prandial dose is delivered accordingly. With these new hybrid pumps, the time in range has increased, and hypoglycemia incidents decreased.

**Dual pumps:** Dual hormone (insulin and glucagon) insulin pumps, which are yet to be approved, provide better glucose control and decreased time in the hypoglycemic range.

**Bionic (artificial) pancreas studies:** The applications of dual hormone pumps with insulin and glucagon infusion capability, closed-loop pump at night, closed-loop systems used under observation in diabetes camps, and finally fully closed-loop pump applications programmed with glucose sensors and algorithms are rapidly progressing.

In addition, Bluetooth-enabled smart pens that record/remind insulin injections, unbending infusion sets and various other applications are among the innovations that enable an easier insulin therapy.

**SEMT RECOMMENDATIONS**

1. **CSII therapy can be used to achieve glycemic control in suitable adults with type 1 diabetes and type 2 diabetics with diminished beta-cell reserve (for type 1 diabetes: A, for type 2 diabetes: D).**

2. **CSII therapy must be started in experienced center, and the patients should be monitored by the same centers (D).**

3. **In CSII therapy of adults with type 1 and type 2 diabetes, preferably fast-acting insulin analogues or short-acting human insulin, should be used (B).**

4. **In type 1 diabetes patients with high hypoglycemia risk, sensor-augmented pumps with insulin infusion pause capability (when the glucose tends to decrease) can reduce hypoglycemia incidents (B).**

**REFERENCES**

Pancreatic transplantation has been performed since 1966. This treatment is particularly administered for type 1 diabetes patients with more 20 years of disease duration, and it aims to eliminate the insulin requirement, prevent acute complications, and improve the quality of life.

According to the reports of transplantation communities, the survival of simultaneous pancreas-kidney transplantation in type 1 diabetes patients is increasing. In the report published between 2014 and 2017, 5-year and 10-year patient survival has been reported to be 93% and 70%, respectively. Kidney survival, 1-year >95%, 10-year 66%; pancreas survival, 1-year 86%, 5-year 75%, and 10-year has been reported to be 53%. In long-term studies, simultaneous kidney-pancreas transplantation has been shown to improve quality of life and provide slight remission in microvascular [retinopathy in particular] complications. However, it is less preferred due to organ rejection, problems related to lifelong immunosuppressive drug use, and complications caused by exocrine pancreas function. The data on long-term outcomes of pancreas transplantation in type 2 diabetes patients is inadequate.

Pancreatic and islet cell transplantations should be performed in facilities with required infrastructure, and an interdisciplinary cooperation must be established that can assume the long-term medical and psychological care of the patients after the transplantation.

In 2006, American Diabetes Association (ADA) and World Health Organization (WHO) prepared a report that contains recommendations for patients who will undergo transplantation. The recommendations on that regard are summarized below:

1. Pancreatic transplantation can be performed as an alternative to chronic insulin therapy in patients with type 1 diabetes who have developed or have a high risk of renal failure.
   - The pancreatic transplantation to be performed simultaneously in these patients do not cause a significant increase in mortality, and even can extend kidney survival.
   - Alternatively, pancreatic transplantation can be performed after renal transplantation.
   - It improves glycemic control.
   - Decelerates the progression of micro and macrovascular complications.
   - The medical and surgical conditions of the patients must be eligible for dual transplantation. The risk/benefit balance must be followed in patients who will undergo simultaneous pancreatic and renal transplantation.

2. If there is no indication for renal transplantation, pancreatic transplantation can be performed in patients who meet the following three criteria.
   - The presence of frequent and severe metabolic complications (hypoglycemia, acute hyperglycemia, DKA) in the history
• Labile diabetes that is difficult to control clinically with exocrine insulin therapy and emotional problems
• Inability to prevent acute complications despite the intensive insulin therapy

3. Pancreatic islet transplantation has significant technical advantages over organ transplantation.
• Recent studies have reported that increasing remission rates without insulin. 1-year survival has exceeded 70%, and 5-year survival has reached 60%.
• Until further advancement in the development of safer immunosuppressants and technical matters, it is recommended to be performed only in equipped facilities.
• In recent years, promising studies are being conducted mainly for islet auto-transplantation in patients with chronic pancreatitis.

Complications of pancreatic and islet transplantations
• Related to pancreatic transplantation: Thrombosis of the graft, bleeding, pancreatitis, delayed healing of the surgical wound, peripancreatic abscess formation, duodenal stump leakage
• Related to islet transplantation: Intraperitoneal bleeding, portal vein thrombosis and perforation of the gallbladder
• Both operations require the patient to use immunosuppressive drugs for life.

SEMT RECOMMENDATIONS

1. Pancreatic and islet transplantations should be performed in facilities with required infrastructure and equipment (D).

2. In type 1 diabetes patients who have end-stage renal failure and will undergo renal transplantation, simultaneous pancreatic transplantation should be considered if the conditions are suitable (C).

3. In patients with preserved renal functions but without metabolic control (e.g., patients with labile glycemia or those with hypoglycemia unawareness and without optimal glycemic control despite all effort) pancreatic transplantation (C) or islet transplantation (C) can be considered.

4. Ineligible patients who will undergo total pancreatectomy due to benign pancreas disease (e.g., chronic pancreatitis), islet auto-transplantation can be considered to prevent the development of diabetes (D).

REFERENCES
Diabetic emergencies still can be the cause of mortality despite all the improvements in monitoring and treatment. Acute complications of diabetes classify in four main topics.

- Diabetic ketoacidosis (DKA)
- Hyperosmolar hyperglycemic state (HHS)
- Lactic acidosis (LA)
- Hypoglycemia

Diabetic ketoacidosis and HHS are two serious metabolic disorders associated with insulin deficiency and severe hyperglycemia. They have very similar pathogenesis and treatment. The main difference is that the major problem is insulin deficiency in DKA and dehydration in HHS. In DKA, lipolysis cannot be suppressed due to absolute insulin deficiency and leads to ketonemia and ketonuria. In HHS, there is a small amount of insulin, and is adequate to suppress lipolysis; therefore, ketone body formation does not take place. The pathogenesis of DKA and HHS is shown in Figure 12.1.

![Pathogenesis of DKA and HHS](image)

**FIGURE 12.1: Pathogenesis of DKA and HHS**

Lactic acidosis is very rare. However, its mortality is significantly high due to accompanied severe (cardiac, renal, cerebral, etc.) diabetes-related health problems.
Hypoglycemia, the most vital condition among diabetic emergencies requiring fast intervention, is a consequence of absolute or relative excess of the anti-diabetic treatment (insulin and/or OAD).

**12.1 | DIABETIC KETOACIDOSIS (DKA)**

Although diabetic ketoacidosis is more frequent in type 1 diabetes cases, patients with type 2 diabetes are also at DKA risk in acute conditions that cause catabolic stress.

**12.1.1. | PRECIPITATING FACTORS**

Main precipitating factors that may cause diabetic ketoacidosis are summarized below:

- Infections
- Newly onset type 1 diabetes (in 20-25% of the cases)
- Errors in insulin therapy (discontinuation of insulin, skipping dose, insufficient dose, erroneous injection technique, expired insulin, malfunction of the insulin pump, etc.)
- Mistakes in nutrition
- Cerebrovascular events
- Alcohol
- Pancreatitis
- Myocardial infarction
- Trauma, burn
- Drugs that disrupt carbohydrate tolerance (corticosteroids, thiazide diuretics, adrenergic agonists)
- Eating disorder (weight gain fear especially in type 1 diabetic young girls with repeating DKA history, fear of hypoglycemia, etc.)
- Hyperthyroidism, pheochromocytoma, acromegaly

However, the cause of DKA is unknown in 25% of the cases.

- In patients with type 1 and type 2 diabetes using SGLT2-I, cases developed DKA, without too much high blood glucose levels, have been reported (euglycemic ketoacidosis). Patients who use SGLT2-I and have DKA symptoms must be evaluated in terms of DKA, even if the blood glucose levels are not high.

**12.1.2. | DIAGNOSIS**

**Symptoms and findings**

In order not to neglect the diagnosis, it is essential to evaluate the symptoms and physical examination findings. DKA symptoms and findings are presented in Table 12.1.

**TABLE 12.1: Symptoms and findings of diabetic ketoacidosis**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Physical Examination Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Loss of appetite, nausea, vomiting</td>
<td>Dry mucous membranes, decreased skin turgor</td>
</tr>
<tr>
<td>Dry mouth, polydipsia, polyuria</td>
<td>Hot and dry skin</td>
</tr>
<tr>
<td>Abdominal pain, cramps</td>
<td>Dehydration, hypotension</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Tachypnea, Kussmaul respirations</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Abdominal tenderness</td>
</tr>
<tr>
<td></td>
<td>Ketone odor on the breath</td>
</tr>
<tr>
<td></td>
<td>Lethargy, mental blunting, coma</td>
</tr>
</tbody>
</table>
In many cases, fever does not occur due to vasodilation despite the presence of infection. Even some patients with poor prognosis are hypothermic.

**Laboratory**

- Plasma glucose level >300 mg/dL (in pregnancy >250 mg/dL)
- Ketonemia ≥3 mmol/L, ketone in the urine ≥2+
- Blood pH ≤7.30
- Serum bicarbonate (HCO₃⁻) level ≤15 mEq/L
- Although serum osmolality is slightly increased, it is still low (<320 mOsm/L)
- Anion deficit is increased (generally >12)
- In many DKA or HSS patients, mild or moderate leukocytosis (10,000-15,000/mm³) can be seen in relation to dehydration and acidosis. Accompanying infection can increase leukocytosis.
- Rarely, amylase and lipase levels may increase up to 2-3 times the normal upper limit.

Diagnostic criteria and fluid-electrolyte changes in DKA and HSS are presented comparatively in Table 12.2.

### TABLE 12.2: Diagnostic criteria and fluid-electrolyte changes in diabetic ketoacidosis and hyperosmolar hyperglycemic state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>&gt;250</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.25-7.30</td>
<td>7.00-7.24</td>
</tr>
<tr>
<td>Serum bicarbonate (mEq/L)</td>
<td>15-18</td>
<td>10-15</td>
</tr>
<tr>
<td>Urinary ketone</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum ketone</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Anion gap (mmol/L)</td>
<td>&gt;10</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Mental state</td>
<td>Awake</td>
<td>Awake/sleepy</td>
</tr>
<tr>
<td>Deficit values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total water (L)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Water (ml/kg)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Na⁺ (mEq/kg)</td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td>Cl⁻ (mEq/kg)</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>K⁺ (mEq/kg)</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>PO₄ (mmol/kg)</td>
<td>5-7</td>
<td></td>
</tr>
<tr>
<td>Mg²⁺ (mEq/kg)</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ (mEq/kg)</td>
<td>1-2</td>
<td></td>
</tr>
</tbody>
</table>

DKA, Diabetic ketoacidosis; HHS, Hyperosmolar hyperglycemic state. Anion deficiency = Na - (Cl + HCO₃⁻); Effective serum osmolality = (2 x Na [mEq/L] + Glucose [mg/dL]/18)
Some formulas used for the diagnosis and follow-up of hyperglycemic emergency cases are shown in Table 12.3.

### TABLE 12.3: Formulas used for the diagnosis and follow-up of DKA and HHS

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anion gap (mmol/L)</td>
<td>[\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)]</td>
</tr>
<tr>
<td>Corrected Na+ (mmol/L)*=</td>
<td>Measured Na+ + 1.6 x (\frac{\left(\text{Glucose} - 100\right)}{100})</td>
</tr>
<tr>
<td>SOsm (mOsm/kg)</td>
<td>(2 \times (\text{Na}^+ + \text{K}^+) + \text{Glucose} / 18 + \text{BUN} / 2.8)</td>
</tr>
<tr>
<td>Effective osmolality (mOsm/kg)</td>
<td>(2 \times \text{Na} + \text{Glucose} / 18)</td>
</tr>
<tr>
<td>Normal TBF (liter)</td>
<td>Body weight x 60%</td>
</tr>
<tr>
<td>Current TBF (liter)</td>
<td>Normal SOsm x Normal TBF / Current SOsm</td>
</tr>
<tr>
<td>Fluid deficit (liter)</td>
<td>Normal TBF ÷ Current TBF liter</td>
</tr>
</tbody>
</table>

S\text{Osm}, Serum osmolality; TBF, total body fluid. *For corrected Na+, some resources recommend adding 2.4 mmol/L to Na+ level for every 100 mg/dL glucose increase especially when PG >400 mg/dL.

### 12.1.3. CLINICAL FEATURES

- In the course of DKA, there is generally acidosis with primary anion deficit. In some cases, hyperchloremic metabolic acidosis may develop within the first 8 hours of the treatment. In some cases, there is a mixed acidosis.
- There are about 5-7 liters of fluid deficit in DKA.
- As Na+ level may initially decrease as a result of water displacement into extracellular space due to hyperglycemia, “corrected Na+” level must be taken into consideration in the treatment.
- In some cases, Na+ level may be measured inaccurately low due to accompanying severe hypertriglyceridemia (pseudo hyponatremia).
- K+ may displace into extracellular space due to severe insulin deficiency, hypertonicity, and acidosis. As a result, serum K+ levels may be found to be higher initially. If the baseline K+ level is found to be at a lower limit or less, then a severe K+ deficiency should be considered.
- Bicarbonate, calcium, phosphate, and magnesium deficiencies can also be seen in DKA.

### 12.1.4. TREATMENT

In DKA/HHS, treatment goals include regulating the circulatory volume and tissue perfusion, restoring serum glucose and osmolality to normal limits, elimination of ketone bodies in urine and serum, and identifying the facilitating factor of metabolic decompensation.

The successful treatment of DKA is possible through achieving fluid and electrolyte balance, recovering hyperglycemia, and treating the accompanying diseases. Clinical and laboratory findings must be frequently monitored during the treatment.
Fluid and electrolyte replacement

Fluid and electrolyte replacement in DKA is summarized in Figure 12.2. According to this method:

- In adults with DKA, fluid therapy aims to correct intra- and extracellular volume and to restore renal perfusion.
- In patients with shock tendency who have no cardiac problems, 0.9% NaCl 1000-1500 ml (or 15-20 mL/kg/hr) can be administered in the first hour of the treatment.
- Fluid administration rate is regulated based on hydration and urine state in the following 2-4 hours. If the corrected Na+ level is low in serum, then 0.9% NaCl can be administered at the same dose. If corrected Na+ is normal or high, 0.45% NaCl (4-14 mL/kg/hr) should be administered by decreasing. Generally, the fluid delivery rate should not be less than 500 mL/hr on average in the first 4 hours.
- Total fluid deficit must be replaced within 24-36 hours.

Insulin therapy

- Continuous i.v. infusion should be preferred for replacement. Insulin therapy in DKA is shown in Figure 12.3.
- In children, insulin infusion should be started 1-2 hours after the initiation of fluid replacement.
- In severe cases, 0.10-0.15 IU/kg i.v. bolus short-acting (regular) insulin can be administered initially, provided that K+ is verified to be >3.5 mEq/L.
130   |   SEMT Clinical Practice Guideline for Diabetes-2019

- In adult patients, continuous i.v. insulin infusion dose is 0.10 IU/kg/hr (or 5-7 IU/hr).
- Despite enough hydration, if PG concentration does not decrease by more than 50 mg/dL (or by 10% compared to baseline) within the first 2 hours, then the insulin infusion rate should be doubled.
- When glycemia is lowered below 250 mg/dL, i.v. insulin dose is decreased to 0.05-0.10 IU/kg/hr (or 2-4 IU/hr) and 5-10% dextrose infusion is initiated. At this stage, “Glucose-Insulin-Potassium” (GIK) infusion can be preferred for its practical use. GIK infusion protocol is described in “Surgery and Diabetes” subject.
- Infusion must be maintained by adjusting the dextrose and insulin doses to keep blood glucose level around 150-200 mg/dL until the acidosis state of the patient is recovered.

**Potassium replacement**

When urine output begins, potassium should be added to the infusion (Figure 12.4).
- In most cases, 20-30 mEq/L K⁺ is given initially. If baseline potassium is lower than the normal value (<3.5 mEq/L), the first aim must be to correct the K⁺ level. Insulin infusion should not be started before K⁺ is achieved to normal.
- In DKA, there is hypophosphatemia together with hyperchloremic acidosis. It is recommended to administer 2/3 of the K⁺ in the form of KCl and the remaining 1/3 as

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**FIGURE 12.3: DKA treatment: Insulin infusion**

- In adult patients, continuous i.v. insulin infusion dose is 0.10 IU/kg/hr (or 5-7 IU/hr).
- Despite enough hydration, if PG concentration does not decrease by more than 50 mg/dL (or by 10% compared to baseline) within the first 2 hours, then the insulin infusion rate should be doubled.
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When urine output begins, potassium should be added to the infusion (Figure 12.4).
- In most cases, 20-30 mEq/L K⁺ is given initially. If baseline potassium is lower than the normal value (<3.5 mEq/L), the first aim must be to correct the K⁺ level. Insulin infusion should not be started before K⁺ is achieved to normal.
- In DKA, there is hypophosphatemia together with hyperchloremic acidosis. It is recommended to administer 2/3 of the K⁺ in the form of KCl and the remaining 1/3 as

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**FIGURE 12.4: DKA treatment: Potassium replacement**

*Since K₃PO₄ is unavailable in Turkey, 7.5% KCl vial, which contains 10 mEq K⁺ per vial, is used.*
K$_2$PO$_4$ to meet the PO$_4$- deficit in DKA. However, K$_2$PO$_4$ is not always available in Turkey. Therefore almost only KCl is used.

- For replacement, generally, 7.5% KCl that contains 10 mEq K$^+$ in one vial is used.
- Serum K$^+$ level should be measured every 2-4 hours. When needed, ECG monitoring should be used to gain insight into intracellular K$^+$.
- If serum K$^+$ level is normal, 20-30 mEq/L KCl, if lower, 40 mEq/L KCl replacement should be administered. Replacement should be paused if K$^+$ is high.
- K$^+$ supplement should be maintained until the patient’s condition becomes stable, and oral intake starts. It should be noted that when insulin is administered, the K$^+$ level will decrease due to permeation into the cell.

**Glucose infusion**

Glucose infusion should be administered when PG level decreases to 250 mg/dL. In rate of 5-10 g/hr glucose can be added into NaCl. Also, 5-10% dextrose can be delivered via a separate vein at 100 mL/hr dose.

**Bicarbonate therapy**

In DKA treatment, routine HCO$_3^-$ administration is not recommended. Except for severely acidic patients, lipolysis will be suppressed by the initiation of insulin therapy, and there will be adequate bicarbonate. Bicarbonate administration principles are summarized below:

- If pH <6.9, then 100 mmol NaHCO$_3$ is performed in 400 ml water and at a rate of 200 mL/hr.
- If pH 6.9-7.0, then 50 mmol NaHCO$_3$ is performed in 400 ml water and at a rate of 200 mL/hr.
- pH is measured every 2 hours, and NaHCO$_3$ infusion is repeated until pH is >7.0.
- If pH >7.0 NaHCO$_3$ should not be administered.

**Alternate practices in insulin therapy**

In mild DKA cases, low dose i.m. or s.c. short-acting (regular) insulin can be administered by starting with i.v. bolus dose. In recent years, successful results have been obtained with s.c. administration of fast-acting insulin analogs in the treatment of DKA.

**Recovering ketonemia**

- Recovering ketonemia in DKA treatment takes longer than the recovery of hyperglycemia.
- The dominant ketone compound in DKA is β-hydroxy butyrate (β-OHB); therefore, the preferred method is direct β-OHB measurement in the blood.
- However, the more commonly used nitroprusside method does not measure β-OHB; it only measures acetoacetic acid and acetone. As β-OHB is converted into acetoacetic acid with the treatment during the course of DKA, if nitroprusside method is used for follow-up, then DKA may exhibit an inaccurate impression of deterioration.

**Maintenance treatment of diabetes after DKA**

- DKA is recovered when glycemia <200 mg/dL, serum HCO$_3^-$ ≥18 mEq/L, and venous pH >7.30.
• If the patient is capable of oral nutrition, basal-bolus multi-dose s.c. insulin injection therapy can be started.
• Insulin infusion should be prolonged for 1-2 hours after the first s.c. insulin injection in order not to cause any interruption in supplementation.
• In newly diagnosed type 1 diabetes cases, s.c. insulin dose should be calculated as 0.3-0.5 IU/kg/day.
• In newly diagnosed type 2 diabetes cases, it is suggested to continue insulin therapy for at least a few months.

12.2. | HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

Approximately 1% of patients hospitalized due to diabetes have HHS. Half of the cases have typical HHS. However, acidosis [pH <7.30] is also present in 1/3 of the cases. In recent years, HHS is thought of as not a specific syndrome but a consequence of metabolic decompensation together with DKA. It is generally seen in patients older than 50 years of age. About 25-35% of the cases are type 2 diabetes patients who haven´t been diagnosed previously.

12.2.1. | PRECIPITATING FACTORS
• Infections
• Myocardial infarction
• Central nervous system diseases (cerebrovascular event)
• Gastrointestinal problems
• Kidney failure
• Endocrine system disorder (hyperthyroidism, acromegaly, etc.)
• Some drugs that disrupt CH tolerance
• Inadequate treatment and care caused by the patient

12.2.2. | PROGNOSIS
• Mortality of HHS ranges between 12-42%
• Mortality is higher in patients >70 years of age particularly who live in nursing homes
• Its slower clinical course than DKA causes delay in admission to hospital (the clinical course may extend from a few days to a few weeks).

12.2.3. | DIAGNOSIS
• It can be easily differentiated from DKA with the absence of ketone bodies in the plasma or urine and very high plasma glucose level and osmolarity.
• Plasma glucose levels >600 mg/dL and osmolarity ≥320 mOsm/kg is adequate for diagnosis.
• Very high levels of PG and osmolarity are accepted as an indicator for poor prognosis.
12.2.4. | CLINICAL FEATURES

Belirti ve bulgular

- Even small, the presence of an insulin reserve provides to suppress lipolysis and thus protection from ketoacidosis in HHS patients
- The aging and dementia-related decreased sense of thirst, and reduced ability of the kidneys to concentrate urine are the additive causes of severe dehydration as distinctive features from DKA
- The absence of ketosis-induced vomiting detainees the patient to be alarmed in terms of fluid loss
- The blood pressure is low, or in cases with known hypertension, it may be decreased to normal range
- Whether diabetic or not, every geriatric case with acute or subacute worsening in the central nervous system functions, and dehydration must be examined for HHS.

Laboratory findings

- In HHS, water and electrolyte losses are more prominent than DKA. The average water loss is around 8-10 liters. Sodium, potassium, chloride, magnesium, calcium, phosphate losses occur
- Thiamine and B-complex vitamin losses can take place concerning increased catabolism
- Mostly, the PG level is as high as 1000 mg/dl, and osmolarity reaches 360 mOsm/kg
- Serum Na⁺ level is generally >140 mEq/L. However, Na⁺ can be measured lower than it is due to severe hyperglycemia and hypertriglyceridemia (pseudo hyponatremia)
- Despite being normal or high initially, serum K⁺ level decreases with fluid replacement and insulin therapy
- Prerenal azotemia (related to advanced age, accompanying conditions, and dehydration) is mostly found
- Moderately increased leukocytosis and hematocrit may be observed due to dehydration
- The concomitant hepato-steatosis may cause an increase in transaminases
- There may be inappropriately normal or low TSH accompanying low T4 and T3 levels due to “Euthyroid sick syndrome”; however, the patient is clinically euthyroid
- Pancreas enzymes may slightly increase
- Creatinine phosphokinase (CPK) levels increase in 25% of the cases and may even exceed 1000 u/L.

12.2.5. | TREATMENT

Treatment principles of hyperosmolar hyperglycemic state are similar to DKA. Because of advanced age and accompanying health problems, some procedures can be often needed, such as nasogastric aspiration, urinary catheter, lumbar puncture, and respiratory support.

Fluid and electrolyte treatment

- The most critical aspect of treatment is fluid support. The content of fluid and speed of replacement are essential for patient survival
- If osmolarity >320 mOsm/kg, 0.45% NaCl solutions should be preferred, 1000-1500 mL should be given in the first hour, and 500-750 mL/hr in 2-4 hours
- If osmolarity <320 mOsm/kg, 0.9% NaCl can be used
- If hypotension does not recover, colloid or pressor agents can be used
• In geriatric patients with cardiac problems, fluid replacement must be performed together with central venous pressure (CVP) monitorization.
• If the patient has renal failure, the amount of fluid should be reduced.
• K+ and other electrolyte losses are replaced as in DKA.
• When glycemia is decreased to 250-300 mg/dL, it is appropriate to add 5% dextrose support.
• Conventional heparin or low molecular weight heparin is recommended to prevent thromboembolic complications if there is no contraindication.

Insulin therapy
• Insulin therapy is done as in DKA; infusion containing “regular insulin” is initiated at a speed of 0.10 IU/kg/hr.
• If glycemia does not decrease by 50 mg/dL at the end of the first two hours, the infusion rate should be doubled.
• When the blood glucose level reaches 250-300 mg/dL insulin infusion is halved and 5% dextrose is started.

12.2.6. COMPLICATIONS DURING THE TREATMENT OF HYPERGLYCEMIC EMERGENCIES

The most common complications are:
• Hypoglycemia due to insulin overload
• Hypokalemia as a result of unnecessary bicarbonate treatment for acidosis without waiting for the response to insulin replacement
• Fluid overload
• Cerebral edema
• Hyperglycemia due to the interruption of insulin infusion without initiating subcutaneous insulin
• Hyperchloremia and transient hyperchloremic acidosis (metabolic acidosis without anion deficit) due to the overload of NaCl, especially during the recovery of DKA.

Rarely, pulmonary embolism, pulmonary edema, aspiration, hypocalcemia (especially after phosphate administration), stroke, acute renal failure, adult respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and deep vein thrombosis may occur.

Cerebral edema

Cerebral edema is a rare but generally fatal complication of DKA. The majority of the cases are newly diagnosed type 1 diabetes patients. Very rarely, it can be seen in the course of HHS. Cerebral edema develops in a short period of time and may progress to brain herniation. Clinically characterized by:
• Headache
• Recurrent vomiting
• Decreased heart rate
• Increased blood pressure
• Decreased oxygen saturation
• Respiratory distress
• Neurological changes (irritability, drowsiness, incontinence, lethargy, etc.)
• Specific neurological findings (e.g., convulsions, cranial nerve palsy, impaired pupillary reflex, postural changes).

**Mechanism of cerebral edema:**
Although not fully understood, it is explained by the osmotic shift of water into the central nervous system following a rapid decrease in plasma osmolality in the treatment of DKA or HHS. Insulin treatment activates membranous Na+ pumps, making the condition more severe.

**Treatment of cerebral edema:**
These patients must be intubated. Mannitol administration (0.26-1.0 g/kg) must be initiated immediately. Alternatively, hypertonic saline water (3% NaCl 5-10 mL/kg/30 min) can be used.

- As with pediatric patients, rapid replacement of water and Na+ should be avoided in adults in order to prevent cerebral edema.
- Reduction in serum osmolality must be maximum 3 mOsm/kg per hour
- In HHS cases, dextrose infusion should be performed to maintain 250-300 mg/dL glycemia.

### 12.3 | LACTIC ACIDOSIS (LA)

Lactic acidosis is a state of acidosis with anion deficit that is seen in cases with increased lactate concentration in the blood.

#### 12.3.1. | DIAGNOSIS AND CLINICAL FINDINGS

It is a severe form of metabolic acidosis resulting from inadequate oxygen distribution and utilization in the tissues, usually seen in patients with an underlying disease. Lactic acid accumulation indicates an imbalance between lactate production and utilization.

- Blood lactate level is >5 mmol/L (normal range 0.5-1 mmol/L. If lactate >2 mmol/L it is considered as hyperlactatemia)
- pH is found to be < 7.30.

LA is a very rare complication in patients using biguanide. Metformin-related LA incidence is < 0.003/1000 patient-year. Most of these patients are actually contraindicated for the use of metformin. Metformin is not recommended in the following conditions due to increased LA risk.

- Conditions that increase tissue hypoxia: congestive heart failure or ischemic heart disease that is uncontrolled or resistant to treatment, chronic obstructive pulmonary diseases, severe infections
- Severe liver failure
- Conditions with decreased renal functions: chronic kidney disease, advanced age (according to some authors > 80 years), shock, severe dehydration
12.3.2. **TREATMENT**

In severe LA with acute development, the prognosis is generally poor in relation to the underlying condition.

- LA cases should be treated in intensive care units.
- The basis of the treatment is the elimination of underlying precipitating factors. First, hemodynamic stabilization must be achieved, and oxygen therapy should be applied with the mask.
- Despite the controversy and uncertainty around the benefits of alkaline treatment, massive doses of i.v. NaHCO₃ may be necessary to improve blood pH in severe LA cases.
- The target of the treatment is to reduce the lactate level to ≤3 mmol/L within 48 hours.
- Hemodialysis is recommended to treat the water and Na⁺ loading that may occur in these patients. Hemodialysis also enables the clearance of the drug in metformin-related LA.
- The use of alternative agents such as dichloroacetate (Carbicarb) that stimulates pyruvate dehydrogenase is controversial.
- The most logical approach is to avoid using risky drugs in type 2 diabetes patients with LA susceptibility.

**SEMT RECOMMENDATIONS**

1. **Unit specific standard treatment protocol should be applied for patients with DKA. A similar treatment protocol should be applied for patients HHS; however, insulin doses must be carefully adjusted depending on PG levels (D).**

2. **In DKA, the administration rate of 0.9% NaCl should be at least 500 mL/hr on average in the first 4 hours (B). Fluid delivery must be faster (1-2 L/hr) in DKA cases in shock (D). In HHS, based on the requirements of the patient, i.v. fluid should be administered (D).**

3. **In patients with DKA, short-acting insulin should be administered as i.v. infusion at 0.1 IU/kg/hr dose. Insulin infusion must be maintained until the ketosis state is recovered (B) and anion deficit is replaced (D).**

4. **In order to protect against hypoglycemia during DKA treatment, i.v. dextrose administration should be started when PG is decreased to 200-250 mg/dL (D).**

5. **Patients who use SGLT2-I and have DKA symptoms must be evaluated in terms of DKA even if the blood glucose levels are not high (D).**

**REFERENCES**

12.4 | HYPOGLYCEMIA

In the treatment of diabetes, the most important obstacle against achieving a strict glycemic control is the risk of hypoglycemia. It is inevitable for a patient using insulin to experience severe hypoglycemia several times a year during the diabetes treatment. Therefore, each patient being treated with insulin and their families must be trained in the prevention, diagnosis and treatment methods of hypoglycemia.

12.4.1. | DIAGNOSIS AND CLINICAL FINDINGS

- In general (including non-diabetic people), the presence of "Whipple triad" is sufficient for the diagnosis of hypoglycemia. (Whipple Triad: Blood glucose <50 mg/dL, symptoms compatible with low glycemia and low blood glucose to go through with a treatment that eliminates)
- However, many patients with diabetes experience symptoms and require treatment even if their PG level is above 50 mg/dL. This occurs especially in patients who do not have good glycemic control for long periods of hyperglycemia.
- Currently, hypoglycemia threshold is accepted as PG <70 mg/dL for patients with diabetes.

Acute hypoglycemia symptoms
There two types of symptoms; adrenergic (neurogenic, autonomic) and neuroglycopenic:

1. Adrenergic symptoms
Develops in relation to the activation of autonomic nervous system and adrenal medulla.
   - Tremor
   - Cold sweat
   - Anxiety
   - Nausea
   - Palpitation
   - Feeling hungry
   - Numbness

2. Neuroglycopenic symptoms
Develops in relation to the decreased glucose presentation to the cerebral cortex.
   - Dizziness
   - Headache
   - Inability to concentrate
   - Difficulty in speaking
   - Weakness
   - Confusion

Classification
Clinically, hypoglycemia can be classified according to severity as; mild, moderate and severe. There are only neurogenic symptoms in mild hypoglycemia; neuroglycopenic symptoms are be added in moderate hypoglycemia.
   - Patients can self-treat mild and moderate hypoglycemia.
• The main clinical difference between mild and moderate hypoglycemia is that activity of patient is significantly affected in moderate attacks.

• And severe hypoglycemia requires external assistance and parenteral treatment, and it may lead to coma.

Hypoglycemia is divided into three groups by “International Hypoglycemia Study Group” of ADA/EASD; high-risk hypoglycemia, clinically significant hypoglycemia, and severe hypoglycaemia (Table 12.4).

<table>
<thead>
<tr>
<th>Degree</th>
<th>Glycemia criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High hypoglycemia risk</td>
<td>≤70 mg/dL</td>
<td>Low BG requiring rapid CH intake and dose adjustment</td>
</tr>
<tr>
<td>2. Clinically significant hypoglycemia</td>
<td>≤54 mg/dL</td>
<td>Severely and clinically significantly low BG</td>
</tr>
<tr>
<td>3. Severe hypoglycemia</td>
<td>No specific threshold</td>
<td>Severely low BG that cause severe cognitive impairment and requires assistance</td>
</tr>
</tbody>
</table>

CH, carbohydrate; BG, blood glucose level.

**Pseudo-hypoglycemia:** Blood glucose measurement >70 mg/dL in the presence of typical hypoglycemia symptoms in patients with diabetes. It can be seen in diabetic patients with poor control

12.4.2. **PRECIPITATING FACTORS**

The main reason of hypoglycemia is the absolute or relative excess of insulin. Main causes:

• Accidental or factitious intake of high dose insulin or insulin-secretagogue drug
• Incompatibility of meal-exercise timing
• Increased bioavailability of insulin (exercise-related increased absorption after injection, anti-insulin antibodies, chronic kidney disease)
• Increased insulin sensitivity (counterregulatory hormone deficiency, weight loss, increased physical activity, postpartum period, menstruation)
• Nutrition deficit (late/small meal, anorexia nervosa, gastroparesis, undernutrition during lactation or exercise)
• Alcohol and drug use (starting OAD treatment that increase insulin secretion and/or addition of OADs that decrease insulin resistance, use of drugs that are not oral anti-diabetic but increase SU effect or insulin secretion)

Risk factors associated with severe hypoglycemia in patients using insulin or insulin secretagogues:

• History of severe hypoglycemia
• Currently low A1C (<6%)
• Hypoglycemia unawareness
• Long-term insulin therapy
• Autonomic neuropathy
• Chronic kidney disease
• Low education level, low income level
• Neurocognitive impairments
Pre-school children, adolescents, pregnant women and geriatric population are especially at risk. Recurrent severe hypoglycemic attacks particularly in geriatrics and pediatric population can cause the following morbidities in various organs:

1. **Brain**: Psychological (cognitive function impairment, automatism, behavioral or personality disorders) and neurological (coma, convulsion, focal involvement, hemiplegia, ataxia, choreoathetosis, decortication) disorders
2. **Heart**: Myocardial infarction, arrhythmias
3. **Eye**: Vitreous bleeding, deterioration of proliferative retinopathy
4. **Other**: Traffic, home or work accidents, hypothermia

### 12.4.3. Treatment and Protection

**1. Patients with open conscious and capable of swallowing**

- 15–20 g of glucose (preferably 3–4 glucose tablet/gel, 4–5 cube sugar or 150–200 mL fruit juice or lemonade) is administered via oral route.
- Fat containing products like chocolate, wafer should not be used.
- If there is no planned meal in the schedule of the patient within 1/2 hours after the hypoglycemic attack, additional 15–20 g of complex CH should be consumed.

**2. Patients with closed conscious and impaired chewing-swallowing functions**

- Parenteral treatment should be administered
- **Glucagon injection**: In severe hypoglycemia, especially in type 1 diabetes patients, 1 mg of glucagon that can be applied by patients’ relatives that can be life-saving: it can be administered as i.v., i.m. or even as s.c. However, in the treatment of SU-related hypoglycemia, glucagon injection is not suitable since it will increase the insulin secretion. It must be noted that the response to be obtained with glucagon is temporary. Therefore, based on the severity of the patient’s clinical condition, dextrose infusion or oral food intake must be planned after the glucagon administration.
- In hospital; i.v. 75-100 mL 20% (or 150-200 mL 10%) dextrose is administered.
- SU group-related severe hypoglycemia attacks that cannot be controlled with glucose infusion, administration of diazoxide or octreotide, which inhibits insulin secretion, together with dextrose infusion, can be beneficial.

**3. Protection**

- After each hypoglycemic episode is treated, the causes should be reviewed and the training should be repeated if needed.
- Especially elderly patients with type 2 diabetes who determined to have long-acting conventional SU-related hypoglycemia should be monitored for 24-48 hours in the hospital.
- **Hypoglycemia unawareness**: Long-term diabetes, strict glycemic control, intense alcohol consumption, recurrent nocturnal hypoglycemia may lead to an inability to recognize the preliminary symptoms of hypoglycemia. Therefore, strict glycemic control targets should be avoided in children, elderly patients and in cases with nephropathy and autonomic neuropathy. In patients with hypoglycemia unawareness, the problem can be significantly improved when glycemic control is loosened for several weeks.
SEMT RECOMMENDATIONS

1. **Mild hypoglycemia** should be treated with 15 g oral CH (four cubes of sugar, or 150 ml fruit juice or lemonade) (B). PG should be measured 15 minutes later, and another 15 g of CH should be given if PG is still <80 mg/dL (D).

2. **Moderate hypoglycemia** should be treated with 20 g oral CH (five cubes of sugar, or 200 mL orange juice or lemonade), PG should be measured 15 minutes later, and another 15 g of CH should be given if PG <80 mg/dL (D).

3. **Subcutaneous or intramuscular glucagon injection** must be administered for unconscious patients over the age of 5 with severe hypoglycemia, and immediate medical care must be sought (D).

4. **In unconscious patients with severe hypoglycemia**, 10-25 g of glucose (50% dextrose 20-50 mL, within 1-3 minutes or 20% dextrose 50-150 mL, within 5-10 minutes) via i.v. route should be administered (D).

5. **To prevent recurrent hypoglycemia**, the main meal and snack should be given at the scheduled times after hypoglycemia has been recovered. If there is more than 1/2 hours for the next meal, then a snack containing 15 g of CH and protein should be given (D).

6. **Relatives of patients at high risk of hypoglycemia** should be trained in the administration of glucagon injection (D).

7. **In patients with severe, recurrent hypoglycemia or with hypoglycemia unawareness**, to ensure the recognition of preliminary indicators of hypoglycemia and to reduce the risk of hypoglycemia:
   - More flexible glycemic targets should be determined not exceed three months (D)
   - CSII (insulin pump) treatment with sensor-augmented pumps that have the feature to stop insulin infusion at low glucose levels (B)
   - Islet (C) or pancreatic (D) transplantation may be considered

REFERENCES

13.1 | MACROVASCULAR DISEASE

Acute coronary syndrome (ACS), myocardial infarction (MI), stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack (TIA) and peripheral arterial disease are classified as atherosclerotic cardiovascular disease (ASCVD). ASCVD is the most important cause of morbidity and mortality in patients with diabetes. Also, directly and indirectly, increases the costs of diabetes. Improvement of the cardiovascular (CV) risk factors in patients with diabetes is crucial to prevent or delay ASCVD.

CV is the most important cause of morbidity and mortality in these patients. In patients with Type 2 diabetes, the risk of coronary artery disease (CAD) is 2-4 times higher than the non-diabetic population. Approximately 60-75% of these patients die because of macrovascular events. The atherosclerosis of patients with diabetes occurs in early age than non-diabetics and more extensive with multi-segmental involvement.

13.1.1. | RISK FACTORS

- Diabetes is an independent risk factor for CAD.
- All the patients with diabetes should be evaluated for CV risk factors (hypertension, dyslipidemia, smoking, early CAD history in the family, the presence of albuminuria) at least once a year, and be treated if needed.

Patients defined below should be considered as high risk for CAD and they should be primarily included in CV protection programs:

- Male patients ≥45 years and female patients ≥50 years of age
- The presence of at least one of the following risk factor for patients younger than 45 years old in men, <50 years old in women:
  - Macrovascular disease (silent MI, silent ischemia, peripheral artery disease, carotid artery disease or cerebrovascular event)
  - Microvascular disease (nephropathy and retinopathy in particular)
  - The presence of multiple additional risk factors in terms of CAD (family history of early coronary event or cerebrovascular event in first degree relatives)
  - The significant dominance of one risk factor (e.g., LDL cholesterol >200 mg/dL or systolic blood pressure [SBP] >180 mmHg)
  - Diabetic patients older than 40 years old with long diabetes duration (>15 years)

13.1.2. | SCREENING OF CORONARY ARTERY DISEASE

In the “Guidelines for Standard Care in Diabetics”, American Diabetes Association (ADA) do not recommend CAD screening for asymptomatic diabetic patients as it would not provide any improvement for CV outcomes. However, European guidelines recommend routine CAD evaluation in patients with diabetes.
The presence of atypical cardiac complaints (unexplained dyspnea, discomfort in the chest, etc.), murmurs over carotid arteries, history of TIA or presence of intermittent claudication requires CAD evaluation.

To identify the individuals with high risk of coronary artery diseases, CV history (dyspnea, chest pain), lifestyle (smoking, sedentary life, imbalanced nutrition), diabetes duration, abdominal obesity, impotency, peripheral artery disease and retinopathy presence, ECG findings, glycemic status, lipid profile, BP value, urinary albumin/creatinine ratio and estimated glomerular filtration rate (eGFR) should be taken into consideration.

For patients with diabetes, CAD screening should be performed by resting ECG. Stress test should be performed for patients having symptoms or other accompanying diseases. Patients having ischemic ECG findings or symptoms during stress tests.

**SEMT APPROACH AND RECOMMENDATIONS**

1. **To reduce CAD risk of patients with type 2 diabetes, in addition to glycemic control, a multifactorial approach (lifestyle modification, lipid and BP control and anti-platelet use, avoiding harmful factors such as smoking) should be employed as well (D).**

2. **Diabetic patients with the following properties should be evaluated by a resting ECG and the test should be repeated in every three years (D):**
   - Age >40 years
   - Patients over 30 years of age with diabetes duration of >15 years
   - End organ damage (micro or macro-vascular)
   - ≥1 CVD risk factor (smoking, HT, family history of early CVD, CKD, obesity)

3. **For the patients described below, the first screening test should be a stress ECG.**
   - Typical or atypical cardiac complaints (unexplained dyspnea, discomfort in the chest, etc.) (C).
   - Peripheral artery disease (deteriorated ankle/brachial index ratio) (D).
   - Murmur over carotid arteries (D).
   - Transient ischemic attack (D).
   - Stroke (D).

4. **In patients with left bundle branch block, abnormal ST-T in resting ECG, pharmacologic (e.g., dipyridamole) stress echocardiography or nuclear imaging should be requested (D). Pharmacologic stress echocardiography or nuclear imaging should be performed for patients who need to undergo stress test but unable to do so due to various reasons such as obesity, sedentary life, neuropathy, peripheral artery disease, diabetic foot (C).**

5. **Patients with ischemic findings in stress tests and patients with low exercise capacity should be referred to a cardiologist (D).**

**REFERENCES**

13.1.3. **CLINICAL PRESENTATION**

Patients may have several of the following clinical properties:
- Classical anginal symptoms (pain and discomfort in the chest, left arm, shoulder and jaw, shortness of breath, cold sweat)
- Myocardial infarction: “Silent” MI is frequent in patients with diabetes.
- Dyslipidemia: Diabetes is considered as an equivalent of CVD.
- Peripheral vascular disease
- Cerebrovascular disease

Half of the patients with CAD admitted to intensive care units due to acute coronary syndrome are found to have IGT or newly onset diabetes. The approach algorithm according to the patient’s primary diagnosis shown in Figure 13.1.

In some patients without known diabetes and presenting with ACS symptoms, stress hyperglycemia may be present initially. Hyperglycemia may recess in a few days in these patients. Therefore, random PG and A1C should be measured for all patients admitting to emergency clinic or hospital with ACS preliminary diagnosis. As shown in Figure 13.2:
- Patients with A1c <5.7% and PG in normal limits during the monitorization at the intensive care unit or in the inpatient clinic, should be followed up by routine diabetes screening recommendations after discharge.

**FIGURE 13.1: Evaluation of the patients with diabetes and coronary artery disease**

- In patients with A1C between 5.7-6.4% should be screened for diabetes after discharge. If there is no diabetes, the patient should be followed up by a routine diabetes screening program.
- In patients with A1C ≥6.5% or random PG ≥200 mg/dL, capillary blood glucose monitoring should be performed before each meal and at bedtime for two days.
  - Compliance with routine diabetes screening program should be maintained for patients with all capillary glucose results <180 mg/dL.
  - Patients with capillary glucose levels >180 mg/dL are recommended to perform SMBG at home with a target PG level of 120-180 mg/dL.
13.1.4. | CARDIOVASCULAR PROTECTION IN PATIENTS WITH DIABETES

The primary and secondary protection against CAD in diabetes patients is summarized below:

**Lifestyle modification**

Weight loss target should be determined for these patients, and they should be ensured to perform lifestyle modification programs such as healthy nutrition, regular physical activity and smoking cessation in order for them to reach and maintain this target.

**Glycemic control**

- In asymptomatic patients, appropriate treatment should be performed based on 10-year CVD risk status.
- In patients with diabetes at risk of CAD, optimal glycemic control (A1C<7%) should be achieved. However, the results of studies such as ACCORD, ADVANCE and VADT, revealed that strict glycemic control in type 2 diabetes do not mitigate the risk of macrovascular event. Moreover, it may actually increase macrovascular event and mortality risk depending on the increase in the risk of severe hypoglycemia. Therefore, more flexible glycemic control should be targeted, particularly in elderly patients with long diabetes duration and high risk of comorbidities and hypoglycemia.

**Anti-platelet therapy**

- For primary protection;
  - In patients with diabetes 10-year CV event risk > 10%, aspirin (80-150 mg) should be administered for primary protection purposes. Apart from diabetes, patients who have at least one additional CV risk factor (family history of CV disease, smoking, dyslipidemia and albuminuria) and patients over 50 years of age are included in this group.
- Aspirin is not recommended for individuals with low CV risk (10-year CV event risk < 5%).
- For individuals with moderate risk (10-year CV risk 5-10%) aspirin may be used depending on the clinical manifestation.
- For secondary protection;
  - In patients with diabetes, aspirin (80-150 mg) should be given for secondary CV prevention.
  - Clopidogrel (75 mg) can be used in patients who can’t tolerate aspirin.
  - After acute coronary syndrome, aspirin and clopidogrel are used in combination in the first 1-2 years.

**β-blocker therapy**

β-blocker should be added to the treatment of patients with previous MI or those who will be referred to surgery. In patients with previous MI, β-blocker treatment should be maintained for at least two years after the incident.

**Statin therapy**

See Chapter 17.

**Blood pressure control**

In patients with diabetes with CAD or at high risk of CAD, BP target should be <130/80 mmHg (see Chapter 16).

ACE-I/ARB therapy should be used

- For patients who have clinical macrovascular disease
- For patients with type 1 and type 2 diabetes over 54 years of age and have clinical macrovascular disease and micro or macrovascular disease
- ACE-I, ARB or statin should be avoided in women of reproductive age who do not use an effective contraception method.

13.1.5. **DIABETES AND HEART FAILURE**

Cardiac failure may develop in 50% of the patients with type 2 diabetes. Metformin, the primary choice of drug in diabetes, can be used in patients with stable cardiac failure whose eGFR is >30 mL/min/1.73 m². However, thiazolidinediones (e.g., PIO) are known to increase the risk of cardiac failure. Therefore, PIO use should be avoided in patients with cardiac failure or at risk of cardiac failure. Metformin is contraindicated in treatment-resistant severe congestive cardiac failure. TZD drugs should not be used in patients with congestive heart failure, severe coronary insufficiency or edema risk or those receiving intensive insulin therapy, unless mandatory.

In the SAVOR-TIMI 53 study, which investigated the long-term CV safety of saxagliptin, a DPP4-I group drug, there was a significant increase in cardiac failure related hospitalizations in comparison to placebo. Similarly, in EXAMINE, where alogliptin was used, there was significantly more cardiac failure related hospitalization incidents than placebo. TECOS study revealed that sitagliptin cause no increase in cardiac failure related hospitalization risk. However, decreased risk of cardiac failure-related hospitalization has been reported with empagliflozin, canagliflozin and dapagliflozin, which are SGLT2-I group drugs.
13.1.6. | **ANTI-HYPERGLYCEMIC DRUGS AND CARDIOVASCULAR SAFETY**

There are no randomized-controlled long-term CV safety studies of SU and metformin in type 2 diabetes patients at high risk of CV.

The meta-analyses published in 2007 revealed that rosiglitazone, a TZD group drug, increase the risk of CV events and CV deaths; and following these publications the drug was prohibited in many countries. However, in a recent meta-analysis, it has been reported that PIO significantly decrease the major adverse CV event (MI and stroke) risk. The separate analysis of the outcomes showed that the decreases in CV death, MI and stroke risk were not significant. The results of PROactive study were published in 2005 and although the secondary endpoint (i.e., death due to any cause, nonfatal MI, stroke) risk significantly decreased with PIO in type 2 diabetes patients with macrovascular event evidence, no significant decrease was determined in individual endpoints.

After the experience with rosiglitazone, FDA and EMA started to require randomized-controlled, long-term CV safety studies for new anti-diabetic drugs. In SAVOR-TIMI 53, EXAMINE and TECOS studies, where DPP4-I group drugs saxagliptin, alogliptin and sitagliptin were used respectively, it has been reported that these drugs do not increase CV risk.

ELIXA study, conducted with lixisenatide (from GLP-1A group), and EXSCEL study, conducted with weekly form of exenatide, showed that these drugs do not increase CV events in patients with high CV risk. In LEADER study with liraglutide and SUSTAIN-6 study with semaglutide, a significant decrease was observed in 3-point adverse CV endpoints (CV death, nonfatal MI, nonfatal stroke). However, the detailed review of the results showed that liraglutide significantly decrease CV and all-cause death and MI risks, and semaglutide decreases nonfatal stroke and revascularization risks.

In EMPA-REG study and CANVAS/CANVAS-R studies, where SGLT2-I group of drugs empagliflozin and canagliflozin were used respectively, revealed similar significant decrease in 3-point adverse CV endpoints (CV death, nonfatal MI, nonfatal stroke). When the CV endpoint outcomes are analyzed in detail, it has been found that empagliflozin and canagliflozin significantly decreased risk of death from any-cause and cardiac failure related hospitalization risk, and that empagliflozin decreased CV death risk (see Chapter 8 and 11).

---

**SEMT RECOMMENDATIONS**

1. **Comprehensive and multifaceted approach to CV risk reduction should be the priority in the prevention of diabetes complications (For all diabetic patients: D, type 2 diabetes patients over 40 years of age with microalbuminuria: A).**

2. **The following approach should be employed to decrease CV risk in diabetic patients:**
   - Lifestyle modification (reaching and maintaining a healthy weight, healthy nutrition, regular physical activity and smoking cessation)
   - Optimal BP control
   - Optimal glycemic control

3. **Other accompanying risk factors should be treated.**
   - **BP target should be <130/80 mmHg in diabetic patients. ACE-I or ARB should be preferred for HT treatment.**
   - **In diabetes patients, statin should be administered according to the CV risk evaluation. The goal should be to ensure 30-50% decrease in LDL cholesterol levels with treatment in patients who are aged between 40-75 and have moderate CV event risk.**
4. In diabetes patients considered to have high risk in terms of CV should use ACE-I or ARB in doses that are appropriate for vascular protection (for patients with vascular disease: A, other high risk patients: B).

5. Low dose aspirin (75–150 mg/day) can be administered to diabetes patients with stable CV disease (D).

6. Clopidogrel (75 mg/day) can be considered for patients who are aspirin intolerant (D).

7. The decision to administer anti-platelet therapy for primary protection purposes against CV events should be based on the individual clinical evaluation of the patients (D).

8. If appropriate, antihyperglycemic drugs (liraglutide, empagliflozin) with proven CV safety should be preferred in patients with type 2 diabetes with CVD (A).

REFERENCES

13.2 | MICROVASCULAR COMPLICATIONS

13.2.1 | RETINOPATHY

The most important cause of blindness in adult people is diabetic retinopathy.

Screening
1. In patients with type 1 diabetes, retinopathy screening should be performed annually starting five years after the diagnosis. In childhood onset cases, annual retinopathy screening is recommended starting from puberty or 15 years of age.
2. In patients with type 2 diabetes, retinopathy screening should be performed at diagnosis and; patients with no or minimal initial retinopathy should be checked once every year and advanced stage patients should be checked once in every 3–6 months. If examination findings are normal at diagnosis, it should be repeated 1 year later. If findings are normal again, follow-up intervals can be extended to two years.
3. A comprehensive fundus and visual field examination should be performed in pregnant women or those planning for pregnancy. The examination should be repeated in every trimester and the patients should be followed up postpartum for at least a year depending on the degree of retinopathy.

Clinical evaluation
Fundus is examined with indirect ophthalmoscopy in dilated pupillae.
1. Non-proliferative retinopathy: Microaneurysms and rigid exudate
2. Pre-proliferative: Exudate, bleeding, IRMA (intraretinal microvascular abnormalities)
3. Proliferative retinopathy: The less functional capillaries in the retinal circulation are replaced with newly formed fragile blood vessels. The risk of bleeding and retinal detachment is high in the developmental process of new vessel formation.
4. Macular edema is the most important cause of vision loss together with tractional retinal detachment and neovascular glaucoma.
Diabetic retinopathy evaluation in adult diabetes patients is summarized in Table 13.1.

**TABLE 13.1: Diabetic retinopathy evaluation in patients with type 2 diabetes**

<table>
<thead>
<tr>
<th>Routine follow-up methods</th>
<th>Referral to ophthalmologist</th>
<th>Referral to ophthalmologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundus examination</td>
<td>I. If there are maculopathy findings:</td>
<td>An urgent examination by an</td>
</tr>
<tr>
<td>During diagnosis and</td>
<td>- Exudate at a disk diameter distance from the center of the fovea center or retinal thickening</td>
<td>ophthalmologist is required</td>
</tr>
<tr>
<td>then once every year;</td>
<td>- Presence of circular or group exudate inside the macula*</td>
<td>in the following cases:</td>
</tr>
<tr>
<td>- Routine visual acuity</td>
<td>- Optimal visual acuity of 6/12 or less due to aneurysm or bleeding at a disc diameter distance from the center of the fovea</td>
<td>- Sudden vision loss</td>
</tr>
<tr>
<td>tests</td>
<td>II. If there are pre-proliferative retinopathy findings**:</td>
<td>- Rubeosis iridis</td>
</tr>
<tr>
<td></td>
<td>- Venous beading</td>
<td>- Pre-retinal and vitreous</td>
</tr>
<tr>
<td></td>
<td>- Venous loops or reduplication - intraretinal microvascular abnormalities (IRMA)</td>
<td>bleeding</td>
</tr>
<tr>
<td></td>
<td>- Multiple deep, circular or stain-like bleeding</td>
<td>- Retinal detachment</td>
</tr>
<tr>
<td></td>
<td>III. Unexplained decreased in visual acuity</td>
<td>- New vascular formations</td>
</tr>
<tr>
<td></td>
<td>*The circle with a center as fovea and a diameter between the temporal edge of the optic disc and the fovea is defined as macula.</td>
<td>must be immediately assessed</td>
</tr>
<tr>
<td></td>
<td>**Cotton wool spots appearance does not indicate pre-proliferative retinopathy..</td>
<td>by ophthalmologist.</td>
</tr>
</tbody>
</table>

**Protection and treatment**

**Glycemic control:** Achieving optimal glycemic control reduces the risk of diabetic retinopathy or decelerates the process of retinopathy development.

**Blood pressure control:** Optimal blood pressure control must be achieved to reduce the risk of retinopathy or to slow down its development process.

Patients with high lipid levels are at high risk of retinopathy.

Laser photocoagulation, vitrectomy, anti-vascular endothelial growth factor (anti-VEGF) and other pharmacologic treatments should be applied. Better outcomes are obtained with anti-VEGF in the treatment of diabetic macular edema. Therefore, intravitreal anti-VEGF use as monotherapy or in combination with laser is recommended as standard care for diabetes patients with macular edema.

Aspirin can be used for primary/secondary CV protection in patients with proliferative diabetic retinopathy.

**SEMT RECOMMENDATIONS**

1. **In type 1 diabetes, retinopathy screening should start from 5 years after the diagnosis or from 15 years of age and performed once in every year (A). In type 2 diabetes, screening should start at the time of diagnosis (A) and repeated annually (A). The screening interval may be once in every two years for patients without retinopathy for two consecutive years (A).**

2. **Optimal glycemia, BP and lipid control must be ensured to prevent or delay the progression of diabetic retinopathy (for glycemia: A; For BP A).**

3. **The eye examination must be performed by an ophthalmologist in severe retinopathy cases (preproliferative and proliferative, maculopathy) (D).**

4. **Laser photocoagulation, vitrectomy and pharmacologic treatments should be considered in retinopathy that threatens the vision (for laser and vitrectomy: A; for pharmacologic treatments: B).**
13.2.2. | NEPHROPATHY (DIABETIC KIDNEY DISEASE)

Nephropathy is one of the most important causes of morbidity and mortality in adult patients with diabetes. It is recommended to use the term “diabetic kidney disease” instead of nephropathy to draw attention to the adverse consequences of diabetes on the kidneys. How to assess the kidney damage in adult diabetes patients is summarized in Figure 13.3.

**Figure 13.3: Evaluation of diabetic kidney disease in adult diabetic patients**

[Flowchart showing the assessment process]
• To investigate early nephropathy in adults, eGFR should be calculated together with microalbuminuria measurement.
• Urinary albumin/creatinine ratio must be measured in first-morning urine for microalbuminuria screening.
• Albuminuria no longer needs to be categorized as microalbuminuria or macroalbuminuria as it reflects a continuous function.
• In addition, eGFR should be calculated based on MDRD, CKD-EPI or Cockroft-Gault formulas by measuring the serum creatinine level (Microalbuminuria evaluation and eGFR calculation has been previously explained under “Care standards for patients with diabetes” section).

Screening
• Diabetic nephropathy screening should be performed with eGFR and urine albumin/creatinine ratio
• once in every year starting from 5 years after the diagnosis in adults with type 1 diabetes, and once in every year starting at diagnosis in type 2 diabetes patients.
• Urinary albumin/creatinine ratio should be measured more frequently in patients with microalbuminuria to monitor the progression of diabetic nephropathy.

If there are any temporary conditions (uncontrolled HT, urinary infection, hypovolemia, etc.) that may cause microalbuminuria or decreased GFR, nephropathy screening tests should not be performed until these conditions are resolved.

Staging
The most important consequence of nephropathy is leading to end-stage kidney failure. In diabetic patients, kidney disease is evaluated according to the following eGFR stages:

  Stage 1: If eGFR >90 mL/min/1.73 m² (for body surface area) then there is kidney damage with normal/high GFR.
  Stage 2: If eGFR 60-89 mL/min/1.73 m² then there is kidney damage with slightly decreased GFR.
  Stage 3: If eGFR 30-59 mL/min/1.73 m² then there is kidney damage with moderately decreased GFR.
  Stage 4: If eGFR 15-29 mL/min/1.73 m² then there is kidney damage with severely decreased GFR.
  Stage 5: If eGFR <15 mL/min/1.73 m² or dialysis is being applied then there is end-stage kidney failure.

In patients with chronic kidney disease, serum creatinine should be measured every 3-6 months to calculate eGFR together with albumin/creatinine ratio in first-morning urine sample.

Clinical findings
• It is characterized by hypertension, edema, proteinuria and kidney failure.
• Chronic kidney failure (CKF) causes other than diabetic nephropathy should be investigated if there is no accompanying diabetic retinopathy, if GFR is very low unconf ormably with the duration of diabetes or GFR is rapidly decreasing, if rapidly increasing proteinuria or nephrotic syndrome has developed, there is treatment-refractory HT, urine sedimentation is rich, if symptoms and findings indicate another systemic disease, if GFR is decreased by more than 30% within 2-3 months after starting ACE-I or ARB.
SGLT2-I drugs and some GLP-1A drugs can be administered for mild and moderate nephropathy as they decrease the risk of CKF and CVD. In EMPA-REG OUTCOME, LEADER, SUSTAIN-6, CANVAS-R and DECLARE-TIMI58 studies delayed progression of nephropathy has been shown as a secondary endpoint. Some studies with this group of drugs, especially in diabetic patients with nephropathy, have confirmed this, and others are still ongoing.

Protection and treatment

**Glycemia control:** In patients with type 1 and type 2 diabetes, optimal glycemic control must be achieved and intensive diabetes treatment should be performed if needed in order to prevent nephropathy or delay its progression.

**Optimal BP control:** Achieving BP control decreases the risk of diabetic nephropathy and slows its progression. BP <140/90 mmHg has been shown to slow the progression of CKD. Lower targets such as <130/80 mmHg can be determined on a patient basis.

**Microalbuminuria:** In diabetes patients, ACE-I or ARB is not recommended for primary protection against nephropathy if there is normal BP and no microalbuminuria (if albumin/creatinine is <30 mg/g).

- If the albumin/creatinine ratio is persistently high (30-299 mg/g) then ACE-I or ARB administration can be considered to delay chronic kidney disease even in the absence of HT.
- If albumin/creatinine ratio is ≥300 mg/g then ACE-I or ARB should be given.
- Combined use of ACE-I and ARB should be avoided due to no additional clinical benefit.
- In patients using ACE-I/ARB or diuretic, serum creatinine and potassium levels should be checked 1-2 weeks after the initiation of the treatment or when dose titration is performed and in cases of acute condition.
- ACE-I or ARB should not be administered to women who may get pregnant as these drugs may cause malformations in the fetus; if women using these drugs are planning for pregnancy, then drugs must be discontinued two months prior to conception.
- In acute conditions such as febrile diseases or diarrhea, and particularly in the presence of suspected intravascular volume reduction, ACE-I/ARB and diuretic treatments may be discontinued.

**Kidney failure:** Thiazide diuretics can be used for sodium and water retention, hyperpotassemia and HT control in diabetes with chronic renal failure. Furosemide can be used in cases where thiazides are inadequate or combination of thiazide and furosemide can be used for patients with severe sodium and water retention or hyperpotassemia

- Drug doses should be adjusted according to GFR when chronic kidney failure develops.
- Electrolytes, hemogram, calcium, phosphorous, bicarbonate and PTH should measured once a year in patients with eGFR 45-60 mL/min/1.73 m² and bone mineral density should be analyzed. If eGFR is 30-44 mL/min, these tests should be repeated in ever 3-6 months.
- Renal replacement treatment should be performed when end-stage kidney failure develops. Renal transplantation should be performed in young and middle age patients (<65 years), and hemodialysis or ambulatory peritoneal dialysis at home should be performed in elderly patients based on their conditions.

**Nutrition:** Daily protein intake should be decreased in patients with diabetic kidney disease (0.8 g/kg/day).

- As there will not be any effect on glycemia, CV risk factor or GFR reduction rate, higher daily protein intake (<0.8 g/kg) is not recommended.
- Vitamin D deficiency should be resolved (if any) (see Chapter 5).
Referral to a nephrologist: Patients should be referred to a nephrologist in the following cases:
- Progressive decrease in kidney functions
- eGFR <30 mL/min
- Albumin/creatinine >300 mg/g creatinine
- Uncontrolled HT
- Hyperpotassemia with ACE-I or ARB or >30% increase in serum creatinine level within 3 months.

SEMT RECOMMENDATIONS

1. It is mandatory to ensure the best possible glycemic control in order to prevent or delay the chronic kidney disease in patients with type 1 and type 2 diabetes (A).

2. Urinary albumin/creatinine (UACR) must be measured and eGFR must be calculated for chronic kidney disease screening in adults (B). Screening:
   - Diabetic nephropathy screening should be performed with eGFR and UACR,
   - And it should be performed once a year starting from the diagnosis in type 2 diabetes patients (B).

3. In patients with chronic kidney disease, serum albumin/creatinine measurements and eGFR calculation should be performed in every 3-6 months (D).

4. If UACR is persistently high, ACE-I or ARB can be administered to delay chronic kidney disease even in the absence of HT (for ACE-I in type 1 and type 2 diabetes, and for ARB in type 2 diabetes: A; for ARB in type 1 diabetes: D).

5. Serum creatinine and potassium levels should be checked in patients using ACE-I/ARB or diuretic (D).

6. In diabetic patients with chronic kidney disease, thiazide diuretics or furosemide can be used when needed (D).

7. If there is suspected intravascular volume reduction, then ACE-I/ARB and diuretic treatments should be discontinued (D).

8. ACE-I/ARB should not be used for women planning to get pregnant (B).

9. In cases involving eGFR <30 mL/min, albumin/creatinine >300 mg/g, uncontrolled HT or hyperpotassemia with ACE-I/AR use or serum creatinine level elevation >30%, patient must be referred to a nephrologist (A).

REFERENCES


13.2.3. **NEUROPATHY**

Neuropathy can involve any system of the body. Distal-symmetrical sensory polyneuropathy, which is characterized by lower extremity involvement, is the most important cause of foot amputation together with infection and ischemia.

**FIGURE 13.4: Treatment of neuropathic pain in adult patients with diabetes**
Screening
- Annual neuropathy screening is recommended, starting 5 years after the diagnosis for patients with type 1 diabetes and starting from the time of diagnosis for patients with type 2 diabetes.
- In addition to physical examination, neuropathy screenings should include simple clinical tests like 10-g monofilament with 10 grams of compression and tuning fork test.

A. Peripheral Polyneuropathy

1. Distal polyneuropathy
It is the most common, progressive presentation.
- Unsteady and ataxic gait, weakness in hand and foot muscles is observed.
- It is associated with decreased proprioception (position and subtle touch) sensation.
- Also, the pain and heat sensations are decreased.
- The abnormal changes in tactile sense (alldynia, pain) may progress up to loss of sensation.
- The “gloves and socks” type involvement from distal to proximal in the hand and feet is typical.
- Extreme hypersensitivity upon a light touch, superficial burning, throbbing pain, deep and tearing pains felt in the bones, become discomforting and disturbing particularly at night.
- Foot ulcers, infections and neuro-osteo-arthritis (Charcot foot: characterized by joint erosions; unnoticed, repeating small fractures; foot edema due to demineralization disorders in the bone, increased temperature and deformations) may develop. The risk can be mitigated with proper foot care.
- Sometimes it can be asymptomatic. When symptomatic, it may manifest a self-limiting or progressive clinical presentation.

2. Focal neuropathies
They have a sudden onset and may spontaneously regress within a few weeks or months.
- Cranial mononeuropathies: It may involve 3rd, 4th, 6th or 7th cranial nerves. The most common type is the 3rd nerve paralysis. It is characterized by unilateral eye pain, diplopia and ptosis. Pupillary functions are preserved.
- Radiculopathy: It causes thoracic, abdominal or truncal pains with band-like expansion due to the involvement of nerve roots.
- Plexopathy: It causes pains expanding to the extremities due to the involvement of brachial and lumbosacral plexus.

3. Autonomic neuropathies
Patients should be inquired in terms of autonomic neuropathy-related symptoms and findings. Hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder and sudomotor dysfunction (increased or decreased sweating) should be investigated in particular.

Neuropathy treatment
- Early and accurate diagnosis is required.
- Treatment of symptoms in neuropathic pain, especially in cardiac autonomic neuropathy, improves the quality of life of the patient.
**Pain treatment:** In neuropathies, the treatment should start with non-specific analgesics and specific pain treatment should be used in unresponsive cases. The drugs listed in Table 13.2 can be used as monotherapy or in combination when needed. Pain treatment can provide 30-50% reduction in the pain.

**Pathogenesis-based treatment:** Based on the pathogenesis of neuropathy, it has been long known that alpha-lipoic acid can partially regress the subjective findings, such as paresthesia, sense of burning, numbness and feeling, with its anti-oxidant effect. In two studies conducted with parenteral form of the drug which is unavailable in our country, it has been claimed that it provided slight relief of pain and it reduced neuropathy symptom scores. However, there is limited clinical data about the ability of oral forms of alpha-lipoic acid to reduce diabetic neuropathy risk (primary protection) or that it can be used for painful neuropathy treatment.

Similarly, the studies conducted with aldose reductase inhibitors, benfotiamine derivates, protein kinase-C inhibitors and anti-oxidants failed to provide adequate clinical results.

**Protection**
- Optimal glycemic control should be achieved. Strict glycemic control has been shown to reduce the risk of autonomic and peripheral neuropathy in patients with type 1 diabetes, and slow its progression in some patients with type 2 diabetes.
- Foot care should not be neglected.

**TABLE 13.2: Pain treatment in diabetic neuropathy**

<table>
<thead>
<tr>
<th>Step</th>
<th>Class</th>
<th>Example</th>
<th>Recommended doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I</td>
<td>Tricyclic antidepressant drugs</td>
<td>Amitriptyline</td>
<td>10-100 mg qd (Night)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline</td>
<td>25-75 mg qd (Night)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipramine</td>
<td>25-75 mg qd (Night)</td>
</tr>
<tr>
<td></td>
<td>5-Hydroxytryptamine and norepinephrine reuptake inhibitors</td>
<td>Duloxetine</td>
<td>30-120 mg qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine</td>
<td>37.5-150 mg bid</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td>Gabapentin</td>
<td>300-600 mg bid to qid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregabalin</td>
<td>75-300 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carbamazepine</td>
<td>200-400 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproic acid</td>
<td>250-500 mg bid</td>
</tr>
<tr>
<td>Step II</td>
<td>Opioids</td>
<td>Dextromethorphan SR</td>
<td>100-200 mg qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Morphine SR</td>
<td>15-60 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxycodone ER</td>
<td>10-40 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tapentadol ER</td>
<td>100-250 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tramadol</td>
<td>40 mg qd</td>
</tr>
<tr>
<td>Other Treatments</td>
<td>Alpha-lipoic acid**</td>
<td>Thiocacid ampoule</td>
<td>600-1200 mg i.v. infusion</td>
</tr>
<tr>
<td></td>
<td>Substance-P inhibitor**</td>
<td>Capsaicin 0.075% cream</td>
<td>0.025-0.075%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topically applied qd to tid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isosorbide dinitrate**</td>
<td>Isosorbide topical cream/30 mg spray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transcutaneous electrical stimulation (TENS)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Dose response is variable. Should be slowly increased by starting from the lowest dose.
**Unavailable in Turkey
SEMT APPROACH AND RECOMMENDATIONS

1. Neuropathy examination should be performed starting from 5 years after the puberty in patients with type 1 diabetes and starting at the time of diagnosis in patients with type 2 diabetes. Screening should be repeated once in every year (B).

2. Peripheral neuropathy screening should include 10-G monofilament test and the tuning fork test that examines the sense of vibration at the dorsum of the toe (128 Hz) (B).

3. Optimal glycemic control must be achieved in order to prevent or delay diabetic retinopathy (for type 1 diabetes patients: A; for type 2 diabetes patients: B).

4. In the treatment of painful diabetic neuropathy:
   - Antidepressant (duloxetine; A)
   - Anticonvulsant pregabalin (A), gabapentin (A) and
   - Opioid analgesics (A) should be used as monotherapy or in combination.

REFERENCES


B. Autonomic Neuropathy

Patients should be inquired in terms of autonomic neuropathy-related symptoms and findings. Hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder and sudomotor dysfunction [increased or decreased sweating] should be investigated in particular.

- **Cardiac autonomic neuropathy [cardiac denervation syndrome]:** It affects the CV reflexes and is related to mortality independently from other CV risk factors. It is often asymptomatic in the early period. The heart rate variability is decreased in deep inspirium.
  - The heart becomes hypersensitive to catecholamines.
  - Dysrhythmias (often resting tachycardia)
- Orthostatic hypotension (A drop in blood pressure when stood up [systolic 20, diastolic 10 mmHg] without a change in the heart rate).
- Decreased exercise tolerance
- Silent (painless) MI
- Sudden death may occur.

• **Gastrointestinal neuropathy:** One or more regions of the gastrointestinal tract may be affected. The most common problems are:
  - Esophageal dismotility (difficulty in swallowing)
  - Delayed gastric emptying (gastroparesis)
  - Decreased motility (difficulty in swallowing, quickly filling up, nausea, vomiting may occur)
  - Delayed absorption of the food (Brittle diabetes: Diabetes regulation deteriorates due to repeating hypo and hyperglycemia attacks with the contribution of gastroparesis)
  - Constipation (colon atony)
  - Fecal incontinence
  - Night diarrhea
  - Cholecystitis, biliary sludge (gallbladder atony)

• **Genitourinary neuropathy:** The following problems may occur.
  - Erectile dysfunction
  - Retrograde ejaculation and infertility
  - Difficulty in sexual arousal, painful sexual intercourse in women
  - Bladder dysfunction (incontinence, infection due to neurogenic bladder)

• **Hypoglycemia unawareness:** Counterregulatory hormone (epinephrine, glucagon) response to hypoglycemia decreases.

• **Autonomic sudomotor dysfunction:** Associated with decreased sympathetic activity of sweat glands. The following problems may occur:
  - Anhidrosis: Uncontrolled sweating loss in the extremities
  - Gustatorial sweating (central hyperhidrosis): Sweating and vasodilation (flushing) in the upper section of the chest, neck and face, especially right after the meal
  - Intolerance to high temperature
  - Dry skin

• **Pupillary dysfunction:** Caused by the impaired pupillomotor function. Pupils cannot dilate in the darkness. Sometimes pupils do not constrict when exposed to light but function of response to distance is still preserved [Argyll Robertson pupil]. In that case pupils are often miotic.

The approach for autonomic neuropathy in patients with diabetes is summarized in Table 13.3.

• Symptoms and findings of cardiac autonomic neuropathy, such as orthostatic hypotension and resting tachycardia, should be investigated in patients with long-term diabetes and clinical microvascular complications.
• For necessary cases, further tests such as Valsalva, ECG and R-R intervals during inspirium and expirium should be performed.
TABLE 13.3: Autonomic neuropathy approach in patients with diabetes

<table>
<thead>
<tr>
<th>Affected system</th>
<th>Treatment approach</th>
<th>Advanced examination and treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroparesis</td>
<td>- Impaired PG with hypo and hyperglycemias</td>
<td>- Suspicion in differential diagnosis&lt;br&gt;- The patient should be referred to a gastroenterologist in case of persistent and severe vomiting.</td>
</tr>
<tr>
<td></td>
<td>- Unexplained abdominal bloating and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Metoclopramide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Domperidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Erythromycin</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>- Necessary evaluations should be performed&lt;br&gt;- The patient should be informed about the contributing factors and treatment options&lt;br&gt;- Phosphodiesterase-5 inhibitor should be administered if there are no contraindications.</td>
<td>If phosphodiesterase-5 inhibitors are inadequate, then in the next step:&lt;br&gt;- Medical treatment&lt;br&gt;- Surgical treatment&lt;br&gt;- Psychological assistance therapy should be planned and the patient should be referred to related experts.</td>
</tr>
<tr>
<td>Hypoglycemia unawareness</td>
<td>Sympathetic nervous system injury should be considered</td>
<td></td>
</tr>
<tr>
<td>Diabetic diarrhea</td>
<td>Autonomic neuropathy affecting the intestines</td>
<td>More advanced tests should be performed and specific treatment should be applied.</td>
</tr>
<tr>
<td></td>
<td>Unexplained diarrhea, especially at night</td>
<td></td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>Autonomic neuropathy affecting the bladder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unexplained problems related to gastric emptying</td>
<td></td>
</tr>
</tbody>
</table>

Erectile dysfunction

The history of sexual functions should be periodically examined for adult male patients with diabetes. First line treatment should include phosphodiesterase-5 inhibitors in patients with erectile dysfunction. Patients who are unresponsive to the treatment should be referred to a urology specialist. The patient should be examined in terms of hypogonadism when needed. Patients with symptomatic hypogonadism may benefit from testosterone replacement in terms of sexual function, well-being, muscle strength, muscle mass and bone density increase. The patients for whom phosphodiesterase-5 inhibitor use is contraindicated, those with retrograde ejaculation, who want fertility and those with normal gonad hormones should be evaluated by an experienced urologist or andrologist.

SEMT APPROACH AND RECOMMENDATIONS

1. Patients with type 1 and type 2 diabetes should be examined in terms of symptoms and findings of autonomic neuropathy, and necessary examinations/tests should be performed (D).
2. The symptomatic treatment of autonomic neuropathy improves the quality of life of the patients (D).
3. Adult men with diabetes should be periodically examined in terms of sexual dysfunction and especially erectile dysfunction (D).
4. If there is erectile dysfunction, phosphodiesterase-5 inhibitors should be used as first line treatment (A).
5. The patients who are unresponsive to phosphodiesterase-5 inhibitors or for whom PDE5 inhibitor use is contraindicated, those with retrograde ejaculation but normal gonad hormone levels, and patients who want fertility should be assessed by an experienced urologist or andrologist (D).

6. Male patients with symptomatic hypogonadism may benefit from testosterone replacement in terms of improved sexual function, well-being, muscle strength, increased muscle mass and bone density (B).

REFERENCES

In patients with diabetes, problems concerning the foot can be reviewed under three sections. These are:
1. Acute infections of the foot,
2. Diabetic foot ulcers (chronic wound) and
3. Charcot neuroarthropathy.

This section is focused on diabetic foot ulcers, and has been prepared in accordance with the International Working Group on the Diabetic Foot (IWGDF) “Guidance on the Diagnosis and Management of Foot Infections in Persons with Diabetes-2015” and “Diagnosis, Treatment and Prevention of Diabetic Foot Wounds and Infections: Turkish Consensus Report -2015”.

It has been reported that every patient with diabetes has a 12-25% risk of diabetic foot ulcer development throughout their lives. Diabetic foot ulcers are important because:
- Diabetic foot ulcers impair the patient’s quality of life, significantly increase the cost of treatment, risk of lower extremity amputations, and mortality.
- Approximately 50-70% of non-traumatic foot amputation operations are performed for patients with diabetes. It has been reported that 85% of the patients who had undergone major amputation had foot ulcers (wounds) prior to the amputation.
- Diabetic foot is the most frequent cause of hospitalization and prolonged hospital stay.
- Amputation of the other extremity is considered for more than 50% of the patients within 3-5 years following the first amputation.
- It has been shown that the mortality risk increases by 2.5 times in diabetic patients with detected new feet ulcers.

Therefore, the goals of the approach to diabetic foot ulcer is to treat the ulcers, enable the patient to be mobile, to improve the quality of life, and to reduce ulcer-related amputations as much as possible. In order to achieve these goals, patients must be closely monitored and treated with a multidisciplinary approach. Moreover, patients, his/her relatives, and the medical team must be regularly trained to prevent the development of new ulcers. Preventive medicine should be at the center of the diabetic foot treatment.

14.1 | ETIOPATHOGENESIS OF DIABETIC FOOT ULCER

Two main factors are playing a major role in the development of foot ulcers: distal symmetrical polyneuropathy (sensory, motor, and autonomic neuropathy) and peripheral artery disease.

Diabetic foot ulcers may be of neuropathic, neuro-ischemic or ischemic origin. While neuropathy has been reported in almost every patient, neuropathy accompanied by ischemia has been reported in half of the patients, and only ischemia in 5-15% of the patients.

Diabetic sensorimotor neuropathy is the most common cause of diabetic foot ulcers. Due to the loss of pain sensation, a minor trauma (e.g., shoe pinch, burn, laceration or bug bite) that disrupts tissue integrity can easily trigger ulcer development in the neuropathic foot. In neuropathic foot (in relation to motor neuropathy), the atrophy of the intrinsic foot muscles
and anatomical deformities cause changes in the load-bearing structures and create extremely high-pressure points in certain areas. The limitation in the range of motion of the joints also contribute to the deformation. Repeating biomechanical traumas caused by the altered load distribution as a result of the deformities in the foot lead to callus formation especially localized in the metatarsal heads. Moreover, Muslim patients who pray (perform salaat) regularly can have pressure sores due to the callus formation in relation to one foot always being under the other foot during salaat. Callus formation poses a severe risk in terms of soft tissue damage and infection. Due to bleeding and ischemia in the soft tissue underneath the callus, ulcers develop over time, and progress into chronic foot ulcers. The deformities like mallet finger and claw toe, which are common in patients with diabetes, can lead to open wounds due to shoe pinch, without callus formation. Superficial ulcers and infections, caused by ischemia, uncontrolled hyperglycemia and recurrent biomechanical traumas, may lead to deep abscess and osteomyelitis formations in a short period of time.

Figure 14.1 shows ulcer development and deepening of the callus base. Ischemia due to peripheral arterial disease worsens tissue recovery and poses a serious risk in terms of gangrene and amputation. Vision loss, sequelae of CV or cerebrovascular disease and disrupted foot hygiene are other predisposing factors for ulcers development in patients with diabetes. Generally, the total loss or decrement of pain sensation delays the diagnosis of neuropathic foot ulcers. Late admission (over 15 days) to the hospital, inadequate treatment, recurrent traumas (continuing to walk on the wounded foot) and hyperglycemia are the main predisposing factors of delayed wound healing in patients with diabetes.

Hyperglycemia is known to impair migration, adhesion, phagocytosis and opsonization of the leukocytes. Therefore, ensuring good glycemic control must be the primary target in all cases with diabetic foot.

**FIGURE 14.1: Ulcer development on the basis of callus**

**Charcot foot:** Charcot foot, defined as diabetic neuro-osteoarthropathy, with neuropathic bone fractures and joint diseases, is one of the most destructive foot complications of diabetes. The warm, red, edematous, and often painless foot of a patient with diabetes should be considered as Charcot’s foot until proven otherwise. Charcot may manifest in different clinical presentations depending on the involvement of front, middle, rear parts of the foot and the ankle. The most common form is “Midfoot Charcot”. First, the foot arcus collapses due to softened bone tissue. It may progress to “rocker bottom foot deformity” of the foot in the advanced stage.
In most cases, the condition is usually misdiagnosed as infection and patients are attempted to treat with antibiotics. Actually, the patients must be referred to a “Diabetic Foot Center” or an experienced orthopedic specialist immediately.

### 14.2 | CLASSIFICATION

The classification of diabetic foot is important in terms of the standardization of treatment. However, there is no widely accepted classification system for foot ulcers. Despite its controversial aspects, the simplest classification still used is Wagner-Megitt classification. In the Wagner classification, cases without foot ulcers but determined to have risk factors are included (Stage 0) and open ulcers are grouped from mild to severe based on the presence of infection or gangrene (1st to 5th Stages) (Table 14.1).

<table>
<thead>
<tr>
<th>TABLE 14.1: Wagner classification in diabetic foot ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
</tr>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 3</td>
</tr>
<tr>
<td>Stage 4</td>
</tr>
<tr>
<td>Stage 5</td>
</tr>
</tbody>
</table>

Source: Wagner FW. Foot Ankle 1981;2:64

In the 2012 guide published by the council formed by Infectious Diseases Society of America (IDSA) and IWGDF, diabetic foot infections are classified as mild (limited to subcutaneous tissues), moderate (wider or involving deeper tissues) and severe (with systemic infection findings and metabolic disorder) ulcers.

The diabetic ulcer assessment of Texas University classification, which is more widely accepted, is shown in Table 14.2.

<table>
<thead>
<tr>
<th>TABLE 14.2: Texas University ulcer classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Pre- or post-ulcerative lesion (completely healed)</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
</tbody>
</table>


Additionally, PEDIS classification that assesses the lesion in terms of perfusion, extent, depth, infection and loss of sensation can be used.
14.3 | CLINICAL EVALUATION

In order to perform a clinical evaluation, first, both feet should be examined, and risk factors should be investigated.

Risk factors of diabetic foot:
- Neuropathic foot
- Peripheral vascular disease
- Deformity
- Infection
- Edema
- Coronary artery disease
- Stroke
- Dyslipidemia
- Poor foot care
- Poor personal hygiene
- Smoking
- Obesity
- Poor glycemic control
- Advanced age
- Nephropathy
- Vision loss
- History of ulcer or amputation in the foot

Risk status is generally classified into four groups:

Low risk: No risk factor, no loss of sensation or pulse

Moderate risk: One risk factor (loss of sensation, lack of pulse, callus or deformation, etc.)

High risk: Previous amputation or ulceration or ≥2 risk factors (loss of sensation, lack of pulse, peripheral arterial disease, callus deformation, pre-ulcerative lesion or end-stage kidney failure etc.)

Active diabetic foot: Foot with active ulcer.

When foot assessment is performed based on the presence of sensory loss, ulcer, deformity and Charcot foot, the examination frequency is recommended to be within the intervals specified in Table 14.3.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Clinical examination</th>
<th>Examination frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No sensory loss</td>
<td>Annually</td>
</tr>
<tr>
<td>1</td>
<td>Sensory loss</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>2</td>
<td>Sensory loss + ulcer</td>
<td>Every 2-3 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Sensory loss + ulcer + deformity</td>
<td>Every 1-2 weeks</td>
</tr>
<tr>
<td>4</td>
<td>Charcot foot deformity</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

The principles of clinical follow-up and treatment in diabetic foot ulcers are summarized below.
- A patient with diabetes with a skin lesion that cannot be healed in two weeks must immediately be referred to a center experienced in diabetic foot management.
- The presence of neuropathy and peripheral arterial disease should be investigated carefully when assessing the ulcer.
- The patient with diabetic foot ulcers must comprehensively be evaluated by noting the duration, width, depth, and odor of the lesion, presence of osteomyelitis, and the administered treatments.
• The etiology of the ulcer must be revealed by performing neurological and peripheral arterial examinations for each patient presenting with diabetic foot wound.

• In suspected cases where there is no pulse, the ankle-brachial index (ABI) should be measured. ABI is calculated by dividing the blood pressure measured over tibialis posterior and dorsalis pedis arteries at the wrist level with a manual Doppler device (whichever is higher) by the systolic blood pressure measured over the brachial artery (proportioning). Normally, ABI should be within 0.91-1.30. ABI <0.90 may indicate peripheral artery disease. If ABI is >1.30 then the presence of severe arterial disease in the upper extremity or inaccurate high-pressure measurement as a result of the tension device not compressing adequately due to the hardened foot arteries caused by medial calcinosis should be considered. Medial calcinosis is common in elderly people and especially in diabetic patients with chronic kidney disease (CKD). In such cases, the patient should be consulted with an experienced vascular surgeon.

• If ABI cannot be measured reliably due to arterial calcification, then toe-brachial index (TBI) can be measured. If TBI measurement, which requires specialized equipment, is higher than 0.70, or the transcutaneous oxygen tension (TcPO2) measured adjacent to the wound is higher than 40 mmHg, then this indicated that there is sufficient arterial circulation in the foot.

• Two- or three-directional X-rays must be performed for all patients with diabetes and foot problems.

• Wound healing is very difficult in tissues with insufficient oxygenation. Because the oxygen requirement of wounded tissues is significantly higher than the healthy tissues. Revascularization by radiological or surgical methods should be performed in patients for whom wound healing cannot be achieved in 4-6 weeks with proper wound care.

• Diagnosis of infection is made clinically. It should be made in the presence of purulent secretion or at least two clinical findings of inflammation (erythema, increased heat, sensitivity, pain, and induration).

• Ischemia or neuropathy related findings may mimic infection. Bad smell, unhealthy appearance or deep penetration of the wound also presents essential evidence for infection.

• Diabetic foot infection often does not cause systemic findings like fever and leukocytosis. The presence of these findings indicates the severity of the clinical condition.

First intervention

When the diabetic foot infection is first observed, the wound must be cleaned, necrotic or gangrenous parts must be debrided, and presence of foreign body and ulcer depth must be evaluated by inserting a sterile blunt-tipped metal probe into the lesion.

• At this stage deep tissue samples must be taken for culture. In the presence of abscess formation or necrotic tissues, debridement and drainage should be performed immediately and biopsies should be taken from the remaining viable tissues.

• Superficial swab cultures are not recommended as they reflect colonization. Culture material from superficial wounds may be collected by curettage or biopsy.

Laboratory tests

• Hemogram, basic biochemical tests and serum markers of inflammation (sedimentation, CRP) are useful for follow-up and treatment modification.

• Two- or three-directional radiographies must be acquired from all patients with ulcer. Direct radiograph provides valuable information such as foreign bodies, air presence in the tissues and findings of osteomyelitis.

• MR imaging may be performed to evaluate the probable deep tissue infection, abscess and osteomyelitis.
The most important pathogens in diabetic foot ulcers are:

- Gram positive cocci (*Staphylococcus aureus* in particular),
- β-Hemolytic streptococci (group B in particular)
- Coagulase negative staphylococci.

Although gram positive cocci mostly cause monomicrobial infection, they may be encountered as part of a mixed infection in chronic ulcers of wounds that had been previously treated or received antibiotics.

Anaerobic bacteria are rare, however, they may be observed as a mixed infection factor especially in ischemic and gangrenous wounds.

Pseudomonas and enterococci strains mostly cause colonization. However, in hot climates including Turkey, it must be noted that pseudomonas strains can be pathogens, and therefore local factor profile must be taken into consideration for the empirical antibiotic treatment.

**Osteomyelitis**

- Diagnosis and treatment of osteomyelitis is difficult. When the bone is clinically exposed or touched by a metal probe, osteomyelitis is present.
- Sedimentation of >70 mm/hr supports the presence of osteomyelitis, however, this test has a low sensitivity.
- Nuclear medicine methods, such as three-phase leukocyte-labeled scintigraphy, are more sensitive than radiography; however, they are relatively less specific and have lower accuracy than MRI.
- The gold standard method for osteomyelitis diagnosis is the histopathological and microbiologic examination of the bone biopsy material.

Clinical approach in diabetic patients with diabetic foot ulcer is shown in Figure 14.2.

![Annual evaluation in terms of foot problems](image)

**FIGURE 14.2: Approach to foot problems in patients with diabetes**
14.4 | TREATMENT

- Wound care, adequate and appropriate debridement, antibiotic administration, relieve pressure on the foot (off-loading), and glycemic control are the essential components of treatment.

- If there are burning, stinging, numbness, and tingling, the patient should be evaluated and treated for neuropathy. Pain is not common. If any, treatment should be performed (see Chapter 13).

- Patients with lower extremity ulcer benefit from the evidence-based treatments that reduce the risk of atherosclerotic diseases. In this regard, cessation of smoking, healthy nutrition, anti-hyperlipidemic, and anti-thrombocyte medication therapies should be into account in addition blood glucose and blood pressure control.

- Diabetic foot ulcers should be evaluated with a multidisciplinary approach. Patients should be assessed and treated in a setting including the specialists on endocrinology, infectious diseases, orthopedics, plastic surgery, vascular surgery, hyperbaric medicine, physiotherapy, diet, and wound care and diabetes nursing.

- A multidisciplinary approach reduces hospital stay, amputation rates and treatment costs. In the first-line treatment, the collaborations with the family practitioner and the specialist of internal diseases should be done for diabetic foot treatment.

**Antibiotic Therapy**

- In patients with good health and no evidence of sepsis, the results of tissue culture and antibiogram should be waited to begin antibiotic therapy.

- In patients with impaired general health conditions and sepsis-related findings, after a tissue culture collected immediately, empirical antibiotic therapies should be started without waiting for the results. The spectrum of antibiotic(s) should be wide, including gram-negative, gram-positive, and anaerobic bacteria.

- Antibiotic treatment is adjusted based on the clinical response, culture results, and antibiotic sensitivity of the patient during follow-up.

- Antibiotic resistance patterns in the medical center of following-up should be considered when choosing the drug (e.g., Methicillin-Resistant *Staphylococcus aureus*: MRSA).

- Antibiotic selection and dosages are also determined based on hepatic and renal functions, and drug allergy history.

- Antibiotic therapy is administered orally in patients with mild infection and intravenously in patients with severe infection.

- There is very limited data on topical antibiotics and they are thought to be only effective in mildly infection superficial wounds.

- For mild wounds without osteomyelitis, antibiotic treatment is administered for two weeks.

- Long-term (4-6 weeks) treatments with agents that can penetrate the bone (e.g., Quinolones) provides successful results in cases with osteomyelitis.

- Some of the antiseptic agents can disrupt the tissue healing.

**Wound care**

- The main purpose of the surgery is the removal of the infected and necrotic tissues to allow the formation of granulation tissue required for secondary healing.
- As ulcers can rapidly become infected and turn into a life-threatening systemic disease, debrided ulcers should be monitored regularly.
- Osteomyelitis is a critical issue of chronic wound. Bone infections are caused by direct spread from soft tissue and become chronic. If a fistula accompanies a chronic wound, there is probably also osteomyelitis. The most definitive treatment is the resection of the infected and necrotic bone. As certain bone resections can cause significant loss of function, the decision should be made and implemented by an experienced orthopedist.
- There are studies suggesting the use of larvae (maggot) for the removal of necrotic tissue from the wound.
- Some studies conducted with growth factors provide data on the benefit of recombinant platelet-derived growth factors (rPDGF) and granulocyte macrophage colony stimulating factor (GMCSF). Both products are unavailable in our country. The epidermal growth factor-IL (EGF-IL) injectable into the lesion is available in Turkey, but it is highly expensive. However, it can be used as an option in cases where revascularization is not possible despite the presence of severe ischemia or cases with unsuccessful revascularization. In recent years, topically applicable forms of epidermal growth factors (e.g., spray) have been developed. These products have been reported to accelerate the healing process in wounds.
- Treatments, such as platelet-rich plasma (PRP), stem cell, and allograft, offered to accelerate wound healing are expensive, and they can be applied for a very limited number of cases in actual practice. It should also be noted that there is still inadequate evidence on the wider use of these methods.

Revascularization
- There is a need for decision-making by experienced multidisciplinary boards for patients with artery disease. Surgical or radiologic treatment of peripheral artery diseases are not required for all patients, and these interventions can be harmful in some cases. In many patients, conservative treatment and proper wound care can alleviate the effects of artery disease.
- Peripheral artery diseases in diabetes patients typically affect the arteries between the knee and the ankle.
- The standard treatment of ischemic and neuro-ischemic ulcers is femoro-distal bypass with autogenous tissue (saphenous vein). If autogenous graft not available, prosthetic grafts can be used. However, re-occlusion and infection risks of prosthetic grafts are relatively high.
- In recent years, there are debates on the selection of either surgical or endovascular revascularization. Generally, a surgical bypass is recommended if the life expectancy is more than two years, and there is a convenient saphenous vein. Endovascular treatment is proposed if the life expectancy is short, and there is no suitable autogenous bypass material. However, in today’s practice, endovascular methods are becoming the first choice due to the constant development and easy application. Some state that surgery should only be used in cases where the endovascular approach fails.
- Excellent results can be obtained with surgical techniques like free autologous tissue transfer. As these are long and complicated surgeries, they can be performed for a limited number of patients who are young and have long life expectancy.
Relieving Pressure (offloading)

- The wound will constantly get damaged and not heal, unless the mechanical load is removed, even if the blood circulation is sufficient.
- Bed rest, using crutches, total contact cast, Scotch-cast boots, special boots with air cushion, and special orthopedic devices provide significant contribution for relieving the pressure on and healing the wound.
- The treatment of the patients with Charcot foot is conservative. These patients should be put to definite rest for a while by applying cast to the foot until the skin temperature reaches normal levels. Supporting shoes with special insoles and ankle cover should be used. There are studies suggesting that parenteral bisphosphonate therapy can benefit these patients.
- Surgical intervention decisions like repairing the deformities or bone protrusion that cause wound opening and resection of the bones with osteomyelitis require attention and should be decided by experienced orthopedists.
- Although the literature data are limited, preventive surgical methods like lengthening or resection of the Achilles tendon or resection of the metatarsal head can be successful in the selected patient.

Adjuvant therapy

In cases that are ineligible for surgical debridement, enzymatic debridement (collagenase in particular) is a very common method. In selected cases with chronic diabetic foot ulcer;

- Hyperbaric oxygen (HBO) treatment,
- Using new techniques capable of continuous or episodic negative pressure wound treatment (NPWT), washing or instillation,
- Using modern wound care materials that are tailored to the requirements of the patient and wound can accelerate the process of wound closing and ulcer healing.

14.5 | PREVENTION OF RECURRENCE

- The recurrent ulcer formation rate is 28% in the first 12 months, whereas, it may increase up to 100% at the end of 40 months.
- Therefore, patients with a diabetic ulcer history or those at high risk should be regularly monitored in specialized diabetic foot clinics.
- Patients with ulcer history or ischemia and their relatives should be trained together, called for a more frequent follow-up visit and the recurrent nature of the foot ulcer should be explained.
- All patients with diabetes should be trained and especially patients without the sense of pain should be told how to protect their feet from mechanical, thermal and chemical traumas.
- At each physical examination, the patient’s feet must be evaluated by removing their socks.
- The principles of ulcer treatment, infection signs and the importance of regular foot care must be explained to the patient.
- The ulcer formation can be reduced by 50% with simple precautions like regular foot care training, moisturizing the foot, basic hygienic practices and proper shoe selection.
- In the prevention of ulcer formation and recurrence, it is important to reduce the foot pressures below the ulcer threshold.
- Patients should not use the shoes that cause ulcer, and they must be ensured to wear proper shoes depending on the level and activity of the deformation.
**SEMT RECOMMENDATIONS**

1. **All patients with diabetes must be trained in foot care and this training should be repeated regularly** (B).

2. **Patients’ feet must be examined at each visit and distal pulses should be checked** (C).

3. **A detailed foot examination should be performed every year in patients with diabetes** (B).

4. **The examinations must be more frequent for patients with sensorial neuropathy, peripheral artery disease and alterations in the foot skin (callus, ulcer, infection) or those with structural deformation** (D).

5. **The diagnosis of diabetic foot infection should be made clinically based on the local and systemic symptoms and findings of inflammation** (D).

6. **The follow-up and treatment of patients with diabetic foot ulcer should be performed by a multidisciplinary “Diabetic Foot Team”** (B).

7. **For the determination of microorganisms and antibiotic sensitivity, after the wound has been thoroughly cleaned by debridement, samples must be collected for deep tissue culture by using new sterile gloves and instruments** (B).

8. **The main components of the treatment include lifestyle modifications like balanced and suitable nutrition, smoking cessation; achieving glycaemia, blood pressure and lipid controls; classifications of the ulcer, maintaining a clean wound bed, applying off-loading precautions, infections control, providing circulation support and (if needed) surgical interventions** (B).

9. **In selected diabetic foot with chronic ulcer, HBO treatment as an ancillary intervention can accelerate the wound healing and can reduce the risk of amputation** (C). Similarly, negative pressure wound treatment (NPWT) can also accelerate the closure of the wound (B).

**REFERENCES**


The combination of pregnancy and diabetes adversely affect each other. Hyperglycemia that first occurs in pregnancy (generally in 2nd or 3rd trimester) is called “diabetes of pregnancy” or “gestational diabetes mellitus” (GDM), whereas, the pregnancy in women with type 1 or type 2 diabetes are called “diabetes in pregnancy”, “overt diabetes in pregnancy”, “pre-gestational diabetes” or “pre-gestational diabetes mellitus” (PGDM). The majority of the diabetes cases observed during pregnancy is GDM. In PGDM, the maternal and infantile mortality and morbidity are more affected in comparison than in GDM.

Today, as in the world, the cases with diabetic pregnancy are increasing in Turkey. According to the data in the Diabetes Atlas published by International Diabetes Federation (IDF) in 2017, 6.2% of the women who have given live birth have hyperglycemia. It is estimated that 93.8% of them are GDM, and 6.2% are PGDM.

The reasons for the increased incidence of diabetic pregnancy are: increased life expectancy and quality of life of women with type 1 diabetes, increased type 2 diabetes prevalence due to obesity, and its frequent onset in the young reproductive ages.

15.1 | PREGESTATIONAL DIABETES MELLITUS

Pregnancy causes extra load on the metabolism even in non-diabetic individuals, and can cause significant problems in diabetic women making it difficult to regulate glycemia as a result of impaired insulin sensitivity. Prior to the discovery of insulin, the pregnancy of a woman with diabetes resulted in 90% fetal mortality and more than 30% maternal mortality. Although the mortality risk decreased after the onset of insulin, pregnancy was not considered appropriate for women with diabetes and was banned until mid-1970s due to high maternal and fetal risk. Today, maternal risks are reduced with development in insulin types and administration techniques, ability to perform self-monitoring glucose measurement at home, and the collaborative of an experienced team involving internal diseases or endocrinology specialist, obstetrician and neonatal health specialist and dietitians and diabetes nurses/instructors. And in parallel with the increased gynecologic care standards, advanced fetal monitoring methods and improved neonatal care conditions have minimized the fetal and neonatal problems.

15.1.1 | THE RISKS OF PREGESTATIONAL DIABETES

Table 15.1 lists the potential risks for mother, fetus and neonate in association with diabetic pregnancy. Especially type 1 and type 2 diabetic women with poor glycemic control may encounter serious health problems and their health-related risks may continue after the birth. In addition, after the diabetic pregnancy, there may be an increased risk of obesity and diabetes for both the mother and the child depending on the type of the diabetes. The children
with type 1 diabetic mother have 2% risk of type 1 diabetes, whereas, children of type 2 diabetic mothers have higher type 2 diabetes risk (25-30%).

In order to minimize the maternal and fetal risks in women with PGDM, good glycemic control must be established prior to the pregnancy. For this purpose, planned pregnancy should be recommended for all women at reproductive age with type 1 and type 2 diabetes, the necessity of contraceptive methods should be explained to avoid unplanned pregnancy and should be trained for the application of a safe method.

**TABLE 15.1: Risks associated with diabetic pregnancy**

<table>
<thead>
<tr>
<th>Maternal Fetal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous aborts</td>
<td>Fetal abnormalities:</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>- Cardiac (transposition of great vessels, VSD), aortic coarctation, ASD</td>
</tr>
<tr>
<td>Progression in diabetic complications (retinopathy, nephropathy)</td>
<td>- Caudal regression syndrome</td>
</tr>
<tr>
<td>Frequent urinary infections</td>
<td>- CNS: Neural tube defects (Anencephaly, microcephaly, hydrocephaly)</td>
</tr>
<tr>
<td>Recurrent hypoglycemia</td>
<td>- Gastrointestinal (duodenal atresia, anorectal atresia, hypoplastic left colon)</td>
</tr>
<tr>
<td>DKA and its complications (hypovolemic shock, aspiration pneumonia, cerebral edema, arrhythmias, pulmonary embolism)</td>
<td>- Musculoskeletal system (drop foot, AMC)</td>
</tr>
<tr>
<td>Obesity, type 2 diabetes in the following years</td>
<td>- Cleft lip/palate</td>
</tr>
<tr>
<td></td>
<td>- Urinary system (double ureter, polycystic kidney, renal dysgenesis, hydronephrosis)</td>
</tr>
<tr>
<td></td>
<td><strong>Macrosomia, intrauterine growth retardation</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Intrauterine death</strong></td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis; VSD, ventricular septal defect; ASD, atrial septal defect; CNS, central nervous system; AMC, arthrogryposis multiplex congenita; RDS, respiratory distress syndrome.

15.1.2 **PROGNOSIS IN PREGESTATIONAL DIABETES**

Factors determining the prognosis of pregnancy: the age of the expectant mother at the time of diabetes diagnosis, duration of diabetes, accompanying macrovascular conditions, microvascular complications like nephropathy and retinopathy and the severity of these. Although it is not commonly used by obstetricians of today, White classification was developed in light of this information and its modified version is summarized in Table 15.2.

Each physician following up diabetic women should evaluate the prognosis of the pregnancy by using this diagram starting from the time when their patient plans for pregnancy. According to White classification, the prognosis of pregnancy is poor in diabetic patients in group D or latter stages. Therefore, pregnancy is unfavorable in diabetic women with early onset or long-term diabetes, or those with serious complications like severe nephropathy, advanced ischemic cardiac disease or retinopathy that is unresponsive to treatment. Additionally, pregnancy should not be allowed for cases with poor glycemic regulation.
15.1.3 | APPROACH TO PATIENTS WITH PREGESTATIONAL DIABETES MELLITUS

In order to minimize the health risks in mother, fetus and neonate, pregnancy should be planned in women with diabetes, and they should be carefully monitored by an experienced multidisciplinary team starting before the conception, during and after the pregnancy and delivery or such a team should be consulted.

TABLE 15.2: Modified White classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>At any age and duration, regulated only with diet</td>
</tr>
<tr>
<td>A2</td>
<td>At any age and duration, regulated with diet + insulin</td>
</tr>
<tr>
<td>Pregestational diabetes</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Age at the time of diabetes diagnosis ≥20 years and diabetes duration &lt;10 years, no complications</td>
</tr>
<tr>
<td>C</td>
<td>Age at the time of diabetes diagnosis or diabetes duration: 10-19 years, no complications</td>
</tr>
<tr>
<td>D</td>
<td>Age at the time of diabetes diagnosis &lt;10 years or diabetes duration ≥20 years</td>
</tr>
<tr>
<td>F</td>
<td>At any age and duration, on insulin therapy, with nephropathy (&gt;500 mg/day proteinuria)</td>
</tr>
<tr>
<td>R</td>
<td>At any age and duration, on insulin therapy, with proliferative retinopathy</td>
</tr>
<tr>
<td>RF</td>
<td>At any age and duration, on insulin therapy, co-existence of the properties of R and F classes</td>
</tr>
<tr>
<td>H</td>
<td>Clinically diagnosed atherosclerotic heart disease</td>
</tr>
<tr>
<td>T</td>
<td>Renal transplantation history</td>
</tr>
</tbody>
</table>

a) Approach in pre-conception period

Although the international institutions like National Institute for Health and Care Excellence (NICE), American Diabetes Association (ADA), American Endocrine Society (ENDO) and Canada Diabetes Association (CDA) have different approaches for pre-conception period, their consensus common view is that prognosis can be improved by achieving good glycemic control prior to pregnancy, applying folate replacement, screening for diabetes complications and management of existing complications, termination of smoking and potentially teratogen drugs, and by providing training for the expectant mother.

The necessity of planned pregnancy and the importance of glycemic control should be explained to the diabetic women. If sexually active women with type 1 and type 2 diabetes at reproductive ages do not desire pregnancy, free-of-charge family counseling service should be provided and a safe contraceptive method should be used. The contraceptive method to be selected is similar to those used by nondiabetic women.

When pregnancy is planned, the tests for rubella, syphilis, hepatitis B and HIV should be performed. The blood group should be tested. Pap smear and cervical culture samples should be collected; TSH, thyroid autoantibodies (anti-TPO, Anti-Tg and B12-vit level) should be analyzed for other autoimmune disease in women with type 1 diabetes. Serum creatinine, ALT and AST, urinary albumin/creatinine ratio (ACO) and fundus oculi examination should be performed. In addition, for women older than 35 years of age, cardiac examination must be performed with ECG and other advanced methods. Counseling for smoking cessation should be provided for women who smoke prior to conception, and women with BMI >27 kg/m² should be recommended to lose weight before pregnancy.
In order to reduce potential risks (congenital malformation in particular) glycemic control must be established prior to conception and A1C ≤6.5% (48 mmol/mol) should be targeted. If hypoglycemia risk is low and the patient is informed then A1C target can even be <6% (42 mmol/mol). However, A1C <7% (53 mmol/mol) is sufficient for women with severe hypoglycemia risk. In women with type 2 diabetes who plan for pregnancy or already pregnant, antihyperglycemics except insulin (e.g., oral antidiabetic; OAD) drugs that they have been using before conception should be discontinued and insulin treatment should be initiated instead. Aside from ovulation induction, there is no consensus on the safe use of metformin in pregnancy.

Teratogen drugs like ACE-I and ARB should be discontinued prior to pregnancy as they may cause fetal renal dysplasia, oligohydramnios and intrauterine growth retardation. Chronic diuretic use should be avoided during pregnancy as it may disrupt the uteroplacental perfusion by decreasing the maternal plasma volume. In pregnancy, blood pressure [BP] targets should be 120-160 mmHg systolic and 80-105 mmHg diastolic; and antihypertensive drugs like methyldopa, labetalol, calcium channel blocker (e.g., diltiazem), which are known to be safer, should be recommended for patients with hypertension.

Statins are contraindicated in pregnancy due to the lack of sufficient teratogenicity data. Especially to avoid fetal neural tube defect in diabetic women who plan for pregnancy, 5 mg/day (0.4-1 mg/day according to some sources) folic acid should be administered for the first 3 months of the pregnancy starting from at least 3 months prior to conception and prenatal vitamins should be started.

In addition, it is recommended to start low-dose aspirin at the end of the first trimester and maintain for the duration of the pregnancy in order to decrease preeclampsia risk in pregnant women with type 1 and type 2 diabetes.

**Maternal follow-up**

In addition to glucose variability, diabetes complications may also develop or worsen due to hemodynamic changes in pregnant diabetics. Therefore, the presence and severity of the complications must be investigated before the pregnancy and patients should be examined in every trimester for retinopathy and nephropathy.

**b) Approach during pregnancy period**

**Glycemic control targets:** Optimal glycemic control must be ensured during the pregnancy. For this purpose, patient-specific medical nutrition and exercise schedule must be prepared and adequate dose of insulin must be prescribed. National/international guidelines recommend the same glycemic targets (by personalizing) for pregnant women with GMD and PGDM. According to this method;

<table>
<thead>
<tr>
<th>Glycemic control targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C 6–6.5% (42–48 mmol/mol),</td>
</tr>
<tr>
<td>FPG and pre-prandial PG &lt;95 mg/dL</td>
</tr>
<tr>
<td>1-hr PG &lt;140 mg/dL</td>
</tr>
<tr>
<td>2-hr PG &lt;120 mg/dL</td>
</tr>
</tbody>
</table>

levels are adopted. In postprandial PG monitoring, 1-hr PG, indicator of postabsorptive period, should be preferred.
A1C target can be lower (<6%, 42 mmol/mol) in the early periods of pregnancy. However, it is recommended to use a less strict and personalized target for patients with high hypoglycemia risk. In that case it is sufficient to maintain A1C <7% (53 mmol/mol). However, as the erythrocyte destruction cycle is fast in pregnant women, A1C level should not be the sole monitoring parameter and patients should be recommended to perform SMBG at least 3 times a week.

SMBG may not be sufficient for monitoring in patients with hypoglycemia unawareness or those with high glycemic variability during the day. In that case, many guidelines recommend the use of subcutaneous glucose sensors (CGM or flash glucose sensors) for more detailed and continuous monitoring of the blood glucose levels.

**Nutrition:** The main principle is using a patient-specific nutrition plan during the pregnancy. The energy intake that is sufficient to provide proper weight gain during pregnancy should be ensured. The daily calorie requirement of pregnant women is calculated based on the ideal weight: 24 kcal/kg in obese diabetics, 30 kcal/kg in the first trimester and 35 kcal/kg starting from the second trimester in non-obese diabetic women. In the second trimester 340 kcal/day, and in breastfeeding period 450 kcal/day additional energy intake is recommended.

Weight loss diets are not recommended for pregnant women, however, mild-moderate energy and carbohydrate (CH) restriction may be suitable for overweight or obese women with GDM.

Nutrients component of the daily total calorie (energy) is calculated. 45-50% of the total energy should be met from CH [minimum 175 g/day], 18-20% from proteins [amount: 1-1.5 g/kg/day, minimum 71 g/day], 30-35% from fats [40-60 g/day]. Moreover, sufficient amount of fibers [28 g/day] should be included in the nutrition plan.

Total number of meals should be planned as 7 (3 main meals and 4 snacks); breakfast should provide the 3/18 of the daily calorie need, 4/18 with lunch and 4/18 with dinner. Throughout the day, three snacks that would provide the 2/18 of the daily energy needs and one snack to cover 2/18 of the daily calorie before bedtime should be consumed.

As glucose tolerance is decreased in the morning, CH intake at breakfast should be <45 g.

**Micronutrients:** Vitamin and mineral supplement should be provided for pregnant diabetics with iron (18 mg/day), folic acid (0.4-1 mg/day), calcium (1200 mg/day), iodine (100-150 μg/day) and 25-OH vitamin D (1000 U/day).

**Weight gain:** During pregnancy, weight gain rate should be 1-2 kg in the first trimester and weekly 250-500 g starting with the second trimester, and the total weight gain should not exceed 10-12 kg.

Weight gain during pregnancy is determined based on the BMI values before pregnancy.
Exercise: If there is no contraindication, 20-30 minutes of tolerable, moderate aerobic (walking, swimming, plates, yoga), resistance or structured muscle strengthening exercise are recommended for diabetic pregnant women. Group sports, diving and flying should be avoided. Exercise has been shown to decrease cardiovascular (CV) risk, preeclampsia and C-section risk.

Medical treatment: Treatment is adjusted according to fasting and PPG targets during pregnancy. Multi-dose insulin may be necessary for type 1 diabetes patients and multi-dose injection therapy may often be required for patients with type 2 diabetes who cannot be controlled with diet and exercise. In pregnant women with type 1 diabetes, for whom multi-dose insulin injection is insufficient, insulin pump (CSII) treatment should be used. Clinical trials have demonstrated no superiority for CSII over multi-dose insulin injection therapy, and under-educated patients or those who do not pay attention to their treatment have risks such as hypoglycemia, hyperglycemia or DKA. However, it is recommended that patients with “Brittle course” diabetes with high daily glucose variability and patients who have achieved glucose regulation during preconception period by using CSII should continue the same treatment for the duration of their pregnancy. Ketosis should be avoided during pregnancy.

There is less need for insulin in early pregnancy, it increases up to 0.8-1.0 IU/kg/day starting from the second trimester and may even reach 1.5 IU/kg/day dose near the term. 40-50% of the daily insulin dose should be basal and 50-60% should be bolus insulin. Today, current insulin products have been shown to not penetrate through the placenta. B category insulins are, detemir or NPH as basal insulin, short-acting regular or fast-acting analog insulins (lispro, aspart) as bolus. Due to the absence of sufficient evidence, the uses of glargine, degludec and glulisine insulins in pregnancy is not recommended.

Although there are studies where sulphonylurea (SU) and metformin are used in pregnancy, they are not recommended during pregnancy as they pass through placenta and there are no long-term safety trial. It is recommended to achieve glycemic control with insulin in patients with PGDM and GDM cases where lifestyle modifications are inadequate.

Fetal monitoring: The requirement for fetal monitoring should not be neglected considering the concurrent maternal hyperglycemia and fetal hypoxia. The mother with PGDM and the fetus should be monitored by a multidisciplinary team. Examinations should be initiated for fetal congenital anomalies at 15-21 gestational weeks. Following the planned triple screening, fetal anatomic screening should be performed at week 18. Since cardiac defects may be unnoticed in 18th week ultrasonography (USG), fetal echocardiography is recommended at 20-22 gestational weeks.

USG should be performed to measure fetal growth and amniotic fluid at 28 gestational weeks. Due to the preterm delivery in third trimester, in addition to maternal monitoring, non-stress test (NST), biophysical profile and fetal movement examinations should be

<table>
<thead>
<tr>
<th>BMI prior to pregnancy</th>
<th>Weight gain in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.6-24.9 kg/m²</td>
<td>11.5-16 kg</td>
</tr>
<tr>
<td>25-29.9 kg/m²</td>
<td>7-11.5 kg</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>5.5-10 kg</td>
</tr>
</tbody>
</table>
initiated to monitor the fetal vitality. The start and frequency of fetal follow-up depends on diabetes control, diabetic nephropathy and hypertension, and fetal growth rate determined on USG. Continuous cardiotocography (CTG) monitoring is not monitoring but it is reassuring. Today, telemetric CTG is being used. In expectant mother with normal pregnancy course and no diabetic complications, fetal monitoring interval can be increased if the initial fetal evaluations are satisfactory.

c) Approach during delivery and postpartum period

The factors that determine the time and type of delivery: maternal obstetric history, maternal vascular disease, glycemic level, cervix status, fetal size/stress exposure probability and the presence of fetal anomaly. The type and time of delivery should be personalized for cases that are accompanied by severe diabetic angiopathy or in the presence of complications of diabetic pregnancy.

In pregnant women with good glycemic control, delivery can be safely delayed to 39th week or term. Although the mode of delivery is still debated normal, spontaneous birth is recommended for diabetic pregnant women.

Conditions require the delivery before 39 weeks of gestation are: poor glycemic control, hypertension or progressive worsening of the mother, intrauterine growth retardation, C-section history, and deterioration of fetal vital signs during antepartum monitoring. In the White classification, delivery is not delayed until the 39 weeks of gestation for PGDM patients in the D-RF class, however, pulmonary maturation of the fetus must be documented by amniocentesis. The presence of lecithin/sphingomyelin <2 in the amniotic fluid indicates RDS in the fetus. Labor induction or C-section can be performed if fetal maturation is shown to be completed.

It is known that maternal-fetal hyperglycemia increases lactate levels and oxygen consumption in the fetus, leads to hypoxia formation that causes cerebral damage and also causes neonatal hypoglycemia. Therefore, glycemic control should be achieved during delivery or before planned C-section. In these cases, a normal evening dose of insulin is given on the day before birth and no morning dose is administered. If the delivery is expected to last long, then glucose infusion should be used to compensate for the energy loss of the expectant mother. Target maternal glucose levels, which will be monitored hourly, should be 80-120 mg/dL. When PG exceeds 120 mg/dL, insulin infusion should be added to glucose infusion as hyperinsulinemia and hypoglycemia may develop in the neonate after the birth.

Patients using subcutaneous insulin infusion pump (CSII treatment) may continue to receive basal insulin provided that the infusion set is placed on the thigh or hip. Basal insulin dose is increased if glycaemia <80 mg/dL. However, if glycaemia is >120 mg/dL then inadequate subcutaneous insulin absorption should be considered due to cold operating room environment, beta agonist drugs, peaked stress hormones etc., pump should be turned off and intravenously glucose and insulin administration should be initiated.

There is no consensus on the content and how to administer glucose and insulin infusion. SEMT adopts the modified “Glucose + Insulin + Potassium” (GIK) infusion (shown in Table 15.3) during the delivery based on the treatment protocol. GIK protocol continues until the oral nutrition starts after delivery.

The treatment is switched back to pre-pregnancy after oral nutrition starts. The treatment of type 1 diabetics should be adjusted based on the pre-pregnancy doses, however, a re-
adjustment should also be performed considering that insulin needs will be decreased after the delivery (removal of placenta).

**TABLE 15.3: Glucose-insulin-potassium infusion protocol**

<table>
<thead>
<tr>
<th>GIK solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An infusion containing 5% Dextrose 500 mL + 15 IU short-acting regular insulin + 10 mmol potassium.*</td>
</tr>
<tr>
<td>• The target is to maintain the hourly glucose levels at 80-120 mg/dL. Therefore, the infusion is initiated with hourly 60 mL (3 gr glucose, 1.8 IU insulin) administration.</td>
</tr>
<tr>
<td>• According to hourly glycemic measurements, infusion is continued until the patient starts oral food intake at the following rates.</td>
</tr>
<tr>
<td>• Infusion solution should be renewed every 5 hours.</td>
</tr>
<tr>
<td>• Electrolytes (especially potassium) should be checked during every infusion that lasts more than 24 hours.</td>
</tr>
<tr>
<td>• The treatment is switched back to pre-pregnancy method after oral nutrition starts.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjustment of infusion rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose (mg/dL)</td>
</tr>
<tr>
<td>≥280</td>
</tr>
<tr>
<td>279-220</td>
</tr>
<tr>
<td>219-180</td>
</tr>
<tr>
<td>179-120</td>
</tr>
<tr>
<td>119-80</td>
</tr>
<tr>
<td>&lt;80</td>
</tr>
</tbody>
</table>

*Includes 5 g glucose, 3 IU short-acting insulin in 100 mL infusion fluid.

**Lactation:** DLactation should be initiated as soon as possible after delivery. Daily energy and CH needs increase during lactation period. Additional 450 kcal/day energy intake is recommended. CH content should be increased by 50 g/day and the daily CH should be >210 g/day.

Lifestyle modifications are essential for type 2 diabetes patients; if these changes are inadequate, then insulin treatment should be maintained for the duration of the lactation period. However, if the patient prefers using metformin during lactation, then 3-4 hours of gap is recommended between breastfeeding time and metformin use.

**15.2 | GESTATIONAL DIABETES MELLITUS**

Gestational diabetes mellitus (GDM) is CH intolerance that occurs in second or third trimester in pregnant women with no overt diabetes prior to pregnancy. However, considering the obesity and type 2 diabetes incidence has increased in younger women, an undiagnosed PGDM may be the case in some women who are determined to have hyperglycemia during pregnancy. It is generally found in 2-4% of all pregnant women, having a higher incidence in populations with high prevalence of diabetes. As the diabetes prevalence is 13.7% among the individuals older than 20 years of age in our country, Turkish population can be considered as a moderate risk population in terms of GDM, the estimated prevalence is around 4-10%.

Insulin resistance and hyperinsulinemia develop during pregnancy. Insulin resistance is caused by some hormones secreted from the placenta along with maternal hormonal changes. GDM occurs in predisposed women when pancreas functions are insufficient to correct insulin resistance during pregnancy.
15.2.1 | THE RISKS OF GESTATIONAL DIABETES

It has been reported that women who had gestational diabetes have approximately 70% risk of developing diabetes (predominantly type 2 diabetes) 22-28 years after the pregnancy.

The main problems encountered in the expectant mother, fetus and neonate in association with GDM and the potential health-related risks that mother and the child may encounter in the later stages of their lives are summarized below:

- In women with GDM: Hypertension, preeclampsia, C-section risk and permanent diabetes
- Fetus: Macrosomia, birth trauma, shoulder dystocia and perinatal mortality
- Neonate: Hypoglycemia, hyperbilirubinemia, hypocalcemia, respiratory distress syndrome (RD) and polycythemia in the neonatal period
- In late adolescent and adult ages of the child: Obesity, glucose intolerance and diabetes

15.2.2 | DIAGNOSTIC CRITERIA

In all pregnant women, risk assessment and FPG measurements should be performed from the first prenatal examination. For all pregnant women in any of the following high-risk groups (Table 15.4), should be screened for diabetes (preferably 75 g glucose OGTT), even if the FPG is normal and results should be interpreted as in nonpregnant women. If diabetes is not detected, then GDM screening should be performed in the following trimesters.

<table>
<thead>
<tr>
<th>TABLE 15.4: Maternal risk factors for gestational diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of factor</strong></td>
</tr>
<tr>
<td>Maternal demographic and physical factors</td>
</tr>
<tr>
<td>Maternal clinical factors</td>
</tr>
<tr>
<td>Previous obstetric history</td>
</tr>
</tbody>
</table>

PCOS, polycystic ovarian syndrome; HT, Hypertension; GDM, gestational diabetes mellitus.

Globally, GDM screening at 24-28 gestational weeks is recommended for all pregnant women who had no diabetes in the early periods of pregnancy. There is no consensus on the use of GDM diagnostic tests and glucose threshold values. As the practices with one-
step diagnostic approach increase, studies report positive perinatal outcomes and the improvement in pregnancy outcomes is “cost-effective”. However, it is also claimed that one-step approach will make GDM diagnosis easier and cause an increase in the number of pregnant women with GDM, potentially leading to economic and emotional issues. The two- and one-step diagnostic approaches used in GDM diagnosis are described comprehensively in Chapter 1.

In our country, both approaches are being used depending on the preferences of the institution and physician. Obstetricians and majority of the endocrinology specialists mostly use the two-step approach. This is because the 50 g glucose screening step in this method is easy to perform and indicates whether there is CH intolerance in a significant number of patients; thus, further tests are required for many patients. Despite the absence of a consensus on which approach to use, reaching a multidisciplinary agreement on a national or regional basis would be useful to eliminate the uncertainties on the subject (see Chapter 1).

15.2.3 | MONITORING IN GESTATIONAL DIABETES

Pregnant women diagnosed with gestational diabetes should be informed about the short and long term adverse effects of the disease on the baby and their health, the importance of blood glucose monitoring and the treatment to be applied. Medical nutrition therapy counseling should be provided by a dietitian for pregnant women diagnosed with GDM.

All pregnant women with gestational diabetes should be trained on the self-monitoring of blood glucose at home. Glycemic targets are the same for pregnant women followed up with GDM and PGDM diagnoses: FPG and preprandial PG <95 mg/dL, bedtime PG 80-100 mg/dL, postprandial 1-hr PG <140 mg/dL and 2-hr PG <120 mg/dL and A1C level 6-6.5% [42-48 mmol/mol] if possible. Peak postprandial glycemia occurs at 90th minute during pregnancy. It is recommended to utilize FPG and 1-hr PG levels in GDM follow-up.

15.2.4 | TREATMENT OF GESTATIONAL DIABETES

It has been shown that good glucose control by treatment of gestational diabetes to current standards (medical nutrition therapy, exercise and insulin if necessary) reduces maternal and fetal complications. The prevalence of hypertension and preeclampsia has also decreased with GDM treatment.

The main principle of gestational diabetes treatment is nutrition and exercise-based lifestyle modifications. The nutrition program should be prepared according to the targeted weight level and physical capacity of pregnant women as well as by considering the fetal requirements and its extent should allow for achieving targeted normoglycemia without causing ketosis.

If the target glucose levels cannot be reached within two weeks by diet and exercise, it is recommended to start an optimal insulin therapy for the patient. The insulin therapy can be intensified if needed. In GDM, the treatment approach for cases where glycemia targets cannot be reached with lifestyle modifications is similar to that of PGDM. The recommendations on nutrition therapy and the regulation of blood glucose levels during pregnancy and delivery are provided in the “Pregestational diabetes” section in detail.

The insulin requirements of the women with gestational diabetes are generally less than in cases with PGDM and vary according to the degree of hyperglycemia and obesity. Total
dose can change between 0.1-0.5 IU/kg/day. The recommended insulin treatment schedule based on fasting and 1-hr PG levels is shown in Table 15.5.

**TABLE 15.5: Insulin treatment protocol in GDM**

<table>
<thead>
<tr>
<th>FPG (mg/dL)</th>
<th>1-hr PG (mg/dL)</th>
<th>Insulin therapy</th>
<th>Dose (IU/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>105-120</td>
<td>&lt;140</td>
<td>Single dose intermediate-acting at bedtime [NPH/detemir]</td>
<td>0.1-0.15</td>
</tr>
<tr>
<td>&gt;105</td>
<td>120-160</td>
<td>Two times a day, intermediate-acting insulin [NPH/detemir]: 2/3 of the total dose in the morning, 1/3 before the dinner</td>
<td>0.3-0.4</td>
</tr>
<tr>
<td>&gt;120</td>
<td>&gt;180</td>
<td>Multi-dose (basal-bolus) insulin therapy: Intermediate-acting [NPH/detemir] in the morning and evening, Short/fast-acting [crystallized/aspart, lispro] in the morning-noon-evening</td>
<td>0.5</td>
</tr>
</tbody>
</table>

FPG, Fasting plasma glucose; 1-hr PG, Postprandial plasma glucose 1-hr after the meal; NPH, Neutral Protamine Hagedorn.

**15.2.5 | POSTPARTUM APPROACH**

Postpartum blood glucose monitoring should be performed for women with gestational diabetes and 75-g glucose standard OGTT screening is recommended between 4-12 weeks in postpartum period even if the values are back to normal range (A1C is also recommended for suspected cases). These women have high risk of developing type 2 diabetes in the future. Individuals with GDM history and HbA1C >5.7% (39 mmol/mol) should be included in lifestyle modification programs (healthy nutrition, ensuring weight loss if necessary and increasing the physical activity level). These precautions can decrease the risk of progression to diabetes. The risk of progression to diabetes decreases by 35% in women with GDM history who are followed up for 10 years with lifestyle modifications, and it has been shown that this risk can be decreased by 40% with the addition of metformin to the lifestyle modifications. For women with a history of GDM, it is recommended to perform diabetes screening every 1-3 years by using any method. Women who have been previously diagnosed with GDM should be evaluated for DM when they are planning a pregnancy again.

**SEMT APPROACH AND RECOMMENDATIONS**

1. **In type 1 or type 2 diabetic women with PGDM, counseling should be provided in the reproductive ages (A):**
   - A safe contraceptive method should be recommended for sexually active diabetic women who do not want pregnancy (A).
   - Women with diabetes should be informed about the necessity of planned pregnancy and the importance of glycemic control (B).

2. **In order to reduce pregnancy-related adverse outcomes / risks in all women with type 1 and type 2 diabetes who plan to conceive, the following measures should be applied before pregnancy:**
   - Women with diabetes should be assessed before pregnancy in terms of nutrition program and optimal diabetes treatment, additionally, they should be monitored by a multidisciplinary pregnancy team or such a team should be consulted in order to mitigate the potential risks for the mother and the neonate (B).
• Glycemic control must be achieved prior to conception. Optimal A1C should be ≤6.5%; if hypoglycemia risk is not high and the patients is educated then the A1C target can be 6%. However, A1C <7% is adequate for patients with severe/recurrent hypoglycemia risk (B).
• Prior to conception, OAD drugs should be discontinued and insulin treatment should be initiated for women with type 2 diabetes who plan to conceive (D).
• Potentially teratogenic drugs (ACE-I, ARB, statin, diuretic, etc.) should be discontinued prior to pregnancy (B).
• If the patient is smoking, necessary assistance should be provided for cessation (C).
• Patients should be informed about potential adverse outcomes (spontaneous abortus, congenital malformation, preeclampsia or progression of the existing retinopathy, etc.) that may occur during pregnancy (C).
• At least 3 months before the pregnancy 5 mg/day folic acid should be started (C).
• Patients should be examined by an ophthalmologist before conception (B).
• Nephropathy screening tests (urinary albumin/creatinine) should be performed (B); if there is microalbuminuria or overt nephropathy, then optimal glycemic and BP control must be achieved in order to prevent maternal and fetal complications (B).
• TSH and if needed other thyroid function tests should be performed before pregnancy (C).

3. The following approach should be employed to achieve glycemic control during pregnancy and to successfully complete the pregnancy:

• Nutrition counseling should be provided during the pregnancy for type 1 and type 2 diabetes patients and starting from the diagnosis for women with GDM (C).
• The weight gain target for the pregnancy period should be determined based on the pre-pregnancy BMI (D).
• In cases with pregestational diabetes and GDM, fasting and postprandial (pre-prandial and at night, if needed) SMBG should be performed at least 3 times a week (C). Especially for the glycemic monitoring of the GDM cases, 1-hr PPG should be preferred (D).
• Glycemic targets: Fasting and preprandial PG <95 mg/dL, 1-hr PG <140 mg/dL, 2-hr PG <120 mg/dL and A1C should 6-6.5% (A).
• Basal-bolus (multi-dose) intense insulin or CSII therapy should be used during pregnancy for type 1 diabetic pregnant women (A).
• OAD drugs are not recommended for the duration of pregnancy. Insulin therapy should be started for women with type 2 diabetes who get pregnant without planning (D).
• BP targets should be 120-160 mmHg systolic and 80-105 mmHg diastolic during pregnancy (B).
For pregnant women with hypertension, drugs known to be safe for pregnancy [metildopa, calcium channel blocker (diltiazem), labetolol, hydralazine, clonidine, prazosin etc.] should be used (B).

For pregnant women with type 1 and type 2 diabetes, low dose aspirin (60-150 mg/day) should be used starting from the 1st trimester and continued until the birth in order to lower the risk of preeclampsia (A).

Patients should be examined by an ophthalmologist in every trimester (B).

In every trimester, nephropathy screening tests (serum creatinine, eGFR, urinary albumin/creatinine) should be performed (B); if there is microalbuminuria or overt nephropathy, then optimal glycemic and BP control must be achieved in order to prevent maternal and fetal complications and delay the progression of nephropathy (B).

5 mg/day folic acid should be administered until the 12th week of gestation (C), and it should be maintained by lowering the dose to 0.4-1 mg/day from the 12th week of gestation (C).

4. The following precautions should be taken to ensure a problem-free postpartum period:

- Nutrition counseling should be provided during the pregnancy for type 1 and type 2 diabetes patients and starting from the diagnosis for women with GDM and continued in the postpartum period (D).
- Breastfeeding should be started as soon as possible after the birth, and it should be encouraged to breastfeed the infant for at least 6 months (D).
- Folic acid should be continued for 6 weeks after the delivery (for the duration of breastfeeding for breastfeeding women) at a dose of 0.4-1 mg/day (C).
- Patients should be examined by an ophthalmologist in the first postpartum year (B).
- Women with type 1 diabetes should be monitored in terms of postpartum thyroiditis, and TSH should be measured at postpartum 6th week (D).

REFERENCES
Hypertension is a very common disease in the adult population. Therefore, it is possible that the patient with diabetes may have HT incidentally.

- In type 2 diabetes patients, HT is generally seen as a component of “metabolic syndrome”. HT is often present prior to the development of diabetes in these cases. These cases are generally accompanied by central obesity and dyslipidemia, other components of metabolic syndrome.
- In patients with type 1 diabetes, HT usually occurs as a result of the development of nephropathy and contributes to further progression of nephropathy.

16.1.1 OTHER CAUSES OF HYPERTENSION IN PATIENTS WITH DIABETES

In every HT case, secondary causes should be investigated based on the clinical and laboratory characteristics. The following are the possible causes in a diabetic patient diagnosed with hypertension:

I. Essential hypertension
II. Secondary hypertension
   1. Renal parenchymal diseases
      • Primary glomerulopathies, pyelonephritis, etc.
      • Diabetic nephropathy
   2. Renal vascular diseases
   3. Endocrine causes
      • Obesity, metabolic syndrome, sleep-apnea syndrome
      • Other endocrine causes (hyperaldosteronism, Cushing’s disease/syndrome, acromegaly, pheochromocytoma)
   4. Drugs that may increase the diabetes risk
      • Corticosteroids, oral contraceptives, beta blockers, thiazide diuretics,
sympathomimetic agents, atypical antipsychotics, herbal products (ephedra, ginseng, licorice root etc.)

16.1.2 | CO-EXISTENCE OF DIABETES AND HYPERTENSION

The following factors explain why hypertension is more common in type 2 diabetes patients:

- Central obesity
- Albuminuria
- Atherogenic lipid profile (low HDL cholesterol, high triglyceride and small density LDL cholesterol)
- Hyperinsulinemia and insulin resistance
- Endothelial dysfunction
- Hyperuricemia
- Increased inflammation indicators (e.g., CRP)
- Disappearance of nocturnal decrease in BP (non-dipper)
- Left ventricular hypertrophy
- Early onset coronary artery disease (CAD)

16.2 | BLOOD PRESSURE TARGETS

According to “Turkish Consensus Report on Hypertension” prepared in 2015 by the members of Turkish Society of Cardiology (TKD), Turkish Association of Internal Medicine (TIHUD), Society of Endocrinology and Metabolism of Turkey (SEMT), Turkish Society of Nephrology (TND) and Turkish Society of Hypertension and Renal Diseases, hypertension (high BP) is defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg in adults (>18 years of age) as measured by a physician with standard measurement method. Systolic BP is particularly important and it is essential for diagnosis in most patients. BP has been reported to be acceptable up to 150 mmHg in patients older than 80 years of age. The classification based on BP level in general population is shown in Table 16.1.

**TABLE 16.1: Hypertension classification in the adult population according to Turkish Consensus Report on Hypertension**

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mmHg)</th>
<th>Diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Normal</td>
<td>130-139</td>
<td>and/or</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>and/or</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>160-179</td>
<td>and/or</td>
</tr>
<tr>
<td>Stage 3 Hypertension</td>
<td>≥180</td>
<td>and/or</td>
</tr>
<tr>
<td>Isolated Systolic Hypertension</td>
<td>≥140</td>
<td>and</td>
</tr>
</tbody>
</table>

**Blood pressure targets in hypertensive diabetics:** BP targets should be individualized in a diabetic patient with hypertension. The primary BP target should be <140/90 mmHg. Especially in individuals with high CV risk, if it can be safely reduced, achieving BP <130/80 mmHg levels will provide additional benefit. However, it is important to avoid hypotension. The safe lower limit of BP should be 120/70 mmHg. Levels lower than this threshold should be avoided. Similarly, systolic BP 130-139 mmHg should be considered sufficient in patients 65 years and older.
16.3 | CLINICAL EVALUATION OF DIABETES PATIENTS WITH HYPERTENSION

Arterial BP should be measured and recorded at each outpatient clinic examination. Patients with high BP should be asked to perform BP monitoring at home. It is important to apply standard approaches during both outpatient clinic and home measurements. In the diagnosis of HT, no laboratory method other than BP measurement is used. Therefore, measurement should be carried out very carefully and in accordance with standards. The person to be measured should be sitting for the last 5 minutes prior to test, both feet should be on the floor and the arm to be measured should be supported by keeping it at heart level. The sleeve cuff size should be appropriate for the upper arm circumference. If the BP is high, then the patient should be told to monitor BP at home and the BP measurement should be repeated on the next visit while the self-monitoring results are being evaluated.

Blood pressure monitoring at home: Blood pressure monitoring at home is a method that is useful for the differential diagnosis of “white coat HT” (BP values high at the clinic, normal at home) or “masked HT” (BP values normal at the clinic, high at home), and for monitoring the response to and compliance with the treatment.

In addition, especially for the determination of postural changes related to autonomic neuropathy in the elderly patients, blood pressure and heart rate measurement both in lying and standing positions is a valuable examination method.

After diagnosing and staging based on repeated measurements at outpatient clinic and home (Table 16.1), it is essential to investigate whether HT is associated with a secondary cause and if there is HT-related tissue damage. These investigations begin with a careful history (BP severity, accompanying clinical presentations, presence of attacks, previous illnesses, drug history, etc.). Other accompanying cardiovascular (CV) risk factors (smoking and use of other tobacco products, sedentary life, overweight or obesity, etc.) should be inquired during the history. Then, potential secondary causes and complications are screened with physical examination. Height and weight measurements, cardiac and pulmonary sounds, peripheral pulses, thyroid gland examination, murmur in the renal artery tracing and fundus oculi examination should be performed within the scope of physical examination. For the screening of secondary causes and complications, as indicated by the data obtained through history and physical examination, the last step is the necessary laboratory tests. Laboratory tests to be required from a diabetic patient diagnosed with HT are given below:

- ECG (left ventricular hypertrophy, ischemic changes, arrhythmia)
- Tele-radiography (size of the cardiac silhouette, left ventricular hypertrophy)
- Urinary assay
- Biochemical analyses (urea, creatinine, eGFR, electrolytes, fasting lipid profile, A1C, uric acid)
- Albumin/creatinine ratio in the spot urine (UACR)
- Fundus oculi examination
- Echocardiography (left ventricular hypertrophy, ischemic dyskinesia)
- Advanced tests if needed (glomerular filtration rate, abdominal ultrasonography, urine catecholamines, aldosterone, plasma renin activity, cortisol, etc.)

16.4 | TREATMENT

As shown in Figure 16.1, according to the general approach recognized by SEMT, the target in diabetic HT patients should BP ≤140/90 mmHg. In eligible cases without severe hypotension risk, BP targets that are as low as the patient can tolerate (≤130/80 mmHg) should be considered.
16.4.1. **NONPHARMACEUTICAL TREATMENT**

- Nonpharmaceutical treatment contains lifestyle modifications, including nutritional therapy aimed at weight loss, restriction of salt, tobacco and alcohol consumption, and exercise programs.
- If systolic BP is 130-139 mmHg or diastolic BP is 80-89 mmHg, then lifestyle modification and behavioral treatment should be performed for a maximum of 3 months.
- During the treatment process, initially, lifestyle modifications should be planned and applied.
- HT is associated with obesity and salt intake.
- BP decreases with weight loss and salt restriction.
- It is recommended to increase the consumption of fresh vegetables, fruits, and low-fat products (e.g., DASH diet).
- For the nutrition of a diabetic individual with HT, recommended Na⁺ amount <2.3 g/day (as salt 5-6 g/day), K⁺ amount >5.9 g/day.
- There is not enough scientific data on the benefit of Ca²⁺ and Mg²⁺ supplementation in hypertensive individuals.
- An active daily life has many benefits. Besides, moderate intensity, ≥3 days a week, 30-
60 minutes of dynamic activities (walking, slow-paced running, cycling, swimming, etc.) per day, is recommended. Exercise should be appropriate to the person’s habits and sustainable.

- Weight loss has an important role among the lifestyle modifications. According to TEMD study, 90% of the type 2 patients with diabetes in Turkey are either overweight or obese. In these patients, even 5% of weight loss can provide improvements in BP levels. Achieving 10% sustainable weight loss significantly increases the chance of reaching the BP levels. Weight loss should be ensured if BMI >25 kg/m² in HT patients.
- Waist circumference should be <102 cm in men and <88 cm in women. According to TEKHARF, TURDEP-II and Metabolic Syndrome studies conducted in Turkey in the past two decades, the normal waist circumference specific to Turkish society is <96 cm in men and <90 cm in women.
- Achieving weight loss increases the efficacy of pharmaceutical treatment.
- A healthy and balanced social life, adequate sleep time and stress management are crucial for healthy BP and glycemia control.
- It is recommended to use relaxation methods for stress management and decrease alcohol consumption (maximum 4 units/week for men, 2 unit/week for women).

### 16.4.2. PHARMACEUTICAL TREATMENT

- Drug therapy should be initiated if the target BP levels cannot be achieved despite the lifestyle modifications and behavioral training.
- If white coat hypertension is suspected, 24-hour monitoring is recommended.
- If systolic BP ≥140 or diastolic BP ≥90 mmHg, then lifestyle modifications and medical treatment should be initiated simultaneously.
- There are six main groups of anti-hypertensive drugs with proven benefits in treatment of hypertension. These are angiotensin converting enzyme blockers (ACE-I), angiotensin receptor blockers (ARB), diuretics (thiazide group and similar), calcium channel blockers (CCB), β-blockers and mineralocorticoid receptor antagonist (aldosterone antagonist) drugs.

Advantages and disadvantages of the drugs to be used in HT treatment of diabetic patients are summarized in Table 16.2. These should be carefully reviewed for each case.

#### TABLE 16.2: Drug treatment in diabetic hypertension

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>Inexpensive</td>
<td>Hyperglycemia, dyslipidemia, sexual dysfunction</td>
</tr>
<tr>
<td>β-blocker</td>
<td>Inexpensive, proven benefit after MI</td>
<td>Can suppress hypoglycemia symptoms, sexual dysfunction</td>
</tr>
<tr>
<td>ACE-I</td>
<td>Specific efficacy in nephropathy</td>
<td>Coughing, hyperkalemia</td>
</tr>
<tr>
<td>ARB</td>
<td>Specific efficacy in nephropathy</td>
<td>Expensive</td>
</tr>
<tr>
<td>CCB</td>
<td>Effective</td>
<td>Edema</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers.

HT treatment algorithm for diabetic patients is shown in Figure 16.1. According to this:

- Monotherapy is started in patients with BP <160/100 mmHg.
- The most important factor that determines the primary drug selection in HT patients with diabetes is the presence of albuminuria.
**In patients who do not have albuminuria, either one of ACE-I, ARB, diuretic or dihydropyridine group may be started.**

**In patients with albuminuria, ACE-I or ARB group drugs that blocks the renin-angiotensin system (RAS) are recommended.**

**ACE-I has been shown to delay progression to clinical nephropathy in adults with type 1 diabetes with persistent albuminuria, with or without HT.**

**In the presence of HT in type 2 diabetes patients, ACE-I or ARB use is thought to potentially delay the progression of microalbuminuria.**

**ARBs delay the progression to end-stage renal failure in type 2 diabetic HT patients with macroalbuminuria or clinical renal failure (serum creatinine >1.5 mg/dL).**

**If a RAS-blocker drug is not tolerated, then it should be changed with another.**

**In patients with baseline BP ≥160/100 mmHg, a combination therapy including one ACE-I or ARB group and one diuretic or CCB group should be initiated. In suitable cases, fixed dose, ready-mixed (e.g., diuretics in combination with ACE-I or ARB) preparations may be preferred.**

**β-blockers can be used in patients with myocardial infarction (MI) history, active angina or heart failure. Except these conditions, β-blockers have not been shown to reduce mortality when used to reduce BP.**

**If BP targets cannot be reached with dual combination (e.g. ACE-I + diuretic) treatment, then a third drug (CCB from dihydropyridine) should be added to the treatment.**

**ACE-I and ARB combination should not be used.**

**BP control becomes more difficult with longer duration of hypertension. Several studies have shown that 3.2 different drugs should be used on average to reach the target values in HT treatment of patients with diabetes.**

**In cases where HT cannot be controlled with the addition of the third drug, then a mineralocorticoid receptor antagonist (e.g., spironolactone) should be added and secondary hypertension causes should be investigated.**

**Resistant HT: Despite the administration of three types of antihypertensive (provided that one is a diuretic) if BP is still ≥160/100 mmHg, then noncompliance with treatment, white coat HT and secondary causes should be excluded. If elevated BP persists despite these are excluded, then the condition is considered as resistant HT.**

**In resistant HT cases, HT can be controlled with the addition of spironolactone. This approach decreases albuminuria, and can provide additional CV benefits.**

**When mineralocorticoid receptor antagonist (e.g., spironolactone) is used in combination with ACE-I or ARB, the risk of hyperpotassemia and renal dysfunction may increase. Therefore, it requires close monitoring of serum creatinine and K levels.**

**In elderly patients with good functional and mental capacity, BP target and treatment approach should be similar to those in young adults, and BP target should be <150/90 mmHg in elderly patients with restricted functional/cognitive capacity and treatment decision should be made based on the risk/benefit balance.**

### 16.4.3. Hypertension and Its Treatment in Pregnancy

**In pregnant women with chronic HT and diabetes, the BP target of 120-160/80-105 mmHg should be considered optimal to prevent long-term health problems and to reduce the risk of fetal growth retardation.**

**ACE-I and ARB are contraindicated as they may cause fetal damage.**

**Chronic diuretic use may impair utero-placental perfusion by reducing maternal plasma volume.**

**Methyldopa, labetalol, diltiazem, clonidine and prazosin are safe and effective drugs for use in pregnancy.**
<table>
<thead>
<tr>
<th>SEMT RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> BP should be measured at every visit. The measurement should be repeated on another day if BP &gt;140/90 mmHg. High values in home measurements also confirm the diagnosis (B).</td>
</tr>
<tr>
<td><strong>2.</strong> In diabetic patients with HT, systolic and diastolic BP target should be &lt;140 and &lt;90 mmHg, respectively (A).</td>
</tr>
<tr>
<td><strong>3.</strong> Lower BP targets (&lt;130/80 mmHg) can be determined for individuals with high CVD risk (C).</td>
</tr>
<tr>
<td><strong>4.</strong> Diabetic patients with HT should be ensured to perform BP monitoring at home (B).</td>
</tr>
<tr>
<td><strong>5.</strong> In pregnant women with known diabetes and HT, the BP target of systolic 120-160 mmHg and diastolic 80-105 mmHg has no adverse effects on the maternal health and the growth/development of the infant in the long term (D).</td>
</tr>
<tr>
<td><strong>6.</strong> The threshold to start antihypertensive treatment is BP &gt;160/105 mmHg in pregnancy (C).</td>
</tr>
<tr>
<td><strong>7.</strong> To lower BP, lifestyle modifications (e.g., DASH diet, reaching and maintaining the ideal weight, restricting the sodium intake, increasing the potassium intake and lowering alcohol consumption) should be initiated simultaneously with pharmaceutical interventions (B).</td>
</tr>
<tr>
<td><strong>8.</strong> If BP is ≥140/90 mmHg in diabetic patients without chronic kidney disease or persistent albuminuria, treatment can be started with either one of ACE-I, ARB, CCB or diuretic groups (A).</td>
</tr>
<tr>
<td>- If BP targets cannot be reached with monotherapy, then additional antihypertensive drugs should be added (B).</td>
</tr>
<tr>
<td>- Multi-drug treatment is generally required for patients with diabetes. However, ACE-I and ARB group drugs should not be used in combination (A).</td>
</tr>
<tr>
<td><strong>9.</strong> In diabetic patients with persistent albuminuria, ACE-I or ARB is recommended as first drug (A).</td>
</tr>
<tr>
<td>- If BP is ≥140/90 mmHg despite the lifestyle modifications, ACE-I or ARB, additional antihypertensive drugs should be used to achieve target BP values (B).</td>
</tr>
<tr>
<td><strong>10.</strong> In patients treated with ACE-I, ARB or diuretics, eGFR (calculated based on serum creatinine) serum K should be measured once a year (B).</td>
</tr>
<tr>
<td><strong>11.</strong> If confirmed BP ≥160/100 mmHg during clinical examination, dual antihypertensive drugs (e.g., fixed combination) should be started in addition to lifestyle modifications, and it should be titrated until the targets are achieved (A).</td>
</tr>
<tr>
<td><strong>12.</strong> Mineralocorticoid receptor antagonist (e.g., spironolactone) may be added to the treatment of patients for whom BP targets cannot be achieved despite the triple antihypertensive treatment (A).</td>
</tr>
<tr>
<td><strong>13.</strong> BP targets and treatment selection for elderly patients with good functional and mental capacity should be similar to those in young adults (A). BP target should be &lt;150/90 mmHg in elderly patients with restricted functional/cognitive capacity (A) and treatment decision should be made based on the risk/benefit (D).</td>
</tr>
<tr>
<td><strong>14.</strong> The treatment drug should be switched to methyldopa, nifedipine or labetalol in women with HT and diabetes who plan for pregnancy or already pregnant (C). ACE-I and ARB are contraindicated in pregnancy (C).</td>
</tr>
</tbody>
</table>
REFERENCES

17 | DYSLIPIDEMIA AND ITS TREATMENT IN DIABETES

17.1 | DEFINITION OF DIABETIC DYSLIPIDEMIA

Diabetic dyslipidemia (atherogenic dyslipidemia) is a characteristic lipid disorder of type 2 diabetics developing as a component of metabolic syndrome. Lipid profile is generally found to be normal in type 1 diabetes if the glycemic control is good (LDL cholesterol and triglyceride levels are closer to lower limits and HDL cholesterol is closer to upper limit). In patients with type 2 diabetes, LDL cholesterol levels are similar to those of nondiabetic individuals; however, triglyceride levels are higher and HDL cholesterol levels are lower.

The main problem in diabetic dyslipidemia is the overproduction of VLDL cholesterol in the liver due to insulin resistance. Even if the LDL cholesterol levels are normal in these patients, small density LDL particles with atherogenic characteristics are increased. Also, HDL particles are small density particles rich in triglycerides, and the anti-atherosclerotic and anti-oxidant effects of these HDL particles are weak.

Patients with diabetic dyslipidemia have increased postprandial triglyceride levels. Elevation of postprandial triglycerides increases the risk of atherosclerotic cardiovascular disease (ASCVD). Since the main problem related to the lipoprotein dysfunction, it is difficult to demonstrate the atherogenic lipid profile by using conventional serum lipid measurements. The ideal indicators that reflect the atherogenic lipid profile in these cases are the increase in Apo-B and non-HDL cholesterol levels.

Atherogenic lipid profile observed in type 2 diabetes onsets years before the diagnosis of diabetes. Poor glycemic control leads to further worsening of the lipid profile. Achieving glycemic control is very important in terms of controlling the atherogenic lipid profile. However, even with good glycemic control, atherogenic dyslipidemia persists in many cases of diabetes, and lipid-lowering treatment is indicated in these cases.

17.2 | LIPID TARGETS

Conventionally, the following optimal lipid levels should be targeted. However, in recent years, risk evaluation has become more prominent instead of lipid levels.

- LDL cholesterol <100 mg/dL
- Triglyceride <150 mg/dL
- HDL cholesterol for men ≥40 mg/dL (for women ≥50 mg/dL)
- Non-HDL cholesterol <130 mg/dL

Lipid profile should be requested at the first medical evaluation during the diagnosis of diabetes in patients not using statin, and then every 5 years in patients under 40 years of age and more frequently in patients over 40 years of age (total cholesterol, HDL cholesterol and triglyceride measurement), and also non-HDL and LDL cholesterol values should be calculated.
Patients at very high risk: In these cases, the 10-year CV risk of death is greater than 10%. The patients in this group have ASCVD or stage 3-4 chronic kidney disease (CKD) or multiple uncontrolled risk factors. LDL cholesterol should be <70 mg/dL in these patients. To achieve these targets, it is appropriate to use high-potency statins.

Patients at high risk: In these cases, the 10-year CV risk of death is 5-10%. Patients without macrovascular complications, eGFR >60 mL/min/1.73 m² and LDL cholesterol >100 mg/dL and without uncontrolled risk factors were included in this group. LDL cholesterol should be <100 mg/dL in these cases. Statins with intermediate potency can be used primarily for treatment. If the treatment target is not achieved, then statin doses are increased.

In diabetic patients using lipid-lowering drugs, it is recommended to measure lipid profile when the medication is started and 4-12 weeks after the treatment initiation or after dose adjustments, and to monitor the lipid profiles annually if the target cannot be reached.

Other secondary hyperlipidemia causes, such as hypothyroidism, should be investigated especially in patients with high LDL cholesterol.

### 17.3 | DYSLIPIDEMIA TREATMENT

#### 17.3.1. | NONPHARMACOLOGICAL TREATMENT

The adoption of a healthy lifestyle should always be given priority in the treatment of diabetic dyslipidemia. Therefore, regular exercise, weight control and cessation of smoking are very important. LDL cholesterol and triglycerides levels decrease with non-pharmacological approaches, while HDL cholesterol levels increase. More importantly, lipoprotein functions improve in these cases regardless of the lipoprotein levels.

**Healthy nutrition:** A reduction of 300-500 kcal/day in daily calorie intake will provide weight control in the long term. With weight loss, insulin resistance decreases, and triglycerides levels may decrease by 20-30%. Besides, a slight increase can be achieved in HDL cholesterol levels. The macro nutrient components of the diet have a very important effect on lipid profile. The habit of excessive carbohydrate (CH) consumption is one of the most critical factors causing dyslipidemia in Turkey. CH weighted nutrition decreases insulin sensitivity and increases triglycerides levels. In order to decrease this effect, CH intake should be limited to 45-55%, and CH with low glycemic index and high fiber content should be preferred instead for fast-absorbed refined CH. High-fiber nutrients cause 5-19% decrease in total cholesterol levels and 8-24% decrease in LDL cholesterol levels. Less than 35% of the daily energy intake should be supplied from fats. Otherwise, saturated fat intake would increase, and this would affect lipid profile negatively.

In this context, the intake of dietary omega-3 fatty acids, fibers, herbal stanols, and sterol is recommended to be increased to improve the lipid profile.

**Aerobic exercise:** An average of 3-6 mg/dL increase in HDL-cholesterol levels can be achieved in people who walk 25-30 km per week or do aerobic physical activity. However, the effect of regular physical activity on LDL-cholesterol is limited. Regular exercise increases flexibility, and muscle strength decreases insulin resistance and hsCRP levels and helps to lose weight. And therefore, regular exercise reduces the risk of type 2 diabetes, hypertension, ASCVD, and many other important diseases. Physically active individuals have been found to have low ASCVD chance independently from CV risk factors.
**Cessation of smoking:** ASCVD risk of smokers is two times higher than non-smokers. Smoking decreases HDL cholesterol level. In addition, smokers have elevated postprandial lipid parameters, especially triglycerides, due to increased insulin resistance. HDL cholesterol levels slightly increase in patients who quit smoking. This effect occurs within one month after cessation of smoking.

**Alcohol restriction:** Excessive alcohol consumption increases triglycerides levels. This effect is more overt in patients with high triglycerides levels. Mild amount of alcohol consumption may be acceptable for patients without high triglycerides. This is 20 g/day [2 units] for men and 10 g/day [1 unit] for women.

### 17.3.2. PHARMACOLOGICAL TREATMENT

Achieving the targeted lipid profile in patients with diabetes is often not possible only through lifestyle modifications. Therefore, medical treatment of dyslipidemia required for many cases of diabetes. The exception to this is: Patients with diabetes under 40 years of age, with no other risk factors other than diabetes, no macro and microvascular complications and LDL cholesterol <100 mg/dL. All diabetes patients outside this definition require treatment to achieve target LDL cholesterol levels.

**Statins**

The first choice of drug is statin in diabetic dyslipidemia treatment. Studies on statin revealed that patients with type 2 diabetes benefit greatly from treatment in terms of CV prevention. The risk of 5-year CV event is decreases by 23% with every 40 mg/dL decrease in LDL cholesterol levels achieved with statin treatment. Statins decrease LDL cholesterol levels based on their types and doses. There are three groups of statins used in diabetic dyslipidemia treatment: high-potency statins that decrease LDL cholesterol levels by more than 50%; moderate-potency statins that cause 30-50% reduction and low-potency ones that cause less than 30% decrease in LDL cholesterol levels [Table 17.1]. The drug preference is determined based on the target LDL cholesterol levels. Generally, moderate or high-potency statins are used in treatment based on the risk status of the patients.

<table>
<thead>
<tr>
<th>High-potency statins (LDL chol. &gt;50 % reduction)</th>
<th>Moderate-potency statins (LDL chol. 30-50% reduction)</th>
<th>Low-potency statins (LDL chol. &lt;30% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td>Simvastatin 20-40 mg</td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td>Pravastatin 40-80 mg</td>
<td>Pravastatin 40 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Pitavastatin 2-4 mg</td>
</tr>
</tbody>
</table>

LDL-chol., Low-density lipoprotein cholesterol.

Statin therapy algorithm for patients with diabetic dyslipidemia is shown in Figure 17.1.

Clinicians should consider patient-specific conditions (e.g., side effects, tolerability) and LDL-cholesterol levels when selecting statin therapy and dosing. Maximum tolerable statin dose should be used for patients who cannot tolerate the statin with recommended potency. Use of statin in pregnancy is contraindicated.
In a large-scale meta-analysis conducted in 2010, increased risk of new diabetes development has been reported with statin use for more than four years. Even though there is a small increase in the development of new diabetes, the benefits with statin use would provide for CV event risk appear to be more important.

Non-statin Therapies

Combination therapies may be tried in cases where LDL cholesterol targets are not achieved despite the highest tolerable statin therapy in cases of diabetic dyslipidemia. The first option to consider in this case should be ezetimibe for its low cost. IMPROVE-IT study has shown additional CV benefits with the addition of ezetimibe to statin therapy. If there is statin intolerance (due to muscle pain, myositis, etc.), the dose of statin may be reduced, and ezetimibe may be added to the treatment. If the targets cannot be achieved despite the addition of ezetimibe, proprotein convertase subtilisin/kexin 9 (PCSK-9) inhibitors may be used. The studies conducted with PCSK-9 inhibitors (evolocumab and alirocumab) have shown that they can be used effectively and safely in patients with diabetes and have beneficial effects on CV outcomes.

Fibrate treatment may be considered to lower non-HDL-cholesterol if LDL cholesterol targets are reached, but non-HDL cholesterol levels are still elevated. Non-HDL cholesterol targets are <100 mg/dL for patients with diabetes at very high risk, and <130 mg/dL for other patients with diabetes. This strategy can be important, especially in people who develop CV events or have uncontrolled risk factors in spite of achieving the target levels. However, it should be noted that the evidence in this regard is not very strong. ACCORD and FIELD studies with fibrates revealed no significant benefit at primary CV endpoints. The subgroup
analyses of these studies have shown that CV events are prevented with both fibrate-only treatment and fibrate+statin combination in cases with triglyceride >200 mg/dL and HDL cholesterol <40 mg/dL. In light of this information, using fenofibrate for the combination instead of gemfibrozil is safer and better tolerated when considering the addition of fibrate to statins, The combination of statin with fibrate or niacin is not recommended for dyslipidemia treatment as these combinations have been shown to not change ASCVD outcomes and cause increase side effect risk (myalgia, increased muscle enzymes, rhabdomyolysis, stroke risk with niacin).

In randomized controlled REDUCE-IT study, administration of 4 gr/day (2x2) icosapent ethyl to patients with known CVD or at least one CVD risk factors in addition to diabetes and have controlled LDL cholesterol but mildly-moderately increased triglyceride (135-499; median 216 mg/dL) while receiving statin therapy, has decreased the compound CV outcome (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, coronary revascularization or unstable angina) risk by 25% in comparison to placebo (p<0.001). The study showed 26% lower risk of classic combined CV outcome (CV death, nonfatal MI, or nonfatal stroke) in comparison to placebo, and no difference was found between placebo and icosapent ethyl groups in terms of side effects. It is unknown whether other omega-3 fatty acids have similar effects.

<table>
<thead>
<tr>
<th>SEMT RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diabetic patients must be ensured to follow healthy lifestyle recommendations (building healthy eating habits, reaching normal weight, regular physical activity and cessation of smoking) (A).</td>
</tr>
<tr>
<td>2. Fasting lipid profile should be requested for young adults younger than 40 years of age at the time of diabetes diagnosis, at first medical evaluation and then in every 5 years (total cholesterol, HDL cholesterol, triglyceride measurement and LDL cholesterol calculation) and it should be repeated every 5 years thereafter. More frequent controls are required for patients receiving dyslipidemia treatment (D).</td>
</tr>
<tr>
<td>3. In patients receiving lipid-lowering therapy, the lipid profile should be evaluated 4-12 weeks after initiation of treatment, when dose adjustment is made and thereafter annually (D).</td>
</tr>
<tr>
<td>4. The primary target in dyslipidemia should be lowering LDL cholesterol (A). The secondary target is to reduce non-HDL-cholesterol in high-risk cases where the atherosclerotic event risk persists even though the LDL-cholesterol target is achieved (C).</td>
</tr>
<tr>
<td>5. In patients with high triglyceride or low HDL-cholesterol levels, lifestyle modifications should be intensified and optimal glycemic control should be achieved (C).</td>
</tr>
<tr>
<td>6. High-potency statin therapy should be initiated in all diabetic patients with ASCVD in addition to lifestyle treatment (A).</td>
</tr>
</tbody>
</table>
7. Statin therapy may not be required for patients with diabetes under 40 years of age, have no other risk factors, no macro and microvascular complications and have LDL cholesterol < 100 mg/dL (B).

8. In addition to lifestyle therapy, moderate-potency statin therapy should be initiated in patients younger than 40 years with ASCVD risk factors in addition to diabetes (C).

9. Moderate-potency statin therapy should be initiated in addition to lifestyle modifications in patients with diabetes aged 40 years or older without ASCVD (40-75 years of age: [A]; >75 years of age: [B]).

10. The highest tolerable dose of statin should be used in patients with diabetes who cannot tolerate the recommended statin dose (D).

11. If LDL cholesterol target cannot be reached despite the use of highest tolerable statin dose in diabetic patients with ASCVD, preferably ezetimibe or if needed PCSK9 inhibitors may be initiated in addition to statin (A).

12. Addition of fenofibrate to statin therapy may be useful in selected cases with very high CVD risk where target non-HDL cholesterol levels are not achieved despite the LDL cholesterol targets are achieved (C).

13. Statin therapy is contraindicated in pregnancy (B).

14. If triglycerides level is very high (>500 mg/dL) despite the glycemic control and lifestyle modifications (weight loss, restriction of processed carbohydrates and alcohol) fibrate may be added to treatment to reduce the risk of pancreatitis (C).

15. The outcomes of ASCVD have been shown to not change when fibrate or niacin combination is added to statin in dyslipidemia treatment. It should be noted that the risk of side effect will be increased in combination therapy (myalgia with fibrate, increase in muscle enzymes, rhabdomyolysis, and hemorrhagic stroke with niacin) (A).

16. Addition of icosapent ethyl to the treatment decreases the CV risk in patients whose LDL cholesterol is controlled but have mildly-moderately increased triglycerides (135-499 mg/dL) while receiving statin therapy and have known ASCVD or other cardiac risk factors (A).

REFERENCES


In patients with diabetes, problems related to operation, pregnancy, infection, need for medication due to accompanying diseases and social life (travel, driving, habits, etc.) may disrupt the glycemic regulation.

The treatment and follow-up protocols that should be performed in special conditions encountered by patients with diabetes are summarized here.

**18.1 | DIABETES AND SURGERY**

**18.1.1. | PREPARATION OF DIABETIC PATIENTS FOR SURGERY**

Beyond the common causes in the population, patients with diabetes often undergo surgical procedures for many reasons such as diabetic foot, vitrectomy, cataract, creating arteriovenous (AV) fistula for treatment of end stage renal failure. Glycemic regulation is a major problem in these patients. In addition to the general surgical risks, diabetic patients undergoing surgery may experience issues in four main areas. These issues are summarized below:

1. **Hyperglycemia and ketosis**
   Stress caused by surgery stimulates the secretion of counterregulatory hormones. These hormones reduce the insulin sensitivity and inhibit insulin secretion particularly in patients with insulin deficiency. These changes may accelerate catabolism and rapidly lead to hyperglycemia and ketosis.

2. **Hypoglycemia**
   Perioperative fasting, and long-acting insulin or insulin secretagogue drug (e.g., glibenclamide) administered prior to the operation may cause hypoglycemia. There can be serious consequences for patients who have been given anesthesia or sedation as they will not be able to recognize the warning signs of hypoglycemia or seek help. Therefore, the risk of hypoglycemia should be avoided, especially in elderly patients referred to surgery.

3. **Perioperative complications**
   Infection and myocardial infarction (MI) are common complications in patients with diabetes.

4. **Suboptimal metabolic control**
   Negligence or incomplete application of the protocols to be followed during surgery, inadequate glucose monitoring, and failure to correct obvious deviations are main causes of suboptimal metabolic control.

   It is recommended to maintain plasma glucose (PG) levels around 100-125 mg/dL in the perioperative period. In patients who are susceptible to hypoglycemia due to certain
complications, such as severe autonomic neuropathy or nephropathy, achieving a glycemic target of 120-180 mg/dL is a safer approach.

For adequate regulation during surgery, simple and safe protocols must be created, and all team members must completely learn these protocols (Table 18.1).

**TABLE 18.1: Surgery preparation protocol for patients with type 1 and type 2 diabetes**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1.   | Glycemic control should be obtained in the preoperative period;  
      |   - If the patient undergoes minor surgical procedure using long-acting SU, it must be replaced with short-acting drugs,  
      |   - Patient who will undergo major surgical procedure should be hospitalized 2 days before the operation, and if the patient has type 2 diabetes, medication should be replaced with short-acting forms of insulin. |
| 2.   | Anesthesia consultation should be obtained. |
| 3.   | If possible, operation should be planned in elective conditions and performed in the morning. |
| 4.   | Patients, for whom elective operation is planned, should not have breakfast on the morning of the operation day, not take the non-insulin antihyperglycemic drugs and especially avoid short/fast-acting insulins. Before minor surgeries or short major surgeries, low dose basal insulin can be administered if necessary. |
| 5.   | If minor surgical procedure is planned for patients with type 2 diabetes who do not use insulin, the patient should be monitored with PG measurements in every 2 hours on the operation day. If the patient is capable of meeting at least 50% of their daily calorie orally, has no acute kidney failure, if contrast agent administration is not planned and discharge is scheduled in 24-48 hours following the procedure, then they can return to their routine treatment regimen starting from the first meal after the procedure. |
| 6.   | A standard glucose and insulin (e.g., glucose-insulin-potassium, GIK) infusion protocol should be applied to all patients with type 1 diabetes and for type 2 diabetes patients undergoing major surgical procedures. As an alternative to GIK infusion, insulin infusion and glucose can be administered via separate routes.  
      |   - **GIK solution:** Solution is prepared with 500 ml 5% dextrose + 10 IU short-acting insulin + 10 mmol K (1 vial of 7.5% KCl).  
      |   - The infusion starts at 08:00-09:00 on the day of the operation.  
      |   - Infusion rate is set at 100 mL/hr.  
      |   - Infusion solution is renewed every 5 hours.  
      |   - PG level is measured in every 1-2 hours and infusion rate is adjusted to maintain 100-125 mg/dL. |
| 7.   | GIK infusion continues until the patient starts oral nutrition and then the regular treatment is continued again. If infusion lasts over 24 hours, then Na⁺ and K⁺ should be checked. |

SU, sulphonylurea; PG, plasma glucose; GIK, glucose-insulin-potassium.  
*In patients with high hypoglycemia risk target PG (plasma glucose level) should be 120-180 mg/dL.*

The operation of the patients with diabetes should be planned and performed in elective conditions and in the morning if possible. In recent years, the subject of how to arrange the antihyperglycemic treatment on the day of surgical intervention of the patients undergoing elective operation has gained importance with the discovery and use of novel drugs and insulins. Table 18.2 summarizes the recommended arrangements for antihyperglycemics on the morning of the operation of patients with diabetes who will undergo surgery under elective conditions.

Protocols for glycemia regulation during surgery are different for patients using and not using insulin.

**A. Patients with type 2 diabetes not using insulin**

- In order to reduce hypoglycemia risk, long-acting sulphonylurea (SU) drugs should be replaced with shorter-acting new agents several days prior to the operation.
- Frequent glucose monitoring during minor surgical procedures is adequate in many patients with well-controlled diabetes. However, the anesthesia team should be informed that dextrose-containing fluid should not be administered in these patients during the operation.
- Patients whose diabetes is uncontrolled or who will undergo major surgical intervention should be treated and followed up like patients using insulin.

- In patients using metformin and sodium glucose co-transporter-2 inhibitor (SGLT2-I) it is recommended to stop these drugs at least 24 hours (48 hours if possible) before the surgery and to ensure adequate hydration.

**TABLE 18.2: Treatment plan in the morning of the operation day for patients undergoing elective surgery**

<table>
<thead>
<tr>
<th>Diabetic patient to undergo elective operation</th>
<th>Treatment plan for the morning of the surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Do not administer the drug</td>
</tr>
</tbody>
</table>

**Type 2 diabetes patients with optimal glycemic control**

- No insulin use

- Combination of insulin and noninsulin drug
  - Long/intermediate-acting basal insulin: X
  - Short/fast-acting insulin + noninsulin drug: X

**Type 1 diabetes patients with poor glycemic control**

- Short/fast-acting insulin + intermediate-acting insulin
  - Short/fast-acting insulin: X
  - Intermediate-acting insulin: X

- Short/fast-acting insulin + long-acting insulin
  - Short/fast-acting insulin: X
  - Long-acting insulin at appropriate dose: X
  - Long-acting insulin at inappropriate dose*: X

**Patients using insulin pump**

- Patient not required to used insulin pump in the perioperative period: X (start I.V. insulin infusion)

- Patient required to used insulin pump in the perioperative period**: X (decrease by 25-50% if basal rate is high)

*Indicators of long-acting insulin use at inappropriate dose: Frequent hypoglycemia, especially at night and/or in the morning, decreasing in blood glucose more than 40 mg/dL at midnight, need for snack prior to bedtime in order to avoid hypoglycemia or more than 60% of the insulin need is long-acting insulin.

**Patients required to use insulin pump in the perioperative period: Patients who are used to insulin pump and have good glycemic control, who will undergo an operation shorter than 2 hours and expected to be completed in a short period of time, patients without hemodynamic problems or those whose pump infusion sites are not close to the surgical site.


**B. Type 1 or insulin using type 2 diabetes patients**

- During surgery, both insulin and glucose should be given as continuous infusion. Glucose and insulin infusions reduce intraoperative metabolic disruptions and increase the success of the surgery.

- Glucose and insulin can be administered from different veins as well as can be given together as a glucose-insulin-potassium (GIK) solution to avoid hypopotassemia:
18.1.2. **GLUCOSE - INSULIN - POTASSIUM (GIK) INFUSION**

In this common method, glucose and insulin are given together via the same route. This method is practical and safe. Infusion rate is adjusted based on blood glucose level according to the following protocol (Table 18.3):

**TABLE 18.3: GIK infusion protocol**

<table>
<thead>
<tr>
<th>Blood glucose (mg/dL)</th>
<th>Infusion rate (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥280</td>
<td>140</td>
</tr>
<tr>
<td>279-220</td>
<td>120</td>
</tr>
<tr>
<td>219-180</td>
<td>100</td>
</tr>
<tr>
<td>179-120</td>
<td>80</td>
</tr>
<tr>
<td>119-80</td>
<td>60</td>
</tr>
<tr>
<td>&lt;80</td>
<td>Infusion is paused for 2 hours.</td>
</tr>
</tbody>
</table>

GIK solution, glucose-insulin-potassium solution.

Alternatively, if fluid loading poses risk for the patients, infusion can be prepared by adding 20 IU short-acting insulin and 10 mmol KCl into 500 ml of 10% dextrose. In that case, infusion rate is initiated by reducing 50% of the original protocol. The infusion rate is then adjusted based on the PG levels in order to avoid fluid overload through less fluid administration.

18.1.3 **ADMINISTRATION OF GLUCOSE AND INSULIN VIA SEPARATE ROUTES**

500 ml of 5% dextrose solution should be administered at 100 ml/hr rate and insulin should be administered at 2-4 IU/hr rate to maintain blood glucose levels at 100-125 mg/dL (120-180 mg/dL in patients with high risk of hypoglycemia). To prepare the insulin solution, 30 IU short-acting insulin is added into 150 ml of 0.9% NaCl. Insulin infusion should not be administered directly into the vein; it should be delivered via the set of 5% dextrose, and blood glucose level should be checked hourly (Table 18.4). In patients with fluid overloading risk, 10% dextrose solution is preferred instead of 5%.

**TABLE 18.4: Protocol for perioperative insulin and glucose infusion via separate routes**

<table>
<thead>
<tr>
<th>Blood glucose (mg/dL)</th>
<th>Insulin infusion (mL/hr)</th>
<th>Insulin infusion (IU/hr)</th>
<th>5% dextrose (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>1.0</td>
<td>0.5</td>
<td>150</td>
</tr>
<tr>
<td>71-100</td>
<td>2.0</td>
<td>1.0</td>
<td>125</td>
</tr>
<tr>
<td>101-150</td>
<td>3.0</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td>151-200</td>
<td>4.0</td>
<td>2.0</td>
<td>75</td>
</tr>
<tr>
<td>201-250</td>
<td>6.0</td>
<td>3.0</td>
<td>50</td>
</tr>
<tr>
<td>251-300</td>
<td>8.0</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;300</td>
<td>12.0</td>
<td>6.0</td>
<td>0</td>
</tr>
</tbody>
</table>
ENSURING GLYCEMIC REGULATION IN SPECIFIC SURGICAL INTERVENTIONS

Insulin requirements vary during surgical interventions in different clinical settings (Table 18.5).

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Insulin (IU/1 g glucose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal body weight</td>
<td>0.25 - 0.35</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.40</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0.40 - 0.60</td>
</tr>
<tr>
<td>Steroid use</td>
<td>0.40 - 0.50</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.50 - 0.70</td>
</tr>
<tr>
<td>Cardiopulmonary problems</td>
<td>0.90 - 1.20</td>
</tr>
</tbody>
</table>

Glycemia regulation during open heart surgeries

- Hypothermia due to the glucose-rich solutions and inotrope agents used in cardiopulmonary by-pass operations, the insulin requirement is significantly increases.
- For these patients, adequate glycemic control may not be achieved with GIK solution.
- Separate administration of glucose and insulin, and more frequent monitoring of blood glucose (e.g., every 1/2 hours) is required.
- During the operation infusion rate should be maintained at a low level, and soon after the operation it should be immediately increased up to conventional doses.
- It has been proven that GIK infusion used during open-heart surgery reduces the need for inotropic agents, reduces the risk of atrial fibrillation, and shortens the length of hospital stay.

Laparoscopic abdominal surgery

- Metabolic disorders and insulin resistance (e.g., for cholecystectomy) that may occur during such procedures are similar to those seen in open surgery. Therefore, surgical preparation rules should be strictly followed and the same protocols should be used.

Caesarean section (C-section)

- In pregnant women with diabetes using insulin, it is recommended to give glucose and insulin via separate access routes during delivery.
- GIK protocol is simpler and safer if elective C-section is to be performed.
- GIK solution should be prepared by adding 20 IU insulin into 500 ml of 10% dextrose and infusion rate should be adjusted according to blood glucose level.
- $\alpha$-Adrenergic agonists (used to delay the delivery) and corticosteroids (used to accelerate fetal pulmonary maturation) may increase the insulin requirement.
- As the insulin requirement rapidly decreases after the placenta is out, GIK infusion should be stopped but glucose monitoring should be continued.
- If necessary, GIK infusion can be started by decreasing the insulin dose to 1/2 or 1/3, following the delivery.
- When the patient starts oral nutrition, s.c. insulin doses are usually reset to the doses before the pregnancy.
SEMT RECOMMENDATIONS

1. If possible, elective surgery should be performed for patients with diabetes (D).
2. Patients should be consulted with anesthesia department prior to operation (B).
3. Elective surgery should be performed in the morning (D).
4. Patients with poor glycemic control should be admitted to hospital at least 3 days before the surgery and glycemic control must be established by switching to insulin (D).
5. Every institution should have a consensus algorithm on how to adjust insulin and non-insulin antihyperglycemic drugs about the patients undergoing elective surgery, and all departments should apply that protocol (D).
6. Insulin infusion is not required for patients with good glycemic control undergoing minor surgical procedure. Surgery can be performed with frequent plasma glucose monitoring (D).
7. If OADs (particularly metformin, SU or SGLT2-I) are used for patient undergoing major surgical intervention, these drugs should be stopped at least 24 hours before the operation (C).
8. In patients undergoing major surgical intervention, i.v. insulin infusion should be administered starting from several hours before the surgery, and continue during the operation until oral nutrition restarts. Administration of glucose and potassium supplementation within insulin infusion (e.g., Glucose - Insulin - Potassium, GIK infusion) can be beneficial to avoid hypopotassemia and ketosis (C).
9. Insulin and glucose can be administered via separate routes in major surgeries that may last long (e.g., cardiac, plastic and cerebral surgery) (C).

REFERENCES


18.2 | PATIENTS UNDERGOING ENDOSCOPIC PROCEDURE

Endoscopic intervention may be necessary for patients with diabetes due to various indications. Diabetes has a negative effect on gastrointestinal peristalsis. Although hyperglycemia is thought to be responsible for this condition, its effect is controversial. Autonomic neuropathy may also be an important cause of prolonged colon emptying.

- As colon cleansing process will be long with classical protocols in a patient undergoing endoscopy, more potent agents like polyethylene glycol (PEG) is recommended.
In addition to laxatives, it is recommended to have a low-fiber diet for 1-4 days and liquid diet on the last day, before colonoscopy.

In this period, patients should be monitored in terms of hypoglycemia and hyperglycemia, and SMBG should be used more frequently. The protocol to be followed in the colonoscopy preparation according to antihyperglycemic treatment in patients with diabetes is summarized in the “SEMT Recommendations” section below.

**SEMT RECOMMENDATIONS**

1. **Patients treated with only diet do not require additional measures, routine bowel cleansing protocol is applied.** In patients with diabetes, a strong agent such as polyethylene glycol (PEG) is preferred (B) as colon cleansing can be prolonged (A). In addition to laxative use before colonoscopy, it is recommended to have a low-fiber diet for 1-4 days and liquid diet on the last day (D).

2. **In patients using OAD(s), if any, the evening dose should not be used one day before colonoscopy. OAD should not be given also on the day of colonoscopy and the dose should be postponed until after colonoscopy (D).**

3. **The following approach is recommended for the patients using insulin:**
   - If the patient is using OAD combined to insulin, above recommendations should be performed for OAD.
   - The following approach can be used for insulin:
     - Patients using single-dose morning basal insulin should take their routine dose on the day before colonoscopy. On the day of colonoscopy, the routine dose should be administered after the procedure (D).
     - Patients using single dose basal insulin in the evening or night time, should take the half of the dose on the day before colonoscopy. After procedure, the routine insulin dose is performed on the colonoscopy day (D).
     - Patients using two doses of insulin should take their routine morning insulin dose and half of evening/night dose on the day before colonoscopy. On colonoscopy day, the morning insulin dose is canceled and after procedure, the routine insulin dose in the evening is taken (D).
     - Patients using basal-bolus insulin regimens should take their routine morning and noon insulin doses until evening of the day before colonoscopy, not take fast/short-acting insulin in the evening and administer the half of the long-acting insulin dose at night. Fast-acting insulin should not be used in the morning of the day of colonoscopy, and the medication should be switched back to routine insulin program when normal nutrition starts after the procedure (D).

**REFERENCES**

Patients with diabetes may require positron emission tomography/computed tomography (PET/CT) imaging for cancer and other causes. Fluorine 18-fluorodeoxyglucose (18F-FDG) is the most common radioactive isotope used in PET/CT. 18F-FDG is grabbed by the tumor cells via sodium-independent diffusion of glucose. Intense 18F-FDG uptake indicates the presence of neoplastic cells that produce energy especially through anaerobic glycolysis. Glucose and 18F-FDG compete for glucose receptors on the cell membrane. Hyperglycemia decreases the 18F-FDG uptake of tumor cells. Exogenous insulin administration prior to 18F-FDG PET/CT imaging increases the FDG uptake in muscle, fat and liver. Insulin acts on GLUT-4 receptors in striated muscle and adipose tissue whereas it is ineffective on GLUT-1 and GLUT-3 in tumor tissues.

- During the preparation process, patients should be fasting for at least four hours prior to FDG-PET/CT injection.
- If the imaging will be performed towards noon or in the afternoon, the patients can have a light breakfast in the morning provided that there will be a 4-hr fasting window prior to the procedure.
- Hydration should be sufficient before imaging. The patients should be given took one liter of water starting from two hours before the injection. Hydration may also reduce glucose slightly. Other fluids (especially coffee and caffeinated beverages) and solid foods are not to be consumed before the procedure.
- In patients receiving parenteral nutrition, glucose-containing i.v. fluids should be discontinued at least four hours prior to FDG injection.
- Patients should be in a seated or lying position and kept warm during FDG injection and latter stages.
- The bladder should be emptied before PET/CT to prevent bladder activity.
- Before FDG administration, blood glucose level should be measured using a valid glucometer calibrated based on PG levels. Imaging can be performed if PG level is <200 mg/dL. If PG level >200 mg/dL the imaging may be delayed or glycemia can be reduced with short-acting insulin, however, at least 4 hours must elapse between insulin administration and FDG injection.
- Although there is no consensus, some authors recommend correction based on PG level when calculating SUVmax in FDG PET imaging. If such a correction is made, it should be indicated in the report along with the PG level at the time of imaging.

The rules about diabetes drugs in patients undergoing 18F-FDG PET/CT imaging are summarized below.

I. Type 2 diabetes patients using OAD:
- SU group of drugs should be discontinued before imaging as they increase insulin secretion.
- Thiazolidinediones do not affect the imaging procedure.
- Metformin can increase the FDG uptake of the lumen in small intestine and colon images as it reduces glucose output from the liver and increases the uptake and use of glucose in the cell. In this regard, it is recommended to stop metformin at least 48 hours before PET procedure, especially in case of intraabdominal lesions.
- Metformin should also be discontinued 48 hours before the procedure if contrast agent is to be administered.
II. Type 1 diabetic patients and Type 2 diabetic patients using insulin:

For FDG PET/CT imaging in these patients, one of the following approaches should be taken.

- If the imaging is going to take place in the morning, intermediate-acting insulin should be injected the night before instead of long-acting insulin; the patient can continue with his routine insulin doses after the imaging and have breakfast.
- If the imaging is in the afternoon, the patient can have breakfast after injecting his routine fast-acting insulin. FDG can be given at least 4 hours after fast-acting and 6 hours after short-acting insulins. If medium or long acting insulin is performed that day, FDG injection cannot be made.
- In patients that use pumps, imaging should preferentially take place in the morning. The pump should be turned off at least 4 hours before FDG injection. The patient can turn on the pump after the imaging and have breakfast.

SEMT RECOMMENDATIONS

1. Patients must have their last meal at least four hours before the 18F-FDG PET/CT procedure (B).
2. Patients are required to have at least 1 liter of fluid two hours before the procedure (D).
3. PG level prior to procedure should be <200 mg/dL (D).
4. In order for FDG injection to be administered, at least four hours must pass after fast-acting insulin and at least six hours after short-acting insulin (D).
5. If intermediate or short-acting insulin injection is performed, FDG PET/CT is not performed on the same day (D).
6. In type 2 diabetes patients using OAD:
   - SU group of drugs should be discontinued 24-48 hours before the procedure (D).
   - Thiazolidinediones do not affect the imaging procedure (D).
   - Metformin may increase FDP uptake in the bowels. Therefore, especially in intraabdominal lesions, it is recommended to be discontinued at least 48 hours before PET procedure (A).
   - Metformin should also be discontinued 48 hours before the procedure as the contrast agent may increase the risk of nephropathy (D).
7. In type 1 diabetes patients and type 2 diabetes patients using insulin:
   - Intermediate-acting insulin is used if the imaging is planned for morning. Patients can have routine insulin dose and eat breakfast after the imaging procedure (D).
   - If the imaging is to be performed in the afternoon, the patient can have their routine insulin dose in the morning and eat breakfast (D).
   - Imaging procedure is recommended to be performed in the morning for patients using pump. Pump is turned off at least four hours before FDG injection. After the imaging, the patient can turn on the pump, apply insulin and have breakfast (D).
18.4 | PATIENTS RECEIVING TOTAL PARENTERAL AND ENTERAL NUTRITION

18.4.1 | PATIENTS RECEIVING TOTAL PARENTERAL NUTRITION

Total parenteral nutrition (TPN) may be required in some patients with diabetes in the postoperative period. TPN can lead to very serious metabolic problems if the patient is not properly monitored and treated.

- Treatment should be started with continuous insulin infusion and PG measurement per hour.
- Since TPN solutions contain high levels of glucose, there is no need for additional glucose infusion.
- Initially, insulin infusion should be administered in a separate route from TPN solution.
- Once the insulin infusion dose is adjusted and stabilized (generally 12-24 hours) according to hourly PG measurements, the total insulin dose given in the last 24 hours can be divided into 4 and added to the TPN solution every 6 hours.
- From this point, the PG level should be measured in every 2-4 hours.
- Depending on the patient’s metabolic status and insulin resistance, the required insulin dose for regulation may be >100 IU/24 h.

18.4.2 | PATIENTS RECEIVING ENTERAL NUTRITION

Enteral nutrition may be required for various reasons in diabetic patients. This process must be managed without causing hyperglycemia and hypoglycemia. Insulin therapy is adjusted based on the patient’s weight, diabetes type, and whether the enteral nutrition program is continuous or intermittent.

Basal and nutritional requirements should be taken into account when calculating the insulin dose and correction doses should be administered in every 4-6 hours.

Especially in patients with type 1 diabetes, basal insulin should not be discontinued and adjustments should be made by using fast/short-acting insulin based on glucose monitoring as long as the enteral nutrition continues.

In a randomized controlled trial of hospitalized patients receiving enteral nutrition, the treatment program including low-dose insulin glargine and short-acting analog (Lispro, Aspart or Glulisine) insulin with sliding scale correction doses had similar efficacy to NPH and regular insulin.

Table 18.6 shows the commonly accepted and recommended approach by ADA for patients with diabetes receiving enteral or parenteral nutrition.
TABLE 18.6: Insulin doses in enteral and total parenteral nutrition

<table>
<thead>
<tr>
<th>Solution</th>
<th>Basal/nutritional</th>
<th>Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous enteral nutrition</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| BASAL             | • Maintain the previous basal dose or calculate based on TID (Basal dos = 30-50% x TID).  
• If there is no prior insulin use then start 2 x 5 IU NPH/Detemir or 1 x 10-12 IU Glargine.  
NUTRITIONAL       | • Regular insulin s.c. every 6 hours or short-acting analog insulin [Lispro, Aspart or Glulisine] s.c. every 4 hours. |
|                   | • By calculating 1 IU insulin for 10-15 g CH; start regular insulin in every 6 hours or short-acting analog insulin (Lispro, Aspart or Glulisine) in every 4 hours. Start 1 IU insulin for 10-15 g CH, adjust daily. |
| **Bolus enteral nutrition** |                                                                                |                                                                                               |
| BASAL             | • Maintain the previous basal dose or calculate based on TID (Basal dos = 30-50% x TID).  
• If there is no prior insulin use, start 2 x 5 IU NPH/Detemir or 1 x 10-12 IU Glargine.  
NUTRITIONAL       | • Regular insulin s.c. every 6 hours or short-acting analog insulin s.c. [Lispro, Aspart or Glulisine] every 4 hours. |
|                   | • By calculating 1 IU insulin for 10-15 g CH; start regular insulin or short-acting analog insulin (Lispro, Aspart or Glulisine) s.c. before each meal time, adjust the dose daily. |
| **Parenteral nutrition** |                                                                                |                                                                                               |
| DIRECT ADDITION   | • By calculating 1 IU for 10 g CH (dextrose) add regular insulin directly into TPN IB solution and adjust insulin doses daily. | • Regular insulin s.c. every 6 hours or short-acting analog insulin s.c. [Lispro, Aspart or Glulisine] every 4 hours. |

s.c., subcutaneous; TID, daily total insulin dose; IU, international unit; CH, carbohydrate; TPN, total parenteral nutrition.

SEMT RECOMMENDATIONS

1. Patients who will receive TPN:
   • Initially, insulin infusion should be administered in a separate route from TPN solution (D).
   • In the first 24 hours, once the insulin infusion dose is adjusted and stabilized according to hourly PG measurements, the total insulin dose given in the last 24 hours can be divided into 4 and added to the TPN solution every 6 hours (D).

2. Patients who will receive enteral nutrition, basal and nutritional requirements should be taken into account when calculating the insulin dose and correction doses should be administered in every 4-6 hours (D).
   • In patients who have previously used insulin, the previous basal dose may be maintained or basal insulin may be decreased to achieve a dose that is 30-50% of total daily insulin dose (TID) (D).
   • If enteral nutrition will be used for type 2 diabetes patients who have not used insulin before, 2x5 IU NPH/detemir or 1x10-12 IU glargine may be started for basal insulin requirement (C).
• In enteral nutrition, nutritional insulin requirement is calculated as 1 IU insulin for 10-15 gr of CH and readjusted daily (D).

• Insulin correction doses: Met by using short-acting insulin (lispro, aspart or glulisine) in every 4 hours or s.c. bolus regular insulin in every 6 hours (A).

REFERENCES

18.5 | HYPERGLYCEMIA TREATMENT IN PATIENTS IN HOSPITAL AND INTENSIVE CARE UNITS

Hospitalized patients: All diabetes patients admitted to hospital for any reason should have written diabetes diagnosis in their medical records, blood glucose monitoring should be requested and the results should be available to health personnel.

• In non-critical patients, glycemic targets should be adjusted on an individual basis according to the condition of the patient’s diabetes and other concomitant diseases.

• Blood glucose levels should be closely monitored in all patients without diabetes but who use medications that increase the risk of hyperglycemia.

• Every hospital, even every department, should develop and implement a unique protocol for the treatment of hypoglycemia.

• If not examined in the past 3 months, A1C measurement should be requested from all hospitalized diabetic patients and patients with blood glucose levels >140 mg/dL without known diabetes.

• Patients who had no previously known diabetes but had hyperglycemia while hospitalized should be recalled for a control visit 6-8 weeks after discharge and laboratory tests should be repeated.

Intensive care patients: Hyperglycemia treatment is one of the important determinants of mortality and morbidity in previously known diabetes or newly onset diabetes cases followed up in internal and surgical intensive care units. Initially, good outcomes were reported with intensive insulin therapy, especially in patients followed up for acute MI in Coronary Intensive Care Units, however later studies demonstrated conflicting results. However, with the results of NICE-SUGAR and similar studies published in 2009, as a result of the new meta-analyses on the subject, it has been accepted that the glycemic targets should not be strict in order to avoid hypoglycemia episodes that may increase the mortality risk in these patients.
NICE-SUGAR is widest randomized-controlled study to date. In this study, the effects of strict control to keep blood glucose levels within narrow limits (81-108 mg/dL) were investigated in 6104 critically ill patients. Mechanical ventilation was required in 95% of the patients.

- The 90-day mortality was significantly higher in the strict glycemic control group than in the conventional follow-up (target blood glucose level 144-180 mg/dL) group in both surgical and internal intensive care patients (mortality in strict and conventional groups: 27.5% vs 24.2%, p=0.02, difference: 78 more deaths in the strict follow-up group).

- In the strict control group, CV-related deaths were higher (41.6% vs 35.8%, p=0.0276, difference: 76 more CV-related deaths in the strict follow-up group).

- The incidence of severe hypoglycemia episodes was higher in the strict control group (6.8% vs 0.5%; p<0.001).

The results of this study show that it is safe to maintain blood glucose levels in the range of 140-180 mg/dL for critically ill hospitalized patients. However, in selected patients, a tighter target of 110-140 mg/dL can be used if it does not increase the risk of hypoglycemia. Overtreatment and negligence of hyperglycemia is unacceptable in hospitalized patients.

**SEMT APPROACH AND RECOMMENDATIONS**

1. If the nutritional condition and glycemic control are adequate, the treatment of hospitalized and non-serious diabetes patients should not be altered to the extent that the medical condition permits. (D).

2. Patients requiring critical care in the hospital:
   - If PG is higher than 180 mg/dL in patients with persistent hyperglycemia, insulin therapy should be initiated (D).
   - To achieve and maintain glycemic control i.v. insulin infusion should be preferred (D).
   - PG levels should be kept in the range of 140-180 mg/dL in critical care patients receiving insulin therapy (A). However, in some selected patients, a tighter target of 110-140 mg/dL may be considered if it does not increase the risk of hypoglycemia (C).
   - For safety and efficacy, proven protocols with low probability of hypoglycemia should be applied (D).
   - Frequent glycemia monitoring is required to reduce the risk of hypoglycemia and to achieve optimal glycemic control in IV insulin protocols (D).
   - Continuous IV insulin infusion should be applied alone (B) or in combination with glucose and potassium infusion (B) to maintain PG levels around 100-180 mg/dL during bypass graft operation for CAD.
3. Hospitalized patients not requiring critical care
   • Preprandial PG <140 mg/dL and random PG level <180 mg/dL should be targeted in the majority of patients in this group. These targets are easy to achieve and safe (D).
   • Lower (110-140 mg/dL) glycemia levels can be achieved in patients who have previously had strict glycemic control, unless they increase the risk of hypoglycemia (B).
   • It may be sufficient to target higher glycemia levels in patients with terminal-stage or concomitant diseases (D).
   • Pre-planned basal-bolus s.c. insulin therapy that will be applied with correction doses should be preferred instead of sliding scale therapy where only short or fast-acting insulin is applied (A).
   • Non-insulin anti-hyperglycemic agents are not suitable for most hospitalized patients requiring hyperglycemia treatment.
   • In the treatment of hyperglycemia, the clinical condition should be assessed and treatment decision should be made daily.

4. Safety
   • Standard and easily applicable protocols that are specific to department and training of healthcare personnel are necessary for the safe application of hyperglycemia treatment in the hospital and to reduce the risk of hypoglycemia (D).
   • Care should be taken in interpreting the results displayed on bedside glucometers (measuring capillary blood glucose) in patients with conditions such as anemia, polycythemia or hypoperfusion (B).

5. Cost
   • Treatment of hyperglycemia is cost-effective in hospitalized patients (A).

6. Discharge from the hospital
   • Discharge planning, training of the patient and informing the clinic staff are necessary for successful and safe discharge of the patient (D).

REFERENCES
18.6  HYPERGLYCEMIA TREATMENT IN PATIENTS RECEIVING CORTICOSTEROIDS

Some commonly used drugs, especially corticosteroids, cause hyperglycemia in people without diabetes and lead to disruption of glycemic control in patients with known diabetes (Table 18.7).

**TABLE 18.7: Drugs causing hyperglycemia**

<table>
<thead>
<tr>
<th>Strong potency</th>
<th>Mild potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drugs containing low-dose thiazide diuretic (≤12.5 mg/day)</td>
</tr>
<tr>
<td>Contraceptives containing high-dose estrogen</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Levonorgestrel (combination)</td>
<td>ACE-I</td>
</tr>
<tr>
<td>Drugs containing high-dose thiazide diuretic (&gt; 25 mg/day)</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>β₁-adrenoreceptor antagonists</td>
<td>α1-antagonists</td>
</tr>
<tr>
<td>β₂-adrenoreceptor agonists</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Somatostatin analogs</td>
</tr>
<tr>
<td>Ritodrine</td>
<td>SSRI</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
</tr>
<tr>
<td>Other hyperglycemic drugs</td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td></td>
</tr>
<tr>
<td>Streptozotocin</td>
<td></td>
</tr>
<tr>
<td>Diazoxide</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
</tr>
</tbody>
</table>

ACE-I, Angiotensin converting enzyme inhibitors; SSRI, Selective serotonin re-uptake inhibitors; HIV, Human immune deficiency virus.

Hyperglycemia is a common complication of glucocorticoid (corticosteroid) therapy. Hyperglycemia occurs in 20-50% of patients who have no diabetes but use corticosteroids. Glucocorticoids reduce peripheral and partially hepatic insulin sensitivity by affecting post-receptor mechanisms. Insulin response to glucose decreases in OGTT.

- The use of high-dose prednisolone (≥30 mg/day) in patients with known diabetes disrupts glycemic control and increases the need for short-acting insulin. Insulin resistance and hyperglycemia in patients receiving prednisolone over a physiological dose (>7.5 mg/day) may return to normal after discontinuation of the drug.

• There is no consensus on the optimal treatment of hyperglycemia associated with high-dose corticosteroid use. However, it is useful to monitor PG levels for 48 hours after starting steroids.
• OAD or better insulin should be used in case of mild/moderate hyperglycemia due to glucocorticoid.
• Patients with diabetes using high-dose glucocorticoids should switch to insulin.
• In patients with diabetes already using insulin, the dose should be increased (~50%).
• In order to control hyperglycemia, correction doses should be administered together with basal-bolus insulin therapy. Such treatment is safer and more effective than the administration of a sliding scale insulin intended to correct only hyperglycemia. Adding 1-4 doses of NPH per day to the sliding scale insulin administration did not provide additional benefit in correcting hyperglycemia.

Patients on corticosteroids should be instructed on how to reduce steroid doses and regulate insulin therapy when discharged, and should be advised of precautions to avoid hypoglycemia especially when they reduce steroid doses.

**SEMT APPROACH AND RECOMMENDATIONS**

1. **FPG is relatively normal in patients with diabetes using glucocorticoids, however, noon and evening postprandial glycemia levels increase and they may even have hypoglycemia in the morning (D).**

2. **In the treatment of hyperglycemia due to high-dose glucocorticoids, the basal bolus treatment protocol (intermediate/long-acting insulin in combination with short/fast-acting insulin) should be preferred and correction doses should be given according to PG results (D).**

3. **Basal (NPH or detemir) or short-acting insulin may also be required in patients using single-dose steroids (D).**

4. **In patients receiving a steroid dose in the morning, the basal insulin dose taken at night may be switched to morning to prevent hypoglycemia towards morning (D).**

5. **Basal-bolus insulin therapy should be preferred in hospitalized diabetes patients using steroid (D).**

6. **Insulin requirement may increase up to ~50% in patients with diabetes who have previously used insulin (D).**

7. **The success of treatment with OADs (gliclazide, metformin and PIO) is low in patients with newly onset steroid-induced diabetes. It is recommended to switch to insulin treatment immediately (D).**

**REFERENCES**


### 18.7 | DIABETES IN THE ELDERLY

In our country, with the extended life expectancy, the elderly population with diabetes is increasing and the care and treatment of this group poses problems. It is beneficial to classify elderly diabetic patients into three groups for the determination of metabolic control targets:

**1. Healthy elderly:** Glycemic control targets of elderly patients with normal functional and cognitive capacity and have life expectancy (e.g. >10 years) long enough to allow for the utilization of treatment benefits should be as in young diabetes patients: A1C 7-7.5% (53-58 mmol/mol), fasting and preprandial PG 80-130 mg/dl, night PG 90-150 mg/dL and BP <140/90 mmHg. Patients in this group should use statins if there is no contraindication or intolerance.

**2. Elderly patients with mildly/moderately deteriorated health:** Survival is shortened in elderly patients with multiple chronic diseases and mild to moderate cognitive dysfunction. In this group of patients targets should be A1C 7.5-8% (58-64 mmol/mol) fasting and preprandial PG 90-150 mg/dL, night PG 100-180 mg/dL and BP <140/90 mmHg and statin should be used in the absence of contraindications/intolerance.

**3. Elderly patients with well deteriorated health:** Glycemic and metabolic targets should be more flexible in elderly patients with advanced complications, accompanying major cardiac problems, short life expectancy, fragile and limited functional or cognitive capacity. In these patients recommendations are: A1C 8-8.5% (64-69 mmol/mol), fasting or preprandial PG 100-180 mg/dL, night time PG 110-200 mg/dL, BP <150/90 mmHg. In this group of patients, excessive aggressive treatment should be avoided, hypoglycemia prevention should be the main target and treatment should be preferred with uncomplicated, easy to use and simple drugs. Cognitive problems should be evaluated before starting insulin, especially in patients requiring insulin therapy. Statin can only be used for secondary protection in eligible patients in this group.

Low dose aspirin (60-150 mg/day) should be given to patients 65 or older with CVD history. Especially in the follow-up of patients older than 75 years of age, the risk-benefit balance should be considered for the treatment of co-morbid conditions (selection of HT and lipid therapy, administration of aspirin).

**Complication screenings:** It should be kept in mind that complications of diabetes may limit functional capacity and complication screenings should be continued in accordance with current approaches. Comprehensive retinal examination should be performed annually for eye problems related to diabetes or other causes.

However, in patients with very limited life expectancy, since it will not be possible to see the additional benefits of complication screening and early diagnosis, all screening programs may not be required.

**Other problems:** It is recommended that elderly people with diabetes should be evaluated periodically (every 2-3 years) for cognitive dysfunction, malnutrition and sarcopenia. Elderly people with limited cognitive functions should be examined once a year and diabetes treatment should be simplified when cognitive dysfunction is detected.

Sedatives that may increase the risk of falls or drugs that may cause orthostatic hypotension and diabetes drugs that may cause hypoglycemia should be avoided in people with diabetes in this age group. Patients with gait and balance disorders due to peripheral neuropathy or...
vascular disease should be referred to the related department (physical therapy, vascular surgery, podologist, etc.).

Considering the high risk of depression in elderly people, especially those living alone, depression screening and treatment should be performed if necessary.

In addition, seasonal influenza and pneumonia vaccinations should not be neglected in elderly people with diabetes. The SEMT approach and recommendations are summarized below.

<table>
<thead>
<tr>
<th>SEMT APPROACH AND RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>In order to decrease the risk of type 2 diabetes, as with other risk groups, older patients with IGT should be advised to follow healthy lifestyle modifications (slight weight loss, regular physical activity)</strong> (A).</td>
</tr>
<tr>
<td>2. <strong>Elderly individuals who have additional health problems other than type 2 diabetes should be ensured to have metabolic control (glycemia, BP and lipid) targets that are close to those in young type 2 diabetes patients</strong> (D).</td>
</tr>
<tr>
<td>• <strong>Metabolic control targets should be more flexible in elderly patients with various co-morbidities, limited functional capacity, cognitive dysfunction or low life expectancy</strong> (D).</td>
</tr>
<tr>
<td>3. <strong>Elderly patients with diabetes staying in nursing homes or senior centers should be evaluated by different disciplines when necessary</strong> (D).</td>
</tr>
<tr>
<td>4. <strong>If there are no contraindications, elderly patients with type 2 diabetes should be advised to perform mild aerobic exercises and resistance exercises to avoid sarcopenia</strong> (B).</td>
</tr>
<tr>
<td>• <strong>Since the risk of hypoglycemia due to SU drugs increases exponentially with age, it should be avoided to give SU to elderly patients with type 2 diabetes. DPP4-I should be preferred instead of SU in these patients</strong> (D).</td>
</tr>
<tr>
<td>• <strong>If SU is required in an elderly patient, half of the dose used for young patients should be started and should be increased more slowly or alternatively administration of a GLN group drug should be considered</strong> (D).</td>
</tr>
<tr>
<td>• <strong>Controlled release gliclazide (B) and glimepiride (C) which are known to have lower risk of hypoglycemia, should be preferred.</strong></td>
</tr>
<tr>
<td>• <strong>DPP4-I and GLN (repaglinide and nateglinide) drugs may be used in elderly patients with irregular eating habits</strong> (B).</td>
</tr>
<tr>
<td>5. <strong>It should be kept in mind that hypoglycemia risk can be seen with SU; edema, cardiac insufficiency and fracture risks with TZD; pancreatitis with DPP4-I; CI-related hospitalization with saxagliptin; genitourinary infection, dehydration (especially in those using diuretic) and DKA risks with SGLT2-I; and pancreatitis and gastrointestinal side effects with GLP-1A and gastrointestinal side effect can be seen with acarbose.</strong></td>
</tr>
<tr>
<td>6. <strong>Long-term basal insulins and single-use (discarded) insulin pens should be preferred in older patients to prevent insulin dose errors and provide optimal glycemic control</strong> (B).</td>
</tr>
<tr>
<td>7. <strong>Elderly diabetic patients with a history of CVD should be prescribed medications with proven CV safety from the GLP-1A or SGLT2-I groups if clinically appropriate.</strong></td>
</tr>
</tbody>
</table>
8. In diabetic patients younger than 75 years of age who have mildly/moderately decreased kidney functions or heart failure, SGLT2-I group drugs may slow the progression to chronic kidney disease and reduce the risk of hospitalization (C).

9. Patients with diabetes ≥65 years of age should be monitored for depression, neurocognitive functions, and sarcopenia at regular intervals (D).

REFERENCES

• Insulin administration schedule should be changed for long flights.
• During the travel, glucose levels should be measured every 3-4 hours and at time zone changes, and the treatment should be maintained as to keep glycemia at 120-180 mg/dL.

18.8.1. | TRAVELING FOR PATIENTS WITH DIABETES USING INSULIN

1. As generally there won’t be time change on north-south direction (and vice versa) there will be no major changes in meal and insulin injection timings.
2. As the day will be longer on westbound flights
   • Before the flight: Normal dose.
   • During flight: Additional insulin dose if the flight is longer than 8 hours.
   • Upon arrival: Next dose is administered as it is in accordance with the time scheduled for the new local time.
3. As the day will be shorter on eastbound flights
   • Before the flight: Normal dose is reduced.
   • During flight: Glucose is measured, additional insulin can be administered if needed.
   • Upon arrival: Next dose is administered as it is in accordance with the time scheduled for the new local time.

18.8.2. | TRAVELING IN PATIENTS WITH DIABETES NOT USING INSULIN
Short-acting drugs (GLN, etc.) can be safer and thus recommended for long travels.

18.9 | VACCINATION IN PATIENTS WITH DIABETES


18.9.1. | SEASONAL FLU (INFLUENZA) VACCINE

From the age of six months, every patient with diabetes should be vaccinated against influenza once a year. The protection provided by influenza vaccine is short term (6-8 months) particularly in elderly people.

• Influenza vaccines available in Turkey are trivalent and quadrivalent inactivated vaccines. Trivalent vaccines provide protection against two influenza A strains and one influenza B strain, while, quadrivalent vaccines include protection against one more influenza B strain in addition to trivalent vaccines. Therefore they can be preferred.
• The protective effect of the vaccine starts 1-2 weeks after administration and in healthy adults the protection lasts for 6-8 months or longer. In the elderly and immunosuppressed patients, this period is shorter and can be as low as 100 days.
• Considering that flu season starts in November-December and lasts until April-May in our country, it is reasonable to start vaccination in October-November.
18.9.2. **PNEUMOCOCCAL VACCINE**

There are two pneumococcal vaccines (13-valent conjugate pneumococcal vaccine: PCV13 and 23-valent pneumococcal polysaccharide vaccine: PPSV23) available in our country for protection against pneumococcal infections and pneumococcal pneumonia.

- PCV13 should be used in childhood.
- As stronger protection can be provided with dual vaccination between the ages 19-64, it is recommended to administer first PCV13 and at least 1 year later PPSV23. If only single vaccination is possible, then PPSV23 is chosen, or whichever vaccine is available.
- For patients aged 65 or older, first PCV13 and one year later PPSV23 is administered. If the patient had been vaccinated with these before the age 65 and 5 or more years have passed after PPSV23 administration, then PPSV23 vaccination is repeated.

18.9.3. **HEPATITIS B VACCINATION**

Patients with diabetes aged 19-59 who have not been vaccinated before should receive 3 doses of hepatitis B vaccine (HBV). Although the protection provided by the vaccine is lower in diabetic individuals older than 59 who have not been vaccinated before, 3 doses of HBV can be administered.

18.9.4. **OTHER VACCINES**

- Some guidelines recommend the administration two doses of recombinant herpes zoster vaccine (RZV) with an interval of 2-6 months for patients with diabetes aged 50 years and older. In addition, patients with diabetes who will travel to endemic areas should receive region-specific vaccines.

SEMT opinion on the subject is summarized below.

### SEMT RECOMMENDATIONS

1. **Routine vaccination program should be maintained for children with type 1 diabetes** (D).
2. **The complication risk and mortality due to influenza and particularly pneumonia infections is high in people with diabetes** (C).
3. **In order to reduce the risk of influenza-related complications in diabetes patients, influenza vaccines should be administered every year (preferably in October-November)** (B).
4. **People with diabetes are susceptible to pneumococcal infection and at increased risk for the morbidity and mortality of pneumonia. Therefore, they should be vaccinated** (D).
   - 23-Valent polysaccharide pneumococcal vaccine (PPSV23) should be administered to all diabetic individuals aged 19-64 and if dual vaccination is preferred for stronger protection, first PCV13 and then at least 1 year later PPSV23 administration is recommended (D).
   - For patients aged 65 or older, one dose of PCV13 should be administered first, then single dose PPSV23 should be repeated one year later. If the patient was vaccinated with these before the age 65, and 5 years have passed after the PPSV23 administration, it is recommended to repeat PPSV23 vaccination (D).
   - **Pneumococcal vaccine should be repeated in patients with suppressed immune system, nephrotic syndrome, chronic renal failure or transplantation** (D).
5. All patients with diabetes aged 19-59 who haven’t been vaccinated previously should be vaccinated against HBV infection (B). HBV vaccination can be considered for diabetic patients also aged 60 or older.

6. Individuals with diabetes should be included in all social protection and eradication programs (D).

7. Patients with diabetes traveling to endemic areas should be vaccinated based on the destination specific vaccine program (D).

REFERENCES

18.10 | DIABETES AND NATURAL DISASTERS

SEMT approach to the subject is summarized below (D).

SEMT RECOMMENDATIONS
1. An “Emergency Bag” to be used in cases of hypoglycemic or hyperglycemic emergencies (DKA, HHS) during disasters like earthquake and flood should be prepared. The amount and expiry date of the contents should be checked at least two times a year (D).

2. Considering that Turkey is located in a seismic belt, this kind of bag should be stored in day care centers, schools, nursing homes and in infirmaries of all institutions where diabetic individuals work (D).

3. Emergency bags of the institutions must include adequate amounts of insulin (short- and long-acting insulin) vials, insulin injectors, glucagon vials, glucometer, and blood sugar strips, urinary ketone strips, i.v. solutions (10% dextrose, 0.9% NaCl etc.) and essential OAD group drugs (SU, metformin) (D).

4. Similarly, a small “Emergency Bag” containing drugs and insulins being used by the diabetic patients and their caretakers should be prepared and stored at a place known to all family members to be used in hypoglycemic and hyperglycemic emergencies (D).
### 18.11 | DIABETES AND RELIGIOUS TASKS

#### 18.11.1 | HAJJ (PILGRIMAGE)

The general rules that diabetes patients must comply with during their travels are also applicable for Hajj. SEMT opinion on the subject are summarized below (D).

<table>
<thead>
<tr>
<th>SEMT RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Elderly diabetics and diabetic patients with complications must consult with their physician and have their health tests checked before going to Hajj.</td>
</tr>
<tr>
<td><strong>2.</strong> People performing the Hajj duty should be provided with the vaccinations recommended for patients with diabetes.</td>
</tr>
<tr>
<td><strong>3.</strong> All diabetic individuals must increase frequency of SMBG during the Hajj duty.</td>
</tr>
<tr>
<td><strong>4.</strong> Especially being in hot environment in the summer may cause unexpected hypoglycemia in patients with diabetes. Therefore, patients should have sugar, fruit juice, etc. with them.</td>
</tr>
<tr>
<td><strong>5.</strong> Fluid intake should be increased and exposure to direct sunlight should be avoided.</td>
</tr>
<tr>
<td><strong>6.</strong> Patients with diabetes should be warned about the risk of hypoglycemia due to increased physical activity during the Hajj, they should make insulin/OAD dose adjustments if necessary, and pay attention to time differences.</td>
</tr>
<tr>
<td><strong>7.</strong> During collective prayers in crowded places (e.g. circumambulation of Kaaba), patients must wear lightweight, safe and hygienic shoes or booties that are suitable for religious rules, and barefoot or slippers should be avoided as they increase the risk of trauma and infection.</td>
</tr>
</tbody>
</table>

#### 18.11.2 | DIABETES AND FASTING (RAMADAN)

Although some small-scale studies conducted in Islamic countries have reported that fasting does not impair metabolic control in diabetic patients who are monitored with diet or OAD, findings of other studies do not support this conclusion. ADA and IDF have published reports on diabetes management during Ramadan in 2015 and 2016. SEMT recommendations were revised by taking the recommendations in these reports into consideration.
SEMT opinion on the subject is summarized below and in Figure 18.1 (D).

**Risk evaluation 1-2 months before Ramadan**

**VERY HIGH RISK**
- Patients with type 1 diabetes, pregnancy, acute disease, dialysis, cognitive disorder, intense physical activity, severe/recurrent hypoglycemia, FPG >300 mg/dL, A1C >10% DKA/HHS

**HIGH RISK**
- Patients with FPG 150-300 mg/dL, A1C 8-10%, moderate hypoglycemia, severe retinopathy, nephropathy, neuropathy, macrovascular disease, who live alone, use insulin/SU, have serious health problems, older than 75 years

**MODERATE RISK**
- Patients whose A1C is <8% with lifestyle modifications and non-insulin antidiabetic drugs (except SU; i.e., metformin, AGI, PIO, DPP4-I, GLP-1A, GLN) and have no serious health problems

**LOW RISK**
- Patients whose A1C is <7% with lifestyle modifications, AGI, PIO and DPP4-I and have no serious health problems

**CANNOT FAST**

**CAN FAST**

**Treatment adjustments**
- Metformin dose is 2x1000 mg; no need for PIO, AGI and DPP4-I dose change. SU and insulin are not recommended due to the risk of hypoglycemia, and SGLT2-I is not recommended as it poses hypovolemia risk, especially in those using diuretics and the elderly patients.

**FIGURE 18.1: Diabetes management in Ramadan**

FPG, fasting plasma glucose; A1C: glycated hemoglobin A1c; DKA, Diabetic ketoacidosis; HHS, hyperglycemic hyperosmolar state; AGI, alpha glucosidase inhibitor; PIO, Pioglitazone; DPP4-I, dipeptidyl peptidase-4 inhibitor; SU, Sulphonylurea; GLN, Glinide; GLP-1A, glucagon-like peptide 1 agonist.

**SEMT RECOMMENDATIONS**

1. Diabetic patients who want to fast should be evaluated by the physician 1-2 months before Ramadan. Patients are asked to perform frequent SMGB measurements. Firstly, the risk group of the patient is determined, and recommendations are made based on the risk group (D).

2. There may not be any significant concern for low-risk patients to fast. Fasting may be inconvenient for patients with moderate risk, and patients in this risk group must increase the frequency of SMBG and exercise caution. Fasting is not recommended for very high and high-risk patients and is very detrimental (D).

3. The drugs (diabetes and non-diabetes drugs) that patients use should be reviewed. Patients receiving SU and insulin therapy have the highest risk in terms of hypoglycemia. These treatment protocols must be rearranged, otherwise, patients should be recommended not to fast (D).
4. Metformin, AGI, PIO and DPP4-I group drugs are considered to be more reliable. Therefore, no major dose adjustment is required. If three doses of metformin is used per day, it should be reduced to two doses a day (C).

5. GLP-1A may be helpful for suppressing appetite and regulating blood glucose during Ramadan, particularly for obese patients (D).

6. There is insufficient data on the efficacy and safety of SGLT2-I in fasting patients. These drugs are not recommended during Ramadan due to risk of hypovolemia and euglycemic DKA, especially in patients using diuretics (D).

7. Based on the risk group, special attention should be put on patient training in terms of calorie and fluid intake and potential complications (D).

8. Patients should be warned about hyperglycemia attacks and monitored for glucose after fasting during the Ramadan holiday (D).

9. After Ramadan, patients return to their routine treatment (D).

REFERENCES

18.12 | DIABETES CARE FOR INDIVIDUALS LIVING UNDER SPECIAL CONDITIONS

18.12.1 | DIABETICS LIVING IN ORPHANAGE AND NURSING HOME OR OBLIGED TO RESIDE IN PRISON AND DETENTION CENTER

SEMT opinion and recommendations on care and treatment of people with diabetes living in orphanage or nursing home and those obliged to reside in prison and detention center are summarized below.

SEMT RECOMMENDATIONS

1. Medical history of the person admitting to the institution (prison/detention center, orphanage or nursing home) should be inquired by the physician or nurse and physical examination should be performed as soon as possible (D).

2. Glycemia levels should be measured within 1-2 hours after first admission to the institution in patients using insulin.

3. MNT and drug treatments of patients should be continued without interruption, insulin-meal timing should not be changed, snack should be provided and physical activity opportunities should be ensured (D).

4. Symptoms and treatment of hypoglycemia and hyperglycemia should be explained to institution staff and they should be trained on how to make glucagon injections when needed (D).

5. If the patient’s PG level is <50 or >350 mg/dL, the on-duty staff should inform the physician and the patient should be referred to the hospital immediately if needed (D).

6. Patient should periodically be referred to a hospital with diabetes department for screening of complications (D).
7. **Insulin and OAD medications should be provided to the patient with diabetes, glycemia should be monitored in proper intervals or the patient should be provided with SMBG means and should be sent to hospital for A1C measurement every 3-6 months (D).**

8. **Epicrisis should be prepared for diabetic patients who are discharged or transferred, and diabetes history and treatment should be written in detail (D).**

9. **People without known diabetes living in nursing homes or prison should be examined for diabetes risk factors and included in the diabetes screening programs (C).**

18.12.2. | **DIABETES AT WORKPLACE**

As diabetic population increases and better care opportunities are offered, the number of diabetic individuals working at various professions is also increasing. Some issues must be taken into consideration in order to reduce the problems that people with diabetes encounter in their business life. SEMT recommendations on the subject are summarized below (D):

---

**SEMT RECOMMENDATIONS**

1. **In order to break the prejudices and prevent negative discrimination against individuals with diabetes during the process of job applications and safe environment in the workplace, healthcare authorities and non-governmental organizations related to diabetes should provide necessary information to employers (D):**
   - A diabetic person applying for a job should be evaluated on an individual basis, taking into consideration his/her medical history, disease stage, medications and the specific conditions required by the applied job.

2. **If there are doubts about the suitability of the applicant for work due to diabetes, a physician specialized in diabetes treatment should be asked to assess the situation.**

3. **Whether the work environment and the work poses a risk to the person with diabetes should be evaluated on an objective basis, and protective measures and positive discrimination should be implemented if needed.**

4. **People with well-controlled diabetes and no severe complications can work at any job. However, it may be risky for individuals with recurrent severe hypoglycemia to work at certain jobs requiring special attention (working at high-altitude, firearm use, heavy duty vehicles etc.)**

5. **Appropriate care opportunities (main and intermediate meals suitable for MNT, physical activity arrangements, SMBG and treatment opportunities, etc.) must be provided for individuals with diabetes in order for them to work efficiently at workplace.**

6. **Especially those using intense insulin therapies should not be assigned to works with variable shifts.**

7. **Workplace physician should collaborate with the physician responsible for the diabetes care of the individual.**
19.1 | EPIDEMIOLOGICAL DATA

The association between diabetes and cancer has been a subject of interest for a long time. Meta-analyses of various studies have revealed higher cancer rates in patients with diabetes in comparison to nondiabetics with the same age and sex. The coexistence of diabetes and cancer can be explained by shared many features identified as risk factors (e.g., aging, obesity, sedentary life, smoking, etc.) for both health problems.

Aging is an important factor that increases the risk of both diabetes and cancer. According to the data of WHO, 25-30% of individuals older than 65 years of age have diabetes, and %60 of them have an increased risk for cancer.

Observational data suggests an association between increased BMI and various types of cancer. High BMI is associated with increased endogenous insulin (hyperinsulinemia), insulin-like growth factor (IGF), inflammatory cytokines, and other growth factors, and thus exhibit a precancerous effect. Epidemiological data show some types of cancer are more significantly increased in obese and diabetic patients.

Risk increase in terms of liver, pancreas, and endometrium cancers is approximately two times higher in patients with diabetes than the healthy population. Furthermore, a 20-30% risk increase has been reported in diabetic patients in terms of colon, bladder, and women breast cancer. Surprisingly, the risk of prostate cancer is relatively decreased in people with diabetes. Considering the probability that the control group included in these meta-analyses might have individuals who have undiagnosed diabetes, one can estimate a higher risk.

As another point, antihyperglycemic, antihypertensive, and anti-lipid treatments, diet, and metabolic factors may also be considered to play a part in the increased prevalence of cancer in diabetes.

Cancer prognosis is poor in people with known diabetes. Cancer-related death risk is approximately 40% higher in comparison to nondiabetic individuals. Obesity, physical inactivity, insulin resistance, chronic low-grade inflammation, and hyperglycemia are considered to be factors in increased risks of cancer and mortality in patients with diabetes.
As diabetic patients have several accompanying medical problems, routine screening tests may be interrupted, and complications related to cancer treatment can occur more frequently due to accompanying diseases.

Pancreatic adenocarcinoma must be taken into account in a middle-aged, overweight patient with a new onset of atypical diabetes without a family history of diabetes. However, routine pancreas cancer screening (abdominal ultrasonography, tumor markers) is not recommended for patients without complaints like weight loss, abdominal pain, etc.

To prevent potential cancers in diabetic patients, weight control must be provided to reduce insulin resistance and hyperinsulinemia, and proper nutrition and exercise must be emphasized. Besides, routine cancer screenings should not be neglected in all diabetes patients, high-risk individuals should closely be monitored with proper early diagnostic methods, and the diabetes treatment of patients with cancer must be readjusted in consideration of cancer.

**Drugs used in diabetes treatment and cancer:** Recently published mostly observational or retrospective studies have claimed that high-dose insulin and various novel antihyperglycemic drugs (PIO, SGLT2-I, DPP4-I, GLP-1A) are associated with increased cancers risk including breast, colon, pancreas, liver, thyroid and breast; however, the results of various meta-analyses and 3-5 years CV safety studies haven´t been able to verify this association. Therefore, potential associations between antihyperglycemic drugs and certain types of cancer must be revealed.

However, diabetes medication metformin has been shown not to increase the risk of cancer, and it was even claimed that it decelerates the cancer development rate. Metformin is thought to it`s prevent progression to cancer by slowing cell growth due to its positive effects on 5’ adenosine monophosphate-activated protein kinase (AMPK).

### 19.2 MANAGEMENT OF DIABETES IN PATIENTS WITH CANCER

The administrations of high-dose corticosteroids during the treatment of patients receiving chemotherapy may increase blood glucose levels. In USA, National Institute of Cancer recommends the classification of chemotherapy-related glucose increase in 4 stages. According to this:

- **Stage 1:** PG 126-160 mg/dL
- **Stage 2:** PG 160-250 mg/dL
- **Stage 3:** PG 250-500 mg/dL (requires hospitalization)
- **Stage 4:** PG >500 mg/dL (requires emergency intervention).

#### 19.2.1 CANCER PATIENTS WITHOUT KNOWN DIABETES

In patients without previous diabetes diagnosis and have chemotherapy-induced mild hyperglycemia, metformin should be started primarily, and OAD should be added if necessary. Insulin must be given to cases with high blood glucose levels.

Nausea, vomiting, and loss of appetite are common problems in patients with cancer, and during chemotherapy treatment. Therefore, special attention must be paid for hypoglycemia, and long-acting drugs that may cause hypoglycemia should be avoided.
Corticosteroid treatment is frequently used during chemotherapy. Corticosteroids are generally administered as a single high dose and in most cases, has no long time effect on glycemia. In long time glucocorticoid treatment, postprandial hyperglycemia occurs frequently. Basal insulin administration in the morning is suitable for patients using single-dose steroid. And short-acting or fast-acting insulin can be added, especially before lunch and dinner against post-prandial elevations. Biphasic insulin can be beneficial for patients using divided steroid doses.

Insulin preference can also change based on the type of used corticosteroid. If a corticosteroid with moderate potency like prednisolone is given as a single dose per day, an intermediate-acting insulin ensures glycemia regulation, and long-acting basal insulins can be preferred for longer-acting steroids like dexamethasone. If hyperglycemia cannot be controlled, basal-bolus insulin therapy can be started.

19.2.2 | CANCER PATIENTS WITH KNOWN DIABETES

Among OADs that can be used for the diabetic patients with cancer, metformin (if there is no contraindication or intolerance) should be preferred. SU group drugs that controlled release can be helpful in glucocorticosteroid-related hyperglycemia. And GLN group drugs can be used for the treatment of steroid-related postprandial hyperglycemia. Acarbose, from AGI group, is not preferred due to its gastrointestinal side effects. DPP4-I group of drugs can also be used. GLP-1A group is not preferred because of its side effects on gastrointestinal system and weight loss. There is no sufficient data on SGLT2-I.

For PET/CT imaging in cancer patients, glycemia must be in appropriate range and metformin must be discontinued prior to procedure (See Chapter 18).

Terminal-stage patients: It may be required to lower the bolus doses in order to avoid hypoglycemia in type 1 diabetics, and maybe even use basal insulin alone; and basal insulin may be needed to prevent complications that can cause metabolic decompensation like HHS in type 2 diabetics. Strict glycemic control should be avoided and glycemic targets (e.g. A1C 8-8.5%, 64-69 mmol/mol) should be kept flexible. Dose adjustment must be made for OADs and insulin.

SEMT RECOMMENDATIONS

1. The prevalence of various cancers has increased in patients with diabetes compared with those without diabetes (B).
2. Metformin does not increase cancer risk; on contrary, some studies have shown that it reduces the cancer risk (B).
3. Routine cancer screenings in patients with diabetes should not be neglected (D).
4. It is recommended that cancer screenings should be done carefully in the first five years, especially in newly diagnosed older patients with diabetes (D).
REFERENCES

PREVENTION OF TYPE 1 DIABETES

Today, there is no effective and reliable method developed according to evidence-based medical data to prevent type 1 diabetes. The results of two placebo-controlled, large-scale, multi-center, and prospective preclinical trials were published in 2003. According to these, no successful results were obtained during type 1 diabetes prevention studies with parenteral and oral insulin in the USA (DPT: Diabetes Prevention Trial) and with nicotinamide (ENDIT: European Nicotinamide Diabetes Intervention Trial) in Europe. The absence of effective prevention programs creates an ethical debate about family and community screening in determining prediabetes.

After the DPT and the ENDIT studies, monoclonal antibody therapies designed for T-cells or to stunt the development of diabetes by blocking various interleukins, vitamin D replacement, peptide treatment design similar to heat shock proteins, vaccination developed against Coxsackie B virus, and all studies that used oral or nasal insulin administration have also failed to prevent type 1 diabetes. More than 200 studies have been conducted in Juvenile Diabetes Research Foundation (JDFR), National Institute for Diabetes, Digestive and Kidney Disease (NDDK) and TrialNet Groups in the United States and their collaboration centers in Germany, Australia, Finland, Sweden and Italy. Although these studies were completed with unsuccessful results for prevention, important information has been acquired with regards to identifying type 1 diabetes in the preclinical stage. Today, it is possible to identify type 1 diabetes in high-risk individuals (eg., first-degree relatives of people with type 1 diabetes) at an early stage by autoantibody assays (glutamic acid decarboxylase [GADA], tyrosine phosphatase [IA2] and insulin autoantibodies [IAA]) and tests for determination of β-cell reserve (IV glucose tolerance test [IVGTT] and C-peptide stimulation tests). Currently, those at risk may be encouraged to participate in type 1 diabetes prevention trials because no further intervention is possible. In this way, it will be possible to recognize Type 1 diabetes before the stage of DKA and start treatment before the endogenous insulin reserve is completely depleted.
Epidemiological studies have shown that children who are breastfed or prepared with cow milk-based formula in the first six months of life have a higher risk of type 1 diabetes. To protect infants against type 1 diabetes, they should be supported to be breastfed only for the first six months and to continue breastfeeding until the age of 2 after switching to supplementary foods.

20.2 | PREVENTION OF TYPE 2 DIABETES

The role of environmental factors in the development of type 2 diabetes is clear. Modern lifestyle adopted by many societies has led people to less active lives and rapidly changed their eating habits. In the past 25 years, the increased use of high-calorie and ready to eat foods that are fat-rich and low in fibers has caused a rapid increase in the prevalence of diabetes.

- Studies on type 2 diabetes prevention with lifestyle modifications have gained particular importance in recent years.
- "Da Qing Diabetes and IGT" study published in 1997 showed that the risk of type 2 diabetes could be decreased by almost 40% through diet and exercise in patients with IGT living in China.
- The results of Diabetes Prevention Study (DPS), published in 2001, demonstrated that the risk of type 2 diabetes can be decreased by 58% through programmed exercise and calorie restriction in obese or overweight patients with IGT living in Finland.
- In the Diabetes Prevention Program (DPP), conducted in United States of America and Canada, included overweight or obese individuals with IFG or IGT and published in 2003, it has been reported that the risk of diabetes is decreased by 58% through intense lifestyle modifications and by 31% using metformin. The study also highlighted the importance of pharmacological prevention in the prediabetes period. In addition to these metformin experiences obtained in DPP, acarbose was also used for the same purpose.
- In the STOP-NIDDM (prevention of type 2 diabetes with acarbose) study conducted in European countries and Canada, acarbose has been shown to decrease the risk of diabetes by 32% and reduced CV event risk in obese or overweight individuals with IGT.
- In the TRIPOD study, where troglitazone was used in women with GDM history, development of type 2 diabetes was found to be decreased.
- In studies planned to reduce obesity (XENDOS study) and CV problems (MICRO-HOPE study), it has been reported that the number of cases with type 2 diabetes development was significantly less than the placebo group with orlistat and ramipril, respectively.
- In DREAM study (Diabetes Reduction Assessment with rampiril and rosiglitazone Medication Trial), where ramipril and rosiglitazone was used in prediabetes (IFG/IGT) period results have showed that the risk of diabetes development could be reduced by 60% by using rosiglitazone.
- The results of NAVIGATOR study (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial), where valsartan and nateglinide were used, revealed that nateglinide did not decrease the incidence of diabetes in median 6.5 years; however, valsartan reduced new diabetes cases by 16% but had no effect in terms of decreasing CV events. The hope is that the subject can be better clarified once these and similar studies are concluded.
In the ORIGIN study published in 2012, prediabetic or type 2 diabetes patients with high cardiovascular risk were followed up for more than six years with insulin glargine or standard therapy, and there was no significant difference in cardiovascular outcomes and cancer development. Although the number of new-onset diabetes decreased with glargine, it was found that the rate of hypoglycemia and body weight (slightly) increased.

In Table 20.1 FINDRISK survey, which is easily applicable in a social scale and developed to identify individual at high risk in terms of type 2 diabetes, is presented and the evaluation of the responses given to the survey is shown in Table 20.2. Individuals with diabetes risk score >20 should also be included in the prevention programs.

**TABLE 20.1: Type 2 Diabetes Risk Survey (FINDRISK)**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: &lt;45 years</td>
<td>2 point: 45-54 years</td>
<td>3 point: 55-64 years</td>
</tr>
<tr>
<td>4 point: &gt;64 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Body mass index (BMI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: &lt;25 kg/m²</td>
<td>1 point: 25-30 kg/m²</td>
<td>3 point: &gt;30 kg/m²</td>
</tr>
<tr>
<td>3. Waist circumference</td>
<td>MALE</td>
<td>FEMALE</td>
</tr>
<tr>
<td>0 point:</td>
<td>&lt;94 cm</td>
<td>&lt;80 cm</td>
</tr>
<tr>
<td>3 point:</td>
<td>94-102 cm</td>
<td>80-88 cm</td>
</tr>
<tr>
<td>4 point:</td>
<td>&gt;102 cm</td>
<td>&gt;88 cm</td>
</tr>
<tr>
<td>4. Do you usually have daily at least 30 minutes of physical activity at work and/or during leisure time (including normal daily activity)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: Yes</td>
<td>2 point: No</td>
<td></td>
</tr>
<tr>
<td>5. How often do you eat vegetables-fruits?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: Every day</td>
<td>1 point: Not every day</td>
<td></td>
</tr>
<tr>
<td>6. Have you ever taken medication for high blood pressure on regular basis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: No</td>
<td>2 point: Yes</td>
<td></td>
</tr>
<tr>
<td>7. Have you ever been found to have high blood glucose (e.g., in a health examination, during an illness, during pregnancy)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: No</td>
<td>5 point: Yes</td>
<td></td>
</tr>
<tr>
<td>8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 point: No</td>
<td>3 point: Yes; grandparent, uncle, aunt, cousin or niece/nephew (Second degree relatives)</td>
<td>5 point: Yes; parent, sibling or child (First degree relatives)</td>
</tr>
</tbody>
</table>
Based on our current knowledge, lifestyle modifications are considered as inexpensive, easy methods that can be applied on a social scale to prevent type 2 diabetes.

Can interventions that prevent the progression of IFG/IGT into diabetes also prevent diabetes-related microvascular complications, cardiometabolic risk factors (e.g., hypertension, hyperlipidemia) or the development and progression of cardiovascular diseases?

Although intense lifestyle modifications have been shown to delay or prevent the development of diabetes, they have mild effect on cardiovascular disease risk. However, it is unknown whether they reduce cardiovascular diseases. Interventions aimed at delaying or preventing diabetes through pharmacological approaches have weaker effect on cardiovascular diseases and related risk factors.

Do we have adequate data to recommend specific interventions in order to delay or prevent the progression of IFG/IGT to diabetes?

Today, lifestyle modification programs (approximately 7% weight loss and at least 150 minutes of moderate intensity physical activity per week, smoking cessation, etc.) are considered as the most appropriate approach to be preferred for IFG/IGT and high-risk groups with A1C 5.7-6.4% [39-47 mmol/mol]. Among pharmacological agents, metformin is the only option that can be used for patients with BMI ≥35 kg/m² at this stage, individuals younger than 60 years of age and women with gestational diabetes (GDM).

In order to delay or prevent the adverse outcomes of IFG/IGT for whom and with which method and frequency should we perform screening?

The most effective way is to examine the presence of IFG/IGT by first measuring the fasting plasma glucose, and then performing OGTT on another day. Individuals with prediabetes are recommended to be examined for at least once every year. If there is combined glucose tolerance (CGI), then metformin should be added to the treatment together with lifestyle modification (Table 20.3).

- As we gain more diagnostic experience about A1C, we develop a better understanding that high-risk individuals with A1C elevation at limit (A1C: 5.7-6.4%) actually have impaired metabolic profile and therefore their inclusion in prevention programs should be prioritized. If metformin is being used, then those cases should be monitored with A1C twice a year, patients who do not use metformin should be examined once a year.

- In order to facilitate compliance with lifestyle modification programs, technological applications like online monitoring, diabetes prevention applications, online physical activity software, pedometer, etc. should be used.

- Program compliance and sustainability can be easier for the individuals if the healthcare insurance system covers lifestyle modification programs.

### TABLE 20.2: Diabetes risk score according to FINDRISK

<table>
<thead>
<tr>
<th>Total score</th>
<th>Risk degree</th>
<th>10-Year risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>Low</td>
<td>1% (1/100)</td>
</tr>
<tr>
<td>7-11</td>
<td>Mild</td>
<td>4% (1/25)</td>
</tr>
<tr>
<td>12-14</td>
<td>Moderate</td>
<td>16% (1/6)</td>
</tr>
<tr>
<td>15-20</td>
<td>High</td>
<td>33% (1/3)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Very high</td>
<td>50% (1/2)</td>
</tr>
</tbody>
</table>
### TABLE 20.3: Treatment recommendations for impaired fasting glucose, impaired glucose tolerance and combined glucose intolerance (impaired fasting glucose + impaired glucose tolerance)

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals diagnosed with IFG or IGT</td>
<td>Lifestyle modification program (e.g., 5-10% weight loss and 30 min/day [or ≥150 min/week] moderate intensity physical activity)</td>
</tr>
</tbody>
</table>
| Individuals having CGI (IFG + IGT) or HRG (A1C: 5.7-6.4%) together with either one of the following risk factors: | • Metformin* can be started simultaneously with the lifestyle modification program summarized above.  
• This can be changed in patients with HT, dyslipidemia, obesity etc. CV risk factors should be examined and treated if any.  
• The participation of these individuals in protection programs designed to ensure lifestyle modification must be prioritized.  |
  | • <60 years                              |                                                                           |
  | • BMI ≥35 kg/m²                           |                                                                           |
  | • Diabetes history in first-degree relatives |                                                                           |
  | • Hypertriglyceridemia                    |                                                                           |
  | • Low HDL-cholesterol                    |                                                                           |
  | • Hypertension                           |                                                                           |
  | • GDM history                            |                                                                           |
  | • Physical inactivity                    |                                                                           |

*Metformin 2x850 mg.

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CGI, combined glucose intolerance; HRG, high risk group; BMI, body mass index; HDL, high-density lipoprotein; A1C, Glycated hemoglobin A1c

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**SEMT RECOMMENDATIONS**

1. **Individuals at high risk of diabetes should be recommended lifestyle modification programs that are designed to ensure mild weight loss and increased physical activity (for IGT: A, for IFG: D).**

2. **Pharmacological treatment may be administered to patients with IGT (especially in the presence of IFG+IGT) to reduce the risk of diabetes (for metformin: A, for Acarbose: A).**

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ABBREVIATIONS

1-hr PG: 1st-hour plasma glucose
2-hr PG: 2st-hour plasma glucose
3-hr PG: 3st-hour plasma glucose
18F-FDG: Fluorine 18-fluorodeoxyglucose
A1C: Glycated hemoglobin A1c (HbA1c)
ABI: Ankle-brachial index
ACCORD: Action to Control Cardiovascular Risk in Diabetes
ACE-I: Angiotensin converting enzyme inhibitor
ACE/AACE: American College of Endocrinology and American Association of Clinical Endocrinologists
ACCHOIS Study: Australian Carbohydrate Intolerance Study in Pregnant Women Study
ACOG: American College of Obstetricians and Gynecologists
ACS: Acute coronary syndrome
ADA: American Diabetes Association
ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGI: Alpha-glucosidase inhibitors
ALLHAT: Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
ALT: Alanine aminotransferase
AMC: Arthrogryposis multiplex congenita
AMPK: 5’ adenosine monophosphate-activated protein kinase
Anti-GAD: Anti-glutamic acid decarboxylase antibody
Anti-Tg: Anti-thyroglobulin antibody
Anti-TPO: Anti-thyroid peroxidase antibody
Anti-VEGF: Anti-vascular endothelial growth factor
Anti-ZnT8: Zinc transporter-8 antibody
ARB: Angiotensin receptor blocker
ARDS: Adult respiratory distress syndrome
ASA: Acetylsalicylic acid
ASCVD: Atherosclerotic cardiovascular disease
ASD: Atrial septal defect
ASH: American Society of Hypertension
AST: Aspartate aminotransferase
BMI: Body mass index
BP: Blood pressure
BPD-DS: Biliopancreatic diversion with duodenal switch
CAD: Coronary artery disease
CANVAS Program: Canagliflozin Cardiovascular Assessment Study (CANVAS) plus CANVAS-Renal (CANVAS-R)
CANVAS: Canagliflozin Cardiovascular Assessment Study
CARMELINA: Cardiovascular and Renal Microvascular Outcome Study with Linagliptin
CDA: Canada Diabetes Association
CGI: Combined glucose intolerance (impaired fasting glucose + impaired glucose tolerance)
CGM: Continuous glucose monitoring
CH: Carbohydrate
CH/I: Carbohydrate/Insulin ratio
CHF: Congestive heart failure
CKD: Chronic kidney disease
CKF: Chronic kidney failure
CNS: Central nervous system
CPK: Creatinine phosphokinase
CSII: Continuous subcutaneous insulin infusion
CTG: Continuous cardiotocography
CV: Cardiovascular
CVD: Cardiovascular disease
CVP: Central venous pressure
DCCB: Dihydropyridine calcium channel blocker
DCCT: Diabetes Control and Complications Trial
DECLARE-TIMI 58: Dapagliflozin Effect on Cardiovascular Events-TIMI 58
DIC: Disseminated intravascular coagulation
DIDMOAD syndrome: Syndrome characterized by diabetes insipidus, diabetes mellitus, optical atrophy and deafness (Wolfram syndrome)
DKA: Diabetic ketoacidosis
DKD: Diabetic kidney disease
DL: Dyslipidemia
DM: Diabetes mellitus
DPP-4: Dipeptidyl peptidase-4
DPP: Study on prevention of type 2 diabetes through lifestyle modifications and pharmacological treatment (Diabetes Prevention Program)
DPP4-I: Dipeptidyl peptidase-4 inhibitors
DPS: Study on prevention of type 2 diabetes through lifestyle modifications (Diabetes Prevention Study)
DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication trial
DTS: Drug Tracking System
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### APPENDIX TABLE 1.1: Non-insulin medicines (oral antidiabetics and insulin-mimetic drugs)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial name and form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanides</strong></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Glucotard 850 mg; Glucophage, Matofin 500, 850, 1000 mg; Diafor-</td>
</tr>
<tr>
<td></td>
<td>min, Diabest, Glange, Glifor, Gluforce, Metvel 850, 1000 mg; Glukofen</td>
</tr>
<tr>
<td></td>
<td>retard 850 mg; Glukofen 1000 mg tb; Metfull 500, 850, 1000 mg eff tb</td>
</tr>
<tr>
<td>Extended-release Metformin</td>
<td>Matofin XR 500, 1000 mg; Glifor SR 1000 mg; Glinext MR 500, 850, 1000 mg eff tb</td>
</tr>
<tr>
<td><strong>Insulin secretagogues</strong></td>
<td></td>
</tr>
<tr>
<td>Sulphonylurea group (second-generation) (SU)</td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>Minidiab 5 mg tb</td>
</tr>
<tr>
<td>Controlled-release Glipizide</td>
<td>Glucotrol XL 2.5, 5, 10 mg tb</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Betanorm, Diamicron, Glikron, Glumikron, Oramikron 80 mg tb</td>
</tr>
<tr>
<td>Gliclazide with modified release form</td>
<td>Betanorm MR, Diamicron MR, Diaway MR, Efikas MR, Glicla MR 30, 60 mg; Diaklazid MR, Dialive MR, Hipoglis MR, Melidys MR 30 mg; Diatime MR 60 mg tb</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>Dianorm, Gliben 5 mg; Dyaben 3.5 mg tb</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Insuprid 2 mg; Mepiriks 1, 2, 3 mg; Diameprid, Glimax, Sanprid 1, 2, 3, 4 mg; Amaryl 1, 2, 3, 4, 6 mg; Tideca 6, 8 mg tb</td>
</tr>
<tr>
<td>Glibornuride</td>
<td>Glutril 25 mg tb</td>
</tr>
<tr>
<td>Glitazone</td>
<td>Glurenorm 30 mg tb</td>
</tr>
<tr>
<td><strong>Glínid grubu (GLN, Meglitinidler, kısa etkili sekretogoglar)</strong></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Diafree, Novade, Novonorm, Repelit, Replic, 0.5, 1, 2 mg; Repafix 0.5, 1, 2 mg eff tb</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Naglid 60, 120 mg; Dialix, Teglix 120 mg; Incuria, Natelix, Starlix 120, 180 mg tb</td>
</tr>
<tr>
<td><strong>Thiazolidinediones (TZD)</strong></td>
<td></td>
</tr>
<tr>
<td>Pioglitazon</td>
<td>Pixart 15 mg; Actos 15, 30 mg; Dropia, Dyndion, Glifix, Pioforce, Piofox, Pioctan, Piondia 15, 30, 45 mg; Dialic 15, 30, 45 mg eff tb</td>
</tr>
<tr>
<td><strong>Alpha glucosidase inhibitors (AGI)</strong></td>
<td></td>
</tr>
<tr>
<td>Akarboz</td>
<td>Acnor, Glucar, Glucobay, Glynose, Oador 50, 100 mg tb</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE 1.1: Non-insulin medicines (oral antidiabetics and insulin-mimetic drugs)

<table>
<thead>
<tr>
<th><strong>Incretin-based drugs</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucagon-like peptide-1 receptor agonists (GLP-1 analogs, GLP-1A)</strong></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Byetta 5, 10 μg injection pen</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza 6 mg/ml injection pen</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity 0.75 mg/0.5 ml, 1.5 mg/0.5 ml injection pen</td>
</tr>
<tr>
<td><strong>Dipeptidyl peptidase-4 inhibitors (DPP-4-I)</strong></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia 100 mg tb</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Galvus 50 mg tb</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza 2.5, 5 mg tb</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Trajenta 5 mg tb</td>
</tr>
<tr>
<td><strong>Sodium-glucose co-transporter 2 inhibitors (SGLT2-I)</strong></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Forziga 10 mg tb</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Jardiance 10, 25 mg tb</td>
</tr>
</tbody>
</table>

### APPENDIX TABLE 1.2: Oral antidiabetic combinations

<table>
<thead>
<tr>
<th><strong>Generic name</strong></th>
<th><strong>Commercial name and form</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin/Glibenclamide</td>
<td>Glucovance 500/5, 500/2.5 mg; Duplax 1.25/500 mg; Glibomet 400/2.5 mg tb</td>
</tr>
<tr>
<td>Gliclazide/Metformin</td>
<td>Duodia 80/500 mg tb</td>
</tr>
<tr>
<td>Gliclazide with modified release/Metformin</td>
<td>Dialive plus, Glifor plus 30/500, 30/850, 30/1000 mg tb</td>
</tr>
<tr>
<td>Repaglinide/Metformin</td>
<td>Pareglin, Sergilex-Met 1/500, 2/500 mg tb; Repamef 1/500, 1/1000, 2/500, 2/1000 eff tb</td>
</tr>
<tr>
<td>Pioglitazone/Metformin</td>
<td>Acort, Preko, Prenorm MR 15/850 mg; Dropia-Met, Duepio 15/500, 15/850 mg; Glifix plus 15/850, 15/1000 mg; Pio-Met 15/850, 30/1000 mg; Glipirom 15/1000, 30/500, 30/1000 mg, Piocomb 15/1000, 30/1000 mg tb</td>
</tr>
<tr>
<td>Sitagliptin/Metformin</td>
<td>Janumet 50/500, 50/850, 50/1000 mg tb</td>
</tr>
<tr>
<td>Vildagliptin/Metformin</td>
<td>GalvusMet, GaliptinMet 50/850 mg, 50/1000 mg tb</td>
</tr>
<tr>
<td>Saxagliptin/Metformin</td>
<td>Komboglyze 2.5/850, 2.5/1000 mg tb</td>
</tr>
<tr>
<td>Linagliptin/Metformin</td>
<td>Trajenta Duo 2.5/850, 2.5/1000 mg tb</td>
</tr>
<tr>
<td>Dapagliflozin/Metformin</td>
<td>Xigduo XR 5/1000, 10/1000 mg tb</td>
</tr>
</tbody>
</table>
### APPENDIX TABLE 1.3: Insulin and “Basal insulin + GLP-1 analog” combinations

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Commercial name and form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prandial (bolus) insulins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting (Human regular)</strong></td>
<td></td>
</tr>
<tr>
<td>Crystallized human insulin</td>
<td>Humulin R vial, Humulin R cartridge; Actrapid HM vial, Actrapid HM penfill</td>
</tr>
<tr>
<td><strong>Fast-acting (Prandial analog)</strong></td>
<td></td>
</tr>
<tr>
<td>Glulisine insulin</td>
<td>Apidra solostar injection pen</td>
</tr>
<tr>
<td>Lispro insulin</td>
<td>Humalog cartridge, Humalog kwikpen</td>
</tr>
<tr>
<td>Aspart insulin</td>
<td>NovoRapid vial, NovoRapid flexpen</td>
</tr>
<tr>
<td><strong>Basal insulins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate-acting (basal human NPH)</strong></td>
<td></td>
</tr>
<tr>
<td>NPH human insulin</td>
<td>Humulin N vial, Humulin N cartridge; Insulatard HM vial, Insulatard HM cartridge</td>
</tr>
<tr>
<td><strong>Long-acting (basal analog)</strong></td>
<td></td>
</tr>
<tr>
<td>Detemir insulin</td>
<td>Leveir flexpen injection pen</td>
</tr>
<tr>
<td>Glargine 100 U/ml insulin</td>
<td>Lantus solostar injection pen</td>
</tr>
<tr>
<td>Glargine biosimilar insulin</td>
<td>Basaglar kwikpen; Glarin cartridge</td>
</tr>
<tr>
<td>Glargine 300 U/ml insulin</td>
<td>Tuojeo injection pen</td>
</tr>
<tr>
<td><strong>Pre-mixed (biphasic) insulins</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-mixed human (Regular + NPH)</strong></td>
<td></td>
</tr>
<tr>
<td>30% crystallized + 70% NPH human insulin</td>
<td>Humulin M 70/30 cartridge; Mixtard HM 30 cartridge</td>
</tr>
<tr>
<td><strong>Pre-mixed analog (Lispro + NPL)</strong></td>
<td></td>
</tr>
<tr>
<td>25% lispro + 75% insulin lispro protamine</td>
<td>Humalog Mix 25 cartridge, Humalog Mix 25 kwikpen</td>
</tr>
<tr>
<td>50% lispro + 50% insulin lispro protamine</td>
<td>Humalog Mix 50 cartridge, Humalog Mix 50 kwikpen</td>
</tr>
<tr>
<td><strong>Pre-mixed analog (Aspart + NPA)</strong></td>
<td></td>
</tr>
<tr>
<td>30% aspart + 70% aspart protamine</td>
<td>NovoMix 30 penfill, NovoMix 30 flexpen</td>
</tr>
<tr>
<td>50% aspart + 50% aspart protamine</td>
<td>NovoMix 50 flexpen</td>
</tr>
<tr>
<td>70% aspart + 30% aspart protamine</td>
<td>NovoMix 70 flexpen</td>
</tr>
<tr>
<td><strong>Pre-mixed analog (Aspart + Degludec)</strong></td>
<td></td>
</tr>
<tr>
<td>30% aspart + 70% degludec</td>
<td>Ryzodeg flextouch</td>
</tr>
<tr>
<td><strong>Basal insulin + GLP-1 analog combinations</strong></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine 100 pg/ml + lixisenatide 33 pg/ml</td>
<td>SOLIQUA SoloStar 100 U/ml + 33 pg/ml injection pen</td>
</tr>
<tr>
<td>Insulin glargine 100 pg/ml + lixisenatide 55 pg/ml</td>
<td>SOLIQUA SoloStar 100 U/ml + 50 pg/ml injection pen</td>
</tr>
</tbody>
</table>
Normal ranges of the data presented here may vary based on kit being used. Also, it must be noted that interpretations related to hormones like cortisol and insulin should be based on the associations with clinical condition, not the reference ranges of the test kit.

### APPENDIX TABLE 2.1 | CLINICAL BIOCHEMICAL TESTS*,**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>S</td>
<td>35-55 g/L</td>
<td>3.5-5.5 g/dL</td>
</tr>
<tr>
<td>Aldolase</td>
<td>S</td>
<td>0-100 nkat/L</td>
<td>0-6 U/L</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin</td>
<td>S</td>
<td>0.8-2.1 g/L</td>
<td>85-213 mg/dL</td>
</tr>
<tr>
<td>Alpha fetoprotein (AFP) (Adult)</td>
<td>S</td>
<td>&lt;15 μg/L</td>
<td>&lt;15 ng/ml</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>S</td>
<td>0.5-2.0 μg/L</td>
<td>30-120 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>S</td>
<td>0.8-3.2 μg/L</td>
<td>60-180 U/L</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate (AST, SGOT) Alanine (ALT, SGPT)</td>
<td>S</td>
<td>0-0.58 μkat/L</td>
<td>0-35 U/L</td>
</tr>
<tr>
<td>Ammonia (NH3)</td>
<td>P</td>
<td>6-47 μmol/L</td>
<td>10-80 μg/dL</td>
</tr>
<tr>
<td>Angiotensin converting enzyme (ACE)</td>
<td>S</td>
<td>&lt;670 nkat/L</td>
<td>&lt;40 U/L</td>
</tr>
<tr>
<td>Anion gap</td>
<td>S</td>
<td>7-16 mmol/L</td>
<td>7-16 mmol/L</td>
</tr>
<tr>
<td>Apolipoprotein A-1 (Apo A-1)</td>
<td>S</td>
<td>1.2-2.4 g/L</td>
<td>119-240 mg/dL</td>
</tr>
<tr>
<td>Apolipoprotein B (Apo B)</td>
<td>S</td>
<td>0.52-1.63 g/L</td>
<td>52-163 mg/dL</td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum.
*Conversion between conventional and international (SI) unit systems can be calculated based on the following equation: \( \text{mmol/L} = 10 \times \frac{\text{mg/dL} \times \text{Atom (or molecular weight)}}{10} \)

### APPENDIX TABLE 2.1 (cont’d): Clinical biochemical tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate [HCO₃⁻]</td>
<td>A</td>
<td>21-28 mmol/L</td>
<td>21-30 mEq/L</td>
</tr>
<tr>
<td>pCO₂</td>
<td></td>
<td>4.7-5.9 kPa</td>
<td>35-45 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>7.38-7.44</td>
<td>7.38-7.44</td>
</tr>
<tr>
<td>pO₂</td>
<td></td>
<td>11-13 kPa</td>
<td>80-100 mmHg</td>
</tr>
<tr>
<td>Apo B/Apo A-1</td>
<td>S</td>
<td>0.35-0.98</td>
<td>0.35-0.98</td>
</tr>
<tr>
<td>Acetoacetate</td>
<td>P</td>
<td>&lt;100 µmol/L</td>
<td>&lt;1 mg/dL</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>S</td>
<td>0.90 nkat/L</td>
<td>0-5.5 U/L</td>
</tr>
<tr>
<td>Beta-hydroxybutyrate</td>
<td>P</td>
<td>&lt;300 µmol/L</td>
<td>&lt;3 mg/dL</td>
</tr>
<tr>
<td>Beta-2-microglobulin</td>
<td>S</td>
<td>1.2-2.8 mg/L</td>
<td>1.2-2.8 mg/L</td>
</tr>
<tr>
<td></td>
<td>U</td>
<td>≤200 µg/L</td>
<td>≤200 µg/L</td>
</tr>
<tr>
<td>Brain natriuretic peptide (BNP)</td>
<td>P</td>
<td>Varies based on age and sex: &lt;167 ng/L</td>
<td>Varies based on age and sex: &lt;167 pg/mL</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>S</td>
<td>5.1-17 µmol/L</td>
<td>0.3-1.0 mg/dL</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1.7-5.1 µmol/L</td>
<td>0.1-0.3 mg/dL</td>
</tr>
<tr>
<td>Indirect</td>
<td></td>
<td>3.4-12 µmol/L</td>
<td>0.2-0.7 mg/dL</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>S</td>
<td>0-30 kU/L</td>
<td>0-30 U/mL</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>S</td>
<td>0-37 kU/L</td>
<td>0-37 U/mL</td>
</tr>
<tr>
<td>CA 27-29</td>
<td>S</td>
<td>0-32 kU/L</td>
<td>0-32 U/mL</td>
</tr>
<tr>
<td>CA 125</td>
<td>S</td>
<td>0-35 kU/L</td>
<td>0-35 U/mL</td>
</tr>
<tr>
<td>C-peptide</td>
<td>S</td>
<td>0.17-0.66 nmol/L</td>
<td>0.5-2.0 ng/mL</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>S</td>
<td>9-27 µmol/L</td>
<td>50-150 µg/dL</td>
</tr>
<tr>
<td>Iron binding capacity</td>
<td>S</td>
<td>45-66 µmol/L</td>
<td>250-370 µg/dL</td>
</tr>
<tr>
<td>Iron binding saturation, total</td>
<td>S</td>
<td>0.2-0.45</td>
<td>20-45%</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>S</td>
<td>5-36 U/L</td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>S</td>
<td>10-200 µg/L</td>
<td>10-200 ng/mL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>15-400 µg/L</td>
<td>15-400 ng/mL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorous, inorganic (P.)</td>
<td>S</td>
<td>1.0-1.4 mmol/L</td>
<td>3-4.5 mg/dL</td>
</tr>
<tr>
<td>Gama glutamyl transferase (GGT)</td>
<td>S</td>
<td>1-94 U/L</td>
<td>1-94 U/L</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>P</td>
<td>4.2-5.6 mmol/L</td>
<td>75-100 mg/dL</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>&gt;7.0 mmol/L</td>
<td>&gt;125 mg/dL</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum; U, Urine.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, 2nd hour postprandial</td>
<td>P</td>
<td>&lt;6.7 mmol/L</td>
<td>&lt;120 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin A1c (A1C)</td>
<td>W</td>
<td>18-38 mmol/mol</td>
<td>3.8-5.6%</td>
</tr>
<tr>
<td>Homosstein (Hey)</td>
<td>P</td>
<td>4-12 µmol/L</td>
<td>4-12 µmol/L</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>U, 24-hr</td>
<td>0-10 µmol/L</td>
<td>0-1.3 mg/day</td>
</tr>
<tr>
<td>Calcium, ionized (Ca ionized)</td>
<td>W</td>
<td>1.1-1.4 mmol/L</td>
<td>4.5-5.6 mg/dL</td>
</tr>
<tr>
<td>Calcium (Ca)</td>
<td>S</td>
<td>2.2-2.6 mmol/L</td>
<td>9-10.5 mg/dL</td>
</tr>
<tr>
<td>Carbondioxide content (tCO₂) (at sea level)</td>
<td>P</td>
<td>21-30 mmol/L</td>
<td>21-30 mEq/L</td>
</tr>
<tr>
<td>Carbondioxide pressure (tCO₂) (at sea level)</td>
<td>A</td>
<td>47-5.9 kPa</td>
<td>35-45 mmHg</td>
</tr>
<tr>
<td>Carbonmonoxide content (CO)</td>
<td>W</td>
<td>Symptoms occur with 20% saturation of Hb</td>
<td></td>
</tr>
<tr>
<td>Carsinoembryonic antigen (CEA)</td>
<td>S</td>
<td>0.0-3.4 ug/L</td>
<td>0.0-3.4 ng/mL</td>
</tr>
<tr>
<td>Chlorine (Cl)</td>
<td>S</td>
<td>98-106 mmol/L</td>
<td>98-106 mEq/L</td>
</tr>
<tr>
<td>Cholinesterase</td>
<td>S</td>
<td>5-12 kU/L</td>
<td>5-12 U/mL</td>
</tr>
<tr>
<td>Coproporphyrin (Type-I and Type-III)</td>
<td>U</td>
<td>150-460 µmol/day</td>
<td>100-300 µg/day</td>
</tr>
<tr>
<td>Creatinine kinase (Total CK)</td>
<td>S</td>
<td>0.67-2.50 µkat/L</td>
<td>40-150 U/L</td>
</tr>
<tr>
<td>Creatinine kinase-MB (CK-MB)</td>
<td>S</td>
<td>0-7 µg/L</td>
<td>0-7 ng/mL</td>
</tr>
<tr>
<td>Creatinin kinase, relative index [(ng/ml) / (total CK U/l)] X100</td>
<td>S</td>
<td>Based on the method Based on the method</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>S</td>
<td>&lt;133 µmol/L</td>
<td>&lt;1.5 mg/dL</td>
</tr>
<tr>
<td>Ketone (Acetone)</td>
<td>S, U</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Lactate</td>
<td>P, V</td>
<td>0.6-1.7 mmol/L</td>
<td>5-15 mg/dL</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>S</td>
<td>1.7-3.2 µkat/L</td>
<td>100-190 U/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase isoenzymes</td>
<td>S</td>
<td>0.14-0.25</td>
<td>14-26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.29-0.39</td>
<td>29-39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.20-0.25</td>
<td>20-26%</td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum; U, Urine; W, Whole blood; A, Arterial blood; V, Venous blood.
### APPENDIX TABLE 2.1 (cont'd): Clinical biochemical tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fraction 4</td>
<td></td>
<td>0.08-0.16</td>
<td>8-16%</td>
</tr>
<tr>
<td>Fraction 5</td>
<td></td>
<td>0.06-0.16</td>
<td>6-16%</td>
</tr>
<tr>
<td>Lipase</td>
<td>S</td>
<td>0-2.66 µkat/L</td>
<td>0-160 U/L</td>
</tr>
<tr>
<td>Lipid fractions, Adult HDL cholesterol Male</td>
<td>S, fasting</td>
<td>&gt;1.0 mmol/L</td>
<td>&gt;40 mg/dL</td>
</tr>
<tr>
<td>Lipid fractions, Adult HDL cholesterol Female</td>
<td></td>
<td>&gt;1.3 mmol/L</td>
<td>&gt;50 mg/dL</td>
</tr>
<tr>
<td>Lipid fractions, Adult LDL cholesterol Diabetes mellitus</td>
<td></td>
<td>&lt;3.4 mmol/L</td>
<td>&lt;130 mg/dL</td>
</tr>
<tr>
<td>Lipid fractions, Adult LDL cholesterol Diabetes mellitus + Cardiovascular event</td>
<td></td>
<td>&lt;2.6 mmol/L</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Lipid fractions, Adult LDL cholesterol Diabetes mellitus + Cardiovascular event</td>
<td></td>
<td>&lt;1.8 mmol/L</td>
<td>&lt;70 mg/dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>S</td>
<td>&lt;1.8 mmol/L</td>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td>Lipoprotein lal</td>
<td>S</td>
<td>0-300 mg/L</td>
<td>0-30 mg/dL</td>
</tr>
<tr>
<td>Magnesium (Mg)</td>
<td>S</td>
<td>0.8-1.2 mmol/L</td>
<td>1.8-3 mg/dL</td>
</tr>
<tr>
<td>Microalbuninuric (UAE) 26-hr</td>
<td>U</td>
<td>&lt;0.2 g/L or ≤0.031 g/24-hr</td>
<td>&lt;20 mg/L or ≤30 mg/24-hr</td>
</tr>
<tr>
<td>Spot, first-morning urine</td>
<td>U</td>
<td>&lt;30 mg albumin/g creatinine</td>
<td>&lt;30 mg albumin/g creatinine</td>
</tr>
<tr>
<td>Myoglobin Male</td>
<td>S</td>
<td>19-92 µg/L</td>
<td>19-92 µg/L</td>
</tr>
<tr>
<td>Myoglobin Female</td>
<td></td>
<td>12-76 µg/L</td>
<td>12-76 µg/L</td>
</tr>
<tr>
<td>S'-Nucleotidase</td>
<td>S</td>
<td>0.02-0.18 ukat/L</td>
<td>0-11 U/L</td>
</tr>
<tr>
<td>N-telopeptide (cross bond), NTx</td>
<td>U</td>
<td>3-65 nmol/mmol creatinine</td>
<td>3-65 nmol/mmol creatinine</td>
</tr>
<tr>
<td>Oxygen level (at sea level) W, A</td>
<td>W, A, V, forearm</td>
<td>17-21</td>
<td>17-21%</td>
</tr>
<tr>
<td>Oxygen level (at sea level) W, A</td>
<td>W, A, V, forearm</td>
<td>10 - 16</td>
<td>10-16%</td>
</tr>
<tr>
<td>Oxygen saturation percentage (at sea level) W, A</td>
<td>W, A, V, forearm</td>
<td>0.97 mol/mol</td>
<td>97%</td>
</tr>
<tr>
<td>Oxygen saturation percentage (at sea level) W, A</td>
<td>W, A, V, forearm</td>
<td>0.60-0.85 mol/mol</td>
<td>60-85%</td>
</tr>
<tr>
<td>Oxygen pressure ($pO_2$)</td>
<td>W</td>
<td>11-13 kPa</td>
<td>80-100 mmHg</td>
</tr>
<tr>
<td>pH</td>
<td>W</td>
<td>7.38-7.44</td>
<td>7.38-7.44</td>
</tr>
<tr>
<td>Osmolality</td>
<td>P</td>
<td>285-295 mmol/kg</td>
<td></td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum; U, Urine; W, Whole blood; A, Arterial blood; V, Venous blood.
### APPENDIX TABLE 2.1 (cont’d): Clinical biochemical tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>U</td>
<td>300-900 mmol/kg</td>
<td>300-900 mmol/kg</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>S</td>
<td>3.1-14 ug/mL</td>
<td>3.1-14 ng/mL</td>
</tr>
<tr>
<td>Parathyroid hormone-related peptide (PTHrP)</td>
<td>S</td>
<td>&lt; 2 pmol/L</td>
<td></td>
</tr>
<tr>
<td>Potassium (K)</td>
<td>S</td>
<td>3.5-5.0 mmol/L</td>
<td>3.5-5.0 mEq/L</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>S</td>
<td>195-358 mg/L</td>
<td>19.5-35.8 mg/dL</td>
</tr>
<tr>
<td>Prostate-specific antigen (PSA), total</td>
<td>S</td>
<td>&lt;0.5 µg/L</td>
<td>&lt;0.5 ng/mL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0.0-2.0 µg/L</td>
<td>0.0-2.0 ng/mL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.0-4.0 µg/L</td>
<td>0.0-4.0 ng/mL</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td></td>
<td>&gt;0.25 (BPH-related)</td>
<td>&gt;25% (BPH-related)</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA, free, Male aged 45-75, between 4-20 µg/mL PSA</td>
<td>S</td>
<td>&lt;0.5 µg/L</td>
<td>0.0-2.0 ng/mL</td>
</tr>
<tr>
<td>Protein, total</td>
<td>S</td>
<td>55-80 g/L</td>
<td>5.5-8.0 g/dL</td>
</tr>
<tr>
<td>Protein fractions:</td>
<td></td>
<td>35-55 g/L</td>
<td>3.5-5.5 g/dL (50-60%)</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td>20-35 g/L</td>
<td>2.0-3.5 g/dL (40-50%)</td>
</tr>
<tr>
<td>Globulin</td>
<td></td>
<td>2-4 g/L</td>
<td>0.2-0.4 g/dL (4.2 -7.2%)</td>
</tr>
<tr>
<td>Alpha-1</td>
<td></td>
<td>5-9 g/L</td>
<td>0.5-0.9 g/dL (6.8 -12%)</td>
</tr>
<tr>
<td>Alpha-2</td>
<td></td>
<td>6-11 g/L</td>
<td>0.6-1.1 g/dL (9.3-15%)</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td>7-17 g/L</td>
<td>0.7-1.7 g/dL (13-23%)</td>
</tr>
<tr>
<td>Gama</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyruvate</td>
<td>P, V</td>
<td>60-170 µmol/L</td>
<td>0.5-1.5 mg/dL</td>
</tr>
<tr>
<td>Free fatty acids (FFA) (non-esterified)</td>
<td>P</td>
<td>0.28-0.89 mmol/L</td>
<td>&lt;8-25 mg/dL</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>S</td>
<td>270-370 mg/L</td>
<td>27-37 mg/dL</td>
</tr>
<tr>
<td>Transferrin</td>
<td>S</td>
<td>2.3-3.9 g/L</td>
<td>230-390 mg/dL</td>
</tr>
<tr>
<td>Troponin-I</td>
<td>S</td>
<td>0-0.4 µg/L</td>
<td>0-0.4 ng/mL</td>
</tr>
<tr>
<td>Troponin-T</td>
<td>S</td>
<td>0-0.1 µg/L</td>
<td>0-0.1 ng/mL</td>
</tr>
<tr>
<td>Urea nitrogen (BUN)</td>
<td>S</td>
<td>3.6-7.1 mmol/L</td>
<td>10-20 mg/dL</td>
</tr>
<tr>
<td>Uric acid</td>
<td>S</td>
<td>150-480 µmol/L</td>
<td>2.5-8.0 mg/dL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>90-360 µmol/L</td>
<td>1.5-6.0 mg/dL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum; U, Urine; V, Venous blood; BPH, Benign prostate hypertrophy.
### APPENDIX TABLE 2.1 (cont’d): Clinical biochemical tests

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urobilinogen</td>
<td>U</td>
<td>1.7-5.9 µmol/day</td>
<td>1.3-3.5 mg/day</td>
</tr>
<tr>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>P</td>
<td>&lt;75 ng/L</td>
<td>&lt;75 pg/L</td>
</tr>
</tbody>
</table>

P, Plasma; U, Urine.

### APPENDIX TABLE 2.2 | ENDOCRINOLOGY AND METABOLISM TESTS *

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropin (ACTH)</td>
<td>P</td>
<td>1.3-16.7 pmol/L</td>
<td>6.0-76.0 pg/mL</td>
</tr>
<tr>
<td>Aldosterone (Adult)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laying Normal sodium diet</td>
<td>S, P</td>
<td>55-250 pmol/L</td>
<td>2.9 ng/dL</td>
</tr>
<tr>
<td>Standing Normal sodium diet</td>
<td>S, P</td>
<td></td>
<td>2.5 times the value at laying position</td>
</tr>
<tr>
<td>Laying low sodium diet</td>
<td>S, P</td>
<td>6.38-58.25 nmol/day</td>
<td>2.3-21.0 μg/24 h</td>
</tr>
<tr>
<td>Random low sodium diet</td>
<td>U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androstenedione (Adult)</td>
<td>S</td>
<td>1.75-8.73 nmol/L</td>
<td>50-250 ng/dL</td>
</tr>
<tr>
<td>Growth hormone (GH) (at rest)</td>
<td>S</td>
<td>0.5-17.0 µg/L</td>
<td>0.5-17.0 ng/mL</td>
</tr>
<tr>
<td>C-peptide (Adult)</td>
<td>S, P</td>
<td>0.17-0.66 nmol/L</td>
<td>0.5-2.0 ng/mL</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA) (Adult)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>S</td>
<td>6.24-41.6 nmol/L</td>
<td>180-1250 ng/dL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>4.5-34.0 nmol/L</td>
<td>130-980 ng/dL</td>
</tr>
<tr>
<td>DHEA sulphate</td>
<td>S</td>
<td>100-6190 µg/L</td>
<td>10-619 µg/dL</td>
</tr>
<tr>
<td>Male (Adult)</td>
<td></td>
<td>120-5350 µg/L</td>
<td>12-535 µg/dL</td>
</tr>
<tr>
<td>Female (Adult, premenopausal)</td>
<td></td>
<td>300-2600 µg/L</td>
<td>30-260 µg/dL</td>
</tr>
<tr>
<td>Female (Adult, postmenopausal)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P, Plasma; S, Serum; U, Urine.

*Conversion between conventional and international (SI) unit systems can be calculated based on the following equation: \( \text{mmol/L} = \frac{\text{mg/dL} \times 10}{\text{Atom (or molecular weight; mg/dL} \times \text{Atom (or molecule) weight)/10}} \)


---

264 | SEMT Clinical Practice Guideline for Diabetes-2019
### APPENDIX TABLE 2.2 (cont’d): Endocrinology and metabolism tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deoxycorticosterone (DOC) (Adult)</td>
<td>S</td>
<td>61.576 nmol/L</td>
<td>2-19 ng/dL</td>
</tr>
<tr>
<td>11-Deoxycortisole (Adult) (S content) (at 08:00 in the morning)</td>
<td>S</td>
<td>0.34-4.56 nmol/L</td>
<td>12-158 ng/dL</td>
</tr>
<tr>
<td>Dihydrotestosterone</td>
<td>S, P</td>
<td>1.03-2.92 nmol/L</td>
<td>30-85 ng/dL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.14-0.76 nmol/L</td>
<td>4-22 ng/dL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>P</td>
<td>&lt;475 pmol/L</td>
<td>&lt;87 pg/mL</td>
</tr>
<tr>
<td>Hormone (Adult)</td>
<td>U</td>
<td>425-2610 nmol/day</td>
<td>65-400 g/day</td>
</tr>
<tr>
<td>Epinephrine (Adrenaline)</td>
<td>P</td>
<td>&lt;273 pmol/L</td>
<td>&lt;50 pg/mL</td>
</tr>
<tr>
<td>Laying (30 min)</td>
<td></td>
<td>&lt;328 pmol/L</td>
<td>&lt;60 pg/mL</td>
</tr>
<tr>
<td>Sitting</td>
<td></td>
<td>&lt;4914 pmol/L</td>
<td>&lt;900 pg/mL</td>
</tr>
<tr>
<td>Standing (30 min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine (Adrenaline)</td>
<td>U</td>
<td>0-109 nmol/day</td>
<td>0-20 µg/day</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
<td>S, P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>3.0-20.0 IU/L</td>
<td>3.0-20.0 U/L</td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td>9.0-26.0 IU/L</td>
<td>9.0-26.0 U/L</td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td>18.0-153.0 IU/L</td>
<td>18.0-153.0 U/L</td>
</tr>
<tr>
<td>Ovulation phase</td>
<td></td>
<td>1.0-12.0 IU/L</td>
<td>1.0-12.0 U/L</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.15 nmol/L</td>
<td>5-250 ng/dL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0.6-3.0 nmol/L</td>
<td>20-100 ng/dL</td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td>3-7.5 nmol/L</td>
<td>100-250 ng/dL</td>
</tr>
<tr>
<td>Mid-cycle peak value</td>
<td></td>
<td>3-15 nmol/L</td>
<td>100-500 ng/dL</td>
</tr>
<tr>
<td>Luteal phase</td>
<td></td>
<td>≤2.1 nmol/L</td>
<td>≤70 ng/dL</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructosamine</td>
<td>S</td>
<td>1.61-2.68 mmol/L</td>
<td>1.61-2.68 mmol/L</td>
</tr>
<tr>
<td>Gastrin</td>
<td>S</td>
<td>&lt;100 ng/L</td>
<td>&lt;100 pg/mL</td>
</tr>
<tr>
<td>Glucagon</td>
<td>P</td>
<td>20-100 ng/L</td>
<td>20-100 pg/mL</td>
</tr>
<tr>
<td>5-Hydroxy-indole acetic acid [5-HIAA]</td>
<td>U</td>
<td>10.5-36.6 µmol/day</td>
<td>2-7 mg/day</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone Adult</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td>0.15 nmol/L</td>
<td>5-250 ng/dl</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>0.6-3.0 nmol/L</td>
<td>20-100 ng/dl</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>3-7.5 nmol/L</td>
<td>100-250 ng/dl</td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td>3-15 nmol/L</td>
<td>100-500 ng/dL</td>
</tr>
<tr>
<td>Mid-cycle peak value</td>
<td></td>
<td>≤2.1 nmol/L</td>
<td>≤70 ng/dL</td>
</tr>
</tbody>
</table>

P: Plasma, S: Serum, U: Urine.
### APPENDIX TABLE 2.2 (cont’d): Endocrinology and metabolism tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td>S, P</td>
<td>14.35-143.5 pmol/L</td>
<td>2-20 µU/mL</td>
</tr>
<tr>
<td><strong>17-Ketosteroids</strong></td>
<td>U</td>
<td>10-42 µmol/day</td>
<td>3-12 mg/day</td>
</tr>
<tr>
<td><strong>Cortisol</strong></td>
<td>S</td>
<td>138-690 nmol/L, 138-414 nmol/L, 0-276 nmol/L</td>
<td>5-25 µg/dL, 5-15 µg/dL, 0-10 µg/dL</td>
</tr>
<tr>
<td>Fasting, at 08:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noon-20:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20:00-08:00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cortisol, free</strong></td>
<td>U</td>
<td>55-193 nmol/24-hr</td>
<td>20-70 µg/24 hr</td>
</tr>
<tr>
<td><strong>Estradiol</strong></td>
<td>S, P</td>
<td>184-532 pmol/L, 411-1626 pmol/L, 184-885 pmol/L, 217 pmol/L, 184 pmol/L</td>
<td>&lt;20-145 pg/mL, 112-443 pg/mL, &lt;20-241 pg/mL, &lt;59 pg/mL, &lt;20 pg/mL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-cycle peak value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Estrone</strong></td>
<td>S, P</td>
<td>55-555 pmol/L, 55-740 pmol/L, 55-204 pmol/L, 55-240 pmol/L</td>
<td>1.5-15 pg/mL, 1.5-20 pg/mL, 1.5-5.5 pg/mL, 1.5-6.5 pg/mL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Human chorionic gonadotropin (HCG)</strong></td>
<td>S</td>
<td>&lt;5 IU/L</td>
<td>&lt;5 mIU/mL</td>
</tr>
<tr>
<td>(except pregnancy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Luteinising hormone (LH)</strong></td>
<td>S, P</td>
<td>2.0-15.0 U/L, 22.0-105.0 U/L, 0.6-19.0 U/L, 16.0-64.0 U/L, 2.0-12.0 U/L</td>
<td>2.0-15.0 U/L, 22.0-105.0 U/L, 0.6-19.0 U/L, 16.0-64.0 U/L, 2.0-12.0 U/L</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstruation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: Plasma, S: Serum, U: Urine.
<table>
<thead>
<tr>
<th>Test</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (Noradrenaline)</td>
<td>U</td>
<td>89-473 nmol/day</td>
<td>15-80 µg/day</td>
</tr>
<tr>
<td>Norepinephrine (Noradrenaline) Laying (30 min)</td>
<td>P</td>
<td>650-2423 pmol/L</td>
<td>&lt;110-410 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>709-4019 pmol/L</td>
<td>120-680 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>739-4137 pmol/L</td>
<td>125-700 pg/mL</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>S</td>
<td>10-60 ng/L</td>
<td>10-60 pg/mL</td>
</tr>
<tr>
<td>Progesterone</td>
<td>S, P</td>
<td>&lt;3.18 nmol/L</td>
<td>&lt;1.0 ng/mL</td>
</tr>
<tr>
<td>Female Follicular</td>
<td></td>
<td>9.54-63.6 nmol/L</td>
<td>3-20 ng/mL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>&lt;3.18 nmol/L</td>
<td>&lt;1.0 ng/mL</td>
</tr>
<tr>
<td>Prolactin</td>
<td>S</td>
<td>0-20 µg/L</td>
<td>1.9-25.9 ng/mL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0-15 µg/L</td>
<td>1.6-23 ng/mL</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renin (Adult, normal Na diet)</td>
<td>P</td>
<td>0.08-0.83 ng/L/second</td>
<td>0.3-3.0 ng/mL/hr</td>
</tr>
<tr>
<td>Laying</td>
<td></td>
<td>0.28-2.5 ng/L/second</td>
<td>1-9.0 ng/mL/hr</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex hormone binding globulin (SHBG) (Adult)</td>
<td>S</td>
<td></td>
<td>13-71 nmol/L</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>18-114 nmol/L</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>W</td>
<td>0.28-1.14 µmol/L</td>
<td>50-200 ng/mL</td>
</tr>
<tr>
<td>Serotonin</td>
<td>W</td>
<td>0.7-2.8 µmol/thrombocyte</td>
<td>125-500 ng/10^9 thrombocyte</td>
</tr>
<tr>
<td>Somatomedin-C (IGF-1) (Adult)</td>
<td>S</td>
<td>182-780 µg/L</td>
<td>182-780 ng/mL</td>
</tr>
<tr>
<td>16-24 years</td>
<td></td>
<td>114-492 µg/L</td>
<td>114-492 ng/mL</td>
</tr>
<tr>
<td>25-39 years</td>
<td></td>
<td>90-360 µg/L</td>
<td>90-360 ng/mL</td>
</tr>
<tr>
<td>&gt;54 years</td>
<td></td>
<td>71-290 µg/L</td>
<td>71-290 ng/mL</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>P</td>
<td>&lt;25 ng/L</td>
<td>&lt;25 pg/mL</td>
</tr>
<tr>
<td>Testosterone, free, morning sample</td>
<td>S</td>
<td>6.9-107.5 pmol/L</td>
<td>0.2-3.1 pg/mL</td>
</tr>
<tr>
<td>Female, Adult</td>
<td></td>
<td>416-1386 pmol/L</td>
<td>12.0-40.0 pg/mL</td>
</tr>
<tr>
<td>Male, Adult</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: Plasma, S: Serum, U: Urine, W: Whole blood
### APPENDIX TABLE 2.2 (cont’d): Endocrinology and metabolism tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample type</th>
<th>SI unit</th>
<th>Conventional unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone, total, morning sample</td>
<td>S</td>
<td>0.21-2.98 nmol/L</td>
<td>6.86 ng/dL 270-1070 ng/dL</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>9.36-37.10 nmol/L</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>6-86 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>S</td>
<td>0-60 µg/L</td>
<td>0-60 ng/mL</td>
</tr>
<tr>
<td>Thyroxine binding globulin (TBG)</td>
<td>S</td>
<td>206-309 µg/L</td>
<td>16-24 µg/dL</td>
</tr>
<tr>
<td>Thyroid hormone binding index (THBI or T3RU)</td>
<td>S</td>
<td>0.83-1.17 mol ratio</td>
<td>0.83-1.17</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>S</td>
<td>0.5-4.7 mUI/L</td>
<td>0.5-4.7 µU/mL</td>
</tr>
<tr>
<td>Free thyroxine index (FT4I)</td>
<td>S</td>
<td>4.2-13</td>
<td>4.2-13</td>
</tr>
<tr>
<td>Free thyroxine (FT4)</td>
<td>S</td>
<td>12-20 pmol/L</td>
<td>0.8-1.7 ng/dL</td>
</tr>
<tr>
<td>Total thyroxine (T4)</td>
<td>S</td>
<td>58-140 nmol/L</td>
<td>4.5-10.9 µg/dL</td>
</tr>
<tr>
<td>Free triiodothyronine (FT3)</td>
<td>S</td>
<td>0.22-6.78 pmol/L</td>
<td>1.4-4.4 pg/mL</td>
</tr>
</tbody>
</table>

S, Serum.