



2023 Clinical Practice Guidelines for Diabetes Management in Korea: Full Version Recommendation of the Korean Diabetes Association

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Table 1. Levels of evidence and recommendation grades

	Notation
Levels of evidence: Classification based on study design	
Systematic review, meta-analysis, randomized controlled trial	Randomized controlled trial
Non-randomized controlled studies	Non-randomized controlled trial
Case series etc.	Uncontrolled studies
Expert opinion	Expert opinion
Recommendation grades: Classification based on the balance of benefits and harms and the scope of application	
When it is recommended to apply to most subjects	General recommendation
When it is recommended to apply with limitations based on certain conditions among the subjects	Limited recommendation

PREFACE

The 2023 Diabetes Clinical Practice Guidelines, developed by the Korean Diabetes Association (KDA), aim to provide evidence-based recommendations for the diagnosis, screening, prevention, and treatment of diabetes and its complications (Table 1). The target population for these guidelines includes adult patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), pediatric and adolescent patients with T2DM, gestational diabetes, and adults with prediabetes. The guidelines have been restructured and updated from the ‘2021 Diabetes Management Guideline’ to serve as a comprehensive resource for a wide range of healthcare professionals involved in diabetes care, including general physicians, specialists, private practitioners, diabetes care physicians in educational institutions, nurses, nutritionists, exercise therapists, social workers, policy makers and other professionals. By promoting effective treatments, providing alternatives to risky or unnecessary interventions, and incorporating essential information on crucial aspects of diabetes care, these guidelines strive to enhance the overall quality of diabetes care in Korea, optimize patient outcomes, and reduce healthcare costs. Ultimately, the guidelines aim to empower healthcare professionals to make informed decisions and deliver the best possible care to patients with diabetes, thereby improving their quality of life and reducing mortality rates.

Composition and role of multidisciplinary groups for the development of guidelines

The writing committee comprised a diverse group of qualified experts to ensure comprehensive coverage of both T1DM and T2DM guidelines. The committee included diabetes special-

ists, nurses, nutritionists, and social workers, as well as experts from various research societies under the KDA, focusing on exercise, neuropathy, nephropathy, geriatric diabetes, gestational diabetes, pancreas transplantation, and fatty liver disease. Additionally, experts from relevant specialist societies, such as the Korean Society of Infectious Diseases, the Korean Ophthalmological Society, the Korean Society for the Study of Obesity, the Korean Society of Hypertension, and the Korean Society of Paediatric Endocrinology, were involved. The working committee members of the KDA and the director of the Clinical Practice Guidelines Committee also participated in the guideline development process. Experts in guideline development methodology (systematic review experts) were also included to ensure a rigorous and evidence-based approach. The committee members were assigned roles based on their areas of expertise to derive recommendations and draft initial proposals using the evidence extracted from the research.

Target users of the guidelines

The target users of these guidelines include general practitioners, practicing physicians, specialists, physicians treating diabetes patients in educational institutions, nurses in clinics and educational institutions, nutritionists, social workers, and other diabetes care professionals. The guidelines are intended for use in primary, secondary, and tertiary medical institutions, as well as outpatient and inpatient settings. The detailed fields of target users encompass general physicians, family medicine physicians, pediatricians, internal medicine physicians (endocrinology, nephrology, cardiology, geriatrics, etc.), hospitalists, orthopedic surgeons, ophthalmologists, obstetricians, and gynecologists, among others.

Table 2. Content and steps of the Korean Diabetes Association's diabetes clinical practice guidelines production process

Stepwise development content of content of guidelines adaptation	
Guideline development planning	Organization of guideline committees (development groups, working committees) Planning and consensus on revision direction in the development planning phase
Guideline development preparation	Search for guidelines Evaluation of guidelines Evaluation of literature selected through systematic review
Guideline development step I (recommendation development)	Drafting initial recommendations Survey and incorporate user feedback (utilization, acceptance, adoption, etc.) Agree on a way to adopt recommendations
Guideline development step II (guideline writing)	Drafting a guideline 1. present a summary (table) of the finalized recommendations 2. description of the development process and methods 3. describe the rationale or background 4. presentation of evidence 5. presentation of summary and appendices
Review and guideline finalization	Internal reviewed by users: Korean Diabetes Association Executive Board and Primary Care Committee External review: related societies (Korean Association of Internal Medicine, Korean Endocrinology Society, Korean Society for the Study of Obesity, Korean Ophthalmological Society, Korean Society of Hypertension, Korean Society of Lipid Atherosclerosis, Korean Society of Nephrology, Korean Society of Pediatric Endocrinology, Korean Society of Infectious Diseases) Disclosed to members through the Korean Diabetes Association website Finalization of the guideline
Accreditation and distribution	Certification after external review Publication Apply for evaluation for accreditation by the Korean Medical Association Disseminate and spread: publications, courses, releasing materials on homepage, web online production

1. DIAGNOSIS AND CLASSIFICATION OF DIABETES MELLITUS

1. Normal blood glucose level

The normal 8-hour fasting plasma glucose (FPG) level is <100 mg/dL, and the normal 2-hour plasma glucose during 75 g oral glucose tolerance test (OGTT) is <140 mg/dL.

2. Diagnostic criteria for diabetes

- 1) Glycosylated hemoglobin (HbA1c; HbA1c should be measured using the standardized method) $\geq 6.5\%$, or
- 2) 8-hour FPG level ≥ 126 mg/dL, or
- 3) 2-hour plasma glucose during 75 g OGTT ≥ 200 mg/dL, or
- 4) Presence of typical symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) with random plasma glucose level ≥ 200 mg/dL
-If an individual meets any of 1)–3) of the diagnostic criteria, tests should be repeated on different days. However, an immediate diagnosis can be made if the individual meets at least two criteria from the tests simultaneously performed.

3. Diagnostic criteria for prediabetes

- 1) Impaired fasting glucose (IFG): FPG level 100–125 mg/dL, or
- 2) Impaired glucose tolerance (IGT): 2-hour plasma glucose during 75 g OGTT 140–199 mg/dL, or
- 3) HbA1c: 5.7%–6.4%

1.1 Diagnostic criteria for diabetes

Fasting plasma glucose

In 2007, the Diagnostic Subcommittee of the KDA reviewed the results of several previous studies conducted in Korea, including 6,234 subjects (2,473 in Yeoncheon, 774 in Mokdong, 1,106 in Jeongup, and 1,882 in Ansan), 40.9% of whom were male [1,2]. The subcommittee reported that a FPG level of 110 mg/dL corresponds to a 2-hour plasma glucose level of 200 mg/dL. However, because of the absence of large epidemiologic studies that suggest the level of FPG that can predict the incidence of diabetic complications in Koreans, it is reasonable, as suggested in the KDA guidelines, to set the diagnostic criterion for diabetes at a FPG level of 126 mg/dL or higher, and the normal FPG standard as less than 100 mg/dL, similar to the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) [3–5].

Oral glucose tolerance test

The OGTT is a test method that is cumbersome, time-consuming, has low reproducibility, and is relatively high in cost. Because of this, it is difficult to recommend it uniformly for diabetes diagnosis in primary healthcare centers. However, Korean adults with diabetes are less obese than their Western counterparts, have relatively low insulin secretion capacity, and often only present with postprandial hyperglycemia, especially in the elderly. Therefore, screening with FPG alone may miss diagnosing diabetes in a significant number of cases. In contrast, lowering the FPG cutoff to overcome the issue reduces diagnostic

specificity.

The OGTT commonly uses the World Health Organization (WHO) method, which involves blood collection at fasting and 2 hours after a 75-g glucose load [6,7]. The Japanese Diabetes Society (JDS) recommends simultaneous measurement of plasma glucose and insulin at 30 and 60 minutes after a glucose load, along with fasting and 2-hour measurements [8]. Although a fasting and 2-hour postprandial test may be more convenient, additional tests at 30, 60, and 90 minutes may be necessary [9]. Specific methods for OGTT based on the WHO recommendations [7] are shown in Table 3.

Individual national diabetes societies or associations and international organizations generally recommend OGTT for people with IFG despite subtle differences between countries. The IDF recommends an OGTT to diagnose diabetes if FPG levels are 100 to 125 mg/dL and also recommends FPG measurement or OGTT if random glucose levels are 100 to 199 mg/dL [3,4].

Considering the recommendations of other countries and the characteristics of diabetes in the Korean population, the KDA recommends that OGTT be conducted for patients with IFG, high diabetes risks despite showing normal FPG levels, and individuals over 60 for whom FPG may not be a practical diagnostic test, equivocal blood glucose test results, pregnant individuals, and in epidemiologic studies [1,2,10,11]. OGTT is also helpful for diagnosing IGT, which is a high-risk condition for diabetes. IGT is more common than IFG and is associated with more cardiovascular events and overall mortality. As appropriate interventions can prevent the progression of T2DM

Table 3. Oral glucose tolerance test methods

1	Maintain usual physical activity and consume an unrestricted diet (greater than 150 g of carbohydrate daily) for at least 3 days before the test.
2	An overnight fast of 10–14 hours should be preceded for fasting plasma glucose measurement.
3	Drink 75 g of glucose in 250–300 mL of water or 150 mL of a commercially available dextrose solution over 5 minutes.
4	Blood samples are collected 2 hours after the test load (The time at which drinking began is considered 0 minute).
5	If appropriate, samples may also be taken in 30, 60, and 90 minutes.

and the development of cardiovascular disease (CVD) in individuals with IGT, it is worth screening for prediabetes. Therefore, it is clinically meaningful to diagnose not only diabetes but also IGT through OGTT.

Glycosylated hemoglobin

The HbA1c test is a widely used, convenient means for determining glycemic status. It is available irrespective of fasting or meals and correlates well with FPG and postprandial blood glucose levels. In 2009, the International Expert Committee recommended that an HbA1c level of 6.5% or higher should be included as a new diagnostic criterion for diabetes when tested by a standardized method (Diabetes Control and Complication Trial [DCCT] reference assay) and certified by the National Glycohemoglobin Standardization Program. This is because it more accurately reflects long-term glycemic control, correlates well with the risk of diabetic complications, and is more reliable than blood glucose measurement. The ADA [3] and JDS [8] also included this criterion in their diagnostic guidelines.

In Korea, it has been found that using FPG of 126 mg/dL or higher alone as a diagnostic criterion for detecting diabetes could diagnose 55.7% of all diabetic patients, suggesting that the HbA1c criterion should also be considered [12]. The concordance of FPG and HbA1c levels as the diagnostic criteria for diabetes detection has been confirmed. Considering the low specificity of FPG and concordance between FPG and HbA1c levels, it is appropriate to use an HbA1c of 6.5% or more as a diagnostic criterion for diabetes in Korea [13]. This has been reflected in the guidelines of the KDA since 2013. However, the diagnosis rate of diabetes when using HbA1c alone was only 30% of that when using a combination of FPG and 2-hour plasma glucose after OGTT [14]. It is important to pay caution while interpreting the HbA1c results because HbA1c levels do not accurately reflect blood glucose status in certain situations such as hemoglobinopathies, pregnancy, glucose-6-phosphate dehydrogenase deficiency, human immunodeficiency virus in-

fection, hemodialysis, recent blood loss or transfusion, and hematopoietic drug treatment.

1.2 Classification of diabetes

With the revisions made by the ADA in 1997 and the WHO in 1999, the terms of insulin-dependent and insulin-independent diabetes based on treatment perspectives have been revised to T1DM and T2DM. There have been no significant changes to the classification of diabetes mellitus since then (Table 4). Based on the findings that the incidence of IGT was common (12% to 40%) in liver disease (hepatitis, cirrhosis), the recommendation by the Committee of the JDS in 2002 added liver disease as one of the causes resulting in 'other diabetes.' As the prevalence of diabetes among individuals with chronic liver disease increased to 15% to 30% in Korea as well [15], liver disease was added as a cause of 'other diabetes' also in the KDA guideline since 2011.

Measurement of autoantibodies (glutamic acid decarboxylase [GAD] autoantibody, insulin autoantibody, islet autoantibody, etc.), insulin, and C-peptide may help differentiate between T1DM and T2DM. Several Korean studies have classified fasting serum C-peptide levels below 0.6 ng/mL (0.2 nmol/L) as indicative of T1DM and above 1.0 ng/mL (0.33 nmol/L) as indicative of T2DM.

The presence of autoantibodies increases the likelihood of immune-mediated T1DM. However, it has been reported that 4% to 25% of individuals diagnosed with T2DM tested positive for GAD autoantibody. In such cases, insulin treatment is more likely to be initiated [16–19]. Among diabetes caused by autoimmune mechanisms, cases that progress slowly, as opposed to the rapidly progressing T1DM, are separately classified as 'latent autoimmune diabetes in adults' [20]. Atypical diabetes, which is difficult to classify at the time of onset, is relatively common in Korea [21]. The clinical course, C-peptide, and autoantibodies should be monitored and re-evaluated in this case.

Table 4. Classification of diabetes

1	Type 1 diabetes mellitus: diabetes caused by insulin deficiency due to β -cell destruction
	1-1. Immune-mediated
	1-2. Idiopathic
2	Type 2 diabetes mellitus: diabetes caused by insulin resistance and progressive insulin secretion defect
3	Gestational diabetes mellitus: diabetes diagnosed during pregnancy
4	Other diabetes
	4-1. Genetic defects in β -cell function
	MODY3 (chromosome 12, HNF-1 α), MODY1 (chromosome 20, HNF-4 α), MODY2 (chromosome 7, glucokinase)
	Other rare forms of MODY (MODY4: chromosome 13, IPF-1; MODY5: chromosome 17, HNF-1 β ; MODY6: chromosome 2, NeuroD1; MODY7: chromosome 2, KLF11; MODY8: chromosome 9, CEL; MODY9: chromosome 7, PAX5; MODY10: chromosome 11, INS; MODY11: chromosome 8, BLK), transient neonatal diabetes (chromosome 6, ZAC/HYAMI imprinting defect), permanent neonatal diabetes (KCNJ11 gene encoding Kir6.2 subunit of β -cell K_{ATP} channel), mitochondrial DNA
	4-2. Genetic defects in insulin action
	Type A insulin resistance, leprechaunism, Rabson-Mendenhall syndrome, lipotrophic diabetes
	4-3. Diseases of the exocrine pancreas
	Pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
	4-4. Endocrinopathies
	Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
	4-5. Liver disease: chronic hepatitis, cirrhosis
	4-6. Drug- or chemical-induced
	Vacor, pentamidine, glucocorticoids, nicotinic acid, thyroid hormone, diazoxazole, β -adrenergic agonist, thiazides, dilantin, γ -interferon, atypical antipsychotics (olanzapine, clozapine, risperidone, etc.), immune checkpoint inhibitor
	4-7. Infections: congenital rubella, cytomegalovirus, others
	4-8. Uncommon forms of immune-mediated diabetes
	Stiff-man syndrome, anti-insulin receptor antibodies
	4-9. Other genetic syndromes sometimes associated with diabetes
	Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

MODY, maturity onset diabetes of the young; HNF, hepatocyte nuclear factor; IPF-1, insulin promoter factor 1; KLF11, KLF transcription factor 11; CEL, carboxyl ester lipase; PAX5, paired box 5; INS, insulin; BLK, BLK proto-oncogene, src family tyrosine kinase; ZAC/HYAMI, zinc finger protein associated with apoptosis and cell cycle arrest/imprinted in hydatidiform mole; KCNJ11, potassium inwardly rectifying channel subfamily J member 11.

2. SCREENING AND DIAGNOSIS OF GESTATIONAL DIABETES

1. The first hospital visit after confirming pregnancy
 - 1) All pregnant women should undergo either fasting plasma glucose (FPG), random plasma glucose, or HbA1c testing at their first hospital visit after confirming pregnancy. [Non-randomized controlled trial, general recommendation]
 - 2) If pregnant women meet any of the following criteria during the first hospital visit after confirming pregnancy, they are considered to have pre-existing diabetes—If an individual meets any of the 2-1) to 2-3) criteria, diagnosis requires two abnormal test results obtained at the same time or these criteria should be confirmed by repeat testing on a different day.
 - 2-1) HbA1c \geq 6.5%
 - 2-2) 8-hour FPG \geq 126 mg/dL
 - 2-3) 2-hour plasma glucose during 75-g OGTT \geq 200 mg/dL
 - 2-4) Presence of classic symptoms of hyperglycemia (polyuria, polydipsia, and unknown weight loss) with random plasma glucose level \geq 200 mg/dL
2. 24 to 28 weeks of gestation
 - 1) Pregnant women who have never been diagnosed with diabetes or gestational diabetes should be tested using one of the following methods between 24 to 28 weeks of pregnancy. [Non-randomized controlled trial, general recommendation]
 - 1-1) 75-g OGTT: gestational diabetes mellitus (GDM) is diagnosed if one or more of the following criteria are met (one-step approach).
 - FPG \geq 92 mg/dL
 - 1-hour plasma glucose during OGTT \geq 180 mg/dL
 - 2-hour plasma glucose during OGTT \geq 153 mg/dL
 - 1-2) If the plasma glucose level measured 1 hour after load during a 50-g OGTT is \geq 140 mg/dL (\geq 130 mg/dL for pregnant women at high risk), proceed to a 100-g OGTT; GDM is diagnosed if two or more of the following criteria are met (two-step approach).
 - FPG \geq 95 mg/dL
 - 1-hour plasma glucose during OGTT \geq 180 mg/dL
 - 2-hour plasma glucose during OGTT \geq 155 mg/dL
 - 3-hour plasma glucose during OGTT \geq 140 mg/dL

Recommendation 2.1 The first hospital visit after confirming pregnancy

- 1) All pregnant women should undergo either FPG, random plasma glucose, or HbA1c testing at their first hospital visit after confirming pregnancy. [Non-randomized controlled trial, general recommendation]
- 2) If pregnant women meet any of the following criteria during the first hospital visit after confirming pregnancy, they are considered to have pre-existing diabetes—If an individual meets any of the 2-1) to 2-3) criteria, diagnosis requires two abnormal test results obtained at the same time or these criteria should be confirmed by repeat testing on a different day.
 - 2-1) HbA1c \geq 6.5%
 - 2-2) 8-hour FPG \geq 126 mg/dL
 - 2-3) 2-hour plasma glucose during 75-g OGTT \geq 200 mg/dL
 - 2-4) Presence of classic symptoms of hyperglycemia (polyuria, polydipsia, and unknown weight loss) with random plasma glucose level \geq 200 mg/dL

Level of evidence

Early diagnosis of glycemic abnormalities during pregnancy is crucial as hyperglycemia during pregnancy can lead to fetal malformations, death, and increased complications at birth [22-24].

Benefits

Early detection of diabetes in pregnant women is critical for minimizing obstetric risks by reducing the fetal exposure to

high blood glucose levels during organ development.

Risks

It remains uncertain whether it is appropriate to use the same diagnostic criteria for diabetes in the general population for the diagnosis of gestational diabetes [25]. Screening all pregnant women without assessing their diabetes risk could result in unnecessary tests.

Balancing the benefits and risks

Considering the impact of high blood glucose on the fetus in early pregnancy, the benefits of testing outweigh the risks.

Alternatives and considerations

Women planning pregnancy should be considered for screening for diabetes in advance, as diagnosing and treating diabetes early can reduce the risk of obstetric complications [26,27].

Recommendation 2.2 24 to 28 weeks of gestation

1) Pregnant women who have never been diagnosed with diabetes or gestational diabetes should be tested using one of the following methods between 24 to 28 weeks of pregnancy. [Non-randomized controlled trial, general recommendation]

1-1) 75-g OGTT: GDM is diagnosed if one or more of the following criteria are met (one-step approach).

- FPG ≥ 92 mg/dL
- 1-hour plasma glucose during OGTT ≥ 180 mg/dL
- 2-hour plasma glucose during OGTT ≥ 153 mg/dL

1-2) If the plasma glucose level measured 1 hour after load during a 50 g OGTT is ≥ 140 mg/dL (≥ 130 mg/dL for pregnant women at high risk), proceed to a 100-g OGTT; GDM is diagnosed if two or more of the following criteria are met (two-step approach).

- FPG ≥ 95 mg/dL
- 1-hour plasma glucose during OGTT ≥ 180 mg/dL
- 2-hour plasma glucose during OGTT ≥ 155 mg/dL
- 3-hour plasma glucose during OGTT ≥ 140 mg/dL

Level of evidence

The 50-g OGTT, utilized in the two-step screening strategy, does not require fasting and effectively screens for GDM. Setting the 1-hour plasma glucose threshold at 140 mg/dL identifies approximately 80% of GDM cases. Lowering this threshold to 130 mg/dL enhances the detection rate to 90% [28]. In a study of 2,776 Korean women, the application of the Carpenter-Coustan criteria within the two-step approach significantly increased the frequency of obstetric complications and macrosomic infants compared to the National Diabetes Data Group criteria within the same approach [29]. The KDA adopted the two-step approach using the Carpenter-Coustan criteria, following the recommendations of the ADA. However, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated that increased glycemia during pregnancy is associated with

a sequential increase in the frequency of obstetric complications [30]. Based on these findings, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has set the cutoff for the one-step approach at a blood glucose level that corresponds to a 1.75-fold increase in the odds ratio (OR) of complications relative to the general pregnant population [31]. This one-step approach has been shown to double the diagnosis rate of gestational diabetes when compared to the two-step approach [32].

Benefits

Both protocols can efficiently diagnose gestational diabetes, prevent obstetric complications caused by hyperglycemia, and serve as evidence for advocating routine diabetes screening, as women are at risk for diabetes after giving birth.

Risks

The OGTT may induce nausea and/or vomiting in some individuals and can lead to hypoglycemia in individuals who have undergone gastrointestinal (GI) bypass surgery.

Balancing the benefits and risks

Considering the impact of hyperglycemia during pregnancy on both the mother and fetus, the advantages of screening surpass the associated risks. However, a randomized controlled trial (RCT) comparing the one-step to the two-step approach revealed no significant differences in the risk of maternal or perinatal complications, despite the former identifying twice as many gestational diabetes cases [33]. Additionally, using a less stringent cutoff of 99 mg/dL for fasting glucose or 162 mg/dL for 2-hour postprandial glucose in the two-step method, as opposed to the 92–180–153 mg/dL criteria of the one-step approach, resulted in diagnosing less than half the number of gestational diabetes cases, with no variation in the risk of large for gestational age (LGA) births [34]. This indicates that the increased diagnosis rate of gestational diabetes through the one-step approach may lead to unnecessary healthcare demands, suggesting the need for further investigation.

Alternatives and considerations

It should be considered that the one-step approach, according to HAPO study results, better predicts direct complications related to pregnancy, while the two-step approach is based on the incidence of future diabetes.

3. SCREENING FOR DIABETES

1. Screening for diabetes based on FPG, HbA1c, or 2-hour plasma glucose 75-g OGTT is assessed. [Non-randomized controlled trial, general recommendation]
2. Annual screening for diabetes [Expert opinion, general recommendation] should be considered for adults aged ≥ 35 and adults aged ≥ 19 who have one or more risk factors (Table 5). [Uncontrolled studies, general recommendation]
3. Additional tests are indicated if FPG or HbA1c levels meet any of the following. [Expert opinion, general recommendation]
 - 1) FPG level 100 to 109 mg/dL or HbA1c 5.7% to 6.0%: test FPG or HbA1c levels annually, and consider 75-g OGTT if body mass index (BMI) is ≥ 23 kg/m²
 - 2) FPG level 110 to 125 mg/dL or HbA1c 6.1% to 6.4%: consider 75-g OGTT
4. Screen individuals with GDM for diabetes at 4 to 12 weeks postpartum, using the 75-g OGTT. [Randomized controlled trial, general recommendation]

Table 5. Risk factors for type 2 diabetes mellitus

Overweight or obese (body mass index ≥ 23 kg/m ²)
Abdominal obesity (waist circumference ≥ 90 cm for men, ≥ 85 cm for women)
Family history of type 2 diabetes mellitus in first degree relative (parents, siblings)
History of prediabetes
History of gestational diabetes mellitus or delivery of a macrosomia baby (≥ 4 kg)
Hypertension ($\geq 140/90$ mm Hg or on therapy for hypertension)
High-density lipoprotein cholesterol level ≤ 35 mg/dL or triglyceride level ≥ 250 mg/dL
Conditions associated with Insulin resistance (e.g., polycystic ovary syndrome, acanthocytosis nigricans)
History of cardiovascular disease (e.g., stroke, coronary artery disease)
Medications (e.g., glucocorticoids, atypical antipsychotics)

Backgrounds

The goal of screening for diabetes is to identify individuals at high risk for developing diabetes and to detect diabetes at the early stage. T2DM frequently remains undiagnosed until complications occur, as it often presents without specific symptoms. It is estimated that approximately one-third of the individuals with this condition are unaware of their diabetes condition. Therefore, it is crucial to implement diabetes screening to identify diabetes or prediabetes in high-risk populations. Criteria defining high-risk groups vary slightly between countries. The risk factors for T2DM in Koreans are shown in Table 5.

In recent years, obesity, prediabetes, and diabetes have become more prevalent among young adults under the age of 40 [35,36]. This necessitated an update to the diabetes screening guidelines, previously focused on adults aged 40 and above or those aged 30 and above with additional risk factors. Consequently, the ADA revised its guidelines in 2022 [37] to start diabetes screening

from the age of 35 instead of 45. The Clinical Practice Guideline Committee of the KDA conducted a cross-sectional study to establish the appropriate age for initiating diabetes screening in adults. This study utilized data from the Korea National Health and Nutrition Examination Survey (KNHANES) for the years 2016 to 2020 and the National Health Insurance Service National Sample Cohort for 2012 to 2017 [38]. Upon evaluating the number needed to screen (NNS) to identify one individual with diabetes, a significant difference in NNS by age group was observed, starting from the 35 to 39 age group (Fig. 1). Additionally, an evaluation of the NNS for diabetes based on risk factors for T2DM in adults aged 20 to 34, using data from the KNHANES (2016 to 2020), revealed that the lowest NNS was 17 (with hypertension), while the highest was 48 (with being overweight). Notably, the NNS for abdominal obesity (waist circumference ≥ 90 cm for men, ≥ 85 cm for women) was 23, which is lower than the NNS of 34 for general obesity. Based on these findings,

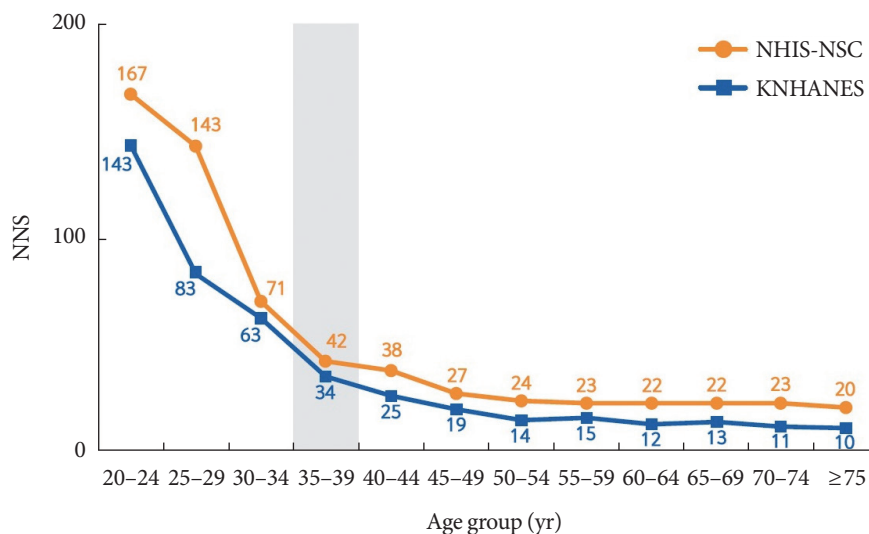


Fig. 1. Number of people who should be screened for diabetes by age group [38]. NNS, number need to screen; NHIS-NSC, National Health Insurance Service-National Sample Cohort; KNHANES, Korea National Health and Nutrition Examination Survey.

KDA recommends diabetes screening for adults aged 35 and older, as well as for adults aged 20 and older with risk factors for T2DM. The revised age threshold substantially reduced the percentage of individuals with undiagnosed diabetes missed by screening, from 4.0% to 0.2%, without significantly increasing the NNS compared to the criteria set by the current guidelines. The KDA also considered the recent trend of the steadily increasing prevalence of prediabetes and diabetes in Korean children and adolescents [39] and the recommendation that screening for diabetes in children and adolescents should be considered at the age of 10 years or after the onset of puberty if risk factors are present. The Committee of Clinical Practice Guideline of KDA thus decided to recommend screening for diabetes in all adults aged 35 years or older and all adults aged 19 years or older with risk factors. Additionally, abdominal obesity has been added as a criterion for the risk factors of T2DM.

Testing for HbA1c, regardless of fasting status, is an effective approach for assessing glycemic control. However, it was initially excluded from diabetes diagnosis and screening protocols due to concerns over standardization and the accuracy of measurement techniques. With advancements in the accuracy and standardization of HbA1c testing methods, an International Expert Committee endorsed the utilization of the HbA1c test as a method for diabetes screening in 2009 [40-42]. In 2010, the ADA guidelines were updated to include “HbA1c $\geq 6.5\%$ ” as part of the diagnostic criteria for diabetes and “HbA1c 5.7% to

6.4%” to identify individuals at high risk for diabetes. Concurrently, in Korea, significant research has been published regarding the diagnostic utility of HbA1c [12,43]. In 2009, the Diagnostic Subcommittee of the KDA undertook a study across eight hospitals, measuring FPG, 2-hour plasma glucose, and HbA1c levels in over 1,000 individuals with no previous diabetes diagnosis. The established HbA1c cutoff points for diagnosing diabetes and IGT are 6.1% and 5.7%, respectively [44]. Therefore, adults presenting with an HbA1c level of 6.1% or higher are categorized as having a very high risk for developing diabetes and are recommended to undergo an OGTT. Analyzing fasting and post-glucose load blood glucose levels, data from four extensive Korean cohort studies—comprising 2,473 subjects from Yeoncheon, 1,106 from Jeongeup, 774 from Mokdong, and 1,881 from Ansan, totaling 6,234 subjects between 1993 and 2000—revealed that classifying IFG into two distinct stages improves diabetes diagnosis rates. For individuals with stage 1 IFG, characterized by FPG levels between 100 and 109 mg/dL, annual screening is advised. If risk factors are present, an OGTT is recommended. For those identified with stage 2 IFG, where FPG levels range from 110 to 125 mg/dL, an immediate OGTT is recommended [2].

According to the recently published Korean Diabetes Prevention Study (KDPS), among 446 individuals newly diagnosed with diabetes and having a BMI of 23 kg/m² or above, 76.2% FPG levels under 126 mg/dL. A 59.2% exceeded the criteria only

with their 2-hour post-glucose load plasma glucose levels, while their FPG and HbA1c levels were below the threshold. When categorizing FPG levels as <100 mg/dL (normal), 100–109 mg/dL (stage 1 IFG), and 110–125 mg/dL (stage 2 IFG), the percentages of subjects with a 2-hour plasma glucose level of ≥ 200 mg/dL were found to be 9.5%, 19.0%, and 43.5%, respectively [45]. The JDS guidelines [46] recommend considering an OGTT for individuals with FPG levels at or above 100 mg/dL, or an HbA1c at or above 5.6%. Similarly, the Canadian Diabetes Association [47] advises an OGTT for individuals with FPG levels at or above 100 mg/dL and one or more risk factors. Based on these Korean and international studies, it is recommended for adults with a BMI of 23 kg/m² or higher to consider an annual measurement of FPG or HbA1c along with an OGTT if FPG levels are 100 to 109 mg/dL or HbA1c is 5.7% to 6.0%, and to undergo an OGTT if FPG levels are 110 to 125 mg/dL or HbA1c is 6.1% to 6.4%. The 40% to 50% of women diagnosed with gestational diabetes are at risk of developing T2DM over time [48,49]. Therefore, these individuals are considered high risk for the onset of diabetes and should implement necessary lifestyle modifications for prevention. Women with a history of gestational diabetes are advised to undergo a 75-g OGTT between 4 to 12 weeks postpartum. If the results are normal, annual screening for diabetes is recommended.

A study in Korea has introduced a self-scoring system designed to evaluate the risk of diabetes. This method involves assigning scores to various risk factors, including smoking, age, abdominal obesity, family history of diabetes, alcohol intake, and high blood pressure, to estimate the probability of having undiagnosed [50].

A self-scoring method has been developed to estimate the

percentage likelihood of developing diabetes within the next 10 years, utilizing data from 8,740 adults without diabetes. These participants were involved in the Anseong-Ansan cohort study, a long-term epidemiological research project in Korea, where they were subjected to 75-g OGTT and HbA1c tests at 2-year intervals. The estimation method could be referred in [51].

Blood sample for screening test

The principle for diagnosing diabetes is to use plasma collected from venous blood. Glucose concentrations vary according to the type of blood collected, that is, venous, arterial, or capillary blood, and can change based on fasting status and meal times. Generally, arterial blood has the highest glucose concentration, followed by capillary and then venous blood. The difference in glucose levels between arterial and venous blood in the morning while fasting is approximately 10 mg/dL, but this gap can widen to 20 to 50 mg/dL after meals. Additionally, glucose levels vary depending on the type of specimen collected: whole blood, plasma, or serum. Plasma glucose concentrations are generally 10% to 15% higher than those in whole blood. It's also noteworthy that red blood cells, which contain glycolytic enzymes, can decrease blood glucose levels by about 10 mg/dL per hour. Therefore, if testing with serum is unavoidable, the serum should be separated within 30 minutes of blood collection, and blood collection tubes containing sodium fluoride (NaF) should be used to inhibit this action [52,53]. Especially in mass screenings where a large number of samples are analyzed simultaneously, serum is often used, so careful management of the samples is necessary.

4. PREVENTION OF TYPE 2 DIABETES MELLITUS

1. Educate individualized lifestyle modifications for diabetes prevention. [Randomized controlled trial, general recommendation]
2. Provide constant motivation to maintain lifestyle modifications and monitor them through various methods, including education and information and communication technology (ICT)-based interventions. [Expert opinion, general recommendation]
3. For diabetes prevention, adults with prediabetes should follow individualized diet plans, considering each person's eating patterns. [Expert opinion, general recommendation]
4. Adults with prediabetes should engage in at least moderate-intensity physical activity for ≥ 150 minutes per week to prevent diabetes. [Randomized controlled trial, general recommendation]
5. Overweight or obese adults with prediabetes should achieve and maintain a weight reduction of at least 5% of their initial body weight to prevent diabetes. [Randomized controlled trial, limited recommendation]
6. Metformin can be considered to prevent diabetes in overweight or obese adults with prediabetes. [Randomized controlled trial, limited recommendation]

Recommendation 4.1 Educate individualized lifestyle modifications for diabetes prevention. [Randomized controlled trial, general recommendation]

Recommendation 4.2 Provide constant motivation to maintain lifestyle modifications and monitor them through various methods, including education and ICT-based interventions. [Expert opinion, general recommendation]

Level of evidence

Recommendation for lifestyle modification education to prevent the development of T2DM in adults with prediabetes was based on the results of 11 RCTs on lifestyle interventions [54-64]. The evidence for the long-term effects of the lifestyle interventions was based on studies that identified differences in diabetes or diabetes complication development upon longer follow-up in participants of T2DM prevention studies [65-73]. The evidence for the effectiveness of ICT-based interventions in preventing the development of T2DM was based on the results of five RCTs [74-78].

All of these study participants were people with prediabetes, but there were differences in the criteria, such as IGT, IFG, overweight, and obesity across each study. The lifestyle interventions used in the studies varied in terms of the expertise of the educators (physicians, nurses, dietitians, etc.), the intensity of the intervention, the number of visits, and the duration of the intervention. However, all included dietary, exercise, and behavioral interventions. Studies also differed in the number of participants and diagnostic methods for defining the devel-

opment of diabetes. Most studies were individually randomized into intervention groups, but one study [54] was cluster-randomized. The reference studies were well-designed and conducted and, therefore, have a high level of evidence. However, due to the nature of these studies, it was not feasible to blind the intervention and control groups completely, and the management of control groups varied. Long-term prognostic observational studies after the end of the intervention have a lower level of evidence than randomized trials. Still, these studies have reported important implications of the long-term effects of interventions and, therefore, were reflected in the recommendations.

Benefits

Although the studies varied in terms of participants characteristics, methods, duration, intensity of the lifestyle interventions, and methods of diagnosing diabetes, systematic interventions to modify lifestyle behaviors significantly reduced the incidence of T2DM in adults with prediabetes. In the references used to develop this guideline, the risk of developing diabe-

tes after lifestyle interventions was reduced by 28.5% to 68% compared to the control group. Most of the lifestyle interventions used in the studies included a comprehensive diet, exercise, and behavioral therapy; one study compared the effects of the interventions by dividing them into three groups: diet alone, exercise alone, and diet and exercise combined. This study reported no differences in diabetes prevention among the three groups [54].

After the end of diabetes prevention studies, studies regarding long-term outcomes of interventions, with 10 to 30 years of follow-up in selected participants, have been published. In these studies, participants were encouraged to maintain a healthy lifestyle through various methods after the end of the intervention study and by observing the course. The risks of developing T2DM, diabetes-related complications, and mortality were reduced in the lifestyle intervention group [65-73,79,80]. However, the difference in the effect of diabetes prevention compared with the control group decreased with longer follow-up, therefore, continued motivation and monitoring using various methods to maintain lifestyle modification are required.

The effect of lifestyle interventions using ICT-based interventions, such as Internet-based programs, voice or text messages, or smartphone applications, in preventing the development of T2DM was unclear. In the literature used for evidence, no consistent results were found when comparing intervention and control groups on key endpoints such as weight, HbA1c, and risk of diabetes development. Some studies using Internet or mobile-based educational programs as adjunct means have shown significant improvements in key clinical indicators such as body weight and BMI over a certain period [77,78]. In the future, it is necessary to develop a systematic method to maintain the effectiveness of lifestyle interventions utilizing ICTs.

Risks

No serious adverse events related to the conduct of the research or the interventions occurred in the studies used to develop the recommendations.

Balancing the benefits and risks

The results of the reference studies of this recommendation show that in adults with prediabetes, the benefits of lifestyle interventions to prevent the development of T2DM are substantial, and the potential risks are low. The long-term effects of diabetes prevention using ICT-based means are unclear, and the

potential risks are not high.

Alternatives and considerations

Lifestyle interventions for preventing T2DM should be tailored to the specific characteristics and environment of different countries and ethnic groups. This means that directly applying lifestyle interventions from studies cited in current guidelines may not be suitable for the Korean population. The KDPS was initiated as a national project by the Ministry of Health and Welfare of South Korea in collaboration with the National Evidence-based Healthcare Collaborating Agency and the Korea Centers for Disease Control and Prevention. It aims to develop diabetes prevention strategies suitable for the Korean context and assess their effectiveness in preventing T2DM among Korean adults with prediabetes. The KDPS is a RCT co-developed by the KDA and conducted by 15 medical institutions from 2016 to 2023 [81]. Eight hundred and forty-four overweight or obese adults with prediabetes (30 to 70 years old) were enrolled and randomized to three different groups: the lifestyle intervention group, the metformin group, and the standard care group (control group). The hospital-based lifestyle modification (KDPS-hLSM), used in the KDPS, is the first multidisciplinary lifestyle intervention for diabetes prevention in Korea, and a recent interim analysis of the 6-month intervention reported positive effects on body weight and metabolic markers in the lifestyle intervention group compared to the control group (paper yet to be published). Although the diabetes prevention effect has yet to be confirmed, the KDPS-hLSM, which has been applied for more than 3 years, has not reported any risks but has shown a tendency for a beneficial effect. Therefore, it can be considered for application as a lifestyle intervention method for adults with prediabetes in Korea. Meanwhile, a large-scale and long-term study on the effectiveness of ICT-based diabetes prevention interventions that can be utilized in various settings is required.

Recommendation 4.3 For diabetes prevention, adults with prediabetes should follow individualized diet plans, considering each person's eating patterns. [Expert opinion, general recommendation]

Recommendation 4.4 Adults with prediabetes should engage in at least moderate-intensity physical activity for ≥ 150 minutes per week to prevent diabetes. [Randomized controlled trial, general recommendation]

Recommendation 4.5 Overweight or obese adults with prediabetes should achieve and maintain a weight reduction of at least 5% of

their initial body weight to prevent diabetes. [Randomized controlled trial, limited recommendation]

Level of evidence

The 11 RCTs [54-64] on lifestyle interventions on which the recommendations were based all included adults with prediabetes who were overweight/obese (BMI ≥ 23 kg/m²), and five of the trials [54,56,58,63] also included participants with BMI lower than 23 kg/m². All studies were systematically designed and conducted and had a high level of evidence. Due to the nature of the studies, complete blinding of the intervention and control groups was not feasible. The detailed selection criteria, number of participants, and duration of the intervention varied by study. In particular, the lifestyle interventions utilized in the studies varied regarding educators, intervention intensity, number of visits, and duration, but all included a systematic diet and exercise regimen.

Benefits

In adults with prediabetes, individualized systematic dietary interventions, including individual characteristics and eating patterns, significantly reduced the incidence of diabetes. Physical activity of 150 minutes or more per week of at least moderate-intensity also significantly reduced the incidence of diabetes in adults with prediabetes. The systematic lifestyle interventions used in most studies were developed to include diet and exercise, demonstrating their efficacy in diabetes prevention. One study compared the effects of three interventions: diet alone, exercise alone, and a combination of diet and exercise; all three groups showed similar diabetes prevention effects [54]. In overweight/obese adults with prediabetes, weight loss was an important factor for diabetes prevention. Achieving and maintaining a weight reduction of at least 5% significantly reduced the incidence of diabetes.

Risks

No serious adverse events related to the conduct of the research or the interventions occurred in the studies used to develop the recommendations.

Balancing the benefits and risks

In adults with prediabetes, the benefits of a systematic lifestyle intervention that includes diet and exercise to prevent the development of diabetes are substantial, while the potential risks

are low. In overweight/obese adults with prediabetes, the benefits of weight loss outweigh the risks; however, the benefits of weight loss in adults with a BMI < 23 kg/m² are not clear.

Alternatives and considerations

Although the diet and exercise regimens shown to be effective in the reference studies vary in content and methodology, the lack of such research in Koreans limits the application of these interventions to the Korean population. Additionally, all dietary and exercise regimens should be individualized according to individual characteristics. The KDPS-hLSM used in the KDPS study is a lifestyle intervention with a standardized educational methodology conducted as an interventional study at 15 medical centers and can be considered for application in overweight/obese adults with prediabetes in Korea. KDPS-hLSM is a lifestyle intervention based on intensive nutrition therapy by a clinical nutritionist and 10 healthy lifestyle changes (10 components: one exercise, five diet, and four behavior) by a health coordinator. It aims to achieve and maintain a weight loss of 5% or more. Similarly, education and intervention are individualized according to various individual characteristics, eating patterns, and stages of behavior change. However, since the KDPS study is still in progress, it is necessary to secure evidence of its diabetes prevention and long-term effect, as well as to investigate its application in normal-weight subjects and various community health organizations.

Recommendation 4.6 Metformin can be considered to prevent diabetes in overweight or obese adults with prediabetes. [Randomized controlled trial, limited recommendation]

Level of evidence

Recommendations on the effectiveness of pharmacologic interventions in preventing diabetes in adults with prediabetes are based on 11 RCTs [56,58,82-90]. All of the study participants were people with prediabetes, but each study differed in their inclusion criteria, number of participants, and duration of intervention. The studies used to develop this recommendation were all well-designed, conducted systematically, and had a high level of evidence. However, due to the nature of the studies, complete blinding of the intervention and control groups was not feasible. Studies involving currently unavailable drugs were excluded.

Benefits

Although studies differed in terms of patient characteristics, intervention methods, and duration, pharmacologic interventions significantly reduced the risk of developing diabetes (Table 6). Currently, metformin, acarbose, orlistat, pioglitazone, voglibose, liraglutide, phentermine/topiramate extended-release, and valsartan have been reported to prevent the development of diabetes [56,58,82-90]. Particularly, pioglitazone, liraglutide, and phentermine/topiramate extended-release have been shown to have a preventive effect of over 50% [86-89].

However, no studies have compared the superiority of these drugs. Long-term observational studies have confirmed the prevention of the development of diabetes and diabetic complications and reduced mortality in metformin users [73,79,80].

Risks

There is a potential risk of developing adverse effects related to the drugs used in the intervention. Adverse effects of metformin include lactic acidosis, dyspepsia, and vitamin B12 deficiency. Acarbose and voglibose may cause GI disturbances

Table 6. Key evidence for diabetes prevention: pharmacologic interventions

Study	Participants	No.	Intervention	Study duration (yr)	Outcomes
STOP-NIDDM study (2002) [82]	IGT	1,429	Acarbose 100 mg tid	3.3	25% Reduction in intervention group
Diabetes Prevention Program (2002) [56]	Overweight, IFG, or IGT	3,234	Lifestyle modification Metformin 850 mg bid	2.8	31% Reduction in metformin group
XENDOS (2004) [83]	BMI \geq 30 kg/m ² , NGT or IGT	3,305	Orlistat 120 mg tid	4	37.3% Reduction in orlistat group
Indian Diabetes Prevention Programme [58]	IGT	531	Lifestyle modification Metformin 250 mg bid Lifestyle modification & metformin 250 mg bid	3	Lifestyle modification 28.5% Metformin 26.4% Lifestyle modification & metformin 28.2%
Voglibose Ph-3 study (2009) [84]	IGT	1,780	Voglibose 0.2 mg tid	3	40% Reduction in voglibose group
NAVIGATOR (2010) [85]	IGT with cardiovascular disease or cardiovascular disease risk factors	9,306	Lifestyle modification+valsartan 160 mg/day (maximal dose)	5	14% Reduction in valsartan group
ACT NOW (2011) [86]	BMI \geq 25 kg/m ² , IGT	602	Pioglitazone 45 mg qd	2.4	72% Reduction in pioglitazone
SEQUEL substudy (2014) [87]	Prediabetes in SEQUAL trial participants	475	Phentermine Topiramate ER 7.5/46 mg, 15/92 mg	2	70.5% and 78.7% in phentermine/topiramate ER, respectively
IRIS (2016) [88]	Recent ischemic stroke or TIA and insulin resistance (HOMA-IR \geq 3.0) but not diabetes	3,876	Pioglitazone 45 mg qd	4.8	52% Reduction in pioglitazone group
SCALE (2017) [89]	Preidabetes (BMI \geq 30 kg/m ²), dyslipidemia or hypertension with BMI \geq 27 kg/m ²	2,254	Liraglutide 3 mg qd	3	79% Reduction in liraglutide
ACE trial (2020) [90]	IGT with coronary artery disease	6,522	Acarbose 50 mg tid	5	18% Reduction in acarbose group

STOP-NIDDM, The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; IGT, impaired glucose tolerance; tid, three times a day; IFG, impaired fasting glucose; bid, twice a day; XENDOS, XENical in the prevention of diabetes in obese subjects; BMI, body mass index; NGT, normal glucose tolerance; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; ACT NOW, Actos Now for Prevention of Diabetes; qd, once a day; SEQUEL, Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults; ER, extended-release; IRIS, Insulin Resistance Intervention after Stroke; TIA, transient ischemic attack; HOMA-IR, homeostasis model assessment of insulin resistance; SCALE, Satiety and Clinical Adiposity-Liraglutide Evidence in Nondiabetic and Diabetic Individuals; ACE, Acarbose Cardiovascular Evaluation.

such as abdominal bloating. Pioglitazone can cause edema, weight gain, and heart failure (HF). Liraglutide can also cause GI disturbances. Orlistat may cause steatorrhea; phentermine/topiramate extended-release can cause tingling, paresthesias, and insomnia. Valsartan may cause orthostatic hypotension.

Balancing the benefits and risks

The benefits of pharmacologic interventions for diabetes prevention are clear, while the potential risks are not high. However, it is important to note that pharmacologic interventions may have potential drug-related adverse effects.

Alternatives and considerations

Due to the lack of studies on preventing the development of diabetes through pharmacological interventions in Koreans, it

is difficult to generalize and apply the derived recommendations. Therefore, further studies are needed to evaluate the effectiveness and safety of various pharmacological interventions for the prevention of diabetes in Koreans with prediabetes. The ongoing KDPS study includes metformin drug intervention in overweight/obese adults with prediabetes (30 to 70 years old), and the results of the 6-month interim analysis showed positive effects on body weight and metabolic markers compared to the control group. However, it is necessary to secure evidence of its diabetes prevention and long-term effect regarding metformin interventions [81]. Therefore, it is crucial to acknowledge the limitations posed by the absence of drugs approved for diabetes prevention in Korea and the necessity for continuous administration, as the preventive effects are lost once the drug is discontinued.

5. GLYCEMIC GOALS IN ADULTS WITH DIABETES

1. Actively control blood glucose to prevent microvascular and macrovascular complications. [Randomized controlled trial, general recommendation]
2. General glyceic goal in adults with T2DM is HbA1c <6.5%. [Randomized controlled trial, general recommendation]
3. General glyceic goal in adults with T1DM is HbA1c <7.0%. [Randomized controlled trial, general recommendation]
4. Glyceic goals should be individualized based on the patient's physical, psychological, and social conditions, life expectancy, the severity of comorbidities, or the risk of hypoglycemia. [Non-randomized controlled trial, general recommendation]
5. When using a continuous glucose monitoring (CGM) device, time in range (TIR) (70 to 180 mg/dL) should be >70% with time below range (TBR) of <4%, especially the time of hypoglycemia (<54 mg/dL) which should be <1%. [Non-randomized controlled trial, general recommendation]

Recommendation 5.1 Actively control blood glucose to prevent microvascular and macrovascular complications. [Randomized controlled trial, general recommendation]

Level of evidence

Results are based on multiple RCTs and follow-up studies, therefore can be applied to individuals with newly diagnosed diabetes.

Benefits

Based on the results of several clinical trials showing that tight glyceic control early in the course of diagnosis of diabetes can reduce the risk of microvascular and macrovascular complications in adults with diabetes.

1) Glyceic control and microvascular complications

The DCCT, a RCT, demonstrated whether intensive glyceic control in T1DM prevents diabetic complications [91]. Tight glyceic control reduced the development of retinopathy by 76% and slowed the progression rate of retinopathy by 54%. It also reduced the incidence of microalbuminuria by 39%, macroalbuminuria by 54%, and neuropathy by 60%. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a follow-up of the DCCT cohort, demonstrated that the benefits of tight glyceic control persisted for over 20 years, even after glyceic control was no longer being maintained. This suggests a lasting benefit, or "legacy effect," of tight glyceic control in preventing microvascular complications [92,93].

The Kumamoto study [94] and the UK Prospective Diabetes Study (UKPDS) [95,96] targeting T2DM demonstrated that in-

tensive glyceic control was protective against microvascular complications, and the follow-up study of the UKPDS [97,98] showed that the protective effect was sustained over time.

The Kumamoto study reported that the group with intensive glyceic control experienced a 69% reduction in retinopathy, a 70% reduction in nephropathy, and an improvement in nerve conduction velocity. The UKPDS study is divided into two parts: one that examines the effects of intensive glyceic control using sulfonylureas or insulin (UKPDS33) and one that looks at the effects of metformin in overweight individuals (UKPDS34). Over the 10-year study period, tight glyceic control was linked with a 25% reduction in microvascular complications in the UKPDS33 substudy, and there was a trend toward a reduction in retinopathy in the UKPDS34 substudy. These three studies demonstrate that intensive glyceic control can significantly reduce microvascular complications.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [99], the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study [100], and the Veterans Affairs Diabetes Trial (VADT) study [101] aimed to determine whether near-normal glyceic control could protect against cardiovascular events. These studies showed a protective effect against some microvascular complications.

The ACCORD study observed a 15% to 28% reduction in

the risk of albuminuria and some improvement in neuropathy-related endpoints. However, overall, there was no reduction in microvascular complications with glycemic control.

The ADVANCE study showed a 14% reduction in microvascular complications, which was mainly due to a 21% decrease in the risk of diabetic nephropathy development. However, it did not affect the occurrence of retinopathy. On the other hand, the VADT study did not prevent microvascular complications but had some impact on the development and progression of albuminuria. The ADVANCE study suggested in order to minimize microvascular complications, the HbA1c level should be less than 6.5% [102].

2) Glycemic control and cardiovascular disease

In the DCCT study, which involved individuals with T1DM, major vascular complications were rare due to the enrollment of young age subjects. However, not statistically significant, tight glycemic control reduced the risk of cardiovascular and peripheral vascular events by 41% [91]. In the EDIC study, subjects with tight glycemic control had a 57% lower risk of major adverse cardiovascular events, including non-fatal myocardial infarction, stroke, and death from cardiovascular causes, after a total of 17 years of follow-up [103]. Additionally, the overall mortality was reduced by 33% after 27 years of follow-up [104].

In the UKPDS study conducted on individuals with T2DM, although statistically non-significant, tight glycemic control reduced the risk of cardiovascular events such as fatal and non-fatal myocardial infarction and sudden death by 16%. After a decade of monitoring, it was discovered that patients who had achieved tight glycemic control had a significantly lower incidence of myocardial infarction (15% in the sulfonylurea/insulin group and 33% in the metformin group) and overall mortality (13% and 27%, respectively) [97].

Risks

Targeting intensive glycemic control inevitably increased the risk of severe hypoglycemia (SH) by 2- to 3-fold in the DCCT study [91], and significantly increased the risk of uncontrolled hypoglycemia, weight gain, and fluid retention in the ACCORD study [105]. It also increased the risk of cardiovascular events and total mortality in the ACCORD study and cohort studies [105,106]. An analysis of the VADT study suggested that tight glycemic control may be beneficial for CVD prevention in individuals with less than 15 years of diabetes duration.

However, it may be harmful in those with more than 15 years of diabetes duration [107]. The ACCORD study, which attempted to achieve less than 6.0 HbA1c, concluded that near-normoglycemic tight glycemic control has some benefit in preventing microvascular complications, but caution should be exercised in determining glycemic targets as tight glycemic control may have risks of weight gain, SH, and death [99].

Balancing the benefits and risks

The newer classes of diabetes medications, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs), have been introduced since the 2000s when most RCTs of glycemic control were conducted. Compared to older medications, these drugs have a very low risk of causing hypoglycemia. Therefore, it is likely that these newer medications can help achieve more aggressive glycemic control, and efforts aimed at preventing diabetic complications through glycemic control will result in more benefits than harm.

Recommendation 5.2 General glycemic goal in adults with T2DM is HbA1c <6.5%. [Randomized controlled trial, general recommendation]

Level of evidence

These findings are based on multiple RCTs and follow-up studies; therefore, they should be applied to all adults with newly diagnosed diabetes.

Benefits

In the Kumamoto study, the intensive glycemic control group had set the fasting blood glucose target of less than 140 mg/dL, a 2-hour postprandial plasma glucose of less than 200 mg/dL, and HbA1c of less than 7.0%. However, the actual HbA1c level achieved by the tight control group was 7.1%. The authors suggested that keeping HbA1c levels below 6.5% could help prevent the development and progression of microvascular complications.

In the UKPDS, intensive glycemic control, which was defined as having a fasting blood glucose level less than 108 mg/dL, it achieved HbA1c levels of 7.0% and 7.4% in the sulfonylurea/insulin (UKPDS33) study and the metformin (UKPDS34) study, respectively (compared to 7.9% and 8.0% in the control groups, respectively). Intensively Maintaining the HbA1c level of 7.0% or less has been shown to significantly reduce microvascular

events compared to conventionally maintaining a control level of 8.0% to 9.0%. The UKPDS observational study also showed a no-threshold association between glycemic control and microvascular events [98]. A 1.0% reduction in HbA1c was associated with a 37% reduction in microvascular events, with the lowest microvascular events in HbA1c below 6.0%.

In other clinical studies consisting of individuals with nearly 10 years of diabetes duration, the achieved HbA1c levels were 6.4% (7.5% control) in the ACCORD study, 6.5% (7.3% control) in the ADVANCE study, and 6.9% (8.4% control) in the VADT study. In the ADVANCE study, it was analyzed that controlling HbA1c at less than 6.5% can help minimize microvascular complications [102]. These studies suggest that maintaining HbA1c 6.5% can protect both newly diagnosed T2DM and individuals who have had diabetes for 10 years against microvascular complications.

The Diabetes and Aging Study is an observational study based on data from the Kaiser Permanente Northern California (KPNC) diabetes registry in the United States. According to the study, people who had maintained an HbA1c level below 6.5% in the first year of diagnosis had a lower risk of microvascular complications. Specifically, those with an HbA1c level of 6.5% to 6.9% had a 20% increased risk, while those with an HbA1c level of 7.0% to 7.9% had a 39% increased risk. The risk of complications further increased when compared to those who controlled the HbA1c level below 6.5 for 2 years. A similar association was seen for macrovascular complications. Therefore, it is beneficial to begin targeting HbA1c levels below 6.5% at the time of diagnosis to prevent complications [108].

Risks

Tight glycemic control may increase the risk of hypoglycemia and weight gain. The ACCORD study terminated early due to a 1.22-fold increased risk of death (1.41% vs. 1.14% per year) in the intensive glycemic control group in comparison to the control group [105]. However, no effect on cardiovascular events was observed in the ADVANCE-ON study, which followed up on ADVANCE participants for 6 years [109]. A 10-year follow-up of VADT participants showed a 17% reduction in the risk of major cardiovascular events (8.6 fewer events per 1,000 person-years), but it did not show any difference in the risk of death [110].

Balancing the benefits and risks

It is important to balance the benefits of tight glycemic control with the risks of hypoglycemia. DPP-4 inhibitors, SGLT2 in-

hibitors, and GLP-1RAs are associated with a shallow risk of hypoglycemia and may be used to minimize the risk of hypoglycemia while attempting aggressive glycemic control.

The Vildagliptin Efficacy in combination with metformin For early treatment of type 2 diabetes (VERIFY) study was a randomized, controlled trial comparing metformin alone to a combination of metformin and vildagliptin in individuals with T2DM [111]. Early combination therapy is significantly more effective in controlling glycemia for up to 5 years without risk of hypoglycemia and weight gain, compared to using only metformin. The study showed that 39.3% of patients in the early combination arm had HbA1c levels below 6.5%, while only 27.3% of people in the metformin monotherapy arm. Additionally, the time to treatment failure, defined as HbA1c of 7.0% or higher, was 61.9 months in the early combination arm, which is significantly longer than the 36.1 months in the metformin monotherapy one. The incidence of hypoglycemia was also very mild. Although early combination therapy successfully reduces glycemic control failures and achieves glycemic control goals for a more extended period, the VERIFY study does not provide evidence that HbA1c levels lower than 6.5% are necessary. Further research is needed to determine whether early combination therapy can reduce complications.

Alternatives and considerations

T2DM progresses over time. As the disease advances, the pancreas produces less insulin, making it harder to control optimal blood glucose levels. Therefore, although the target HbA1c level at the time of diagnosis is below 6.5%, it is essential to adjust the glycemic control goal according to the patient's condition as the disease progresses.

Blood glucose (self-glycemic testing) is used to assess glycemic control, but HbA1c level should be the ultimate standard of glycemic control. To ensure proper control of blood glucose level, it is recommended to control blood glucose to 80 to 130 mg/dL before meals and less than 180 mg/dL after meals through self-checking or CGM. It is also advised to take the HbA1c test at least every 3 months to assess glycemic control.

Recommendation 5.3 General glycemic goal in adults with T1DM is HbA1c <7.0%. [Randomized controlled trial, general recommendation]

Level of evidence

These results are based on large RCTs and follow-up studies and

should be applied to all adults with newly diagnosed T1DM.

Benefits

The DCCT study was conducted between 1983 and 1989, with 1,441 individuals with T1DM enrolled. The mean age of the participants was 27 years, with 2.6- and 8.6-year diabetes duration in the primary and secondary study, respectively. The control group received one to two insulin injections daily to alleviate hyperglycemia symptoms and facilitate normal growth. The intensive glycemic control group was administered with insulin injections at least three times a day to achieve pre-prandial blood glucose levels between 70 and 120 mg/dL and postprandial blood glucose levels below 180 mg/dL, and HbA1c levels of less than 6.5%, measured monthly. At the start of the study, HbA1c levels ranged from 8.8% to 9.0%. After an average follow-up period of 6.5 years, HbA1c levels were to be 9.0% in the control arm and 7.2% in the tight glycemic control one. Therefore, the ideal glycemic control goal for people with T1DM should be less than 7.0% HbA1c.

Risks

In the DCCT study, tight glycemic control inevitably increased the risk of SH by two to three times [91].

Balancing the benefits and risks

The recent use of long-acting and (ultra-) short-acting insulin analogs, which effectively reduced the risk of hypoglycemia, especially severe or nocturnal hypoglycemia, has created a favorable environment for glycemic control. Furthermore, the use of CGM and insulin pumps have significantly improved glycemic control.

Alternatives and considerations

To achieve the glycemic control goal of having HbA1c levels less than 7.0% in individuals with T1DM, active self-management education is essential. In response, the government, in collaboration with medical institutions, launched the 'Home healthcare pilot project for type 1 diabetics' in January 2020. A medical service system provided by a home healthcare team is anticipated to assist individuals with T1DM in managing their blood glucose levels. The system will offer educational counseling to help them manage their blood glucose levels and provide continuous monitoring and feedback.

Recommendation 5.4 Glycemic goals should be individualized based on the patient's physical, psychological, and social conditions, life expectancy, the severity of comorbidities, or the risk of hypoglycemia. [Non-randomized controlled trial, general recommendation]

Level of evidence

It is based on RCTs or multiple observational studies and should be applied to all individuals with advanced diabetes.

Benefits

Active glycemic control is crucial in preventing microvascular and macrovascular complications. The ideal glycemic control goal for people with T2DM is less than 6.5% HbA1c. It is important to implement more aggressive glycemic control with hypoglycemic agents that pose a low risk of hypoglycemia, particularly in the early stages of diabetes and when the risk of cardiovascular events is not significant. Active glycemic control using hypoglycemic agents with a low risk of hypoglycemia can be very helpful in preventing complications.

Risk

Glycemic control goals should be personalized based on the person's condition and objectives, and subjects should be systematically educated on controlling their blood glucose levels actively. However, individuals with long-standing diabetes, SH or advanced microvascular and macrovascular complications, short life expectancy, or elderly patients may not benefit from aggressive glycemic control to prevent complications. In fact, they may be at greater risk for adverse events such as hypoglycemia, weight gain, and death; thereby, the glycemic control goal may need to be adjusted upward.

Balancing the benefits and risks

T2DM is a disease that worsens over time. The pancreas produces less insulin as the disease progresses, and insulin resistance can worsen with age. As blood glucose control becomes more challenging, even with combination therapy using various medications, including insulin, achieving optimal blood glucose control becomes more challenging. In addition, glycemic variability increases, making it harder for people with diabetes to manage their own blood glucose levels. As diabetic kidney disease progresses and kidney function decreases, available medications become limited. Severe hypoglycemia can increase the risk of brain damage, dementia, cardiac arrhythmias, and sudden death.

The patient's understanding of diabetes is also essential for treatment. Active glycemic control can be challenging depending on socioeconomic status, education level, and living conditions. Many lifestyle modifications such as diet and physical activity may be complex. Ongoing counseling and consultation can help determine the extent to which a person can make lifestyle changes to control their blood glucose.

Alternatives and considerations

In conditions where glycemic control is difficult to achieve, and any improvement effects are unlikely to be seen, it is necessary to set the glycemic goal higher to minimize adverse effects and prioritize the individual's quality of life. It is also necessary to understand the characteristics of the elderly and refer to geriatric medicine guidelines.

Recommendation 5.5 When using a CGM device, TIR (70 to 180 mg/dL) should be >70% with TBR of <4%, especially the time of hypoglycemia (<54 mg/dL) which should be <1%. [Non-randomized controlled trial, general recommendation]

Real-time CGM (rtCGM) is recommended for all adults with T1DM to control blood glucose levels and reduce the risk of hypoglycemia. Adults with T2DM using multiple insulin injections can also benefit from rtCGM for glucose control. However, those who use other types of insulin therapy besides multiple insulin injections or those who only use oral hypoglycemic medications may also benefit from rtCGM for glycemic control.

According to a study based on data from 545 people with T1DM adopting CGM, CGM data shows a 70% TIR with 70 to 180 mg/dL yields to 7% HbA1c, whereas a 50% TIR corresponds to 8% HbA1c [112]. A 10% change in TIR with 70 to 180 mg/dL (2.4 hours of the day) was associated with a 0.6% change in HbA1c. Therefore, if physicians aim for 6.5% HbA1c, a continuous glucose monitor should indicate an 80% time in the target range.

For more information, see section 'Continuous glucose monitoring and insulin pumps.'

6. MONITORING AND EVALUATION OF GLYCEMIC CONTROL

1. Measurement of HbA1c

- 1) Test HbA1c every 2 to 3 months. The test interval can be adjusted based on individual conditions, but the test should be conducted at least twice a year. [Expert opinion, general recommendation]
- 2) Test HbA1c levels more frequently when glycemic fluctuations are severe, when medications are changed, and when tight glycemic control is needed (e.g., in pregnancy). [Uncontrolled studies, general recommendation]

2. Self-monitoring of blood glucose

- 1) Educate individuals on self-monitoring of blood glucose (SMBG), and check methods and accuracy frequently. [Expert opinion, general recommendation]
- 2) Individuals with T1DM or adults with T2DM who are on insulin therapy should perform SMBG. [Randomized controlled trial, general recommendation]
- 3) Adults with T2DM who are not on insulin therapy should consider SMBG. [Expert opinion, general recommendation]
- 4) SMBG can be done before and after the meal, before bedtime, at dawn, before and after exercise, and in the event of hypoglycemia, and the time and frequency of measurements can be individualized based on the patient's condition. [Expert opinion, general recommendation]

3. Continuous glucose monitoring

- 1) A rtCGM device is recommended to control blood glucose and reduce the risk of hypoglycemia in adults with T1DM. [Randomized controlled trial, general recommendation]
- 2) A rtCGM device should be considered to control blood glucose in individuals with T2DM on insulin therapy. [Randomized controlled trial, limited recommendation]

Recommendation 6.1-1) Test HbA1c every 2 to 3 months. The test interval can be adjusted based on individual conditions, but the test should be conducted at least twice a year. [Expert opinion, general recommendation]

Level of evidence

Due to the lack of large RCTs, most recommendations are based on expert consensus.

Benefits

Two large RCTs of T1DM and T2DM, DCCT and UKPDS, showed that glycemic control, as measured by the HbA1c level, was strongly associated with diabetes complications [98,113]. HbA1c is a measure of the degree of glycation of hemoglobin in response to levels of blood glucose, which reflects the average blood glucose over the lifetime of a red blood cell (about 3 months). It determines whether an individual's blood glucose has reached or is being maintained at the desired level and is usually measured every 2 to 3 months. However, it may be tested more frequently in case of significant fluctuations in blood glucose, medication changes, or when closer control is needed, such as during pregnancy, depending on the patient's clinical situation and treatment [114]. Although HbA1c is arguably the

most crucial indicator of glycemic control, the exact number of measurements required is yet to be determined due to insufficient evidence.

Risks

Frequent HbA1c measurements can help manage blood glucose levels and adjust lifestyle modification [115,116], but are costly and require constant blood collection.

Balancing the benefits and risks

There is currently no other marker that can replace HbA1c, so its benefits outweigh its risks.

Alternatives and considerations

In cases where there is anemia, such as hemoglobinopathies, hemoglobin metabolism disorders, and hemolytic anemia, as well as glucose-6-phosphate dehydrogenase deficiency, blood transfusions, increased erythropoiesis, end-stage renal disease

(ESRD), pregnancy, or any other situation where the turnover rates of red blood cells increase, the results of HbA1c may not be completely reliable and should be interpreted with caution. In such cases, it is advisable to test more frequently or use alternative methods such as a SMBG, CGM, fructosamine, or glycated albumin [117]. As a short-term blood glucose monitoring method, the use of 1,5-anhydroglucitol (1,5-anhydrogl, 1,5-AG) is also possible, but there is not enough research to determine how it correlates with average blood sugar or how it relates to prognosis in diabetes patients.

HbA1c is not a reliable indicator of glycemic variability or hypoglycemia in individuals with T1DM experiencing significant fluctuations in blood glucose, in individuals with T2DM with severe insulin deficiency, or individuals requiring multiple insulin injections [118]. Therefore, in such cases, HbA1c should be used in combination with SMBG levels or CGM to evaluate glycemic control. On the other hand, HbA1c is helpful in determining the accuracy of self-glycemic testing or CGM devices, as well as the suitability of testing frequency and duration. An international consensus on TIR published in 2019 recommends using TIR, one of the CGM metrics, as an alternative to HbA1c [119].

Recommendation 6.1-2) Test HbA1c levels more frequently when glycemic fluctuations are severe, when medications are changed, and when tight glycemic control is needed (e.g., in pregnancy). [Uncontrolled studies, general recommendation]

Level of evidence

Due to a lack of large randomized or non-randomized controlled studies, the level of evidence is based on other research.

Benefits

HbA1c levels are usually measured at intervals of 2 to 3 months. However, considering the patient's clinical situation, treatment, and other factors, more frequent HbA1c measurements may be required. This is particularly true when glycemic fluctuations are severe, medications are changed, or more stringent control is needed, such as during pregnancy [114].

Risks

Frequent HbA1c measurements can help manage blood glucose levels and adjust lifestyle modification, but are costly and require constant blood collection.

Balancing the benefits and risks

There is currently no other marker that can replace HbA1c in assessing glycemic control, so its benefits outweigh its risks.

Alternatives and considerations

As mentioned above, alternatives include SMBG, TIR of CGM, fructosamine, glycated albumin, and 1,5-AG. However, there is not enough evidence to substitute HbA1c with other alternatives.

Recommendation 6.2-1) Educate individuals on SMBG, and check methods and accuracy frequently. [Expert opinion, general recommendation]

Level of evidence

Due to the lack of large RCTs, the recommendations provided are based on the opinion of experts.

Benefits

SMBG is a useful method for managing diabetes, as it allows people with diabetes to monitor the response to treatment and ensure whether glycemic control goals are met as recommended. It can also help prevent hypoglycemia and demonstrate the effectiveness of medication, exercise, and medical nutrition therapy (MNT). Clinicians should educate individuals on how to perform SMBG, interpret the results, and take appropriate actions based on those results, enabling patients to monitor their blood glucose levels independently [120]. The number of tests needed will vary depending on the type of diabetes, medications used, commitment to glycemic control, and knowledge of diabetes [121,122]. In studies of individuals with T2DM not treated with insulin, those who underwent systematic education in SMBG exhibited HbA1c levels that were 0.3% to 0.6% lower compared to the control group [123,124].

When performing SMBG, inaccuracies in the glucose meter and lack of proficiency in the measurement technique can lead to errors. There is always a device-dependent discrepancy between blood glucose levels measured by a self-testing glucometer using a finger-stick capillary blood sample and those measured in a laboratory using a venous blood sample. The International Organization for Standardization (ISO) and U.S. Food and Drug Administration (FDA) standards are commonly used as a standard for glucose meter accuracy [120,125].

ISO standards approve a margin of error of ± 15 mg/dL for blood glucose levels below 100 mg/dL and $\pm 15\%$ for levels

above 100 mg/dL [120]. To ensure accuracy, individuals should compare their blood glucose with a lab test at least once a year. Moreover, individuals should compare self-test glucose levels to laboratory glucose values if HbA1c and self-test values are significantly different. Most errors in SMBG are due to inexperience with the method, so regular refresher training is necessary to improve accuracy [126].

Risks

To perform SMBG effectively, systematic training on using the devices and interpreting blood glucose values is important. Unfortunately, some institutions cannot offer this kind of training or provide feedback on self-management. Additionally, it is difficult to compare and evaluate the accuracy and superiority of various self-blood glucose monitoring devices.

Balancing the benefits and risks

Errors can occur in SMBG, but these can be prevented with systematic training and consistent monitoring. In primary care settings where systematic education may be challenging, the effectiveness of lifestyle modifications achievable through SMBG might be limited. To overcome this limitation, various educational resources such as reports and booklets provided by various organizations can be utilized to improve self-management.

Alternatives and considerations

If in-person training is not feasible, individuals with diabetes can utilize Internet resources, booklets, and other training methods.

Recommendation 6.2-2) Individuals with T1DM or adults with T2DM who are on insulin therapy should perform SMBG. [Randomized controlled trial, general recommendation]

Level of evidence

Recommendations are based on RCTs.

Benefits

Large-scale studies targeting patients undergoing insulin therapy have shown that SMBG plays a crucial role in the prevention of diabetes complications that can be achieved through active blood glucose control [91]. A study of 27,000 children with T1DM showed that more frequent SMBG led to lower HbA1c levels and a lower incidence of acute complications [127]. In individuals with T2DM treated with insulin, those who fre-

quently performed SMBG had lower HbA1c levels [128]. There is not enough evidence to show a relationship between the frequency of SMBG and glycemic control for people with T2DM who use basal insulin or oral hypoglycemic agents. However, individuals with T2DM who are treated with basal insulin and self-adjust their insulin dose by measuring their fasting blood glucose have been found to have lower HbA1c levels [129,130].

Risks

People are often deterred by the need for blood draws during SMBG, and the testing is less effective without proper education.

Balancing the benefits and risks

All studies have supported the benefits of SMBG in individuals treated with insulin. Although it is an invasive test, the benefits of glycemic control, prevention of hypoglycemia, and diabetes complications make it appropriate to recommend SMBG.

Alternatives and considerations

If SMBG is challenging, CGM or HbA1c can be used to assess the level of glycemic control. However, CGM is also effective only when sufficient education has been provided.

Recommendation 6.2-3) Adults with T2DM who are not on insulin therapy should consider self-monitoring their blood glucose levels. [Expert opinion, general recommendation]

Level of evidence

Due to the lack of large-scale RCTs or observational studies, recommendations are based on the opinion of experts.

Benefits

The benefits of SMBG in individuals with T2DM who are not using insulin therapy are not well-established. Some studies with well-designed educational programs for self-monitoring showed no improvement in glycemic control [131-135]. Nevertheless, SMBG can help individuals with diabetes become more aware of their diet, exercise, and the effectiveness of their diabetes medication on their blood glucose levels. Therefore, it should be actively encouraged. SMBG is also helpful in detecting hypoglycemia, monitoring blood glucose changes in the presence of other health comorbidities, and determining the degree of discrepancy with the actual blood glucose levels if the accuracy of the HbA1c test is in question.

In a year-long study of T2DM patients not receiving insulin therapy, the HbA1c levels were 0.3% lower in the group that conducted SMBG compared to the control group that did not perform any testing [123]. However, in another study, participants were divided into three groups for a year-long observation: one that performed SMBG once a day, another that conducted SMBG and received education, and a control group that did nothing. There was no difference in HbA1c levels among the three groups [134]. A meta-analysis reported that SMBG led to a 0.30% reduction in HbA1c after 6 months, but there was little effect after 12 months [135]. Moreover, the study revealed that SMBG was more effective when combined with education, but no significant change in glycemic control was observed without treatment modification [136]. Therefore, the effectiveness of SMBG in non-insulin-treated individuals with T2DM may be attributed to adequate education, treatment modification, and its application to self-management rather than the test itself.

Risks

The evidence is not as strong as in studies of insulin-treated individuals, and there are costs and there are costs and efforts required for education and self-management fees that should accompany SMBG.

Balancing the benefits and risks

Despite the lack of evidence, it is recommended that individuals with T2DM learn to test their blood glucose in order to benefit from lifestyle modification effects such as preventing hypoglycemia, improving self-care, and controlling diet.

Alternatives and considerations

If individuals with diabetes have difficulty testing their own blood glucose level, they can use the CGM or HbA1c test. However, CGM is only effective when proper training is provided.

Recommendation 6.2-4 SMBG can be done before and after the meal, before bedtime, at dawn, before and after exercise, and in the event of hypoglycemia, and the time and frequency of measurements can be individualized based on the patient's condition. [Expert opinion, general recommendation]

Level of evidence

Recommendations are based on the opinion of experts.

Benefits

SMBG can be helpful for the patient's self-management and lifestyle modification and can assist in accurate blood glucose measurement. The testing frequency depends on the type of diabetes, the medication prescribed, and the patient's knowledge and proactivity in controlling their blood glucose [121,122]. Although the 2-hour postprandial blood glucose test (2 hours after starting the meal) correlates more with HbA1c, individuals with uncontrolled diabetes are more influenced by fasting glucose level [137,138]. Therefore, if possible, measuring both pre-prandial and 2-hour postprandial blood glucose is recommended.

Risks

SMBG requires blood collection, which may cause discomfort for the patient. If it is not accompanied by sufficient education, its effectiveness can be reduced. Additionally, frequent measurements can cause inconvenience in daily life.

Balancing the benefits and risks

Despite the inconvenience and cost, several studies have shown that frequent testing correlates with better glycemic control. Therefore, frequent testing is recommended.

Alternatives and considerations

CGM is available but is more expensive than self-testing.

Recommendation 6.3-1 A rtCGM device is recommended to control blood glucose and reduce the risk of hypoglycemia in adults with T1DM. [Randomized controlled trial, general recommendation]

See section 'Continuous glucose monitoring and insulin pumps'

Recommendation 6.3-2 A rtCGM device should be considered to control blood glucose in individuals with T2DM on insulin therapy. [Randomized controlled trial, limited recommendation]

See section 'Continuous glucose monitoring and insulin pumps'

7. MEDICAL NUTRITION THERAPY

1. People with diabetes should receive individualized education in MNT. [Randomized controlled trial, general recommendation]
2. Education on MNT should be provided by registered dietitian nutritionists (RDNs) who are qualified for diabetes education. [Randomized controlled trial, general recommendation]
3. Overweight or obese adults should achieve a weight loss of at least 5% and reduce their total calorie intake to maintain it. [Randomized controlled trial, general recommendation]
4. The proportion of intake of carbohydrates, proteins, and fats should be individualized based on treatment goals and personal preferences. [Randomized controlled trial, general recommendation]
5. Eating patterns that have demonstrated long-term benefits, such as the Mediterranean style, vegetarian, low-fat, Dietary Approaches to Stop Hypertension (DASH), and low-carbohydrate eating patterns, may be implemented according to personal preferences and treatment goals. [Randomized controlled trial, limited recommendation]
6. Carbohydrates should be consumed as fiber-rich whole grains, legumes, vegetables, fresh fruits, and dairy products. [Randomized controlled trial, general recommendation]
7. Consumption of sugar-sweetened beverages is discouraged to minimize added sugar intake. [Randomized controlled trial, general recommendation]
8. Protein intake need not be limited, even in people with renal diseases. [Randomized controlled trial, general recommendation]
9. Food rich in saturated and trans fats should be replaced with food rich in unsaturated fats. [Randomized controlled trial, general recommendation]
10. Routine administration of unsaturated fat as dietary supplements is not recommended. [Randomized controlled trial, general recommendation]
11. A sodium restriction of less than 2,300 mg per day is recommended. [Randomized controlled trial, general recommendation]
12. Routine administration of micronutrients, such as vitamins and minerals, as dietary supplements to improve blood glucose levels is not recommended. [Randomized controlled trial, general recommendation]
13. Abstinence from alcohol, when possible, is preferable. [Expert opinion, general recommendation]
14. Insulin or insulin secretagogue users should be educated on preventing hypoglycemia when drinking alcohol. [Randomized controlled trial, general recommendation]

Recommendation 7.1 People with diabetes should receive individualized education in MNT. [Randomized controlled trial, general recommendation]

Recommendation 7.2 Education on MNT should be provided by RDNs who are qualified for diabetes education. [Randomized controlled trial, general recommendation]

Level of evidence

An individualized MNT program provided by RDNs has consistently shown multiple benefits, including improved glycemic control, weight loss, and reduced blood pressure [139]. Most diabetes guidelines recommend active implementation of MNT, and recent systematic reviews and meta-analyses support this recommendation [140].

Benefits

In people with diabetes, MNT reduces HbA1c by 0.3% to 2.0% [139], and has shown also to reduce body weight, waist circumference, cholesterol, and blood pressure [140]. In one study on adults with prediabetes, the MNT-implemented group showed significant glycemic improvement compared to the control group [141]. Furthermore, MNT provided by RDNs has proven to be cost-effective [139,142].

Risks

There are no risks in implementing MNT when educated by an appropriately qualified clinical dietitian.

Balance the benefits and risks

MNT lowers blood glucose and CVD risk without evidence of harm. It is cost-effective when provided by RDNs with expertise in diabetes education.

Alternatives, considerations when using the guidelines

MNT plays an essential role in the prevention and treatment of diabetes. People with diabetes need individualized MNTs based on their medical status, treatment goals, and personal preferences. MNT provided by RDNs should be reimbursed with an appropriate insurance plan in a cost-effective manner. Caregivers and people with diabetes should be actively involved in the whole nutrition therapy process, starting from the nutritional status assessment and meal planning, followed by regular reassessment and education sessions. RDNs should strive for a comprehensive understanding and up-to-date knowledge of diabetes and should receive continuous education to maintain their credentials.

Recommendation 7.3 Overweight or obese adults should achieve a weight loss of at least 5% and reduce their total calorie intake to maintain it. [Randomized controlled trial, general recommendation]

Level of evidence

When overweight or obese adults with diabetes (or prediabetes) lose and maintain a weight loss of at least 5% of their body weight by reducing caloric intake in combination with adequate exercise, insulin sensitivity, blood glucose, hypertension, and dyslipidemia were improved [55,56,143,144]. Short-term, very low-calorie meal plans (<800 kcal/day) have shown to be beneficial in weight loss and glycemic control without significant risks in some people [145], and these improvements remained when a weight loss of 7% or more was maintained for 5 years [146]. As a result, major diabetes guidelines recommend a weight loss of at least 5% in overweight or obese adults. In the Diabetes Remission Clinical Trial (DiRECT), participants (individuals who had been diagnosed with T2DM within the past 6 years) currently taking only oral antidiabetic medications were enrolled in a 1-year weight loss program, which included eating a diet of 825 to 853 kcal/day for the first 3 to 5 months. Results showed that 46% achieved diabetes remission, and this effect was proportional to the amount of weight lost [147].

Benefits

In overweight or obese people with diabetes, a weight loss of at least 5% combined with calorie intake restriction and appropriate lifestyle modifications, including exercise, was associated with improved metabolic markers, such as blood glucose, and reduced CVD risk. Depending on the patient, greater weight loss may result in more significant gains, and maintaining this weight loss results in sustained benefits.

Risks

In people with diabetes who are using insulin or sulfonylureas, low-calorie, and very low-calorie meal plans may increase the risk of hypoglycemia. Excessive dietary restriction can lead to deficiencies in essential nutrients, and the risk of ketoacidosis should be considered in people taking SGLT2 inhibitors [148]. Lower calorie meal plans are more difficult to adhere to, and their long-term effectiveness and safety need to be better established [149].

Balancing the benefits and risks

In overweight or obese people with diabetes (or prediabetes), reducing total caloric intake, losing weight, and maintaining weight loss with an appropriate exercise regimen have significant benefits in preventing diabetes, improving blood glucose levels, and reducing CVD risk. There are concerns about hypo-

glycemia and deficiencies of essential nutrients, but these can be prevented with appropriate medical evaluation and education. Therefore, all people with diabetes (or prediabetes) who are overweight or obese are recommended to restrict their total caloric intake to lose and maintain at least 5% of their body weight. However, this is not recommended in individuals at high risk for malnutrition, older adults, pregnant or lactating women, or those with kidney disease [139], and caution is warranted in SGLT2 inhibitor users.

Alternatives and considerations

Reducing total calorie intake for weight loss is individualized based on the patient's age, gender, height, weight, current intake and activity levels, medical conditions, and personal preferences and sustainability [139]. There are several methods for determining a target intake, but it is only a guide and should be individualized based on an individual's current intake, target body weight, glycaemic goals and feasibility.

Recommendation 7.4 The proportion of intake of carbohydrates, proteins, and fats should be individualized based on treatment goals and personal preferences. [Randomized controlled trial, general recommendation]

Level of evidence

No ideal proportion of carbohydrate, protein, and fat intake has consistently demonstrated benefit in the treatment of diabetes [139]. Therefore, major diabetes guidelines do not provide specific intake proportions for these macronutrients and recommend individualized proportions depending on an individual's metabolic goals, which are based on current medical conditions, eating patterns, and personal preferences. Many studies have reported that reducing carbohydrate intake is effective in improving blood glucose levels [150-152]. Systematic reviews and meta-analyses have also shown consistent results [153-155]. A recent meta-analysis evaluated the dose-dependent effect of carbohydrate restriction; blood glucose decreased linearly with the decrease in carbohydrate intake, and U-shaped effects were observed for serum lipids at 40% carbohydrate intake [156]. Another systematic review and meta-analysis found that consuming a diet with a carbohydrate proportion of $\leq 26\%$ of the total calorie intake was associated with a significantly higher rate of diabetes remission at 6 months compared to the control group, with no difference in adverse events [157].

Benefits

Although there is a lack of evidence that specific proportions of carbohydrates, proteins, and fat are beneficial in diabetes, reducing carbohydrate intake is effective in improving blood glucose levels.

Risks

There is a risk of hypoglycemia when carbohydrate intake is drastically reduced in insulin or sulfonylureas users. Reducing carbohydrate intake alone without reducing total caloric intake means increasing intake of other caloric nutrients such as protein and fat, and the potential for increased intake of animal-derived saturated fats should be considered. Excessive low-carbohydrate meal plans can lead to deficiencies in essential nutrients [139], and the risk of ketoacidosis must be considered in patients taking SGLT2 inhibitors [148].

Balancing the benefits and risks

There are no ideal proportions of carbohydrate, protein, and fat intake that have consistently shown benefits for all people with diabetes. Therefore, individualization based on a careful assessment of each individual's medical condition, metabolic goals, and preferences is recommended. While it may be worthwhile to reduce total carbohydrate intake to improve blood glucose, excessively low-carbohydrate meal plans are not recommended in individuals at high risk for malnutrition, older adults, and pregnant or lactating women [139], and caution is warranted in those taking SGLT2 inhibitors.

Alternatives and considerations

Although prospective studies on the appropriate carbohydrate intake in Korean people with diabetes are lacking, given that 65% to 70% of total energy intake comes from carbohydrates, which is higher than the proportion in other countries [158], recommending a reduction in carbohydrate intake may be beneficial in improving blood glucose levels. Therefore, in Koreans with diabetes, carbohydrate intake should be reduced to $\leq 55\%$ to 65% of total energy [159], but the specific amount should be individualized according to each individual's current medical condition and metabolic goals.

Recommendation 7.5 Eating patterns that have demonstrated long-term benefits, such as the Mediterranean style, vegetarian, low-fat, DASH, and low-carbohydrate eating patterns, may be im-

plemented according to personal preferences and treatment goals.
[Randomized controlled trial, limited recommendation]

Level of evidence

Many previous studies have shown the benefits of Mediterranean style, vegetarian, low-fat, low-carbohydrate, and DASH eating patterns demonstrate benefits in improving blood glucose levels, reducing weight, and reducing CVD risks. Accordingly, the ADA guideline recommends the implementation of these eating patterns in MNT [139]. A network meta-analysis and systematic review have also shown consistent results about the benefits of these eating patterns [151]. Recent studies have shown that time-restricted eating (including intermittent fasting) is beneficial for weight loss and glycemic control [160-162]. However, evidence on the benefits of this eating pattern in people with diabetes is still lacking [163,164]. Although there are reports of increased risk of hypoglycemia despite improved metabolic markers with medication adjustments and education [165], the few intervention studies to date have reported no safety concerns when medications are well monitored [166]. As a result, the recent ADA guidelines include time-restricted eating as a type of eating pattern [167]. However, the specific methods vary across studies, leading to limitations in interpretation and application, and there is still a lack of research on long-term effects.

Benefits

Mediterranean style, vegetarian, low-fat, low-carbohydrate, and DASH eating patterns have been shown to have long-term benefits in glycemic control, weight loss, and CVD risk reduction. Some studies reported the association of time-restricted eating with short-term weight loss and glycemic improvement. However, there is insufficient evidence on the benefits and long-term effects in people with diabetes.

Risks

There are no known harms of the Mediterranean style, vegetarian, low-fat, low-carbohydrate, or DASH eating patterns. Time-restricted eating may increase the risk of hypoglycemia during fasting, and compensatory binge eating may cause postprandial blood glucose to spike, leading to greater glycemic variability. Evidence on the long-term safety of timed eating is lacking.

Balancing the benefits and risks

The Mediterranean style, vegetarian, low-fat, low-carbohydrate, and DASH eating patterns have proven long-term benefits and safety for improving blood glucose and preventing CVD. In addition, these diets offer various meal options that are not too different from everyday meals and can be individualized upon consultation with RDNs to make them feasible and sustainable for people with diabetes. While there is evidence for short-term benefits, time-restricted eating is associated with an increased risk of hypoglycemia and glycemic variability, and there is a lack of evidence on its long-term benefits and safety.

Alternatives and considerations

People with diabetes should not attempt dietary methods that have not proven their efficacy and safety, including time-restricted eating, without doctor consultation, as they are at increased risk of various adverse events compared to the general population. This is particularly true when trying extreme diets that largely deviate from the usual eating patterns or in people who take medications that increase the risk of hypoglycemia, such as insulin or sulfonylureas. People with CVD or complications, elderly at increased risk of malnutrition, and pregnant and lactating women need special consideration.

Recommendation 7.6 Carbohydrates should be consumed as fiber-rich whole grains, legumes, vegetables, fresh fruits, and dairy products. [Randomized controlled trial, general recommendation]

Recommendation 7.7 Consumption of sugar-sweetened beverages is discouraged to minimize added sugar intake. [Randomized controlled trial, general recommendation]

Level of evidence

Many studies have shown that consuming carbohydrates in the form of fiber-rich whole grains, legumes, vegetables, raw fruits, and dairy products instead of refined carbohydrates has a significant effect on preventing diabetes and CVD and improving blood glucose levels [168-170]. In people with diabetes, routine dietary fiber consumption was associated with a significant decrease in mortality [171,172]. In contrast, consumption of sugar-sweetened beverages containing free sugars, such as added sugars used in processing or concentrated fruit juices, was associated with a significant increase in the incidence of diabetes [173,174]. As a result, major diabetes guidelines recommend minimizing added sugar intake and replacing it with

fiber-rich foods, emphasizing the quality of carbohydrates consumed. Recent observational studies, systematic reviews, and meta-analyses have also shown consistent results [175,176]. Previous studies have shown no benefit in glycemic management from nonnutritive sweeteners (NNSs) [177], and results were inconsistent for weight loss [178-180]. Recent systematic reviews and meta-analyses have also shown that NNSs does not improve glycemic management [180].

Benefits

Minimizing added sugar intake and consuming carbohydrates as fiber-rich food have proven to be beneficial in preventing diabetes, improving glycemic management, preventing CVD, and reducing mortality. The benefits of using calorie-free and carbohydrate-free NNSs are inconclusive. Consumption of beverages (carbonated beverages, sports drinks, coffee, tea, cacao beverages, and fruit juices made from concentrated fruit juices) containing added sugars, such as sugar and syrups, is discouraged. Short-term substitution with NNSs has been reported to reduce added sugar intake [181], and a recent network meta-analysis found that postprandial glycemic and metabolic responses to NNSs-sweetened beverages were similar to those seen with water [182].

Risks

While there is no known harm when consuming carbohydrates in the form of fiber-rich foods with minimal intake of added sugars, it is important to be aware of potential risks. Caution is necessary for individuals with severely reduced renal function or those taking certain medications, as electrolyte abnormalities such as hyperkalemia may occur. Recently, there have been increased reports of adverse events regarding NNSs intake [181]. NNSs has been reported to impair glycemic responses depending on the individual's gut microbiome [183] and may also be associated with increased CVD risk [184,185].

Balancing the benefits and risks

Reducing sugar intake and consuming carbohydrates in the form of fiber-rich whole grains, legumes, vegetables, fresh fruits, and dairy products is recommended for glycemic management, CVD prevention, and mortality reduction, as there is no general harm. However, fruits that are high in sugars may raise blood glucose levels and should be consumed in moderation, especially if those consumed in the form of concentrated juices, which may cause a significant increase in blood glucose levels.

Although evidence for NNSs in glycemic improvement and weight loss is insufficient, NNSs may be considered for short-term use in individuals who have difficulties in reducing added sugar consumption.

Alternatives and considerations

Studies in the United States and Canada recommended a dietary fiber intake of at least 14 g per 1,000 kcal to prevent CVD. However, in Korea, the recommended intake is 12 g per 1,000 kcal, calculated based on the estimated average dietary fiber intake in the 1960s to 1970s [159]. The average dietary fiber intake of South Koreans in 2016 to 2018 was 11 g per 1,000 kcal, which is lower than the recommended intake of 12 g [159]. Therefore, despite the lack of scientific evidence for the recommended dietary fiber intake in Korea, this recommendation has remained without further adjustments. The 2020 Korean Dietary Reference Intakes (KDRI) recommends limiting sugars to 10% to 20% of total energy intake and added sugars to 10% of total calories [159]. NNSs can help reduce sugar intake in the short term, but ultimately, it is important to reduce the consumption of all beverages, even those containing NNSs, and replace them with water [181]. To ensure adequate carbohydrate intake, metrics such as the glycemic index and glycemic load can help manage postprandial glucose levels, though they may not be completely reliable [186,187].

Recommendation 7.8 Protein intake need not be limited, even in people with renal diseases. [Randomized controlled trial, general recommendation]

Level of evidence

There is a lack of evidence on the appropriate amount of protein intake and the benefits of protein restriction on glycemic management and CVD risk in people with diabetes [139,188]. Traditionally, protein restriction has been proposed to delay the progression of kidney disease in patients with albuminuria or reduced glomerular filtration rate (GFR), but many studies have shown that even in the aforementioned cases, evidence on protein restriction is insufficient. As a result, major diabetes guidelines recommend the same amount of protein intake for people with diabetic nephropathy as the general population. A recent systematic review and meta-analysis have also shown consistent results [189].

Benefits

Evidence on the benefits of a stricter protein restriction in people with diabetes and those with diabetic nephropathy than the general population is insufficient.

Risks

Limiting protein intake to less than 0.8 g/kg/day can lead to not only protein deficiency but also inadequate intake of various nutrients [190,191].

Balancing the benefits and risks

Protein intake need not be restricted in people with diabetes as the evidence of its benefits is lacking. Even in people with kidney diseases, evidence on protein restriction is insufficient and instead poses an increased potential for harm, including malnutrition; therefore, protein intake need not be more strictly restricted.

Alternatives and considerations

Protein accounts for 13% to 15% of total daily energy intake for adults in Korea, including people with diabetes [158]. In the past, protein intake in Korea was lower than the recommended amount. Recently, except for women of ≥ 75 years old, the average intake has increased to above the recommended amount, though excessive intake is not yet a cause for concern [159]. It is not necessary to generally restrict protein intake in Koreans with diabetes, but the intake should be individualized according to the individual's eating patterns, glycemic management, and metabolic goals. Since protein can increase the insulin response to carbohydrates, carbohydrate sources such as milk with high protein content should not be used to treat hypoglycemia [192].

Recommendation 7.9 Food rich in saturated and trans fats should be replaced with food rich in unsaturated fats. [Randomized controlled trial, general recommendation]

Recommendation 7.10 General administration of unsaturated fat as dietary supplements is not recommended. [Randomized controlled trial, general recommendation]

Level of evidence

Numerous studies have shown that replacing foods high in saturated or trans fats with those rich in unsaturated fats benefits glycemic management and reduces the risk of CVD [193-197]. A recent systematic review and meta-analysis have also shown consistent findings [198]. However, there is insufficient evi-

dence to support the routine administration of unsaturated fat supplementation to improve glycemic management and prevent cardiovascular events in people with diabetes. Previous studies have failed to prove the preventive effect of omega-3 fatty acid supplementation on cardiovascular events in people with diabetes [199]. A recent meta-analysis found that unsaturated fats supplementation had little or no effect on diabetes incidence, HbA1c, fasting blood glucose level, insulin secretion, or insulin resistance [200]. In the Study of Cardiovascular Events in Diabetes, daily supplementation with 1 g of omega-3 fatty acids did not show a preventive effect on cardiovascular events in diabetic people without CVD [201]. However, in the Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial, in which more than 50% of the participants were people with diabetes, daily 4 g eicosapentaenoic acid supplementation lowered the risk of cardiovascular events in patients with atherosclerotic CVD with triglycerides level between 135 and 499 mg/dL, despite the use of statins [202].

Benefits

Reducing the consumption of foods high in saturated and trans fats and replacing them with those rich in unsaturated fats is effective in improving blood glucose levels and preventing CVD. However, supplementation of unsaturated fats in the general diabetes population has not been proven to improve blood glucose levels or prevent CVD.

Risks

Given that the total calories and the proportion of fats are not excessive, limiting the consumption of foods high in saturated and trans fats and increasing consumption of foods rich in unsaturated fats are known to have no harms. There are no known harms in taking unsaturated fats supplementation, but this is not recommended as there is a lack of evidence for its safety.

Balancing the benefits and risks

In terms of fat intake, the quality is more important than absolute quantity or proportion [139]. Limiting the intake of foods high in saturated and trans fats and replacing them with foods rich in unsaturated fats can be generally recommended without significant risks, as it is expected to improve glycemic control and reduce CVD risk. However, supplementation of unsaturated fats, including omega-3 fatty acids, for the prevention and treatment of CVD in all people with diabetes is not recommended because of the lack of evidence of its effects.

Alternatives and considerations

According to the KNHANES, the proportion of energy intake from fat among Koreans ranges from 13% to 26% depending on age, which is lower than that of Western countries [159]. The 2020 KDRI suggested that the appropriate energy intake from fats for adults is 15% to 30% of total calories, and the 2022 Korean Guidelines for the Management of Dyslipidemia recommended limiting fat intake within 30% of daily energy intake. It is recommended to limit cholesterol to within 300 mg per day, to limit saturated fats to within 7% of total energy intake and replace them with unsaturated fats as much as possible, and to avoid the intake of trans fats.

Recommendation 7.11 A sodium restriction of less than 2,300 mg per day is recommended. [Randomized controlled trial, general recommendation]

Level of evidence

Many observational and RCTs have shown that sodium restriction reduces blood pressure and CVD risk [203-207]. A meta-analysis has showed that reducing sodium intake in people with T1DM and T2DM improves blood pressure [208], and another RCT showed that in people with T2DM, limiting sodium intake to an average of 2,310 mg per day, along with the DASH diet, improved CVD risk factors, including blood pressure [209]. Based on these findings, most hypertension and diabetes guidelines recommend limiting sodium intake ideally to within 2,300 mg per day when possible. While the evidence for the benefits of sodium restriction is clear, there is a lack of evidence supporting the recommendation that the appropriate sodium intake is within 2,300 mg.

Benefits

In people with diabetes, hypertension and CVD are among the most critical comorbidities, and controlling blood pressure is essential to delay the development of diabetes complications. Therefore, reducing sodium intake may help lower blood pressure and delay the development of CVD and diabetic complications.

Risks

There is no evidence of harm in restricting daily sodium intake, especially in populations with high-sodium intake, such as Korea.

Balancing the benefits and risks

Reducing sodium consumption may lower blood pressure and reduce the risk of CVD and the occurrence of diabetes complications development without concerns of specific harms. Although prospective studies focusing on Koreans are lacking, clinical benefits may be expected from sodium restriction in a population with high-sodium intake, such as Korea. There is a lack of evidence to warrant more stringent sodium intake restrictions for people with hypertension and diabetes compared to the general population [210,211]; therefore, the same level of recommendation is advised for people with diabetes as for the general population. Although there is insufficient evidence to justify the recommendation of a daily sodium intake limit of 2,300 mg, the consensus should be understood more as a direction to reduce overall excessive sodium consumption, which can help in improving blood pressure and CVD risk, rather than as an absolute target.

Alternatives and considerations

The 2020 KDRI revised the recommended daily allowance of sodium to within 2,300 mg to reduce the risk of chronic diseases [159]. Many clinical guidelines, including those from the ADA, recommended a sodium limit of less than 2,300 mg, and the 2022 guideline from Korean Society of Hypertension recommended a daily salt restriction of 6 g to lower blood pressure. The 2023 diabetes treatment guidelines maintained sodium intake restriction for people with diabetes to within 2,300 mg as revised in 2021. Efforts to reduce sodium intake resulted in a significant decrease in the average daily sodium intake in Korea to 3,038 mg in 2021 from 4,549 mg in 2012, according to the KNHANES [212]. However, this is still above the global recommendation of 2,000 to 2,400 mg, and persistent efforts to reduce sodium intake are necessary.

Recommendation 7.12 Routine administration of micronutrients, such as vitamins and minerals, as dietary supplements to improve blood glucose levels is not recommended. [Randomized controlled trial, general recommendation]

Level of evidence

There are many studies on the benefits of micronutrient supplementation for improving glycemic management, weight loss, and CVD risk in adults with diabetes. However, due to differences in participant characteristics and research methods in these studies, the consistent benefit of micronutrient supple-

mentation has not been proven [139]. Based on observational studies suggesting that vitamin D deficiency increases insulin resistance and the risk of developing T2DM, many prospective studies, systematic reviews, and meta-analyses have been conducted. Some reported that vitamin D supplementation could prevent diabetes [213,214] and improve blood glucose levels [215]. However, these studies often used doses of vitamin D much higher than those used for osteoporosis treatment, typically more than 5,000 IU daily, were short-term and small-scale, and mostly failed to prove the effectiveness of vitamin D supplementation. A recently published large-scale RCT, in which 2,400 people with prediabetes received a daily vitamin D dose of 4,000 IU, has also failed to prove the protective effect of vitamin D against diabetes, regardless of underlying vitamin D deficiency [216]. Therefore, the evidence for vitamin D supplementation to improve glycemic management remains insufficient to recommend it in major diabetes guidelines.

Benefits

The benefits of supplementation with antioxidants such as vitamin C, vitamin E, and carotenes, as well as micronutrients like chromium, magnesium, and selenium are unclear [139]. Despite accumulating research on the benefits of vitamin D on improving blood glycemic control, the evidence is still not sufficient. In addition, a variety of foods and plants (aloe vera, cinnamon, curcumin, Jerusalem artichoke, bitter melon, etc.) and its processed products that have been reported to improve glycemic management in different countries and cultures also do not have enough evidence to support their benefits.

Risks

There is a lack of evidence that the routine administration of micronutrient supplements such as vitamins and minerals is harmful, but there is also a lack of evidence on its safety from long-term consumption in excessive amounts. However, recent reports of the association of β -carotene with increased mortality from lung cancer and CVD [217] have led the ADA guideline to suggest that supplementation of β -carotene may pose a risk to some people [167].

Balancing the benefits and risks

Since there is insufficient evidence that micronutrient supplements prevent diabetes or improve blood glucose levels, their use for improving blood glucose in people with diabetes is generally not recommended. However, supplement use may be

considered in cases where nutrient deficiencies are confirmed or likely, such as pregnant or lactating women, the elderly, vegetarians, and those on very low-calorie or low-carbohydrate eating patterns [139].

Alternatives and considerations

Vitamins and minerals are essential nutrients that constitute and regulate many biological reactions. It is recommended to consume these nutrients in the form of whole grains, fresh vegetables and fruits, and dairy products, rather than in supplements. Rather than focusing on the effects of specific micronutrients and their supplements, it is recommended to consume a variety of nutrients through a diverse diet. The socioeconomic costs associated with the use of unproven micronutrient and dietary supplements, as well as considerations for the manufacturing process and safety of additives, also need to be taken into account. The association between long-term use of metformin, the most widely used oral antidiabetic agent, and vitamin B12 deficiency has been reported. Therefore, it is advised to test for vitamin B12 in patients who have been taking metformin for a long period and exhibit unexplained anemia or peripheral neuropathy [218].

Recommendation 7.13 Abstinence from alcohol, when possible, is recommended. [Expert opinion, general recommendation]

Recommendation 7.14 Insulin or insulin secretagogue users should be educated on preventing hypoglycemia when drinking alcohol. [Randomized controlled trial, general recommendation]

Level of evidence

Previous observational studies, systematic reviews, and meta-analyses have shown a J-shaped association between alcohol consumption and the risk of developing diabetes, where moderate amounts are beneficial, and excessive amounts increase harm. This pattern has also been observed in studies involving people with diabetes [219]. Consequently, many clinical guidelines permit moderate drinking for adults with diabetes, similar to the general population, and recent meta-analyses of cohort studies support this conclusion [220].

Benefits

Some studies have shown that consuming 5 to 25 g of alcohol per day may reduce the risk of diabetes [219,221].

Risks

Systematic reviews and meta-analyses, as well as prospective observational studies in Korea have shown that excessive alcohol consumption (>30 g/day) can increase the risk of diabetes, hyperglycemia, and weight gain [219-221]. Furthermore, alcohol consumption in people on insulin or insulin secretagogues has been associated with a higher risk of hypoglycemia [222].

Balancing the benefits and risks

In patients with diabetes who do not have complications or liver disease and who maintain good glycemic control, it is not necessary to prohibit alcohol consumption outright, and the intake guidelines can be the same as for the general population. The WHO recommends limiting alcohol consumption to no more than one standard drink for women and two standard

drinks for men (based on commonly used glasses for each type of alcohol) and abstaining from alcohol at least 2 days per week [223]. Although there is a lack of evidence on the appropriate amount of alcohol consumption for Koreans, the same guideline may be applied. However, many individuals may find it difficult to control the amount and frequency of their alcohol consumption, and in diabetes, alcohol can exacerbate various health problems that often accompany the disease. Therefore, it is considered more beneficial to encourage abstinence from alcohol rather than permitting it, based on the consensus of numerous experts recommending abstinence where possible. People using insulin or insulin secretagogues should be advised to eat adequately when drinking to avoid SH and to frequently monitor their blood glucose levels before and after drinking to prevent hypoglycemia.

8. EXERCISE THERAPY

1. Individualize the type, frequency, duration, and intensity of physical exercise based on the individual's age, physical capacity, and comorbidities. [Expert opinion, general recommendation]
2. Assessment for CVD and microvascular complications and confirmation of the absence of contraindications before the start of the first training session. [Expert opinion, general recommendation]
 - 1) People with severe retinopathy should avoid high-intensity physical exercise because they are at a high risk of retinal hemorrhage or detachment. [Expert opinion, general recommendation]
 - 2) People with severe peripheral neuropathy or foot diseases should avoid weight-bearing exercises. [Expert opinion, general recommendation]
 - 3) People with CVDs or those at a high risk of CVDs should avoid high-intensity physical exercise. [Expert opinion, general recommendation]
3. Preferably, a professional trainer should prescribe an appropriate exercise regimen. [Expert opinion, general recommendation]
4. Pre-exercise blood glucose levels were measured to determine the exercise method (Table 7). [Expert opinion, general recommendation]
5. Blood glucose levels were measured for hypoglycemia or hyperglycemia when the intensity or duration of exercise increased. [Expert opinion, general recommendation]
6. Engaging in both aerobic and resistance exercises is recommended. [Randomized controlled trial, general recommendation]
7. Engage in ≥ 150 min/week of at least moderate-intensity aerobic exercise, spread over at least 3 days per week, with less than 2 consecutive days without exercise. [Randomized controlled trial, general recommendation]
8. For physically able people with T2DM who cannot exercise as recommended because of time restrictions, high-intensity interval training (HIIT), a time-efficient alternative, is recommended. [Randomized controlled trial, limited recommendation]
9. Engage in resistance exercises at least twice a week. [Randomized controlled trial, general recommendation]
10. Minimize time spent in sedentary behaviors and avoid prolonged sitting. [Randomized controlled trial, general recommendation]

Recommendation 8.1 Individualize the type, frequency, duration, and intensity of physical exercise based on the individual's age, physical capacity, and comorbidities. [Expert opinion, general recommendation]

Recommendation 8.2 Assessment for CVD and microvascular complications and confirmation of the absence of contraindications before the start of the first training session. [Expert opinion, general recommendation]

- 1) People with severe retinopathy should avoid high-intensity physical exercise because they are at a high risk of retinal hemorrhage or detachment. [Expert opinion, general recommendation]
- 2) People with severe peripheral neuropathy or foot diseases should avoid weight-bearing exercises. [Expert opinion, general recommendation]
- 3) People with CVDs or those at a high risk of CVDs should avoid high-intensity physical exercise. [Expert opinion, general recommendation]

Recommendation 8.3 Preferably, a professional trainer should prescribe an appropriate exercise regimen. [Expert opinion, general recommendation]

Level of evidence

Although physical exercise is recommended for glycemic control, physical fitness, and cardiorespiratory fitness, it may be limited to people with CVD or microvascular complications. Precautions are required to avoid additional injuries and harm during exercise. These individualized recommendations are based on high-quality international guidelines and the opinions of diabetes specialists and exercise professionals.

Benefits

When exercising at intensities higher than brisk walking, it is advisable to consider the individual's age and previous physical activity level before starting the exercise and to assess the presence of CVD, severe hypertension, and microvascular complications such as severe retinopathy/autonomic neuropathy/peripheral neuropathy. When beginning an exercise regimen, it is beneficial to receive guidance from a professional to ensure that the exercise is performed accurately, effectively, and safely, and, if possible, to seek an exercise prescription from an exercise specialist.

Risks

Exercise tolerance testing is not necessary for asymptomatic diabetics with a 10-year risk of coronary artery disease of less than 10%, as the harms of false-positive results are greater [224,225].

Balancing the benefits and risks

In people with diabetes with proliferative retinopathy or severe non-proliferative retinopathy, high-intensity aerobic or resistance exercises are contraindicated due to an increased risk of retinal hemorrhage or detachment [226,227]. Reduced pain sensation in the upper or lower extremities increases the risk of skin ulcers, infections, and Charcot's joints. Therefore, diabetic individuals with peripheral neuropathy should be educated to wear appropriate footwear and monitor their feet daily to detect lesions early. Individuals with severe diabetic neuropathy are recommended to engage in low-impact exercises, such as swimming, cycling, and arm exercises [228,229]. Autonomic neuropathy can reduce the cardiac response to exercise and cause orthostatic hypotension, impair thermoregulation, night vision, and thirst, and cause gastroparesis, all of which can lead to various exercise-related adverse events and increase cardiovascular complications. Therefore, diabetic individuals with autonomic neuropathy are recommended to undergo a thorough cardiovascular evaluation before beginning exercise [230,231].

Recommendation 8.4 Pre-exercise blood glucose levels were measured to determine the exercise method. [Expert opinion, general recommendation]

Recommendation 8.5 Blood glucose levels were measured for hypoglycemia or hyperglycemia when the intensity or duration of exercise increased. [Expert opinion, general recommendation]

Level of evidence

Research on the timing and extent of insulin reduction before and after exercise has primarily focused on people with T1DM who use insulin pumps or multiple insulin injections. As the response to exercise varies among individuals, it is not easy to make a general recommendation based on the exercise methods used in each study. Professional opinions and individualized recommendations are essential to identify fluctuations in blood glucose levels and to prevent hypoglycemia in patients at high risk for hypoglycemia.

Benefits

Measuring pre-exercise blood glucose levels can aid in predicting and preparing for hypoglycemia, as it is an important predictor of exercise-induced hypoglycemia.

Risks

Exercise can lead to hypoglycemia in people on insulin or insulin secretagogues. For people with T1DM, the fear of hypoglycemia is one of the main reasons for their hesitation to exercise. A meta-analysis reported that HIIT tends to cause less hypoglycemia in patients with T1DM than continuous aerobic exercises, although the difference was not significant [232]. High-intensity exercise should be avoided in patients with ketoacidosis. However, if there is no ketoacidosis and the overall condition is good, there is no need to delay or avoid exercise due to hyperglycemia [233].

Balancing the benefits and risks

Before and after exercise, when the overall condition changes, the intensity of exercise varies, or the duration of exercise increases, the blood sugar levels should be measured to detect hypoglycemia or hyperglycemia. This is especially important for individuals with diabetes using insulin secretagogues or insulin, as measuring blood glucose before and after exercise helps to understand the changes in blood glucose levels during activity. If there is a high risk of hypoglycemia, it may be necessary to re-

Table 7. Suggested strategies based on pre-exercise blood glucose levels

Pre-exercise blood glucose levels	Carbohydrate intake or other actions
<90 mg/dL	Consume 15–30 g of fast-absorbing carbohydrates prior to the start of exercise, depending on the level of exercise: This may not be necessary for exercises of less than 30 minutes, or high-intensity exercises such as weight training or interval training. Additional carbohydrate intake is required for prolonged moderate-intensity exercise (depending on blood glucose levels, consume an additional 0.5–1 g of carbohydrate per kg body weight every hour of exercise).
90–150 mg/dL	Start consuming carbohydrates at the beginning of most exercise (0.5–1 g of carbohydrates per kg body weight every hour of exercise), depending on the type of exercise or insulin activity level.
150–250 mg/dL	Delay carbohydrate consumption until blood glucose decreases below 150 mg/dL, after starting an exercise.
250–350 mg/dL	Test for ketones and stop the exercise if a medium to high amount of ketones is detected. Start with low- to moderate-intensity exercise. Since high-intensity exercise can lead to hyperglycemia, these exercises should be delayed until blood glucose falls below 250 mg/dL.
≥350 mg/dL	Test for ketones and stop the exercise if a medium to high amount of ketones is detected. If no ketones are detected, adjust the pre-exercise insulin dosage (generally to about 50%) based on insulin activity level. Start with low- to moderate-intensity exercise and avoid strenuous exercise until blood glucose levels fall.

duce the dose of insulin or medication before exercising or to consume a snack before exercising [234].

Recommendation 8.6 Engaging in both aerobic and resistance exercises is recommended. [Randomized controlled trial, general recommendation]

Recommendation 8.7 Engage in ≥150 min/week of at least moderate-intensity aerobic exercise, spread over at least 3 days per week, with less than 2 consecutive days without exercise. [Randomized controlled trial, general recommendation]

Recommendation 8.8 For physically able people with T2DM who cannot exercise as recommended because of time restrictions, HIIT, a time-efficient alternative, is recommended. [Randomized controlled trial, limited recommendation]

Recommendation 8.9 Engage in resistance exercises at least twice a week. [Randomized controlled trial, general recommendation]

Level of evidence

There are many RCTs and meta-analyses analyzing the effects of exercise on glucose control, physical fitness, and cardiorespiratory fitness in people with T1DM and T2DM. However, there were difficulties in interpreting the results uniformly due to differences in the type, method, intensity, and duration of exercise used in each study. Therefore, the evidence for this recommendation was based on studies that analyzed the degree of glycemic control, cardiorespiratory fitness, and metabolic markers in the general population with diabetes, not those focusing on a specific limited patient group.

Benefits

Regular exercise improves glucose control, reduces CVD risk, and contributes to weight loss [235]. It also has a preventive effect on diabetes in people at high-risk groups [56]. Typical aerobic exercises include walking, cycling, jogging, and swimming, whereas resistance exercises involve weight training using equipment to work against weight or resistance [235].

Boule et al. [236] conducted a meta-analysis of studies (12 aerobic and two resistance exercise studies) lasting more than 8 weeks on changes in HbA1c and BMI in people with T2DM, and found that HbA1c was significantly reduced in the exercise group, independent of weight loss. In addition, the reduction in HbA1c was more pronounced in the higher intensity exercise group, suggesting that increasing exercise intensity may lead to improved fitness and better glucose control in currently exercising people [237]. A meta-analysis of 23 clinical studies on Koreans with T2DM also reported a significant reduction in HbA1c with exercise, but no significant weight loss was observed [238].

Evidence on the benefits of exercise on HbA1c and glycemic management is more limited in people with T1DM than in those with T2DM. A meta-analysis of five studies examining the effect of exercise for 12 weeks or longer on people with T1DM found no difference in HbA1c, but did note improvements in key indicators such as body weight, BMI, peak oxygen uptake, and low-density lipoprotein cholesterol (LDL-C) [239]. An 11.4-year prospective observational study involving approximately 2,300 people with T1DM demonstrated that

higher physical activity intensity was associated with a lower risk of cardiovascular mortality [240].

It is ideal to perform moderate-to-vigorous intensity exercise for at least 30 minutes as frequently as possible throughout the week, combining aerobic and resistance exercises unless contraindicated [239]. If daily aerobic exercise is challenging, the duration of exercise per session can be increased. At least 150 minutes of moderate-intensity aerobic exercise per week is recommended. Exercise should be performed at least 3 days a week, and it is important to not skip more than 2 consecutive days since the effect of aerobic exercise on insulin sensitivity lasts 24 to 72 hours [241,242].

HIIT may be beneficial for individuals who exercise regularly or are physically capable. A meta-analysis of 13 RCTs comparing 11 weeks or more of HIIT to moderate aerobic exercise or control (no exercise) groups in people with T2DM found that HIIT had more positive effects on HbA1c, body weight, and BMI than moderate aerobic exercise [243]. However, there are limitations to the level of evidence due to heterogeneity in exercise methods among the included studies and the inclusion of studies with low-quality assessments, indicating the need for more extensive studies to verify long-term effects. Based on the current level of evidence, short-duration HIIT can be recommended for individuals with T2DM who cannot secure sufficient exercise time.

Resistance exercise improves insulin sensitivity to the same extent as aerobic exercise. Since resistance exercise does not increase the risk of cardiac ischemia or stroke compared to aerobic exercise, it can also be recommended for middle-aged and elderly people with diabetes [244,245]. Furthermore, combining aerobic and resistance exercises has additional benefits for glycemic control [246,247]. Unless contraindicated, resistance exercises should be performed at least twice a week [241,242].

Risks

Potential harm from exercise in people with diabetes includes

injuries and soft tissue damage during exercise. Moderate-intensity or prolonged exercise can lead to hypoglycemia, whereas high-intensity exercise may cause hyperglycemia. People with high blood glucose levels should be cautious of rising blood glucose and ketone levels.

Balancing the benefits and risks

The glycemic benefits of exercise in T1DM remain unclear. However, it also improves cardiorespiratory fitness and physical strength. Therefore, unless contraindicated, exercise is recommended with precautions for hypoglycemia.

Recommendation 8.10 Minimize time spent in sedentary behaviors and avoid prolonged sitting. [Randomized controlled trial, general recommendation]

Level of evidence

While there is an accumulating amount of research on the association of sedentary behavior with health and glycemic control, controlled trials with interventions are still limited. Two recent RCTs have shown similar positive results, leading to recommendations for most people with diabetes.

Benefits

A recent study found that avoiding prolonged sitting and engaging in brief walks or light activity every 30 minutes can help improve glycemic control in inactive adults with T2DM [248]. Another study found that light walking for 3 minutes at intervals of 60, 30, and 15 minutes during a 7-hour sitting period improved morning fasting blood glucose and overnight glucose variability. The more frequently participants got up to take short walks, the better the improvement [249]. Therefore, it is recommended to minimize the time spent sitting and frequently stand or engage in light physical activities to break up long periods of sitting.

9. PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES MELLITUS

1. People with T1DM should receive structured education to adjust their insulin doses on their own, allowing for flexible eating. [Randomized controlled trial, general recommendation]
2. The educational understanding and self-management skills of adults with T1DM should be assessed and feedback given consistently and regularly from the time of diagnosis. [Expert opinion, general recommendation]
3. For children and adolescents with T1DM and their parents or caregivers, personalized self-management education appropriate for the developmental stages of children and adolescents should be provided from the time of diagnosis. This should be regularly reassessed as the children or adolescents grow and their capacity for independent self-management evolves. [Expert opinion, general recommendation]
4. Adults with T1DM who have experienced hypoglycemia unawareness or symptomatic hypoglycemia (SH) should receive professional and specialized education to prevent hypoglycemia and restore hypoglycemia awareness. [Randomized controlled trial, general recommendation]
5. Treat adults with T1DM using multiple daily injections (MDIs) of prandial and basal insulin or insulin pumps (continuous subcutaneous insulin infusion). [Randomized controlled trial, general recommendation]
6. In adults with T1DM on multiple daily insulin injection therapy, rapid-acting insulin analogs and basal insulin analogs should be used preferentially. [Randomized controlled trial, general recommendation]

Recommendation 9.1 People with T1DM should receive structured education to adjust their insulin doses on their own, allowing for flexible eating. [Randomized controlled trial, general recommendation]

Recommendation 9.2 The educational understanding and self-management skills of adults with T1DM should be assessed and feedback given consistently and regularly from the time of diagnosis. [Expert opinion, general recommendation]

Recommendation 9.3 For children and adolescents with T1DM and their parents or caregivers, personalized self-management education appropriate for the developmental stages of children and adolescents should be provided from the time of diagnosis. This should be regularly reassessed as the children or adolescents grow and their capacity for independent self-management evolves. [Expert opinion, general recommendation]

Level of evidence

The evidence for Recommendation 1 includes systematic reviews [250,251] and RCTs [252,253]. Among the research, the systematic review conducted by Rytter et al. [251] to determine the effectiveness of educational programs in people with T1DM aged 16 years or older using insulin pumps included only nine studies among which were only one RCT. Another limitation was the excessive heterogeneity among the study designs. However, the included RCT was relatively well-designed and conducted with moderate to high quality; therefore, the level of evidence was rated as a RCT. A general recommendation was rated as benefits outweighed risks.

Benefits

People with T1DM using multiple daily insulin injections or

an insulin pump should be educated to self-monitor blood glucose and appropriately adjust insulin dose based on carbohydrate intake, anticipated activity, and current glucose levels [252,254,255]. It is also recommended that people with T1DM be taught how to cope with circumstances in which insulin sensitivity is reconstituted (stress, infection, steroid use, etc.) or insulin pump use is unavailable [255]. In a meta-analysis of adults with T1DM, carbohydrate counting was associated with a 0.64% reduction in HbA1c levels compared to usual or alternative dietary advice alone [250].

The 5-day Dose Adjustment For Normal Eating (DAFNE) program is a renowned insulin education program. A RCT showed that after receiving structured education on DAFNE, individuals could adjust their mealtime insulin doses according to circumstances with flexible food intake. Also, it had improved diabetes-

related quality of life and HbA1c levels [252]. Similar education programs are available in the United Kingdom, Germany, Australia, and New Zealand. Alimentación Normal con Ajuste de Insulina (ANAIS) is the Spanish version of the DAFNE program and is a therapeutic education program for people with T1DM based on a flexible insulin regimen that adapts to the individual's food intake [253]. In a RCT, ANAIS did not show a significant improvement in HbA1c levels but was found effective in terms of treatment satisfaction and achievement of individual-set goals [253]. In addition, Rytter et al. [251] conducted a systematic review to determine the effectiveness of educational programs in people with T1DM aged 16 years or older using insulin pumps. Although the lack of included studies and the heterogeneity of the study designs limit definitive conclusions, the results suggest that appropriate education in insulin pump users can help improve HbA1c levels, reduce hypoglycemic events, and enhance knowledge and skills on use of insulin pump [251].

The effectiveness of such education is expected to be enhanced with appropriate feedback based on an assessment of the level of understanding and performance of people with diabetes provided on an ongoing basis. Especially in children and adolescents, the help and support of parents/caregivers play an important role in the management of T1DM [256,257], and the role of parents/caregivers changes throughout the life course as the youth grows, develops, and acquires the need and desire for greater independent self-care skills [256-258]. Therefore, to ensure the best outcomes, both children and adolescents and their parents/caregivers should receive tailored education suited to their developmental stage as well as periodic reassessment.

Risks

The RCT assessing the effectiveness of the DAFNE program [252] found no negative impact on cardiovascular risk factors, such as body weight and cholesterol markers, or an increase in symptomatic hypoglycemia (SH). The average number of insulin injections per day increased after the program. In the RCT that examined the effectiveness of the ANAIS education program [253], researchers encountered issues with finding dedicated areas to educate and store training materials, securing staff for teaching, and ensuring participant attendance.

Balancing the benefits and risks

The structured insulin education program for T1DM, DAFNE, has been shown to improve prandial insulin dose adjustment,

dietary flexibility, diabetes-related quality of life, and HbA1c levels, while ANAIS has shown improvements in T1DM treatment satisfaction and user-set goal achievement. In addition, the systematic review by Rytter et al. [251] suggests that education for individuals using insulin pumps can help improve HbA1c levels, reduce the incidence of hypoglycemia, and improve knowledge and skills related to insulin pump use. Although implementing a structured insulin education program may lead to increased costs in terms of health providers, material, and time resources, there is no expected direct harm to individuals with T1DM. Although the average number of insulin injections per day increased in participants who underwent the DAFNE program, it is likely due to the need for more injections to achieve adequate glucose control in T1DM. Therefore, the benefits of the recommendation clearly outweigh the risks.

Recommendation 9.4 Adults with T1DM who have experienced hypoglycemia unawareness or SH should receive professional and specialized education to prevent hypoglycemia and restore hypoglycemia awareness. [Randomized controlled trial, general recommendation]

Level of evidence

The studies included in the analysis were the RCT by Little et al. [259] and their 24-month follow-up [260], where randomization and blinding were well maintained and 76 of 96 participants were followed up to 24 months. The characteristics of those who dropped out were similar to those enrolled. Taken together, the quality of evidence was rated as RCTs. Specialized, structured education for preventing hypoglycemia and reestablishing hypoglycemia awareness in individuals with impaired awareness of hypoglycemia (IAH) and T1DM clearly outweigh the risks; therefore, the level of recommendation was classified as a general recommendation.

Benefits

To determine whether IAH could be improved and SH could be prevented in T1DM, Little et al. [259] conducted a 24-week 2×2 factorial RCT in 96 adults with T1DM and IAH by randomizing them into an insulin pump or MDIs as well as rtCGM or SMBG. All participants received comparable structured education aimed at avoidance of hypoglycemia and restoring hypoglycemia awareness. Regardless of the insulin pump, MDIs use, rtCGM, and SMBG, the study showed decreased

hypoglycemia, including SH, and improved IAH without the relaxing HbA1c levels [259]. After the 24-week study period, the subjects were allowed to return to their usual care and were free to decide to receive either the insulin pump or MDIs. At 24 months from baseline, the improvement in IAH and reduction in SH were sustained. In addition, the improvement in treatment satisfaction and the reduction in fear of hypoglycemia were sustained, with improved HbA1c compared to baseline without significant differences among the intervention groups [260]. These results indicate that providing specialized and professional education to prevent hypoglycemia and restore hypoglycemic awareness can improve IAH and reduce the incidence of SH in individuals with long-standing T1DM complicated by IAH and SH, and that the effects of such education are long-lasting [260].

Risks

In the 24-month follow-up report of a randomized controlled study by Little et al. [260], it was reported that a total of six cases of ketoacidosis requiring hospitalization occurred, all of which recovered without any sequelae. These incidences are unlikely a risk associated with specialized education for preventing hypoglycemia and reestablishing hypoglycemia awareness [260]. Furthermore, 12 serious adverse events were also reported in the study, all of which were unrelated to the study intervention [260]. Professionalized and structured education for hypoglycemia prevention and restoration of hypoglycemia awareness requires adequately trained educational personnel, resources, and secured educational time.

Balancing the benefits and risks

In a 24-week RCT of adults with T1DM with IAH, specialized and structured training to prevent hypoglycemia and restore hypoglycemic awareness resulted in clear benefits in terms of improved hypoglycemia awareness and reduced SH, which were sustained through 24 months. Improvements in HbA1c levels were seen at 24 months, along with improvements in treatment satisfaction and reduced fear of hypoglycemia. On the other hand, the risks of such systematic education are not clear, and the costs of educational personnel, resources, and training time are considered worthy. Therefore, the benefits of providing specialized, structured training for hypoglycemia prevention and restoration of hypoglycemic awareness in adults with T1DM and IAH clearly outweigh the risks.

Recommendation 9.5 Treat adults with T1DM using MDIs of prandial and basal insulin or insulin pumps (continuous subcutaneous insulin infusion). [Randomized controlled trial, general recommendation]

Level of evidence

The studies included in the analysis were the DCCT [91], a RCT, the EDIC studies [103,113] that followed up the DCCT through 2005, and a systematic review of 11 RCTs described by Chico and Corcoy [261]. Upon strict examination, the study by Chico and Corcoy [261] which included 11 RCTs is not a systematic review due to the following reasons: the insufficiently systematic search by using only one database search, no mentions on the inclusion criteria in advance, and no expressions of judgments on the exclusion of individual studies or an assessment of the bias risks of individual studies included in the study. Overall, the quality of evidence was rated as RCTs. As the benefits of the recommendation outweigh the risks, the recommendation was classified as a general recommendation.

Benefits

The DCCT study, conducted on patients with T1DM from 1983 to 1993, examined the impact of intensive insulin treatment, such as multiple daily insulin injections or insulin pumps, on reducing HbA1c levels below 7.0% compared to the conventional insulin treatment where insulin was administered once or twice-daily to control HbA1c levels to 9.0%. The results showed that intensive insulin treatment reduced the incidence and progression of microvascular complications by 50% over 6 years [91]. The EDIC study followed up the DCCT study until 2005 and found that the intensive insulin treatment group resulted in reduced incidence and progression of microvascular complications, macrovascular complications, and mortality [103,113]. A systematic review of 11 RCTs also concluded that intensive insulin treatment was superior in terms of reduction in HbA1c levels [261].

Risks

In the DCCT study, it was found that individuals receiving intensive insulin treatment had two to three times higher incidence of SH requiring assistance from others, as compared to those receiving conventional insulin treatment. During the 1-year observation of 100 subjects, there were 62 episodes of SH in the intensive insulin treatment group and 19 episodes in

the conventional insulin treatment group [91]. The study was carried out with a combination of neutral protamine hagedon (NPH) and regular insulin for its regimen. A review of 11 RCTs [261] that compared intensive insulin treatment with conventional insulin treatment in people with T1DM found that intensive insulin treatment resulted in more frequent hypoglycemia and greater weight gain. However, most of these studies were conducted in the 1980s and 1990s, and intensive insulin treatment in those studies consisted of at least three daily injections of a combination of NPH and regular insulin.

Balancing the benefits and risks

Studies in the past have shown that hypoglycemia occurs more frequently in intensive insulin treatment compared to conventional insulin treatment. However, with the development of insulin analogs including rapid-acting and long-acting insulin analogs, the frequency of SH has been reduced by 1/2–1/3 compared to the DCCT study, even with intensive insulin therapy [262]. A study conducted in Koreans with T1DM also showed a reduction in the frequency of hypoglycemia compared to a study conducted in the West 10 years ago [263]. Meanwhile, large-scale studies of DCCT and EDIC have shown that intensive insulin treatment with multiple insulin injections or insulin pumps leads to an improvement in HbA1c levels, a reduction in micro- and macrovascular complications, and a decrease in mortality. Therefore, it can be concluded that the benefits of intensive insulin treatment outweigh the risks.

Alternatives and considerations

Meta-analyses of studies that compared intensive insulin treatment involving multiple insulin injections and insulin pumps showed no significant difference in the frequency of SH. However, the reduction in HbA1c levels was slightly better in the insulin pump group [264]. At present, there are no consensus recommendations to guide the choice between multiple insulin injections or insulin pumps for specific individuals. Both are recommended as intensive insulin treatment for T1DM [255]. The use of insulin pump treatment is discussed in a separate section (section ‘Continuous glucose monitoring and insulin pumps’).

Recommendation 9.6 In adults with T1DM on multiple daily insulin injection therapy, rapid-acting insulin analogs and basal insulin analogs should be used preferentially. [Randomized controlled trial, general recommendation]

Level of evidence

The evidence considered for this analysis consisted of systematic reviews and meta-analyses [265–271], along with RCTs [272,273]. The evidence level was rated as randomized controlled studies, including systematic reviews and RCTs that were well-planned and conducted with moderate to high quality. The recommendation was classified as a general recommendation because the benefits outweighed the risks.

Benefits

The previous DCCT study comparing intensive insulin treatment versus conventional insulin treatment in people with T1DM reported a 2- to 3-fold increase in the incidence of SH requiring assistance from others in the intensive insulin treatment group. However, the study was conducted using intermediate-acting insulin and regular insulin [91].

Several types of insulin analogs have since been developed. These include rapid-acting insulin analogs such as aspart, lispro, and glulisine, as well as long-acting insulin analogs like glargine 100 U/mL and detemir.

More recently, longer-acting basal analogs like degludec and glargine 300 U/mL, which have longer half-lives than glargine 100 U/mL and detemir, have been developed and are currently in use. In addition, new ultra-rapid-acting insulin analogs like niacinamide combined with aspart (Fiasp, Novo Nordisk, Bagsværd, Denmark) and prostacyclin analog- and citrate-containing lispro (ultra-rapid lispro, Lyumjev, Eli Lilly and Company, Indianapolis, IN, USA) have been developed to accelerate their onset of action and are also being used. Long-acting insulin analogs have a longer duration of action compared to intermediate-acting insulin (NPH) with a flatter, more constant and consistent plasma concentrations and pharmacokinetic profiles. Rapid-acting insulin analogs have a quicker onset and peak, and shorter duration of action compared to regular human insulin. In people with T1DM, the combination of rapid-acting insulin analogs and long-acting insulin analogs is associated with lower risk of nocturnal and postprandial hypoglycemia, lower HbA1c levels, and less weight gain compared with intermediate-acting insulin (NPH) and regular insulin [254,265–268,270,272,273].

In a 24-month RCT, the use of detemir+aspart was superior to NPH+aspart in reducing HbA1c levels and FPG, with added benefits of less major and nocturnal hypoglycemia and less weight gain [272]. A systematic review and network meta-analysis of a total of 39 studies, encompassing 27 RCTs, demon-

strated consistent results. This encompassed studies involving long-acting insulin analogs (glargine, detemir) and intermediate-acting insulin (NPH, lente) adults with T1DM [265]. A literature review of 11 systematic reviews also confirmed that long-acting insulin analogs are superior to intermediate-acting insulin (NPH) in terms of HbA1c levels and incidence of nocturnal hypoglycemia [266]. In a more recent systematic review and meta-analysis, not only traditional long-acting insulin analogs (glargine, detemir), but also degludec, a longer-acting basal analog with a longer half-life, was found superior to intermediate-acting insulin in terms of HbA1c and FPG levels, weight gain, and major, severe, or nocturnal hypoglycemia [270]. Another systematic review and meta-analysis including nine RCTs conducted on people with T1DM found that detemir was superior to NPH for the risk of SH, but the results were inconsistent and there were no clear differences in other interventions, including severe nocturnal hypoglycemia and HbA1c levels [271]. A systematic review and meta-analysis including 22 RCTs demonstrated the superiority of rapid-acting insulin analogs over regular insulin in terms of overall hypoglycemia incidence, nocturnal hypoglycemia, SH, postprandial glycemic control, and HbA1c levels [267].

In addition, a study conducted on individuals with either T1DM or T2DM, among whom 82 were T1DM, found that multiple daily insulin injection with glargine plus premeal glulisine was superior to twice-daily premixed insulin (Humalog mix 75/25, Eli Lilly and Company; or Novomix 70/30, Novo Nordisk) in terms of patient satisfaction and quality of life, glycemic variability, and HbA1c levels [274].

Risks

The 24-month, multi-national RCT showed similar safety profiles between pre-prandial aspart+NPH and aspart+detemir, without unexpected adverse events reported in the aspart+detemir group [272]. A systematic review and network meta-analysis of studies of long-acting insulin analogs (glargine, detemir) and intermediate-acting insulin (NPH, lente) in adults with T1DM found that although the cost-effectiveness varied by studies, long-acting insulin analogs were generally more costly than intermediate-acting insulin [265]. However, a more recent systematic review found that long-acting insulin analogs, especially detemir, were cost-effective compared to NPH [269]. However, these reviews on cost-effectiveness did not include domestic data.

Balancing the benefits and risks

The combination of long-acting insulin analogs and rapid-acting insulin analogs demonstrated to reduce the incidence of hypoglycemia and nocturnal hypoglycemia, improve glycemic indices of HbA1c, FPG, and postprandial glucose levels, and reduce the extent of weight gain, compared to intermediate-acting insulin (NPH, lente) and regular insulin. Meanwhile, there are no clear risks of using long-acting insulin analogs and rapid-acting insulin analogs over intermediate-acting insulin (NPH, lente) and regular insulin. Although few overseas cost-effectiveness analyses report long-acting insulin analogs (glargine, detemir) are more costly than intermediate-acting insulin (NPH) [265], the studies were not conducted in Korea, and recent findings show detemir as more cost-effective than NPH [269]. Therefore, the benefits of using long-acting insulin analogs and rapid-acting insulin analogs compared to intermediate-acting insulin (NPH, lente) and regular insulin clearly outweigh the risks.

Alternatives and considerations

In the EDITION 4 study conducted in the United States and Europe on individuals with T1DM, there was no significant difference in the effectiveness of glargine 300 U/mL and glargine 100 U/mL when used as basal insulin. However, in the EDITION JP1 study involving Japanese individuals with T1DM, glargine 300 U/mL was found to be more effective in reducing the incidence of nocturnal hypoglycemia, compared to glargine 100 U/mL [275,276]. In individuals with T1DM and at least one risk factor for hypoglycemia, degludec significantly decreased nocturnal hypoglycemia and symptomatic SH when compared to glargine 100 U/mL in the United States and Europe [277]. In addition, degludec allows for flexible dosing intervals ranging from 8 to 40 hours, providing comparable glycemic control to daily dosing at the same time [278]. A recent systematic review reported that degludec was cost-effective over a 1-year period compared to glargine [269]. In a study conducted on people with T1DM, it was found that using Fiasp as pre-prandial insulin for 6 months resulted in a decrease of 0.15% in HbA1c levels and a reduction of 12 mg/dL in postprandial blood glucose levels as compared to aspart. The study also found that injection of Fiasp immediately after a meal had similar effects to pre-prandial aspart, all of which were maintained for up to 1 year [279,280]. More recently, ultra-rapid lispro was developed, which includes a prostacyclin analog and citrate in the rapid-acting insulin analog lispro to increase and accelerate absorp-

tion through increased local vasodilation and vascular permeability. Once administered 0 to 2 minutes before meals, it was reported to be more effective in controlling postprandial glycemic levels compared to lispro [281].

Medications other than insulin

The adjunctive role of non-insulin treatments in T1DM is being actively studied. Medications other than insulin in T1DM are studied to evaluate their efficacy as adjunct to insulin therapy. In particular, as the prevalence of obesity in T1DM is increasing, new drugs are being developed to be used alongside insulin, to reduce weight and decrease insulin dose. Pramlintide, a drug based on amylin secreted by pancreatic β -cells, has been approved by the U.S. FDA for use in T1DM, but is not currently imported into Korea. In randomized controlled studies, pramlintide has been shown to reduce body weight by 1 to

2 kg and lower HbA1c levels by 0.0% to 0.3% when used in combination with insulin [282,283]. Several drugs licensed only for T2DM have been studied in people with T1DM. Metformin, when used in T1DM, reduced weight and improved cholesterol levels, but had no significant effect on HbA1c levels [284,285].

Among GLP-1RAs, adding liraglutide or exenatide to insulin was associated with a 0.2% reduction in HbA1c levels and a weight loss of nearly 3 kg [286]. Among SGLT2 inhibitors, the addition of canagliflozin, dapagliflozin, and empagliflozin reduced body weight, HbA1c levels, and insulin dose when used with insulin compared to insulin alone, but increased the frequency of ketoacidosis [287-289]. Sotagliflozin, an SGLT1/2 inhibitor, also reduced body weight, HbA1c, and insulin dose in patients with T1DM when combined with insulin, but increased the incidence of ketoacidosis [290].

10. PHARMACOLOGIC THERAPY FOR TYPE 2 DIABETES MELLITUS

1. Immediately upon diagnosis, actively educate on lifestyle modification and self-management methods and monitor whether it is continued. [Randomized controlled trial, general recommendation]
2. Consider the presence of comorbidities (cardiac failure, atherosclerotic cardiovascular disease [ASCVD], and chronic kidney diseases [CKDs]), hypoglycemic effects, effects on weight, risk of hypoglycemia, side effects, treatment acceptability, age, life value pursued by patients, and cost when selecting drugs. [Expert opinion, general recommendation]
3. Initiate insulin therapy for patients with severe hyperglycemia (HbA1c >9.0%) along with hyperglycemic symptoms (polydipsia, polyuria, weight loss, etc.). [Expert opinion, general recommendation]
4. When initiating drug therapy, a monotherapy or combination therapy should be used, taking into consideration the HbA1c goal and current glucose levels. [Randomized controlled trial, general recommendation]
5. Consider combination therapy from the day of diagnosis to reduce the risk of glycemic control failure. [Randomized controlled trial, limited recommendation]
6. Check medication adherence regularly and adjust the medication if necessary. [Expert opinion, general recommendation]
7. If the HbA1c goal is not achieved, the previous drug should be increased in dose or used in combination with a drug of a different class immediately. [Randomized controlled trial, general recommendation]
8. Use metformin first for pharmacotherapy and maintain it unless there are contraindications or side effects. [Randomized controlled trial, general recommendation]
9. When prioritizing a potent glucose-lowering effect, treatment should incorporate injectable therapies. [Randomized controlled trial, general recommendation]
 - 1) When considering combination therapy based on injectables, GLP-1RAs are prioritized over basal insulin. [Randomized controlled trial, general recommendation]
 - 2) If the target blood glucose level is not achieved with either GLP-1RA or basal insulin alone, combine the two drugs. [Randomized controlled trial, limited recommendation]
 - 3) If the target blood glucose level is not achieved using GLP-1RA or basal insulin treatment, initiate intensive insulin therapy. [Randomized controlled trial, limited recommendation]
10. In patients with HF, SGLT2 inhibitors, which have proven benefits in protecting against HF, should be a priority regardless of HbA1c levels and should continue as long as there are no contraindications or adverse reactions. [Randomized controlled trial, general recommendation]
11. If the patients have albuminuria or reduced estimated glomerular filtration rate (eGFR), SGLT2 inhibitors, which have proven benefits in protecting the kidney, should be used as a priority regardless of HbA1c levels and continued as long as there are no contraindications or adverse effects. [Randomized controlled trial, general recommendation]
12. In patients with ASCVD, SGLT2 inhibitors or GLP-1RAs, which have proven cardiovascular benefits, should be prioritized. [Randomized controlled trial, general recommendation]

Recommendation 10.1 Immediately upon diagnosis, actively educate on lifestyle modification and self-management methods and monitor whether it is continued. [Randomized controlled trial, general recommendation]

Recommendation 10.2 Consider the presence of comorbidities (cardiac failure, ASCVD, and CKDs), hypoglycemic effects, effects on weight, risk of hypoglycemia, side effects, treatment acceptability, age, life value pursued by patients, and cost when selecting drugs. [Expert opinion, general recommendation]

Level of evidence

Recommendations are based on evidence from large RCTs, meta-analyses, and expert opinions.

Benefits

When choosing a glucose-lowering agent, the primary considerations are the presence of comorbidities (HF, ASCVD, and CKD), the glucose-lowering effect of the drug, the effect on weight, the risk of hypoglycemia, and adverse reactions. Since the study on the cardiovascular benefits of empagliflozin was reported in 2015 [291-294], large-scale RCTs have been conducted to verify the cardiovascular safety of SGLT2 inhibitors and GLP-1RAs. The results showed that SGLT2 inhibitors were generally associated with fewer hospitalizations for HF, reduced cardiovascular mortality, reduced albuminuria, delayed decline in eGFR, and ESRD progression. On the other hand, GLP-1RAs significantly reduced the occurrence of major cardiovascular events and composite renal endpoints. Based on these findings, it is recommended that individuals with diabetes with HF, ASCVD, and CKD should include medications that have demonstrated effectiveness in reducing the risk of developing and worsening these comorbidities.

In terms of weight loss, metformin and α -glucosidase inhibitors have a mild effect on weight loss, while SGLT2 inhibitors and GLP-1RAs (liraglutide, dulaglutide) have a moderate weight loss effect of 2% to 5%. Among GLP-1RAs, semaglutide injection has a more substantial weight loss effect. DPP-4 inhibitors are weight-neutral, while insulin and sulfonylureas are associated with weight gain. When weight control is considered in obese individuals with T2DM, SGLT2 inhibitors and GLP-1RAs may be beneficial among antidiabetic medications.

Among antidiabetic medications, GLP-1RAs and insulin have the most potent glucose-lowering effects. They are followed by metformin, sulfonylureas, SGLT2 inhibitors, and thiazolidinediones, which also have high potency, whereas DPP-4 inhibitors have moderate glucose-lowering effects [295]. In addition, choosing medications considering various factors such as adverse reactions including hypoglycemia, compliance, age, the patient's life values, and cost can minimize side effects.

One of the most important but often overlooked aspects of drug selection is engaging in shared decision-making by providing sufficient information to the patient. Reports vary, but nearly half of patients with diabetes lack sufficient adherence to treatment plans, leading to suboptimal glycemic and cardiovascular risk factor control and increased diabetic complications, mortality, hospitalization, and healthcare costs [296-300]. Factors that affect the individual's adherence to treatment include perceived treatment inefficacy, fear of hypoglycemia, treatment complexity, adverse reactions, and cost [301], and have been reported to vary by medication type [302]. It is necessary to put the patients at the center of their care and to identify and acknowledge their comorbidities, preferences, and barriers to specific treatments [303,304].

Risks

In cases where agents deemed most medically beneficial are unavailable due to patient preferences, the benefits of reducing the risk of major morbidity and mortality may have to be foregone.

Alternatives and considerations

It is essential not to rationalize the choice of a less effective treatment simply because the patient declined the recommended medication. Instead, healthcare professionals should focus on educating patients about the medication they need, its anticipated advantages, and how to reduce the expected side effects, with a comprehensive approach. Consistent communication can help change their preferences and improve health outcomes.

Recommendation 10.3 Initiate insulin therapy for patients with severe hyperglycemia (HbA1c >9.0%) along with hyperglycemic symptoms (polydipsia, polyuria, weight loss, etc.). [Expert opinion, general recommendation]

Level of evidence

One RCT and a meta-analysis of seven studies (including five intervention studies) were evaluated. Given the insufficient number of studies, the level of evidence was determined as expert

opinion. The recommendation was classified as a general recommendation because the benefits outweigh the risks [305,306].

Benefits

Since insulin is a potent glucose-lowering agent, it may be the drug of choice for patients with severe hyperglycemia and symptoms such as polydipsia, polyuria, and weight loss [307]. In a study comparing an insulin-administered group and an oral antidiabetic agent-administered group among 382 newly diagnosed T2DM patients (average HbA1c 10.1%) over 2 weeks, the rate of reaching target blood glucose levels was higher when insulin was administered (insulin pump, MDI therapy, and oral antidiabetic agents: 97.1%, 95.2%, and 83.5%, respectively). In the insulin-administered group, β -cell function assessed by the homeostasis model assessment of β -cell function (HOMA- β) improved, and the remission rate over 1 year was also higher (insulin pump, MDI therapy, oral antidiabetic agents: 51.1%, 44.9%, 26.7% respectively) [305]. A meta-analysis of seven studies that included 839 newly diagnosed T2DM patients receiving insulin for 2 to 3 weeks showed the same results. After insulin treatment, HOMA- β increased (1.13; 95% confidence interval [CI], 1.02 to 1.25), and the homeostasis model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, decreased (-0.57; 95% CI, -0.84 to -0.29). Analyzing four studies from the meta-analysis that evaluated remission, the remission rates were maintained at 66.2% at 3 months, 46.3% at 1 year, and 42.1% at 2 years [306].

Risks

The adverse reactions of insulin include a high incidence of hypoglycemia and weight gain, inconvenience due to injection, and the need for blood glucose monitoring. In RCTs, SH and serious adverse reactions were not observed. Although mild hypoglycemia was more common in the insulin group than in the oral antidiabetic agent group, it was quickly recoverable (insulin pump, multiple insulin injection therapy, and oral antidiabetic agents: 31%, 28%, and 19%, respectively).

Balancing the benefits and risks

In cases of severe hyperglycemia accompanied by hyperglycemic symptoms, studies have demonstrated that insulin administration is more effective in improving blood glucose levels and β -cell function and has a higher 1-year remission rate than oral antidiabetic agents, indicating that the benefits of insulin therapy outweigh the risks.

Alternatives and considerations

The initiation and titration of insulin therapy are summarized in Table 8 [308]. For those using multiple daily insulin injections, the total daily insulin requirements should be determined based on the target blood glucose level, typically starting from 0.4 to 0.5 units/kg/day. Half of this amount should be administered as basal insulin at a specific time, while the remaining portion should be divided into thirds and given as prandial insulin before each meal. It is of note that injections should not be given if there is no food intake. The starting dose and dose adjustments should be individualized, and SMBG levels and systematic training are necessary for proper self-management of blood glucose [309,310].

Recommendation 10.4 When initiating drug therapy, a monotherapy or combination therapy should be used, taking into consideration the HbA1c goal and current glucose levels. [Randomized controlled trial, general recommendation]

Level of evidence

The recommendation is based on large-scale RCTs and meta-analyses.

Benefits

In the UKPDS, a study on newly diagnosed T2DM, pharmacotherapy along with aggressive lifestyle modification reduced the incidence of microvascular complications by 25% in the sulfonylurea or insulin treatment arms, and a 1.0% reduction of HbA1c reduced the incidence of microvascular complications by 37% over the 10-year study period [96,98]. Furthermore, a report published 10 years after the end of the study revealed that initial tight glycemic control not only reduces the risk of ongoing microvascular events but also has a legacy effect of reducing myocardial infarction and total mortality [97].

Generally, pharmacologic treatment is initiated with a single oral antidiabetic agent. However, if glycemic targets are unlikely to be reached with monotherapy alone, initial combination therapy of two drugs with different mechanisms may be considered [311,312]. Since the glucose-lowering effect of a single oral antidiabetic agent is generally within 1.0% of HbA1c, combination therapy is recommended when the HbA1c level is more than 1.5% above the target level. Several RCTs and meta-analyses have shown that initial combination therapy with metformin and either DPP-4 inhibitors, SGLT2 inhibitors, or sulfonylureas/glinides showed a significant reduction in HbA1c (ap-

proximately 0.4%) and sustained glycemic control compared to metformin monotherapy [108,311,313,314].

Risks

A variety of adverse drug reactions can occur and increase the burden of costs. Possible side effects include GI symptoms such as dyspepsia and nausea, hypoglycemia, weight gain or loss, urinary tract infections, and transient decreases in eGFR.

Balancing the benefits and risks

Given that the benefits of preventing microvascular and macrovascular complications through glycemic control significantly surpass the risks of side effects or medication costs, vigorous lifestyle modification and proper pharmacotherapy should be initiated right from the point of diagnosis.

There are many antidiabetic agents currently available that have a low risk of hypoglycemia. Therefore, by using these agents, the risk of hypoglycemia, the major concern in initial combination therapy, can be minimized. Although studies on early combination therapy have not demonstrated a direct reduction in complications, as the benefits of tight glycemic control have been well documented in previous studies, early combination therapy may lead to a reduced risk of diabetic complications. While there is a lack of research on the most appropriate combination of antidiabetic agents, the benefits of initial combination therapy are still recognized.

Recommendation 10.5 Consider combination therapy from the day of diagnosis to reduce the risk of glycemic control failure. [Randomized controlled trial, limited recommendation]

Level of evidence

The recommendation is based on observational studies that observed the prognosis in recently diagnosed patients with T2DM who achieved an early HbA1c target and on RCTs and meta-analyses that investigated the effects of initial combination therapy.

Benefits

A stepwise addition of antidiabetic agents to improve hyperglycemia in patients with newly diagnosed diabetes increases the duration of exposure to hyperglycemia. In a 10-year observational study of 34,737 patients with newly diagnosed diabetes, there was an increase in microvascular and macrovascular complications in those with HbA1c $\geq 6.5\%$ in the first year after

diagnosis compared with those with HbA1c $< 6.5\%$ (HbA1c 6.5% to $< 7.0\%$; hazard ratio [HR] for microvascular complications 1.204; 95% CI, 1.063 to 1.365). As mortality increases with HbA1c $\geq 7.0\%$ (HbA1c 7.0% to $< 8.0\%$; HR, 1.290; 95% CI, 1.104 to 1.507), and microvascular complications and mortality increases with more prolonged exposure to hyperglycemia with HbA1c $> 8.0\%$ [108], even if HbA1c is not as high at the time of diagnosis, aggressive glycemic control may reduce the risk of developing diabetic complications [97]. In a 6-year observational study of 194 Koreans with newly diagnosed T2DM, those who achieved target HbA1c levels early had a longer duration of maintained glycemic control (34.5%, 30.0%, and 16.1% in < 3 , 3–6, and ≥ 6 months, $P=0.039$) and fewer complications [315].

The VERIFY study showed that the initial combination therapy prolonged the time to primary and secondary treatment failure compared to the conventional combination therapy, which involves sequential intensification of glucose-lowering agents [111]. In individuals who had been diagnosed with diabetes within 2 years, had an HbA1c of 6.5% to 7.5%, and a BMI of 22 to 40 kg/m², early combination therapy (vildagliptin and metformin, 998 patients), compared to metformin monotherapy (1,003 patients), reduced the time to initial treatment failure (HbA1c $> 7.0\%$ for 6 months) over 5 years (HR, 0.51; 95% CI, 0.45 to 0.58; $P<0.0001$) [316]. The VERIFY study showed that this effect was consistent regardless of age, BMI, HbA1c, gender, or race, and there were no differences in adverse events, safety, or incidence of hypoglycemia between the groups.

A meta-analysis of 15 RCTs involving 6,693 treatment-naïve patients with T2DM (mean age 48.4 to 62.7 years, mean HbA1c 7.2% to 9.9%, mean diabetes duration 1.6 to 4.1 years, mean treatment duration 6 months, total observation 16 to 72 weeks) showed that initial combination therapy including metformin (with thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, sulfonylureas) was more effective in reducing HbA1c levels (-0.43% ; 95% CI, -0.56 to -0.30) and achieving the HbA1c goal of $< 7.0\%$ (HR, 1.40; 95% CI, 1.33 to 1.48) than metformin monotherapy [312]. In another meta-analysis of four RCTs involving 3,749 treatment-naïve patients with T2DM, initial combination therapy of metformin and SGLT2 inhibitors reduced HbA1c by 0.55% (95% CI, -0.37 to -0.43) and weight by 2.0 kg (95% CI, -2.34 to -1.66) compared to metformin monotherapy. Compared to SGLT2 inhibitor monotherapy, the combination therapy reduced HbA1c by 0.59% (95% CI, -0.72 to -0.46) and weight by 0.57 kg (95% CI, -0.89 to -0.25) [317].

In terms of preservation of β -cell function, a meta-analysis including 360 RCTs (total 157,696 participants, mean treatment duration 24 weeks, mean age 56.2 years, mean diabetes duration 6.6 years, mean HbA1c 8.1%) found that in comparison to six other oral glucose-lowering agents, incretin therapy (DPP-4 inhibitors, GLP-1RAs) increased HOMA- β , fasting C-peptide, and decreased fasting glucose and HOMA-IR compared to placebo [318].

Therefore, initial combination therapy for aggressive glycemic control at the onset of diagnosis, as opposed to the sequential addition of antidiabetic medication, may likely improve the long-term prognosis in a subset of T2DM patients.

Risks

Risks to consider when using initial combination therapy over monotherapy include adverse reactions, costs, weight gain, hypoglycemic events, and decreased adherence. In the VERIFY study, the risk of adverse events, weight gain, and hypoglycemic events did not differ from metformin monotherapy. Although the risk of hypoglycemia increased in all metformin-containing dual-combination therapies (HR, 1.56; 95% CI, 1.08 to 2.26), the risk of hypoglycemia was not increased compared to metformin monotherapy (HR, 1.20; 95% CI, 0.91 to 1.56) except for sulfonylureas [312]. In comparison to metformin monotherapy, initial combination therapies with DPP-4 inhibitors+metformin and SGLT2 inhibitors+metformin were associated with similar risks of hypoglycemia, but sulfonylurea+metformin (HR, 8.91; 95% CI, 1.46 to 54.34) and thiazolidinedione+metformin (HR, 1.60; 95% CI, 1.05 to 2.46) were associated with higher risks of hypoglycemia [311]. Regarding weight gain, initial combination of metformin+sulfonylurea and metformin+thiazolidinedione resulted in a weight gain of 2.6 kg (95% CI, 2.40 to 2.80; $P<0.001$) and 1.93 kg (95% CI, 1.88 to 1.97; $P<0.001$) respectively, compared to metformin monotherapy [311].

Balancing the benefits and risks

Specific individuals, specifically those who have been diagnosed with diabetes for less than 5 years, are under the age of 70, have an HbA1c below 7.5%, have a BMI over 22 kg/m², and have no CVDs or diabetic complications while having a low risk of hypoglycemia, early combination therapy using different mechanisms of oral antidiabetic agents to control blood glucose levels appears to increase the possibility of preserving β -cell function and reduce the risk of treatment failure in patients with T2DM. Understanding that diabetes is a progressive chronic disease

and that it is very difficult to maintain HbA1c below 6.5% over the long term with monotherapy, an early combination therapy based on metformin is expected to quickly achieve target blood glucose levels, thereby providing more extended protection from treatment failure, alleviating glucose toxicity immediately after the diagnosis of diabetes, and helping improve β -cell function and insulin resistance. However, most studies supporting the benefits of initial combination therapy do not have long follow-up periods and only focus on glycemic control, including HbA1c, as an endpoint. There are no RCTs to determine how long these early glycemic improvements last and whether they lead to long-term benefits, such as reduced microvascular complications or cardiovascular risks. Meanwhile, it is also unclear whether the benefits observed in the VERIFY study, which had the longest follow-up period, resulted from initially effective glycemic control or the specific drug.

Alternatives and considerations

Recent clinical results suggest that DPP-4 inhibitors may be preferred for long-term use in initial combination with metformin because of their glucose-lowering effects, lower risk of treatment failure, and less risk of discontinuation due to weight gain, hypoglycemia, GI side effects, or infection. However, further studies are warranted on various combination therapies based on metformin, such as sulfonylureas, α -glucosidase inhibitors, thiazolidinediones, GLP-1RAs, DPP-4 inhibitors, and SGLT2 inhibitors for initial combination therapy.

The increase in healthcare costs (drug costs) compared to conventional sequential add-on therapies may be offset by a reduction in diabetic complications and healthcare costs due to treatment failure [319]. In addition, recent advances in using fixed-dose combinations may improve medication adherence. The Committee of Clinical Practice Guidelines of the KDA conducted a brief survey to determine patient preferences for initial combination therapy. A group of 28 recently diagnosed, treatment-naïve patients with T2DM with HbA1c levels less than 7.0% were asked, "Would you try the initial combination therapy to possibly delay the start of insulin treatment and help maintain the target HbA1c levels longer, even if you are likely to reach glycemic targets with the conventional single metformin therapy?" Out of the 28 participants, 25 agreed, while among the three who disagreed, one cited family opposition, and the other two cited the fear of experiencing hypoglycemia-like symptoms.

Recommendation 10.6 During pharmacotherapy, check medication adherence regularly and adjust the medication if necessary. [Expert opinion, general recommendation]

Level of evidence

We included meta-analyses and RCTs that evaluated medication adherence and glycemic control in patients with T2DM.

Benefits

A study on individuals with T2DM revealed that medication adherence was significantly linked to improved glycemic control, showing a 0.16% decrease in HbA1c levels for every 10% increase in adherence [320]. These findings were consistent with another study that analyzed the correlation between medication adherence and clinical outcomes through pharmacy claims data [321]. Patients with poor adherence had statistically and clinically worse outcomes, and a 10% increase in non-adherence to metformin was associated with a 0.14% increase in HbA1c levels [321]. Besides improving glycemic control, enhanced medication adherence can also result in reduced numbers of emergency room visits, hospitalizations, and healthcare costs [322].

A meta-analysis conducted to evaluate medication adherence for six chronic diseases reported a 17% non-adherence rate (95% CI, 15% to 20%) overall, with the highest non-adherence rate in osteoporosis and hyperlipidemia at 25% and the lowest non-adherence rate in diabetes at 10%. Younger age, number of concurrent medications, prescriber specialty, and high medication costs were identified as factors associated with lower adherence [323]. In another study, age, race, medication costs, health insurance coverage, insulin use, and health literacy were identified as factors influencing medication adherence [322]. In older adults aged 60 years and older, increasing age was associated with better adherence, but female gender (OR, 0.92; 95% CI, 0.86 to 0.97), depression (OR, 0.73; 95% CI, 0.62 to 0.87), and high copayments for medication (OR, 0.87; 95% CI, 0.80 to 0.94) were analyzed as factors that lowered adherence [324].

In a study on adherence by the class of antidiabetic medication, better adherence was observed in the following order: DPP-4 inhibitors > thiazolidinediones ≥ sulfonylureas > metformin [302]. In addition, the most significant factor in improving adherence was identified as an adequate response to adverse drug reactions [325]. While some studies demonstrate that improved education and mobile-based interventions can

enhance adherence [326], a meta-analysis of various interventions, including messaging interventions such as text messaging services, web-based feedback, and monitoring devices, and monitoring interventions such as remote self-reporting of medication adherence and telephone calls from healthcare providers, showed inconsistent results [327]. Out of 15 interventions, six improved medication adherence, and two led to improved clinical outcomes [327].

It is crucial to assess medication adherence during every visit, particularly in cases with poorly-controlled blood glucose levels. When initiating a medication, discuss the expected efficacy, side effects, administration methods, and costs with the patient. Identifying and managing barriers to adherence can enhance compliance with the prescribed therapy. Improving adherence can help improve glycemic control and reduce the risk of diabetic complications. It can also reduce side effects and lower costs by preventing the addition of unnecessary medications and improve the collaborative relationship between patients with diabetes and healthcare professionals.

Risks

There is no particular risk involved, apart from the extra time and effort required by healthcare providers to assess medication adherence.

Alternatives and considerations

To improve adherence to medications, reducing the number of tablets and unifying the dosing times for convenience is helpful. Additionally, it is important to listen carefully to the patient's reported adverse events and, if the medication is indispensable, repeatedly explain to the patient the importance and effectiveness of the medication. If possible, switching to an alternative medication should be considered to minimize side effects. If the patient repeatedly forgets to take their medication, consider interventions like using a weekly pillbox or setting alarms.

Recommendation 10.7 If the HbA1c goal is not achieved, the previous drug should be increased in dose or used in combination with a drug of a different class immediately. [Randomized controlled trial, general recommendation]

Level of evidence

Recommendations are based on evidence from large RCTs, meta-analyses, and expert opinion.

Benefits

Numerous studies have demonstrated the additional glucose-lowering effect of treatment intensification with dual-combination therapy compared to metformin monotherapy. In a meta-analysis, adding another class of glucose-lowering agent apart from insulin to metformin resulted in an additional 0.7% to 1.0% reduction in HbA1c [328]. The usefulness of low-dose initial combination therapy with dual drugs has been well reported, as most drugs have a maximal glucose-lowering effect with fewer adverse effects at around 50% of the maximum dose [313]. Therefore, if monotherapy fails to achieve individualized treatment goals, combination therapy with other oral agents can be initiated before increasing the drug to the maximum dose. Unless there are contraindications or adverse drug reactions, dual-combination therapy should first be initiated with metformin, and if the glycemic target is still not achieved, triple-combination therapy should be initiated by adding agents with different mechanisms of action [329-331].

A combination of different classes of drugs that have been well documented for their effectiveness in glycemic control can be used to achieve maximum glycemic control while minimizing the side effects. Furthermore, incorporating drugs that consider individual-specific factors can yield benefits beyond glycemic control. For instance, in patients with comorbidities like ASCVD, CKD, or HF, SGLT2 inhibitors may offer additional advantages, including the prevention of ASCVD, reduction in the decline of kidney function, and decreased hospitalizations due to HF.

Risks

Adverse reactions, including hypoglycemia, weight gain or loss, polyuria, urinary tract infections, and higher costs, may arise depending on the medications added.

Balancing the benefits and risks

Given the importance of glycemic control in diabetes and the established additional glucose-lowering effects of combination therapy, the benefits of combination therapy far outweigh the risks. Therefore, if monotherapy does not achieve glycemic control targets, it is crucial to advance to dual-combination therapy promptly. If dual therapy fails to achieve adequate glycemic control, progressing to triple-combination therapy and other assertive treatments should be considered. If the individualized glycemic targets are unmet, healthcare providers should adjust medication immediately. Healthcare providers should

avoid clinical inertia, which is the practice of maintaining prior treatment instead of initiating or intensifying treatment.

Alternatives and considerations

When treating T2DM with a single oral antidiabetic agent, the dose should be adjusted every 2 to 3 months based on HbA1c measurements. Although there are slight variations by drug classes, a usual reduction in HbA1c levels with a single agent is 0.5% to 1%. Once HbA1c goals are achieved, the dose can be maintained or even reduced in some cases. If the HbA1c is $\geq 7.5\%$ upon diagnosis or glycemic goals are not met within 3 months of the maximum monotherapy dose, combination therapy should be initiated without delay. When choosing additional medications, consider the mechanism of action of the drug, its glucose-lowering potency, adverse reactions, risk of hypoglycemia, impact on weight, cardiovascular benefits, patient compliance, and cost [332]. Metformin, DPP-4 inhibitors, and SGLT2 inhibitors have weight loss or maintenance effects, while sulfonylureas and thiazolidinediones have weight gain effects, and hypoglycemia is most common with sulfonylureas [328,333]. If postprandial hyperglycemia is the major concern, adding a meglitinide, α -glucosidase inhibitor, or DPP-4 inhibitor may be considered [334]. As diabetes progresses, insulin resistance and β -cell dysfunction advance, and a significant proportion of patients will require insulin therapy as the duration of diabetes extends.

Recommendation 10.8 Use metformin first for pharmacotherapy and maintain it unless there are contraindications or side effects.
[Randomized controlled trial, general recommendation]

Level of evidence

The recommendation is based on RCTs and meta-analyses of RCTs analyzing treatment with metformin in patients with T2DM.

Benefits

The UKPDS study found that metformin monotherapy had similar glucose-lowering effects but caused less weight gain and hypoglycemia compared to sulfonylureas or insulin monotherapy in overweight individuals with T2DM [95]. Subsequent observational studies and meta-analyses support metformin as the first-line therapy of choice in terms of HbA1c reduction, adverse reactions, weight gain, hypoglycemic events, cost, and long-term cardiovascular events compared to sulfonylureas,

thiazolidinediones, and DPP-4 inhibitors [328,335,336].

The Practical Evidences of Antidiabetic Monotherapy (PEAM) study, a domestic RCT in Korea, examined the glucose-lowering effects of monotherapy in 349 patients with newly diagnosed drug-naïve T2DM. After 48 weeks of treatment with sulfonylureas (glimepiride), biguanides (metformin), or thiazolidinediones (rosiglitazone) monotherapy, there was no significant difference in HbA1c reduction between the drugs (glimepiride, 7.8%→6.9%, $P<0.001$; metformin, 7.9%→7.0%, $P<0.001$; rosiglitazone, 7.8%→7.0%, $P<0.001$; P for trend=0.62) [337].

Based on such findings, clinical guidelines from various organizations, including the KDA, the ADA, the European Association for the Study of Diabetes, and the IDF, recommend metformin as the first-line antidiabetic agent when lifestyle modifications alone do not achieve target blood glucose levels [336,338]. Metformin has a potent glucose-lowering effect, does not cause weight gain, has a low risk of hypoglycemia, and is inexpensive. Although no studies have included cardiovascular events as an endpoint, the UKPDS study showed the potential to reduce myocardial infarction and mortality, and a recently published meta-analysis reported a reduction in cardiovascular risk and mortality [339].

Risks

Adverse reactions of metformin include GI intolerance due to diarrhea, abdominal discomfort, nausea, and vomiting, and should be titrated from low doses while monitored for adverse effects. Although rare, lactic acidosis can occur, hence it should not be used in cases of severe hepatic or renal impairment (use cautiously if the eGFR is less than 45 mL/min/1.73 m² and contraindicated if less than 30 mL/min/1.73 m²), acute conditions that can affect kidney function, such as severe infections, dehydration, acute myocardial infarction, sepsis, or during cardiopulmonary failure [340]. It may be used in patients with stable HF with normal kidney function but should be avoided in patients hospitalized for HF or with uncontrolled HF. Long-term use of metformin may cause vitamin B12 deficiency, leading to anemia and peripheral neuropathy [341,342].

During examinations involving iodinated radiocontrast, kidney function may decrease, and there have been reports of lactic acidosis in individuals taking metformin. As metformin is eliminated through the kidneys, it is usually contraindicated or temporarily discontinued in individuals with renal dysfunction due to the risk of lactic acidosis. However, clinical cases of lactic acidosis are extremely rare, and the U.S. FDA has recent-

ly revised its guidance, allowing its relatively safe use of metformin in patients with diabetes whose eGFR is greater than or equal to 30 mL/min/1.73 m² [343]. When using iodinated contrast agents, if the eGFR is less than 60 mL/min/1.73 m², it is advisable to discontinue metformin. After 48 hours post-examination, kidney function should be re-evaluated before resuming its use.

Balancing the benefits and risks

In RCTs and meta-analyses, metformin has shown excellent glucose-lowering effects and significantly reduced diabetes-related endpoints, diabetes-related deaths, and total mortality [344]. Additionally, it was associated with a lower risk of weight gain and hypoglycemia, and it is a cost-effective medication. GI side effects can commonly occur during metformin therapy, but they can be minimized by gradually increasing the dose from a low level. The risk of a serious adverse reaction, lactic acidosis, is very low in the absence of other deteriorating factors such as renal impairment. Hence, the therapeutic benefits greatly outweigh the risks.

Alternatives and considerations

The extended-release form of metformin can help reduce GI side effects compared to the immediate-release form. If metformin cannot be used due to GI side effects or severe hepatic or renal impairment, other antidiabetic agents, such as DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, and sulfonylureas, etc., may be used as the initial therapy, depending on the patient's condition [345].

Recommendation 10.9 When prioritizing a potent glucose-lowering effect, treatment should incorporate injectable therapies. [Randomized controlled trial, general recommendation]

Level of evidence

The comparison of the glucose-lowering effects between oral antidiabetic agents and injectables for diabetes was based on a systematic review and network meta-analysis [346]. The analysis included 453 RCTs assessing 21 antidiabetic interventions from nine drug classes (metformin, sulfonylureas, pioglitazone, DPP-4 inhibitors, GLP-1RAs, SGLT2 inhibitors, basal insulin, basal-plus insulin, basal-bolus insulin, premixed insulin, α -glucosidase inhibitors, and meglitinide) with outcomes on blood glucose level, mortality, and cardiovascular events. The intervention period was at least 24 weeks, assessing changes in

HbA1c and mortality rates among the drugs.

Benefits

A pairwise meta-analysis compared HbA1c changes between each drug versus placebo as an add-on to metformin [346]. For glucose-lowering injectables, the mean difference (MD) for subcutaneous semaglutide was -1.33 (95% CI, -1.50 to -1.16), premixed insulin -0.89 (95% CI, -1.08 to -0.71), dulaglutide -0.89 (95% CI, -1.05 to -0.73), basal-bolus insulin -0.89 (95% CI, -1.17 to -0.60), liraglutide -0.80 (95% CI, -0.89 to -0.70), basal insulin -0.71 (95% CI, -0.82 to -0.60), prandial insulin -0.67 (95% CI, -0.86 to -0.47), exenatide -0.6 (95% CI, -0.73 to -0.47), and lixisenatide -0.43 (95% CI, -0.57 to -0.29). For oral antidiabetic agents, the MD for meglitinide was -0.64 (95% CI, -0.85 to -0.43), pioglitazone -0.60 (95% CI, -0.71 to -0.50), ertugliflozin -0.58 (95% CI, -0.79 to -0.36), sulfonylureas -0.57 (95% CI, -0.66 to -0.48), empagliflozin -0.57 (95% CI, -0.71 to -0.42), DPP-4 inhibitors -0.53 (95% CI, -0.58 to -0.47), dapagliflozin -0.51 (95% CI, -0.63 to -0.40), and a α -glucosidase inhibitors -0.50 (95% CI, -0.67 to -0.34).

These results showed that GLP-1RAs, premixed insulin, and basal-bolus insulin had the most significant reductions in HbA1c level compared to placebo as an add-on to metformin, with subcutaneous semaglutide having the most potent effect.

Risks

1) Hypoglycemia

In a combination therapy with metformin, hypoglycemia was significantly higher with sulfonylureas, premixed insulin, and basal-bolus insulin compared to placebo. In comparison between GLP-1RAs and basal insulin, the overall incidence of hypoglycemia and nocturnal hypoglycemia was significantly higher with basal insulin.

2) Weight gain

Among injectables, insulin was associated with weight gain, while GLP-1RAs were associated with weight loss.

3) Other side effects and safety

GI side effects such as nausea, vomiting, diarrhea, and constipation are the most common side effects of GLP-1RAs, while injection site reactions are also reported. Regarding safety concerns with GLP-1RAs, large clinical studies have shown increased gallbladder disease but no significant difference in medullary thyroid cancer, pancreatitis, or pancreatic cancer.

Diabetic retinopathy outcomes were similar across most anti-diabetic agents compared to placebo; however, they were reported to be slightly higher with subcutaneously administered semaglutide (OR, 1.75; 95% CI, 1.10 to 2.78), especially in cases where there was a rapid improvement in blood glucose levels. This phenomenon, which can occur with aggressive glycaemic control, was also observed during insulin treatment in the DCCT. Therefore, additional clinical studies are needed regarding the incidence and safety of diabetic retinopathy.

4) Inconvenience of injections and injection site side effects

According to a survey of Korean healthcare professionals on their perceptions and prescriptions for injectables, including insulin, patients often avoid injectable treatment due to fear of needles, pain, and the inconvenience of the method. While insulin may require monitoring blood glucose levels and corresponding dose adjustments, GLP-1RAs have the advantage of not requiring dose adjustment based on blood glucose. Injection site side effects are possible but not common. In addition, with basal insulin available as once-daily injection and GLP-1RAs as once-weekly injections, minimizing injection frequency can enhance patient and healthcare provider perceptions and increase the accessibility of injectables.

5) Costs

Insulin analogs and GLP-1RAs are more expensive than oral antidiabetic agents. GLP-1RAs, in particular, have very limited reimbursement criteria in Korea and are not in line with current clinical practice. While the use of combination therapy of metformin and sulfonylureas has decreased significantly in recent clinical practice, reimbursement coverage for GLP-1RAs is only available when target blood glucose levels are not achieved despite the combination therapy of metformin and sulfonylureas. This further limits the use of GLP-1RAs in terms of medical costs.

Balancing the benefits and risks

When considering aggressive glucose-lowering effects, injectables are preferred as long-acting GLP-1RAs and insulin generally have more potent glucose-lowering effects than oral antidiabetic agents. However, injectables commonly require discussions with patients regarding the inconvenience or aversion to injections and cost aspects. In conclusion, when prioritizing potent glucose-lowering effects, the recommendation to prefer treatments including injectables, was made as a general recom-

mendation, considering the balance of benefits and risks and the target population.

Alternatives and considerations

If monotherapy or dual-combination therapy fails to achieve the target HbA1c levels, a combination of three or more oral antidiabetic agents may be considered. However, the adverse reactions of each medication and the medical costs associated with the increased number of medications should also be considered. In many cases, insulin eventually becomes necessary. In such cases, combining therapy with SGLT2 inhibitors or once-weekly long-acting GLP-1RAs, in addition to metformin, can reduce the required dose of insulin or mitigate weight gain. However, if intensive glycemic control is required, multiple daily insulin injections should be considered.

Recommendation 10.9-1) When considering combination therapy based on injectables, GLP-1RAs are prioritized over basal insulin. [Randomized controlled trial, general recommendation]

Level of evidence

This recommendation is based on a meta-analysis that conducted a head-to-head comparison between combination therapies based on incretins (short- and long-acting GLP-1RAs, glucose-dependent insulinotropic polypeptide [GIP]/GLP-1RAs such as tirzepatide) and those based on basal insulin in patients with T2DM [347].

Benefits

The analysis included patients who were around 60 years old on average, slightly more likely to be male, had been diabetic for an average of 9 years, and had an average HbA1c of 8.0% to 8.5%. Compared to basal insulin-based combination therapy, incretin-based combination therapy further reduced HbA1c by an average of 0.50% (95% CI, -0.53% to -0.46%). In comparing the average reduction of HbA1c levels by incretin subgroups, while the combination therapy based on short-acting GLP-1RAs showed no significant difference compared to basal insulin (0.01%; 95% CI, -0.13% to 0.12%), the combination therapy based on long-acting GLP-1RAs was significantly more effective by 0.27% (95% CI, 0.12% to 0.42%). Although not yet available in South Korea, tirzepatide, a GIP/GLP-1RA, showed the most potent effect of 0.90% (95% CI, -1.06% to -0.75%).

Risks

1) Hypoglycemia

Compared to basal insulin-based combinations, incretin-based combinations resulted in a 50% lower incidence of hypoglycemia.

2) Weight gain

Overall, weight was reduced with incretin-based combinations and increased with basal insulin-based combinations. There was a significant weight loss of 4.6 kg (-4.7 to -4.5) with combination therapy based on short- and long-acting GLP-1RAs compared with insulin-based combination, with no difference in the weight loss between short- and long-acting GLP-1RAs. GIP/GLP-1RA-based combination therapy resulted in a weight loss of 12.0 kg (-13.9 to -10.1) compared with basal insulin-based combination therapy.

3) Gastrointestinal adverse reactions and drug discontinuation rates

Nausea, vomiting, and diarrhea occurred 6, 3–4, and 2–3 times more frequently with incretin-based combinations compared to basal insulin-based combinations. Drug discontinuation rates were 60% to 71% higher with incretin-based combinations than basal insulin-based combinations.

4) Number of injections

Compared to once-daily basal insulin administration, long-acting GLP-1RAs require once daily or weekly administration. Therefore, weekly GLP-1RAs offer the advantage of reducing resistance due to injection frequency.

Balancing the benefits and risks

Compared to basal insulin-based combination therapy, incretin-based combination therapy has the advantage of better HbA1c reduction, significantly lower risk of hypoglycemia, and less frequent injections, especially among long-acting GLP-1RAs. However, combination therapy based on GLP-1RAs has a significantly higher incidence of GI side effects.

Therefore, when the potent glucose-lowering effect is a priority, incorporating injectable agents, particularly based on GLP-1RAs rather than basal insulin, may be prioritized. However, due to GI side effects, selecting appropriate injectable agents should be tailored to the individual circumstances.

In conclusion, when considering injectable-based combination therapy, prioritizing GLP-1RAs over basal insulin is deter-

mined as a general recommendation based on a comprehensive assessment of the balance between glucose-lowering benefits and adverse reactions, as well as the target population for application.

Various alternatives and considerations

GI side effects are common with GLP-1RAs and may lead to medication discontinuation. Therefore, it is crucial to educate individuals on gradually increasing the dose. GLP-1RAs should be discontinued if side effects occur, and insulin should be considered. If insulin secretory function is impaired, the effectiveness of GLP-1RAs may be limited, and prompt administration of insulin should be considered.

Recommendation 10.9-2) If the target blood glucose level is not achieved with either GLP-1RA or basal insulin alone, combine the two drugs. [Randomized controlled trial, limited recommendation]

Level of evidence

The glucose-lowering effect of GLP-1RA monotherapy compared to the combination therapy of GLP-1RA and basal insulin (either as separate drugs or as a fixed-ratio combination) was assessed through six RCTs with a study duration of at least 24 weeks [348-353]. In addition, the glucose-lowering effect of basal insulin monotherapy compared to combination therapy of GLP-1RA with basal insulin (either as separate drugs or as a fixed-ratio combination) was also evaluated through 14 RCTs with a study duration of at least 24 weeks [350,352,354-365]. GLP-1RAs were evaluated only for four formulations: exenatide twice-daily injection, liraglutide, dulaglutide, and subcutaneous semaglutide. The fixed-ratio combinations of GLP-1RAs and basal insulin were evaluated for two formulations: insulin glargine/lixisenatide and insulin degludec/liraglutide. The level of evidence was classified as a RCT, as it originates from RCTs.

Benefits

Previous RCTs on the efficacy of glycemic control of GLP-1RA+basal insulin compared to GLP-1RA monotherapy (0.4% to 1.0% reduction in HbA1c), and we also reviewed 14 RCTs on the efficacy of glycemic control of GLP-1RA+basal insulin compared to basal insulin monotherapy. There was a significant reduction in blood glucose levels with the combination therapy compared to monotherapy.

Risks

Compared with GLP-1RA monotherapy, GLP-1RA+basal insulin was associated with more frequent hypoglycemia and increased body weight. This trend was also observed in fixed-ratio combinations. The same trends were noted for hypoglycemia when comparing GLP-1RA+basal insulin with basal insulin monotherapy. Other risks of GLP-1RAs and insulin as individual agents are the same as those described in Recommendation 9-1.

Balancing the benefits and risks

If the target blood glucose level is not achieved despite being on treatment that includes one injectable medication, injectables from different classes can be combined. If the patient is on a GLP-1RA, adding basal insulin is feasible, and *vice versa*. Combining a GLP-1RA with basal insulin may have a greater glucose-lowering effect than each agent alone, reduce insulin requirements, and reduce the side effects of hypoglycemia and weight gain. In addition, the number of injections and blood glucose monitoring can be reduced compared to multiple insulin injections, and using fixed-ratio combinations of basal insulin and GLP-1RA can further improve medication adherence.

However, its effectiveness may be limited in patients with a long history of diabetes or reduced insulin secretory function who require additional prandial insulin. In addition, both drugs are expensive compared to oral antidiabetic agents, and the reimbursement criteria for their combined use in Korea is very restricted compared to multiple daily insulin or premixed insulin injections, presenting an economic burden.

In conclusion, when the target blood glucose level cannot be achieved by either GLP-1RAs or basal insulin alone, the recommendation to combine these two medications was determined to be a limited recommendation, based on a comprehensive assessment of the benefits and risks, as well as the target population.

Alternatives and considerations

Apart from combining the two agents, increasing the number of premixed insulin injections or using multiple daily insulin injections could be alternatives.

Recommendation 10.9-3) If the target blood glucose level is not achieved using GLP-1RA or basal insulin treatment, initiate intensive insulin therapy. [Randomized controlled trial, limited recommendation]

Level of evidence

The level of evidence was classified as a RCT, as it originates from RCTs and meta-analyses. The recommendation was rated as limited, as the benefits do not apply in all cases.

Benefits

For those who do not achieve target glycemic levels with GLP-1RA or basal insulin injections, a change in regimen to basal-plus insulin, premixed insulin, or MDI therapy (basal-bolus insulin) is necessary to improve glycemic control [366-368]. In patients with T2DM with HbA1c >7.5% on basal insulin, adding a single prandial insulin to the largest meal of the day resulted in a significant difference in the proportion of patients reaching HbA1c <7% after 3 months (22.4% vs. 8.8%, $P<0.05$) compared to the maintenance treatment arm, and a greater reduction in HbA1c (-0.37% vs. -0.11%, $P=0.03$) [366]. A meta-analysis of 10 prospective RCTs comparing basal insulin with twice-daily premixed insulin in 4,366 patients with T2DM also reported a higher achievement rate of target HbA1c levels in the premixed insulin group than in the basal insulin group [369].

If once-daily prandial insulin with maintaining basal insulin (basal-plus insulin) achieves postprandial glucose control but not HbA1c targets, add a second prandial insulin. If the HbA1c target is still not achieved, switch to multiple daily insulin injections (basal-bolus insulin). In a RCT conducted over 14 weeks with 631 patients with T2DM who had HbA1c levels above 8%, participants were divided into groups receiving 1, 2, or 3 times of prandial insulin. The group receiving three injections had a higher percentage of reaching glycemic control targets (30%, 33%, and 46%, respectively) [370].

A meta-analysis of RCTs comparing GLP-1RA plus prandial or basal insulin therapy with basal-plus insulin/basal-bolus insulin therapy, as well as a RCT comparing GLP-1RA plus basal insulin combination therapy arm with the maintenance arm in patients with T2DM treated with MDIs of insulin, showed no difference in glucose-lowering effects between the two groups. However, the combination of GLP-1RAs and insulin was reported to be effective in weight loss and reducing the occurrence of hypoglycemia. However, due to the limited number of studies and lack of evidence, further research is needed [371,372].

Risks

Compared to GLP-1RA or basal insulin injection therapy, intensive insulin therapy increases the number of injections, the

risk of hypoglycemia, and weight gain. Premixed insulin and multiple daily insulin injection groups, compared to the basal insulin injection group, showed no difference or an improvement in the reduction of HbA1c levels depending on the study duration. However, they experienced more hypoglycemia and weight gain [369,373,374].

Balancing the benefits and risks

Switching to intensive insulin therapy is effective as it improves glycemic control indices, but depending on the injection regimen, it increases the number of injections, the frequency of hypoglycemia, and weight gain. Patients undergoing intensive insulin therapy require an individualized selection of injection regimens and dose adjustments according to their glycemic status, age, and comorbidities, which is in line with Recommendation 2 [375,376]. In conclusion, the recommendation for insulin intensification for glycemic control was determined to be a limited recommendation based on a comprehensive assessment of the benefits and risks, as well as the target population.

Recommendation 10.10 In patients with HF, SGLT2 inhibitors, which have proven benefits in protecting against HF, should be a priority regardless of HbA1c levels and should continue as long as there are no contraindications or adverse reactions. [Randomized controlled trial, general recommendation]

Level of evidence

This recommendation is based on large-scale RCTs that investigated the cardiovascular safety of SGLT2 inhibitors (empagliflozin, dapagliflozin, ertugliflozin, canagliflozin) in patients with T2DM who have CVDs or cardiovascular risk factors, and on the meta-analyses of these studies. Additionally, large-scale RCTs on the effectiveness of SGLT2 inhibitors (empagliflozin, dapagliflozin) in patients with HF, regardless of diabetes status, were evaluated.

Benefits

In patients with T2DM with established CVD or cardiovascular risk, empagliflozin, dapagliflozin, ertugliflozin, and canagliflozin significantly reduced the risk of hospitalization for HF by approximately 30%. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial assessing the cardiovascular safety of empagliflozin showed a 14% signif-

icant reduction in major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), a 38% reduction in cardiovascular death and a 35% reduction in HF hospitalization compared to placebo [291]. The cardiovascular safety study of dapagliflozin, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), reported a 27% lower incidence of hospitalization due to HF over an average study period of 4.2 years (HR, 0.73; 95% CI, 0.61 to 0.88) [292], while the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS-CV) on the cardiovascular safety of ertugliflozin also showed a 30% reduction in hospitalization for HF (HR, 0.70; 95% CI, 0.54 to 0.90) [377]. In the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, canagliflozin also reduced the risk of death and hospitalization due to HF (HR, 0.70; 95% CI, 0.55 to 0.89) and decreased the risk of hospitalization due to HF by 32% (HR, 0.67; 95% CI, 0.52 to 0.87) [378]. The beneficial effect of SGLT2 inhibitors on the worsening of HF was observed regardless of the baseline ejection fraction (EF) status [379,380].

These benefits of SGLT2 inhibitors on HF have been extended to studies on HF patients regardless of the presence of diabetes. The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study, involving 4,744 patients with existing HF (New York Heart Association class II, III, or IV) and reduced EF ($\leq 40\%$), regardless of diabetes status, found that dapagliflozin 10 mg reduced the risk of worsening HF or cardiovascular death by 26% over an average of 18.2-month study period (HR, 0.74; 95% CI, 0.65 to 0.85; $P < 0.001$), with similar outcomes in groups with or without diabetes [381]. Through the Empagliflozin outcome trial in patients with chronic HF with reduced ejection fraction (EMPEROR-Reduced) trial, empagliflozin was shown to reduce the composite endpoint of cardiovascular death or hospitalization due to worsening HF by 25% compared to the placebo group (HR, 0.75; 95% CI, 0.65 to 0.86; $P < 0.001$) over an average study period of 16 months in patients with HF (class II, III, or IV and EF $\leq 40\%$), regardless of the presence of diabetes [381]. The effects of empagliflozin were maintained irrespective of diabetes status. Meta-analysis of the DAPA-HF and EMPEROR-Reduced studies also showed that SGLT2 inhibitor treatment reduced all-cause mortality by 13% (pooled HR, 0.87; 95% CI, 0.77 to 0.98; $P = 0.018$), cardiovascular death by 14% (0.86; 95% CI, 0.76 to 0.98; $P = 0.027$), and the risk of worsening HF or cardiovascular death by 26% (0.74; 95% CI, 0.68 to 0.82; $P < 0.0001$) [382].

The benefit of SGLT2 inhibitors was also demonstrated in patients with HF with preserved EF. In the Empagliflozin outcome trial in patients with chronic HF with preserved ejection fraction (EMPEROR-Preserved) trial involving individuals with class II–IV HF and an EF of 40% or higher, the incidence of the primary composite endpoint of cardiovascular death or hospitalization for worsening HF was 25% lower in the empagliflozin group compared to placebo over an average period of 26 months (HR, 0.79; 95% CI, 0.69 to 0.90; $P < 0.001$) [383].

In all cardiovascular safety studies of SGLT2 inhibitors conducted so far, benefits for HF have been proven, suggesting a class effect of SGLT2 inhibitors. This effect has been proven in patients with and without diabetes. Therefore, it is considered clearly beneficial to use SGLT2 inhibitors in patients with diabetes with HF symptoms to reduce the worsening of HF and cardiovascular death, regardless of the HbA1c levels.

Risks

SGLT2 inhibitors can cause discomfort in daily life due to polyuria and consequent frequent urination. In all studies, a decrease in the eGFR was observed early after the use of SGLT2 inhibitors. Therefore, it is necessary to monitor the eGFR carefully during this period. There is an increased risk of dehydration and orthostatic hypotension without adequate hydration. Especially in elderly patients, close monitoring of symptoms related to hypovolemia is required, and thus, it is necessary to check for associated symptoms after SGLT2 inhibitor administration. The risk of genital infections and urinary tract infections also increases after the use of SGLT2 inhibitors, and there have been reports of cases of Fournier's gangrene. Although rare, the risk of diabetic ketoacidosis (DKA) also increases. In some patients, weight loss due to the medication may be problematic. When adding it to prevent worsening HF in patients who were well-controlled with other antidiabetic agents, hypoglycemia can occur if the dose adjustment of the existing medications is not adequately managed.

Balancing the benefits and risks

In patients with HF, the use of SGLT2 inhibitors, if accompanied by efforts to avoid risks, is thought to prevent the worsening of HF symptoms and potentially reduce mortality. However, since the diagnosis of HF is made chiefly clinically, and extensive testing to diagnose HF could lead to unnecessary health-care expenses socially, it is necessary to select patients who require these tests carefully.

Recommendation 10.11 If the patients have albuminuria or reduced eGFR, SGLT2 inhibitors, which have proven benefits in protecting the kidney, should be used as a priority regardless of HbA1c levels and continued as long as there are no contraindications or adverse effects. [Randomized controlled trial, general recommendation]

Level of evidence

This recommendation is based on large-scale RCTs that investigated the cardiovascular safety of SGLT2 inhibitors (empagliflozin, dapagliflozin, ertugliflozin, canagliflozin) in patients with T2DM who have CVDs or cardiovascular risk factors, and on the meta-analyses of these studies. Additionally, large-scale RCTs on the effectiveness of SGLT2 inhibitors (empagliflozin, dapagliflozin) in patients with CKD, regardless of diabetes status, were evaluated.

Benefits

In RCTs treated with SGLT2 inhibitors, a reduction in albuminuria was observed, along with effects that slow the decline in eGFR and the progression to ESRD. In the EMPA-REG OUTCOME study, empagliflozin demonstrated a 46% reduction in the composite renal endpoints (two-fold increase in serum creatinine, initiation of renal replacement therapy, and death due to kidney disease) compared to placebo [384], and in the DECLARE-TIMI 58 study, dapagliflozin demonstrated a 30% reduction in the same composite renal endpoints compared to placebo [292].

In both studies, the long-term use of SGLT2 inhibitors showed a reduction in the decline of the eGFR compared to placebo. However, these studies have the limitation of confirming renal outcomes as secondary endpoints. The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, conducted on patients with CKD (eGFR 25 to 75 mL/min/1.73 m², urinary albumin-to-creatinine ratio 200 to 5,000 mg/g) with or without diabetes, found that the risk of composite renal endpoints including a sustained decline in the eGFR more than 50%, ESRD, or death due to renal or CVD was reduced by 39% in the dapagliflozin arm over placebo [385]. When the analysis was limited to patients with diabetes, a 36% reduction was also observed. A meta-analysis of large clinical trials on SGLT2 inhibitors reported a 19% reduction in the risk for renal endpoints compared to placebo [386].

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial, recruiting patients with CKD (eGFR 25

to 45 mL/min/1.73 m² or eGFR 45 to 90 mL/min/1.73 m² with urinary albumin-to-creatinine ratio \geq 200 mg/g) regardless of diabetes status, showed an 18% reduction in the primary endpoint of the composite endpoint of worsening renal function or cardiovascular mortality compared to placebo (HR, 0.72; 95% CI, 0.64 to 0.82; $P < 0.001$) [387]. Notably, unlike previous studies, the EMPA-KIDNEY study included patients with reduced eGFR without proteinuria, confirming the beneficial effects on kidney protection.

The KDA and the Korean Society of Nephrology conducted a meta-analysis examining the effect of the domestically available SGLT2 inhibitors on kidney function [388]. This study confirmed the effect of SGLT2 inhibitors in reducing the decline in eGFR compared to the control group, but this effect was found with long-term use of over 2 years. When studies that predominantly included Asians were analyzed separately, no significant effect was observed. Meanwhile, a *post hoc* analysis of 1,517 Asians in the EMPA-REG OUTCOME trial showed that treatment with empagliflozin was associated with a reduction in albuminuria progression (36%) and a decrease in the composite renal endpoint (52%) compared to placebo with the effect on reducing the decline in eGFR becoming apparent after about 66 weeks [389].

When large-scale RCTs and meta-analyses are comprehensively evaluated, SGLT2 inhibitors have been shown to inhibit the progression of kidney diseases (complications) in patients with T2DM. This appears to have a positive impact at various levels, including the progression of albuminuria, the deterioration of eGFR, and the initiation of renal replacement therapy. However, since the large-scale clinical trials that provide the evidence mostly involve patients with CVDs, those at high risk for CVDs, or those with evident kidney diseases, SGLT2 inhibitor treatment can be recommended in these patient groups. Among the commercially available SGLT2 inhibitors in Korea, dapagliflozin and empagliflozin have the highest level of evidence. Ipragliflozin lacks large-scale prospective studies; thus, evidence for its effect on delaying the progression of kidney disease is insufficient.

The renal protective effects of SGLT2 inhibitors have been demonstrated not only in patients with diabetes but also in those with CKD without diabetes. Therefore, it is considered clearly beneficial to use SGLT2 inhibitors in diabetic patients with CKD, regardless of the HbA1c levels, to reduce the worsening of CKD and decrease mortality due to CVDs.

Risks

Identical to the Recommendation 10 as mentioned above.

Balancing the benefits and risks

According to the Korean Ministry of Food and Drug Safety, SGLT2 inhibitors can be used for renal protection in CKD but should not be used if the eGFR is less than 20 mL/min/1.73 m² for empagliflozin and less than 25 mL/min/1.73 m² for dapagliflozin. If the eGFR is less than 45 mL/min/1.73 m², the glucose-lowering effect of SGLT2 inhibitors is reduced, and additional drugs of other classes should be used for glycemic control.

Recommendation 10.12 In patients with ASCVD, SGLT2 inhibitors or GLP-1RA, which have proven cardiovascular benefits, should be prioritized. [Randomized controlled trial, general recommendation]

Level of evidence

1) SGLT2 inhibitors

Recently, large-scale RCTs and meta-analyses on the cardiovascular effects of antidiabetic agents have been published, making cardiovascular benefits an essential factor to consider when selecting oral antidiabetic agents. This recommendation is based on RCTs and meta-analyses involving SGLT2 inhibitors.

2) GLP-1RA

This recommendation is based on three double-blind RCTs on the cardiovascular safety of GLP-1RAs, specifically the currently available in Korea, liraglutide and dulaglutide, and semaglutide, which will be available in the future. The level of evidence is categorized as a RCT because the recommendation was evaluated based on RCTs.

Benefits

1) SGLT2 inhibitors

In the EMPA-REG OUTCOME trial involving 7,020 patients with T2DM and cardiovascular risk factors, empagliflozin administration over an average of 3 years resulted in a 14% reduction in cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) compared to placebo (HR, 0.86; 95% CI, 0.74 to 0.99; $P=0.04$) [291]. Subsequent analysis of Asian participants from the EMPA-REG OUTCOME study also showed a similar effect on all-cause mortality or HF outcomes as in Westerners, with a HR of 0.68 (95% CI, 0.48 to 0.95) for the 3-point major cardiovascular ad-

verse events [390].

A meta-analysis of five RCTs with a duration of over 2 years and involving 351,476 participants, demonstrated that SGLT2 inhibitors reduced the incidence of major cardiovascular events by 20%, all-cause mortality by 33%, and hospitalization for HF by 38% [391].

In a meta-analysis of six randomized placebo-controlled trials on the cardiovascular effects of four SGLT2 inhibitors, SGLT2 inhibitors significantly reduced the risk of major cardiovascular events (HR, 0.90; 95% CI, 0.85 to 0.95; Q statistic, $P=0.27$), and hospitalization for HF and death from cardiovascular causes (HR, 0.78; 95% CI, 0.73 to 0.84; Q statistic, $P=0.09$). Irrespective of the presence of underlying ASCVD, SGLT2 inhibitor treatment was associated with a reduced risk of major cardiovascular events, hospitalization for HF, and death from CVD [386]. The analysis included a total of 46,969 patients with T2DM, 66.2% of whom had ASCVD, with a mean age of 63.7 years, 65.9% male, and 78.5% Caucasian. The EMPA-REG OUTCOME trial, CANVAS program, DECLARE-TIMI 58, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), and VERTIS-CV studies were included.

A meta-analysis of four large trials of SGLT2 inhibitors, including the EMPA-REG OUTCOME trial, CANVAS, DECLARE-TIMI 58, and CREDENCE also reported that SGLT2 inhibitors reduced the risk of major cardiovascular events, death from cardiovascular causes, and all-cause mortality, regardless of the presence of underlying CVD or HF [392,393].

In a meta-analysis of three large-scale clinical trials on SGLT2 inhibitors, including the EMPA-REG OUTCOME trial, CANVAS and DECLARE-TIMI 58, a reduction in the risk of major cardiovascular events was observed only in patients with underlying ASCVD, which presents a slight difference from the previous analysis. However, this analysis also showed that SGLT2 inhibitors reduced the risk of cardiovascular death or hospitalization due to HF regardless of the presence of underlying CVD or HF [394].

Therefore, in patients with diabetes and concomitant ASCVD, the use of SGLT2 inhibitors can significantly reduce major cardiovascular events, cardiovascular death, and hospitalization due to HF, as demonstrated in previous studies.

2) GLP-1RAs

The primary endpoint of large clinical trials on the cardiovascular safety of GLP-1RAs was the incidence of three-point ma-

major cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. There were differences in severity in the three large-scale clinical trials assessed for this recommendation because the proportions of patients with underlying ASCVD varied.

The Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results (LEADER) trial, a double-blind study of 9,340 patients with T2DM, randomized participants to either liraglutide or placebo, where 81% of participants having underlying ASCVD, and the remaining 19% only having risk factors for ASCVD [293]. The total of the three major cardiovascular events, the primary endpoint, decreased by 13% with liraglutide compared to placebo (HR, 0.87; 95% CI, 0.78 to 0.97). This effect was contributed by reductions in cardiovascular death (HR, 0.78; 95% CI, 0.66 to 0.93), asymptomatic/non-fatal/fatal myocardial infarction (HR, 0.86; 95% CI, 0.73 to 1.00), and non-fatal/fatal stroke (HR, 0.89; 95% CI, 0.71 to 1.06). All-cause mortality was reduced by 15% with liraglutide compared with placebo (HR, 0.85; 95% CI, 0.74 to 0.97), primarily due to a reduction in cardiovascular deaths. There was no statistically significant reduction in hospitalization for HF with liraglutide compared to placebo (HR, 0.87; 95% CI, 0.73 to 1.05).

The Trial to Evaluate CV and Other Long-term Outcomes With Semaglutide in Subjects With T2D (SUSTAIN-6) trial used the same inclusion criteria as the LEADER trial, a double-blind study of 3,297 adults with T2DM, randomized to either semaglutide or placebo, where 72% of participants having underlying ASCVD [395]. The aggregate of the three major cardiovascular events, the primary endpoint of the study, was reduced by 26% with semaglutide compared to placebo (HR, 0.74; 95% CI, 0.58 to 0.95). The results for each component were as follows: cardiovascular death (HR, 0.98; 95% CI, 0.65 to 1.48), non-fatal myocardial infarction (HR, 0.74; 95% CI, 0.51 to 1.08), and non-fatal stroke (HR, 0.61; 95% CI, 0.38 to 0.99). There was no statistically significant reduction in all-cause mortality (HR, 1.05; 95% CI, 0.74 to 1.50) or hospitalization for HF (HR, 1.11; 95% CI, 0.77 to 1.61) with semaglutide compared to placebo.

The Researching CV Events With a Weekly Incretin in Diabetes (REWIND) trial was a double-blind study of 9,901 adults with T2DM, randomized to dulaglutide or placebo [294]. Unlike the two studies above, in this study, only 31% of participants had underlying ASCVD, and more than half of the patients had risk factors for ASCVD but did not have the AS-

CVD. The total of the three major cardiovascular events, the primary endpoint of the study, was reduced by 12% with dulaglutide compared to placebo (HR, 0.88; 95% CI, 0.79 to 0.99). There was no statistical significance in cardiovascular death (HR, 0.91; 95% CI, 0.7 to 1.06) or non-fatal/fatal myocardial infarction (HR, 0.96; 95% CI, 0.79 to 1.15), but the risk of non-fatal/fatal stroke was reduced by 24% (HR, 0.76; 95% CI, 0.62 to 0.94). The reduction in major cardiovascular events was consistent regardless of the presence of underlying ASCVD. There was no statistically significant reduction in hospitalization or emergency room visits for HF with dulaglutide compared to placebo (HR, 0.93; 95% CI, 0.77 to 1.12). In the REWIND study, 69% of the participants were T2DM adults without underlying ASCVD. Even in this case, dulaglutide reduced the occurrence of major cardiovascular events to the same extent, suggesting that it could be considered for primary prevention as well as secondary prevention (HR, 0.87; 95% CI, 0.74 to 1.02 for both; *P* for interaction = 0.97). However, because there is no other large-scale RCT yet for patients without underlying ASCVD, it is necessary to confirm whether consistent results will be reported in other studies involving these participants.

In summary, liraglutide, dulaglutide, and semaglutide have been demonstrated to reduce the risk of three-point major cardiovascular events in patients with T2DM who have underlying ASCVD. To date, the GLP-1RAs approved by the U.S. FDA for these cardiovascular effects include liraglutide, dulaglutide, and injectable semaglutide, where liraglutide and dulaglutide are currently available in Korea.

Risks

1) SGLT2 inhibitors

Identical to the Recommendation 10 as mentioned above.

2) GLP-1RA

Identical to the Recommendation 10 as mentioned above.

Considerations

1) SGLT2 inhibitors

SGLT2 inhibitors have a pronounced effect in reducing the risk of major cardiovascular events, deaths due to CVD, and hospitalizations due to HF, as well as improving renal endpoints. Even when considering the adverse reactions of SGLT2 inhibitors, the benefits significantly outweigh the risks, warranting their proactive use in patients indicated for it. However, when prescribing this class of antidiabetic agents, it is essential to dis-

cuss the expected benefits and potential side effects with the patients, ensuring that patients' preferences are considered in the decision-making process. Furthermore, healthcare providers should be aware of the glucose-lowering efficacy of SGLT2 inhibitors (0.5% to 0.8% reduction in HbA1c) and ensure proper medication adjustments when adding or changing drugs.

2) GLP-1RAs

In cases of underlying ASCVD, combination therapy with GLP-1RAs clearly reduces major adverse cardiovascular events. The potent glucose-lowering effect, relatively low risk of hypoglycemia, and the benefits of weight loss are advantages of GLP-1RAs, and the benefits are evident. However, GLP-1RAs, being injectable, have lower accessibility compared to oral medications such as SGLT2 inhibitors. Their high cost can impose significant economic burdens, and they frequently cause GI side effects, which can reduce patient compliance with the medication.

Alternatives and considerations

Through large-scale clinical studies, GLP-1RAs have been shown

to reduce cardiovascular risk to a similar degree as SGLT2 inhibitors. As they can inhibit the progression of kidney disease, they may be an alternative treatment for individuals with a severe decline in renal function or those who cannot use SGLT2 inhibitors due to adverse reactions.

In a prospective RCT targeting patients with T2DM with concomitant macrovascular disease, pioglitazone significantly reduced the concomitant secondary endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke by 16% [396]. Caution is needed in patients with HF due to its adverse reactions, such as edema and weight gain.

In two recently published meta-analyses, DPP-4 inhibitors did not increase the risk of major cardiovascular events (cardiovascular death/non-fatal myocardial infarction/non-fatal stroke), cardiovascular death, stroke, myocardial infarction, all-cause mortality, or hospitalization for HF compared with controls [397,398]. Therefore, DPP-4 inhibitors can also be considered as an alternative to SGLT2 inhibitors when an oral antidiabetic agent with cardiovascular safety is needed.

Table 8. Starting and titrating insulin therapy

	Starting capacity	Scaling	Hypoglycemia
Basal insulin	10 units/day or 0.1–0.2 units/kg/day	To achieve the target fasting glucose level, increments of 2 units every 3 days (other proven titration methods are available)	Analyze the cause; consider 10%–20% reduction without any specific cause
Mealttime insulin	Start with 4 units/day, or 10% of basal insulin; consider 4 units/day or a 10% reduction of basal insulin when A1c <8%	1–2 units twice a week or 10%–15% increase	Analyze the cause; consider 10%–20% reduction without any specific cause
Mixed insulin	If use insulin for the first time, 10–12 units/day or 0.3 units/kg/day Split the basal insulin dose to dosing with 2/3 in the morning and 1/3 in the afternoon; or half and half in the morning and the afternoon	1–2 units once or twice a week, or 10%–15% increase	Analyze the cause; consider 2–4 units or 10%–20% reduction without any specific cause

Adapted from Wu et al. [308].

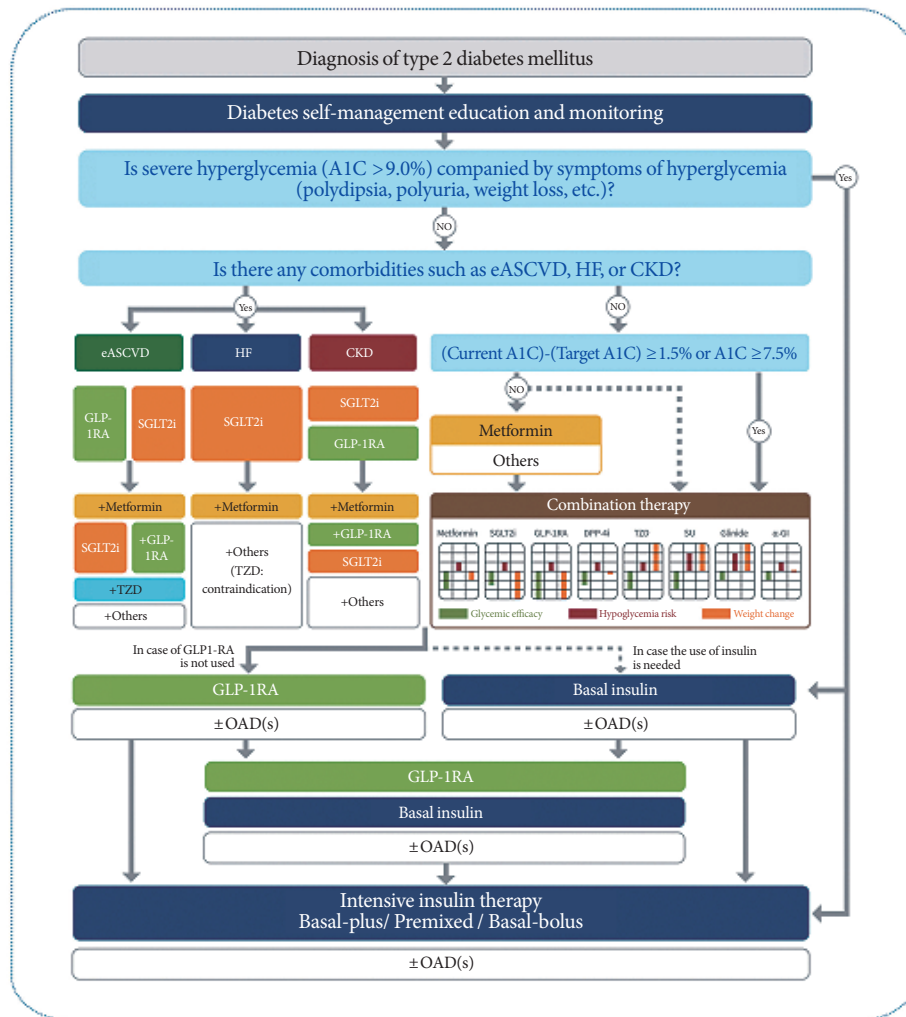


Fig. 2. Pharmacotherapy of type 2 diabetes mellitus algorithm. Implement and monitor diabetes self-management education immediately upon diagnosis. Prioritize treatment, including insulin, for severe symptomatic hyperglycemia. If comorbid atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease (CKD) is present, prioritize sodium-glucose cotransporter-2 inhibitor (SGLT2i) or glucagon-like peptide-1 receptor agonist (GLP-1RA), whichever has demonstrated clinical benefit for each condition. In the absence of these conditions, metformin monotherapy is common, but other members of the class may be used based on patient condition and drug characteristics. If glycemic goals are not achieved with monotherapy, combination therapy with other classes of drugs may be considered based on drug characteristics. Patients with comorbid ASCVD, HF, or CKD who are using an SGLT2i or GLP-1RA may be added to metformin, with preference given to drugs from other classes that have demonstrated clinical benefit for each condition. Combination therapy may be initiated earlier in the course of diagnosis to reduce the risk of glycemic control failure, with early combination therapy strongly considered, especially if glycosylated hemoglobin (HbA1c) is greater than 7.5% or greater than 1.5% above target. If glycemic goals are not achieved with a combination of oral hypoglycemic agents, GLP-1RAs or basal insulin should be considered first, and a combination of GLP-1RAs or basal insulin, or insulin intensification, may be used to improve glycemic control. (1) A history of an acute coronary syndrome or myocardial infarction, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin; (2) Current or prior symptoms of HF with documented HF with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40) or HF with preserved ejection fraction (LVEF >40); (3) Estimated glomerular filtration rate <60 mL/min/1.73 m² or urine albumin-creatinine ratio ≥30 mg/g; (4) Dulaglutide, liraglutide, semaglutide; (5) Dapagliflozin, empagliflozin; (6) Dapagliflozin, empagliflozin, ertugliflozin; (7) Pioglitazone. ASCVD, atherosclerotic cardiovascular disease; TZD, thiazolidinedione; DPP-4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; α-GI, α-glucosidase inhibitors; OAD, oral antidiabetic drug.

11. OBESITY MANAGEMENT

1. Individuals with T2DM and obesity should aim to reduce their weight by at least 5% and maintain it through medical nutrition and exercise. [Randomized controlled trial, general recommendation]
2. Antidiabetic agents may be used as adjunct therapy to support lifestyle modifications for weight reduction in obese individuals with T2DM. [Expert opinion, limited recommendation]
3. If the individual does not lose 5% of their body weight within 3 months after initiating anti-obesity medications, a different medication may be considered, or drug therapy should be discontinued. [Randomized controlled trial, general recommendation]
4. If individuals with T2DM and a BMI ≥ 30 kg/m² fail to reduce weight and exhibit poor blood glucose control on non-surgical treatments, bariatric surgery should be considered. [Randomized controlled trial, limited recommendation]
5. A multidisciplinary medical approach is required before and after surgery to enhance the efficacy and safety of bariatric surgery. [Expert opinion, general recommendation]

Recommendation 11.1 Individuals with T2DM and obesity should aim to reduce their weight by at least 5% and maintain it through medical nutrition and exercise. [Randomized controlled trial, general recommendation]

Level of evidence

Systematic reviews, RCTs, cluster RCTs, and the Korean Society for Obesity's Obesity Guidelines 2022 served as the primary evidence sources for the recommendations [144,147,399-402]. The nature of lifestyle intervention studies often precludes rigorous double-blinding, which may introduce bias due to deviations from the intended intervention. The limitation of DiRECT study of a single ethnic group further restricts the applicability of its evidence. Despite these limitations, the evidence level is classified as a 'RCT', and the recommendation is deemed a 'general recommendation' because the benefits significantly outweigh the risks.

Benefits

A systematic review comparing the effects of weight loss with and without lifestyle interventions in obese individuals with T2DM found that maintaining a weight loss of at least 5% of pre-treatment weight 1-year post-intervention was associated with significant improvements in several metabolic markers, including blood glucose, lipids, and blood pressure [144]. The Look Action for Health in Diabetes (Look AHEAD) study confirmed the effectiveness of active lifestyle modification in people with T2DM and a BMI of 25 kg/m² or higher. This intervention involved limiting total caloric intake to 1,200 to 1,800 kcal per day, aiming for at least 7% weight loss, and en-

gaging in at least 175 minutes of moderate physical activity weekly [399]. After 1 year, the active lifestyle intervention group achieved an 8.6% weight loss, compared to 0.7% in the usual care group and 6.0% versus 3.5% at the study's end [399]. At an 8-year follow-up, the intervention group's average weight loss was 4.7%, with about 50% losing 5% or more and 27% losing 10% or more of their body weight [403]. While the active lifestyle modification did not reduce the risk of major cardiovascular events and death—the primary endpoint—it improved metabolic markers, including blood glucose, and reduced the need for insulin, antihypertensive, and lipid-lowering medications [399]. In a long-term observational study, maintaining a weight loss of 10% or more reduced the risk of death by over 20% compared to those who maintained or gained weight in the first year [404]. The DiRECT study investigated the effects of a dietary intervention on weight loss and diabetes remission in individuals with T2DM, a BMI of 27 to 45 kg/m², and duration of diabetes of 6 years or less, not using insulin. The intervention consisted of an 825 to 853 kcal/day meal replacement for 3 to 5 months, followed by a gradual re-introduction of food over 2 to 8 weeks to maintain weight loss [147]. One-year post-intervention, 24% of the intervention group lost 15 kg or more, and 46% achieved diabetes remission. Two years later, the figures were 11% for the intervention group losing 15 kg or more versus 2% in the control group,

with diabetes remission rates at 36% and 3%, respectively [147, 401]. Moreover, at the 2-year follow-up, 64% of participants who maintained a weight loss of 10 kg or more achieved diabetes remission [401].

Risks

Weight loss is associated with side effects such as biliary stones, cholecystitis, gallbladder pain, loss of muscle mass and strength, water and electrolyte imbalances, liver disorders, increased uric acid, constipation or diarrhea, hair and skin damage, and thermoregulatory disorders [402]. Active lifestyle modification interventions, such as diet and exercise regimens, can potentially increase expense.

Balancing the benefits and risks

The Look AHEAD study investigated severe adverse effects of weight loss, such as hypoglycemia, cholelithiasis, fractures, risk of amputation, and HF, and found no significant increase in harm associated with the intervention [399]. Long-term follow-up showed economic benefits, including reduced hospitalization rates and healthcare costs, in the group undergoing aggressive lifestyle intervention [405]. Similarly, the DiRECT study reported no significant increase in adverse events associated with weight loss interventions [147,401]. Consequently, it can be concluded that the benefits of weight loss and maintenance through active lifestyle modification in obese individuals with T2DM significantly outweigh the potential harms.

Alternatives, and considerations when using the guidelines

In South Korea, obesity is defined as a BMI of 25 kg/m² or greater and a waist circumference of 90 cm or greater for men, and 85 cm or greater for women [402]. Lifestyle modification for weight loss should involve the patient's active participation and be guided by a professional.

For effective glycemic control in obese individuals with diabetes, the impact of hypoglycemic agents on body weight should be considered. Metformin, SGLT2 inhibitors, and GLP-1RAs are associated with weight loss effects. DPP-4 inhibitors have a neutral effect on weight, while insulin, sulfonylureas, and thiazolidinediones are associated with weight gain [406].

Recommendation 11.2 Antidiabetic agents may be used as adjunct therapy to support lifestyle modifications for weight reduction in obese individuals with T2DM. [Expert opinion, limited recommen-

ation]

Recommendation 11.3 If the individual does not lose 5% of their body weight within 3 months after initiating anti-obesity medications, a different medication may be considered, or drug therapy should be discontinued. [Randomized controlled trial, general recommendation]

Level of evidence

A systematic review of drug-specific RCTs, recently published RCTs, and the Korean Society of Obesity's Obesity Guideline 2022 served as the primary sources of evidence for the recommendations [402,407-416]. Although the systematic review encompassed numerous RCTs and meta-analyses, it did not fully address the risk of bias or consider heterogeneity among the individual studies. Recommendation 2, despite its widespread use in clinical practice, lacked sufficient high-level evidence to support its application specifically in the Korean population; hence, the evidence level was classified as 'expert opinion,' and the recommendation was given a 'limited recommendation' grade. For Recommendation 3, the evidence level was designated as 'RCT,' and the recommendation was 'general recommendation' because the benefits outweighed the risks.

Benefits

The following medications are currently licensed in Korea for long-term use beyond 12 weeks: orlistat (Xenical, Roche Pharmaceuticals, Basel, Switzerland), naltrexone/bupropion (Contrave, Orexigen Therapeutics Inc., La Jolla, CA, USA), liraglutide (Saxenda, Novo Nordisk), and phentermine/topiramate (Qsymia, Vivus, Campbell, CA, USA). Pharmacological treatment for obesity is generally associated with a weight loss of 3% to 7%. However, the clinical evidence to judge the benefits of recommendations using a BMI cutoff of 25 kg/m² as a cutoff point is limited. Generally, if an adequate response is not observed after 3 months of initiating an anti-obesity medication, the medication should be switched or discontinued, weighing the risk of adverse drug reactions against the benefit of reduced treatment costs [402,410].

An RCT examining the effects of orlistat 120 mg three times daily in individuals with T2DM on metformin reported a mean weight loss of 4.6% and a HbA1c reduction of 0.61% in the orlistat group over 52 weeks, both significantly higher than those in the placebo group [407]. In the 56-week Contrave Obesity Research-Diabetes (COR-DM) study involving 505 individuals with T2DM and a BMI of 27 kg/m² or greater, 44.5% of the nal-

trexone/bupropion group and 18.9% of the placebo group lost 5% or more of their body weight [408]. Additionally, 44.1% in the naltrexone/bupropion group and 26.3% in the placebo group achieved an HbA1c of less than 7%, a significant difference. The Satiety and Clinical Adiposity-Liraglutide Evidence in Nondiabetic and Diabetic Individuals (SCALE) study, conducted over 56 weeks with 846 individuals with T2DM and a BMI of 27 kg/m² or greater [409], found that liraglutide 3.0 mg/day led to a 4% weight loss compared to placebo. The proportion of individuals losing 5% or more of their weight was 54.3% in the liraglutide group versus 21.4% in the placebo group. For a 10% or more weight loss, the figures were 25.2% in the liraglutide group compared to 6.7% in the placebo group. The CONQUER study randomized individuals with a BMI of 27 to 45 kg/m² and at least two metabolic disease risk factors to placebo, once-daily phentermine/topiramate (7.5/46.0 mg), or phentermine/topiramate (15/92.0 mg) for 56 weeks [411]. Among participants, 16% had T2DM or IGT. In this subgroup, weight loss was 4.9% with the phentermine/topiramate (7.5/46.0 mg) group and 6.9% with the phentermine/topiramate (15/92.0 mg) group compared to placebo, with HbA1c decrease of an average of 0.4% in the drug groups.

Recently, evidence for newer drugs for the treatment of obesity has been introduced. The STEP 2 study randomized 1,210 subjects with a BMI of 27 kg/m² or greater and HbA1c of 7% to 10% to semaglutide 2.4 mg, semaglutide 1.0 mg, or placebo group for 68 weeks [412]. The mean weight loss was 9.6% in the semaglutide 2.4 mg group, 6.9% in the semaglutide 1.0 mg group, and 3.4% in the placebo group. The percentages of subjects achieving 5% or greater weight loss were 68.8%, 57.1%, and 28.5%, respectively. The STEP 6 study, conducted in South Korea and other East Asian populations, randomized 401 subjects with a BMI of 27 kg/m² or greater with two or more risk factors or a BMI of 35 kg/m² or greater with one or more risk factors, to semaglutide 2.4 mg, semaglutide 1.0 mg, or placebo group for 68 weeks [413]. Mean weight loss was 13.2% in the semaglutide 2.4 mg group, 9.6% in the semaglutide 1.0 mg group, and 2.1% in the placebo group. The percentages of subjects achieving 5% or greater weight loss were 83%, 72%, and 21%, respectively. The SURPASS-1 study randomized 478 individuals to placebo and 5, 10, and 15 mg doses of tirzepatide for 40 weeks [414]. HbA1c reductions, corrected for the effect of placebo, were 1.91%, 1.93%, and 2.11% with the 5, 10, and 15 mg doses, respectively. Weight loss was 7.0 to 9.5 kg and dose-dependent. The SURPASS-2 study compared the effects of tirz-

epatide and semaglutide in 1,879 individuals with T2DM inadequately controlled with metformin [415]. Participants were randomized to receive 5, 10, or 15 mg/week of tirzepatide or 1.0 mg/week of semaglutide for 40 weeks. By the end of the study, mean HbA1c decreased by 2.01%, 2.24%, and 2.3% with the 5, 10, and 15 mg doses of tirzepatide, respectively, and by 1.86% in the semaglutide arm. Weight decreased by 7.6, 9.3, and 11.2 kg with the 5, 10, and 15 mg doses of tirzepatide, respectively, and by 5.7 kg in the semaglutide arm. The SURPASS-3 study confirmed the effectiveness of combined treatment with tirzepatide or insulin degludec in 1,444 individuals with T2DM inadequately controlled with oral hypoglycemic agents [416]. After 52 weeks of intervention, HbA1c decreased by 1.93%, 2.20%, and 2.37% with the 5, 10, and 15 mg doses of tirzepatide, respectively, and by 1.34% in the insulin degludec group. A significant dose-dependent decrease in body weight from 7.5 to 12.9 kg was observed in the tirzepatide group, compared to a 2.3 kg increase in the insulin degludec group.

Risks

Harms include drug-related side effects and contraindications. Orlistat may cause fatty stools, abdominal bloating, and gas, increased bowel movements, and fecal incontinence. Naltrexone/bupropion may lead to nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, anxiety, hot flashes, fatigue, tremor, epigastric pain, viral gastroenteritis, tinnitus, urinary tract infections, hypertension, abdominal pain, hyperhidrosis, irritability, increased blood pressure, taste abnormalities, and palpitations. Liraglutide and semaglutide can induce nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, bloating, belching, gastroesophageal reflux disease (GERD), dry mouth, gastritis, hypoglycemia, injection site reactions (redness and itching), fatigue, weakness, dizziness, taste changes, sleep disturbances, gallstones, and elevated lipase/amylase levels. Adverse reactions with phentermine/topiramate may include paresthesias/paresthesia, mood and sleep disturbances, cognitive impairment, decreased serum bicarbonate, decreased serum potassium, increased serum creatinine, and nephrolithiasis. The most common adverse reactions associated with tirzepatide to date have been GI, including nausea and vomiting, occurring at a frequency similar to that observed with semaglutide.

Balancing the benefits and risks

Large clinical studies have demonstrated the efficacy and safety

of long-term anti-obesity medications. However, most of these studies have been limited to individuals with a BMI >30 or >27.5 kg/m² and comorbid risk factors such as hypertension, diabetes, dyslipidemia, and sleep apnea. There is limited evidence to assess the balance of benefits and harms of antidiabetic medications in individuals with T2DM with a BMI of 25.0 kg/m² or greater.

Alternatives, considerations when using the guidelines

Long-term maintenance of weight loss is crucial in obesity pharmacotherapy, both for weight loss itself and for the improvement of related complications. Therefore, drugs approved for long-term use, based on large-scale clinical studies, should be prioritized [402]. Recent RCTs on new obesity treatment drugs have been published, promising to alter the clinical landscape in the future. In clinical practice, there exists a group that is non-responsive to obesity medications. If significant weight loss is not achieved in the initial stages of treatment, continuing the treatment is unlikely to result in weight loss success. In most clinical studies, the response to weight loss within the first 12 weeks indicates of 1-year outcomes. Therefore, if there is less than a 5% to 10% reduction in pre-treatment weight after 12 weeks of medication, individuals may face the risks of side effects and increased costs without benefiting from the treatment.

Recommendation 11.4 If individuals with T2DM and a BMI \geq 30 kg/m² fail to reduce weight and exhibit poor blood glucose control on non-surgical treatments, bariatric surgery should be considered. [Randomized controlled trial, limited recommendation]

Recommendation 11.5 A multidisciplinary medical approach is required before and after surgery to enhance the efficacy and safety of bariatric surgery. [Expert opinion, general recommendation]

Level of evidence

RCTs and systematic reviews of bariatric surgery, meta-analyses focusing on Asian populations, and the Korean Society for Obesity's Obesity Guidelines 2022 served as the primary sources of evidence for these recommendations [402,417-422]. Due to the inherent nature of surgical interventions, the RCTs were not blinded, yet they were unlikely to be biased. Systematic reviews and meta-analyses rigorously analyzed RCTs with a low risk of bias. However, the applicability of these findings may be limited as most studies were conducted in Western populations.

Recommendation 4 is widely used in clinical practice, yet there is insufficient high-level evidence to support its effectiveness, specifically within the Korean population. Consequently, the evidence level for this recommendation is categorized as 'limited evidence from RCTs,' leading to its classification as a 'limited recommendation.' For Recommendation 5, the evidence level is 'expert opinion,' it is designated as a 'general recommendation' due to its widespread use in clinical practice and the overall benefits outweighing the risks.

Benefits

The literature identifies diabetes remission as the primary outcome of interest, with secondary outcomes including weight loss, improvement in metabolic markers, and medication discontinuation. The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) study compared the effectiveness of bariatric metabolic surgery to medication therapy in 150 individuals with T2DM and a BMI of 27 to 43 kg/m² [417]. At a 5-year follow-up, diabetes remission (HbA1c <6.0%) was achieved by 29% of the Roux-en-Y gastric bypass group, 23% of the gastric sleeve group, and 5% of the medication-only group, highlighting a significant benefit in favor of surgery. Additionally, body weight decreased by 23%, 19%, and 5% in the Roux-en-Y gastric bypass, sleeve gastrectomy, and medication groups, respectively, with corresponding reductions in insulin use of 35%, 34%, and 13% [417]. A single-center, randomized, controlled, long-term follow-up study in Italy compared the effectiveness of surgical versus pharmacological treatments in 60 individuals with T2DM of at least 5 years duration, a BMI of 35 kg/m² or greater, and an HbA1c of 7.0% or greater [418]. At the 10-year mark, 37.5% of all surgically treated individuals (25.0% in the Roux-en-Y gastric bypass group and 50.0% in the biliopancreatic diversion group) maintained diabetes remission, defined as fasting glucose <100 mg/dL and HbA1c <6.5%, a stark contrast to the medication arm, where no subjects except one who underwent additional surgery-maintained remission. A meta-analysis assessing the Roux-en-Y gastric bypass's effectiveness in individuals with T2DM and a BMI of 30 to 40 kg/m² found the OR of achieving diabetes remission significantly higher in the surgical group than in the medical treatment group, with an OR of 17.48 (95% CI, 4.28 to 71.35) and notably lower HbA1c levels [419]. Diabetes remission rates at a 3-year follow-up of the 256 participants in the STAMPEDE, TRIABETES, Surgery or Lifestyle With Intensive Medical Management in the Treatment of

Type 2 Diabetes (SLIMM-T2D), and CROSSROADS studies were 37.5% in the bariatric metabolic surgery group versus 2.6% in the control group [421]. Furthermore, significant differences were observed in metabolic markers such as HbA1c, FPG, and BMI. A comprehensive meta-analysis encompassing a population of approximately 170,000 individuals revealed that, compared to controls, bariatric surgery led to a 49.2% reduction in the HR and extended median life expectancy by 6.1 years [422]. The benefits of bariatric surgery were even more notable among people with diabetes, with those undergoing surgery experiencing a median life extension of 9.3 years compared to their non-surgical counterparts.

The existing evidence on racial differences in bariatric surgery outcomes is sparse. A meta-analysis examining bariatric surgery outcomes among Asians (including Chinese, Taiwanese, and Indian populations) reported that the Roux-en-Y gastric bypass group achieved an excess weight loss of 83.4%, while the sleeve gastrectomy group saw a 65.1% loss [420]. Although diabetes remission rates were higher in the Roux-en-Y gastric bypass group, no significant differences were observed between the surgical methods [420].

Additionally, employing a multidisciplinary team approach has proven to enhance the safety and effectiveness of both surgical and perioperative patient care. A retrospective study highlighted that multidisciplinary care significantly improved the quality of perioperative management in bariatric metabolic surgery [423].

Risks

Risks associated with bariatric metabolic surgery encompass surgical site strictures, leaks, fistulas, marginal ulcers, GERD, gastric outlet obstruction, hernias, dumping syndrome, anemia, hypoglycemia, malabsorption of calcium and vitamin D, osteoporosis, deficiencies in protein and micronutrients, depression, anxiety, and suicidal ideation [402]. Additionally, individuals face the risk of needing additional surgery, experiencing weight regain, recurrence of diabetes, and challenges in conducting regular endoscopic surveillance of the bypassed stomach during long-term follow-up. Moreover, there may be an increase in healthcare utilization and associated costs for individuals in the surgical group.

Balancing the benefits and risks

Bariatric surgery is associated with significant weight loss, diabetic remission, and glycemic improvement in individuals

with T2DM, offering additional benefits such as reduced risk of diabetic nephropathy, retinopathy, CVD, and improved quality of life [424,425]. Furthermore, with the advancement of surgical techniques, the rate of complications associated with bariatric surgery continues to decrease. Therefore, it can be concluded that the benefits of bariatric metabolic surgery outweigh the risks. While systematic evidence for multidisciplinary care in bariatric metabolic surgery is lacking, the general benefits of this approach are considered to outweigh the harms. However, there is insufficient evidence to recommend bariatric surgery as a primary treatment for T2DM in Asians with a BMI of 30 to 35 kg/m².

Various alternatives, considerations when using the guidelines

Types of bariatric metabolic surgery include sleeve gastrectomy, Roux-en-Y gastric bypass, and biliopancreatic diversion/duodenal switch. For individuals with T2DM, sleeve gastrectomy and Roux-en-Y gastric bypass are primarily considered, with a preference for Roux-en-Y. There is insufficient evidence to differentiate the effectiveness and safety between these two procedures. Some meta-analyses suggest that Roux-en-Y gastric bypass may be more effective for weight loss compared to sleeve gastrectomy, yet no significant difference in diabetes remission rates has been observed [426,427]. Additionally, a large-scale meta-analysis found no significant difference in treatment effectiveness based on the surgical method [422]. In Korea, sleeve gastrectomy and Roux-en-Y gastric bypass are designated as selective medical coverage for individuals with T2DM who have a BMI of 27.5 kg/m² or more but not exceeding 30 kg/m², and who have not achieved glycemic control through conventional medical treatment and lifestyle modification.

There is ongoing debate regarding the efficacy and safety of bariatric surgery for individuals with T2DM and the specific surgical indications for Asians with a BMI of 35 kg/m² or lower. During the 2011 International Federation for the Surgery of Obesity and Metabolic Disorders Asia-Pacific Chapter (IFSO-APC), it was highlighted that Asians face an increased risk of developing metabolic diseases, including T2DM, at relatively lower BMIs. It was proposed that a BMI of 35 kg/m² or higher, or 30 kg/m² or higher with comorbidities such as uncontrolled T2DM or metabolic syndrome, should be the criteria for considering bariatric metabolic surgery [428]. The 2016 Diabetes Surgery Summit (DSS-II) further suggested lowering the BMI threshold for Asians by 2.5 kg/m², recommending bariatric

surgery for those with a BMI of 27.5 kg/m² or higher who experience poor glycemic control despite lifestyle modifications and medication [429]. In 2018, The American Society for Metabolic and Bariatric Surgery (ASMBS) advised that bariatric surgery should be strongly considered for individuals with T2DM and a BMI of 30 to 35 kg/m², without specifically addressing racial differences [430].

Concerning the age for undergoing surgery, there was tradi-

tionally an age limit of 18 to 65 years. However, recent guidelines have relaxed significant age restrictions. For adolescents, it is recommended that they be at least 14 years old, have completed bone growth, and exhibit secondary sexual characteristics. While bariatric surgery is generally safe, it is crucial to note that the rate of complications can vary based on the surgeon's expertise and the volume of procedures conducted by the healthcare facility.

12. HYPERTENSION MANAGEMENT

1. Blood pressure should be measured in individuals with diabetes at every hospital visit. [Expert opinion, general recommendation]
2. Home blood pressure monitoring is recommended for individuals with diabetes and hypertension. [Randomized controlled trial, general recommendation]
3. It is recommended that individuals with diabetes but without CVDs or risk factors maintain their blood pressure level at <140/90 mm Hg. [Randomized controlled trial, general recommendation]
4. Individuals with diabetes with CVD, end-organ damage (albuminuria, CKD, retinopathy, left ventricular hypertrophy), or risk factors for CVD should maintain their blood pressure at <130/80 mm Hg. [Randomized controlled trial, general recommendation]
5. Individuals with diabetes and blood pressure \geq 120/80 mm Hg should change their lifestyle, including weight control, appropriate exercise, and dietary management, to maintain normal blood pressure. [Randomized controlled trial, general recommendation]
6. Every antihypertensive agent can be used for individuals with diabetes and hypertension as the first-line therapy. [Randomized controlled trial, general recommendation]
7. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are recommended first-line therapy for individuals with diabetes and albuminuria as antihypertensive agents. [Randomized controlled trial, general recommendation]
8. ACE inhibitors or ARBs are recommended first-line therapy for individuals with diabetes and coronary artery diseases as antihypertensive agents. [Randomized controlled trial, general recommendation]
9. If the blood pressure level is not controlled with first-line therapy, a combination therapy using drugs with a different mechanism of action should be employed. However, a combination of ACE inhibitors and ARBs should not be used. [Randomized controlled trial, general recommendation]
10. If blood pressure exceeds 160/100 mm Hg, lifestyle should be corrected aggressively, and a combination of two or more medications should be initiated. [Randomized controlled trial, general recommendation]

Recommendation 12.1 Blood pressure should be measured in individuals with diabetes at every hospital visit. [Expert opinion, general recommendation]

Recommendation 12.2 Home blood pressure monitoring is recommended for individuals with diabetes and hypertension. [Randomized controlled trial, general recommendation]

Level of evidence

Although research on the frequency of blood pressure measurement for early detection of hypertension in individuals with diabetes is lacking, most experts recommend measuring blood pressure at every hospital visit. Therefore, the level of evidence has been assessed as an 'expert opinion.' Since the benefits of the recommendation outweigh any potential harm, making it advisable for most individuals with diabetes, the scope of the recommendation has been assessed as a 'general recommendation.'

Based on evidence from RCTs and meta-analyses that highlight the utility of home blood pressure monitoring for diagnosing hypertension and assessing treatment efficacy, the recommendation for home blood pressure measurement has been assessed as a 'general recommendation.'

Benefits

Hypertension is one of the risk factors for both microvascular and macrovascular complications in individuals with diabetes.

CVD is a major cause of death among people with diabetes, and large-scale RCTs have demonstrated that blood pressure management can significantly reduce mortality. Thus, controlling blood pressure in individuals with diabetes is critical to preventing myocardial infarction, stroke, and renal failure and decreasing the related mortality [431]. The 2022 Diabetes Fact Sheet from the KDA reports that the prevalence of hypertension in Koreans with diabetes aged 30 years and older is 58.6%, increasing to 71.7% in those aged 65 and older. However, the hypertension control rate stands at only 55.5% for those aged 30 and over and 60.9% for those aged 65 and over, indicating that many individuals have inadequately controlled blood pressure [432]. It is very important for individuals with diabetes to have an early diagnosis of hypertension and receive proper treatment according to blood pressure targets. Accurate blood pressure measurement is foundational for hypertension diagnosis, treatment, and prognosis assessment. Given the variability in blood pressure across different settings, sites, and clinical situations, it should be measured using standardized methods, and it should be measured at every hospital visit.

Due to the limitations of office-based blood pressure measurements, the importance of out-of-office blood pressure monitoring is increasingly recognized. Home or ambulatory blood pressure measurements are instrumental in diagnosing conditions such as white coats and masked hypertension and are valuable for assessing the effectiveness of treatment. RCTs and meta-analyses have demonstrated that home blood pressure monitoring can increase treatment adherence, persistence, and blood pressure control in individuals receiving anti-hypertensive medications [433].

Assessing risks and balancing harm and benefit

The potential harm of implementing the recommendation is unclear, indicating that the benefits of the recommendation outweigh the harm.

Alternatives and considerations

When measuring blood pressure, it should be conducted in a standardized manner using a validated sphygmomanometer. Ensure individuals are at rest for at least 5 minutes, with both feet on the ground, arms resting on a table, the cuff positioned at heart level, and using the appropriate cuff size for their arm circumference.

Recommendation 12.3 It is recommended that individuals with diabetes but without CVDs or risk factors maintain their blood pressure level at <140/90 mm Hg. [Randomized controlled trial, general recommendation]

Recommendation 12.4 Individuals with diabetes with CVD, end-organ damage (albuminuria, CKD, retinopathy, left ventricular hypertrophy), or risk factors for CVD should maintain their blood pressure at <130/80 mm Hg. [Randomized controlled trial, general recommendation]

Level of evidence

Based on RCTs and meta-analyses that demonstrate a reduction in cardiovascular events and microvascular complications when systolic blood pressure (SBP) is maintained below 140 mm Hg in individuals with diabetes, the level of evidence has been assessed as a 'RCT' and the scope of the recommendation has been assessed as a 'general recommendation.' RCTs and meta-analyses targeting a SBP lower than 140 mm Hg in individuals with diabetes who have CVD or are at high risk for CVD have shown cardiovascular benefits. Consequently, the level of evidence has been assessed a 'RCT' and the scope of recommendation has been assessed a 'general recommendation.'

Benefits

Numerous studies have investigated blood pressure control targets in individuals with diabetes, with various RCTs and meta-analyses indicating that maintaining SBP below 140 mm Hg can reduce cardiovascular events and microvascular complications [434]. The 2010 ACCORD study, which focused on individuals with T2DM at high cardiovascular risk, found that lowering SBP below 120 mm Hg was associated with an increase in adverse events and did not offer benefits in cardiovascular risk reduction compared to maintaining SBP below 140 mm Hg [435]. Conversely, the 2015 Systolic Blood Pressure Intervention Trial (SPRINT), which excluded individuals with diabetes or stroke but included individuals with high cardiovascular risk, demonstrated that controlling SBP to below 120 mm Hg improved cardiovascular outcomes compared to a target below 140 mm Hg leading to recommendations for lower blood pressure targets [436]. A subsequent re-analysis of the ACCORD participants using the SPRINT inclusion criteria indicated that individuals with diabetes also benefited from maintaining SBP below 120 mm Hg [437]. Consequently, in 2017, the American College of Cardiology and the American Heart Association recommended that individuals with hyper-

tension aim for blood pressure control below 130/80 mm Hg [438]. The 2018 European Society of Hypertension recommendations suggested that the primary target for SBP in individuals with diabetes should be reduced to 130 mm Hg and, if tolerable, maintained below 130 mm Hg but not below 120 mm Hg [439]. The Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) study in 2021 revealed that hypertensive individuals aged 60 to 80 years experienced a 26% reduction in the risk of cardiovascular events when achieving SBP control between 110 and 130 mm Hg, compared to control between 130 and 150 mm Hg [440].

However, no studies have demonstrated a clear advantage in lowering SBP to less than 130 mm Hg over maintaining it below 140 mm Hg in individuals with diabetes who do not have comorbid cardiovascular risk factors. Most of the previously mentioned studies involved individuals with diabetes who had comorbid CVD or numerous cardiovascular risk factors. Consequently, there is still no definitive evidence supporting the maintenance of SBP below 130 mm Hg in the general diabetic population. The Korean Society of Hypertension, in its 2022 revised recommendations, advises controlling blood pressure to below 140/90 mm Hg in individuals with diabetes without cardiovascular risk factors, CVD, CKD stages 3, 4, or 5, and asymptomatic organ damage. It recommends a target of below 130/80 mm Hg for those with diabetes and one or more cardiovascular risk factors, CVD, CKD stages 3, 4, or 5, or asymptomatic organ damage [441]. Similarly, the KDA suggests a blood pressure goal of below 140/90 mm Hg for individuals with diabetes without CVD or cardiovascular risk factors and below 130/80 mm Hg for those with CVD, end-organ damage (such as albuminuria, CKD, retinopathy, or left ventricular hypertrophy), or cardiovascular risk factors.

Few studies have specifically focused on the control target of diastolic blood pressure (DBP) in individuals with diabetes. In the UKPDS, the group with tight blood pressure control achieved a mean DBP of 82 mm Hg and experienced fewer microvascular and cardiovascular complications than the group receiving standard treatment [442]. A subanalysis of the Hypertension Optimal Treatment (HOT) study compared three groups with DBP targets of 90, 85, and 80 mm Hg, respectively. It was observed that lower DBP was associated with a cardiovascular benefit in individuals with diabetes, in contrast to those with hypertension but without diabetes [443].

Risks

Potential adverse events of intensive blood pressure control include hypotension, syncope, falls, acute kidney injury, and electrolyte imbalance. The risk of these adverse events increases in individuals who are elderly, have CKD, or exhibit frailty [435,436,444,445].

Balancing risks and benefits

In a study targeting patients with CVD and hypertension, a further analysis was conducted exclusively on individuals with diabetes. The study was compared between the intensive control group (target SBP <130 mm Hg) and the standard control group (target SBP 130 to 139 mm Hg). The results demonstrated a J-shaped association indicating an increased all-cause mortality and primary endpoints, including non-fatal myocardial infarction and non-fatal stroke in the group with SBP below 110 mm Hg and DBP below 60 mm Hg. This finding suggests that excessively lowering blood pressure in individuals with diabetes, depending on their specific characteristics, may lead to adverse outcomes [446]. Blood pressure management in diabetes is complex and should be individualized, considering factors such as glycemic control status, duration of diabetes, presence of comorbidities, and severity of complications.

Alternatives and considerations

Generally, cardiovascular risk factors include age (male ≥ 45 years, female ≥ 55 years), smoking, obesity, dyslipidemia, and a family history of early CVD. End-organ damage includes albuminuria, CKD, retinopathy, and left ventricular hypertrophy [439,441].

Recommendation 12.5 Individuals with diabetes and blood pressure $\geq 120/80$ mm Hg should change their lifestyle, including weight control, proper training, and dietary management, to maintain normal blood pressure. [Randomized controlled trial, general recommendation]

Level of evidence

Numerous RCTs and meta-analyses demonstrate the effectiveness of lifestyle modifications, including weight loss, restriction of sodium intake, reduction in alcohol consumption, and exercise in reducing blood pressure. Consequently, the level of evidence for the recommendation has been assessed as a 'RCT'. Since the benefits of the recommendation outweigh any potential harm, making it advisable for most individuals with diabe-

tes, the scope of the recommendation has been assessed as a 'general recommendation.'

Benefits

A normal blood pressure is defined as a SBP <120 mm Hg and a DBP <80 mm Hg. Lifestyle modification is recommended to maintain normal blood pressure when blood pressure exceeds these thresholds [437]. Lifestyle modifications such as healthy eating habits, regular exercise, smoking cessation, reduction in alcohol consumption, and weight loss not only have the effect of lowering blood pressure but also can maximize the efficacy of antihypertensive medications and reduce side effects. Additionally, these modifications reduce other metabolic and cardiovascular risks [204,439,447-451].

In individuals with obesity, achieving weight loss can lead to substantial reductions in blood pressure. A meta-analysis of 25 RCTs reported a decrease of 4.44 and 3.57 mm Hg in SBP and DBP, respectively, following a weight loss of 5.1 kg, achieved through dietary calorie reduction and increased physical activity [448]. Additionally, restriction of sodium intake has proven effective in lowering blood pressure and reducing the risk of CVD [449,450]. An RCT investigating the DASH diet, which emphasizes increased intake of fruits, vegetables, and fish while reducing fats, demonstrated a significant reduction in blood pressure [204]. Excessive alcohol consumption is known to elevate blood pressure, which can be mitigated by abstaining from alcohol [451]. Regular exercise also lowers blood pressure, with a recommended regimen that includes both aerobic and resistance training [439].

Risks

The risks associated with lifestyle modifications are not clear. Nonetheless, it is crucial that diet and exercise plans be tailored to the individual's specific needs and conditions.

Balancing harms and benefits

The benefits of lifestyle modification for controlling blood pressure are well-established, while the associated risks remain unclear, indicating that the benefits significantly outweigh the risks. However, maintaining lifestyle modification can be challenging and necessitates sustained motivation and education.

Recommendation 12.6 Every antihypertensive agent can be used for individuals with diabetes and hypertension as the first-line therapy. [Randomized controlled trial, general recommendation]

Level of evidence

Based on RCTs and meta-analyses showing no differences in cardiovascular or renal outcomes across antihypertensive drug classes in diabetes, the evidence level has been assessed as a 'RCT,' and the scope of recommendation has been assessed as a 'general recommendation,' as it is applicable to the majority of the population.

Benefits

How to start and titrate antihypertensive treatment is summarized in Fig. 3. Hypertension is diagnosed when the office blood pressure is repeatedly 140/90 mm Hg or higher, and pharmacologic treatment is administered for individuals diagnosed with hypertension [439,441]. For individuals with diabetes, first-line antihypertensive medications include ACE inhibitors, ARBs, β -blockers, calcium channel blockers (CCBs), and diuretics. No differences in cardiovascular event prevention have been observed among these medication classes, making all of them recommended as first-line therapy [452,453].

Risks

Thiazide diuretics can affect blood sugar, lipids, sodium, and potassium levels. β -Blockers may influence blood glucose and lipid levels, but no evidence that they directly increase cardiovascular death in individuals with T2DM [438,439].

Alternatives and considerations

Diuretics, ACE inhibitors, and ARBs can raise serum creatinine or potassium levels, therefore monitoring is necessary. If creatinine rises by no more than 30% from baseline or potassium remains below 5.5 mEq/L, discontinuation of the medication is unnecessary. Individuals with serum creatinine levels above 3.0 mg/dL should be cautious of hyperkalemia [438,439].

Recommendation 12.7 ACE inhibitors or ARBs are recommended as the first-line therapy for individuals with diabetes and albuminuria as antihypertensive agents. [Randomized controlled trial, general recommendation]

Recommendation 12.8 ACE inhibitors or ARBs are recommended as the first-line therapy for individuals with diabetes and coronary artery diseases as antihypertensive agents. [Randomized controlled trial, general recommendation]

Level of evidence

Based on RCTs and meta-analyses demonstrating the efficacy

of ACE inhibitors or ARBs in slowing renal disease progression in individuals with diabetes and albuminuria, the evidence level has been assessed as a 'RCT', and the scope of recommendation has been assessed as a 'general recommendation.' Similarly, based on RCTs and meta-analyses that reveal ACE inhibitors or ARBs reduce cardiovascular events in individuals with diabetes and coronary artery disease, the evidence level has been assessed as a 'RCT' and the scope of recommendation has been assessed as a 'general recommendation.'

Benefits

The selection of antihypertensive medication for individuals with diabetes should consider clinical characteristics and comorbidities. ACE inhibitors or ARBs are recommended as the first-line treatment in the presence of albuminuria due to their cardiovascular benefits and ability to reduce albuminuria [454-456].

For individuals with diabetes and coronary artery disease, ACE inhibitors or ARBs are recommended as the first-line treatment, supported by their proven ability to reduce cardiovascular events. In the Heart Outcomes Prevention Evaluation (HOPE) study, the group taking ramipril showed a reduction in the occurrence of cardiovascular events compared to the placebo group, indicating that there are RCTs and meta-analyses demonstrating the cardiovascular protective benefits of ACE inhibitors and ARBs in those with coronary artery disease [457-459].

Risks

Serum creatinine and potassium levels may increase in individuals with reduced GFRs during ACE inhibitors or ARBs treatment and should be monitored.

Balancing risks and benefits

In individuals with diabetes, hypertension, albuminuria, or coronary artery disease, the advantages of using ACE inhibitors or ARBs outweigh the risks, offering benefits in decelerating renal disease progression and decreasing cardiovascular events.

Alternatives and considerations

In individuals taking ACE inhibitors or ARBs, maintaining medication when the GFR decreases to less than 30 mL/min/1.73 m² may provide cardiovascular benefit without increasing the risk of progression to ESRD [460].

Recommendation 12.9 If the blood pressure level is not controlled with first-line therapy, a combination therapy using drugs with a different mechanism of action should be employed. However, a combination of ACE inhibitors and ARBs should not be used. [Randomized controlled trial, general recommendation]

Level of evidence

RCTs and meta-analyses that examine the effects of combination antihypertensive therapy on lowering blood pressure, along with studies assessing the heightened adverse effects of using ACE inhibitors and ARBs together. Consequently, the evidence level has been assessed as a 'RCT' and the scope of recommendation has been assessed as a 'general recommendation.'

Benefits and harms

The ACCORD study highlights that many individuals with hypertension do not achieve adequate blood pressure control with a single antihypertensive medication [435], often necessitating a combination of drugs with different mechanisms of action. While it is possible to increase the dosage of the first antihypertension medication if it is ineffective or if the target blood pressure is not reached, combining low doses of drugs with different mechanisms offers the advantages of enhancing the blood pressure-lowering effect and adherence while reducing side effects [461]. Although taking two or more drugs is possible, it remains still uncertain which specific combinations are beneficial in the long-term perspective. Combinations of renin-angiotensin-aldosterone system (RAS) inhibitors, CCBs, and diuretics generally show favorable outcomes, with some evidence suggesting that combining a RAS inhibitor with CCB may be superior in reducing cardiovascular events compared to combining it with a diuretic [462]. However, combining ACE inhibitors with ARBs is not advised due to the lack of added benefit in preventing CVD and the potential for increased adverse effects, such as hyperkalemia and acute kidney injury [463-465].

Alternatives and considerations

Hypertension that remains above 140/90 mm Hg despite the combination of three or more antihypertensive drugs with different mechanisms of action, including a diuretic, is referred to as 'resistant hypertension.' It is necessary first to exclude factors such as treatment compliance, white coat hypertension, and secondary causes of hypertension. In cases of resistant hyper-

tension, adding mineralocorticoid receptor antagonists may be considered. However, when added to patients already taking ACE inhibitors or ARBs, there is a risk of hyperkalemia, necessitating the monitoring of serum potassium and creatinine levels [466].

Recommendation 12.10 If blood pressure exceeds 160/100 mm Hg, lifestyle should be corrected aggressively, and a combination of two or more medications should be initiated. [Randomized controlled trial, general recommendation]

Level of evidence

Based on RCTs indicating that initial combination therapy enhances the probability of reaching target blood pressure goals, the level of evidence has been assessed as a 'RCT', and the scope of the recommendation has been assessed as a 'general recommendation.'

Benefits

Randomized studies indicate that initiating treatment with two

antihypertensive medications leads to quicker achievement of target blood pressure without significant safety issues compared to monotherapy [467-469]. If blood pressure exceeds 160/100 mm Hg or is more than 20/10 mm Hg above the target, it is advised to initially consider using two or more agents to enhance effectiveness and achieve rapid blood pressure control [439].

Risks

Using initial combination therapy to reduce blood pressure might elevate the risk of adverse events, including dizziness and syncope.

Balancing risks and benefits

Considering the importance of blood pressure control, the advantages of reaching target blood pressure levels outweigh the risks associated with potential adverse events. Monitoring blood pressure control through frequent follow-up or home blood pressure monitoring is recommended.



Fig. 3. Hypertension management. BP, blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

13. LIPID MANAGEMENT

1. To evaluate the CVD risk, a serum lipid profile (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides, and LDL-C) should be conducted at the time of initial diabetes diagnosis and annually thereafter. [Expert opinion, general recommendation]
2. A serum lipid profile is conducted 4 to 12 weeks after initiation of pharmacological therapy to evaluate response and adherence to treatment. [Expert opinion, general recommendation]
3. The primary goal of lipid management is the control of LDL-C levels. [Randomized controlled trial, general recommendation]
4. To determine the LDL-C targets, comorbidities including CVD and end-organ damage (albuminuria, eGFR <60 mL/min/1.73 m², retinopathy, and left ventricular hypertrophy), major CVD risk factors (age, family history of premature coronary artery disease, hypertension, smoking, and HDL-C <40 mg/dL), and duration of diabetes should be initially assessed. [Expert opinion, general recommendation]
5. The LDL-C targets are as follows:
 - 1) In the presence of CVD, LDL-C levels should be less than 55 mg/dL, with a more than 50% reduction from the baseline. [Randomized controlled trial, general recommendation]
 - 2) If the duration of disease is 10 years or more, or major CVD risk factors or target organ damage, LDL-C level should be less than 70 mg/dL. [Non-randomized controlled trial, general recommendation]
 - 3) In the presence of target organ damage or three or more major CVD risk factors, LDL-C level should be less than 55 mg/dL. [Non-randomized controlled trial, limited recommendation]
 - 4) If the disease duration is less than 10 years and no major CVD risk factors are present, LDL-C levels should be less than 100 mg/dL. [Randomized controlled trial, general recommendation]
6. Active lifestyle modification is recommended for lipid management, with adherence monitored. [Randomized controlled trial, general recommendation]
7. If the LDL-C target level is not achieved, pharmacological therapy is initiated:
 - 1) Statins should be the first-line therapy. [Randomized controlled trial, general recommendation]
 - 2) If the target is not achieved with the maximum tolerable statin dose, ezetimibe should be added. [Randomized controlled trial, limited recommendation]
 - 3) In diabetic patients with CVD who do not achieve the target after adding ezetimibe, combination therapy with statins and proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors should be considered. [Randomized controlled trial, limited recommendation]
8. For severe hypertriglyceridemia (triglyceride levels ≥150 mg/dL), primary treatment should focus on lifestyle modification, including abstinence from alcohol, weight loss, and secondary factors such as glycemic control. [Non-randomized controlled trial, general recommendation]
9. In cases of severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL), pharmacological therapy with fenofibrates, omega-3 fatty acids, etc., is initiated to reduce the risk of acute pancreatitis. [Non-randomized controlled trial, general recommendation]

Recommendation 13.1 To evaluate the CVD risk, a serum lipid profile (total cholesterol, HDL-C, triglycerides, and LDL-C) should be conducted at the time of initial diabetes diagnosis and annually thereafter. [Expert opinion, general recommendation]

Recommendation 13.2 A serum lipid profile is conducted 4 to 12 weeks after initiation of pharmacological therapy to evaluate response and adherence to treatment. [Expert opinion, general recommendation]

Level of evidence

There are no RCTs regarding the timing and frequency of serum lipid tests for assessing CVD risk in the presence of diabetes [470]. However, CVD is a leading cause of mortality in diabetic patients, and evaluating lipid profiles for concomitant CVD risk factors in diabetic patients is recommended at the time of diabetes diagnosis and annually thereafter, according to accredited domestic and international clinical guidelines. Additionally, it is commonly recommended to conduct follow-up lipid tests before initiating medication for dyslipidemia and 4 to 12 weeks after initiation. Therefore, the level of evidence for this recommendation is considered 'expert opinion,' and since the benefit of the recommendation outweighs the harm, it is evaluated as 'general recommendation.'

Benefits

Dyslipidemia is actively targeted for treatment in diabetic patients because the risk of death from CVD is two to four times higher compared to non-diabetic individuals [471]. According to the Diabetes Fact Sheet 2022 by the KDA, 76.1% of T2DM patients in Korea have hypercholesterolemia, with only 53.5% of them reported to have LDL-C levels controlled within the target range (less than 100 mg/dL) [432].

For diabetic patients, it is recommended to conduct comprehensive serum lipid profile tests (measurement or calculation of total cholesterol, HDL-C, triglycerides, and LDL-C) at the time of diagnosis and annually thereafter to assess CVD risk [472]. Additionally, when initiating pharmacological therapy for dyslipidemia, it is recommended to measure serum lipid profile tests before starting medication and 4 to 12 weeks after administration to evaluate the medication's efficacy and adherence. Subsequently, testing every 3 to 12 months is recommended based on the patient's cardiovascular risk and the degree of lipid reduction after treatment [473].

Balancing the risks and benefits

The harms resulting from the implementation of the recommendation are not evident, and the adverse effects due to difficulties in assessing CVD risk without implementation are greater.

Alternatives and considerations

The dyslipidemia typically includes hypertriglyceridemia and low HDL-C levels in diabetic patients. With an increase in the production of large very low-density lipoproteins (VLDL),

there is a characteristic increase in small dense LDL particles, and an increase in the number of apolipoprotein B (apoB), even if the high LDL-C levels is not high. Therefore, in addition to routine lipid profile tests, evaluation of diabetic dyslipidemia can also involve measuring non-HDL-C and apoB [474]. Particularly, when tested in a non-fasting state, lipid status can be assessed using non-HDL-C (total cholesterol minus HDL-C) rather than LDL-C [473].

Recommendation 13.3 The primary goal of lipid management is the control of LDL-C levels. [Randomized controlled trial, general recommendation]

Recommendation 13.4 To determine the LDL-C targets, comorbidities including CVD and end-organ damage (albuminuria, eGFR <60 mL/min/1.73 m², retinopathy, and left ventricular hypertrophy), major CVD risk factors (age, family history of premature coronary artery disease, hypertension, smoking, and HDL-C <40 mg/dL), and duration of diabetes should be initially assessed. [Expert opinion, general recommendation]

Recommendation 13.5 The LDL-C targets are as follows:

- 1) In the presence of CVD, LDL-C levels should be less than 55 mg/dL, with a more than 50% reduction from the baseline. [Randomized controlled trial, general recommendation]
- 2) If the duration of disease is 10 years or more, or major CVD risk factors or target organ damage, LDL-C level should be less than 70 mg/dL. [Non-randomized controlled trial, general recommendation]
- 3) In the presence of target organ damage or three or more major CVD risk factors, LDL-C level should be less than 55 mg/dL. [Non-randomized controlled trial, limited recommendation]
- 4) If the disease duration is less than 10 years and no major CVD risk factors are present, LDL-C level should be less than 100 mg/dL. [Randomized controlled trial, general recommendation]

Level of evidence

For diabetic patients, the target for LDL-C control based on the presence of CVD has been derived through RCTs of primary and secondary cardiovascular prevention using pharmacological interventions, as well as systematic literature reviews and meta-analyses of these studies [475-479]. The level of evidence for the LDL-C control target based on the presence of CVD is 'RCT,' and since the benefits of the recommendation outweigh the harms, the recommendation grade is evaluated as 'general recommendation' [477-479]. For diabetic patients without CVD but with various target organ damage or CVD

risk factors, the level of evidence for the LDL-C control target is based on review of international clinical guidelines and a large-scale retrospective study conducted in Korean T2DM patients [480]. The threshold of less than 55 mg/dL is evaluated as 'limited recommendation' due to insufficient evidence supporting its universal application in all cases.

Benefits

In the UKPDS, LDL-C was the strongest predictor of coronary heart disease in T2DM patients among several risk factors for CVD, and each 39 mg/dL increase in LDL-C increased the coronary heart disease risk by about 60% [481]. The Heart Protection Study (HPS) showed that LDL-C lowering with statin therapy reduced the risk of major cardiovascular events by 22% compared to placebo in diabetic patients, regardless of the presence of previous CVD [482]. Subsequent analysis of the HPS secured evidence for the LDL-C target of less than 100 mg/dL in diabetic patients without CVD. Furthermore, in a meta-analysis of 14 RCTs conducted by the Cholesterol Treatment Trialists' Collaboration, it was found that for every approximate reduction of 39 mg/dL (1 mmol/L) in LDL-C with statin therapy, there was a 23% decrease in major cardiovascular events over 5 years, irrespective of baseline LDL levels or other baseline characteristics [483]. Since T2DM patients had a similar relative risk (RR) reduction as non-diabetic patients in this meta-analysis, considering that diabetic patients have a higher absolute risk of CVD, it can be inferred that the absolute benefit of LDL-C lowering with statin therapy may be even more significant.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER), and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trials have demonstrated that even when lowering LDL-C to below 70 mg/dL, further reduction in LDL-C reduces the risk of major cardiovascular events [484-486]. Moreover, subgroup analyses have shown that the reduction in RR is even greater in cases of diabetes [487] or similar to those without diabetes [488,489]. Therefore, diabetic patients with concomitant CVD are recommended to control LDL-C to below 55 mg/dL and achieve a reduction of over 50% from baseline, similar to other high-risk patient groups. In diabetic patients without CVD, the risk of CVD varies among patients. Factors such as duration of dis-

ease (over 10 years), albuminuria (urine albumin/creatinine ratio >30 mg/g), CKD (eGFR <60 mL/min/1.73 m²), retinopathy, neuropathy, and an ankle-brachial index <0.9 are well-known risk factors for CVD in diabetic patients [490]. The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines recommend to evaluate risk and provide treatment targets based on the presence of target organ damage, age, three or major risk factors (hypertension, dyslipidemia, smoking, obesity), and duration of diabetes [491].

Whether the risk of CVD in Korean diabetic patients can be evaluated using the same criteria as international guidelines is not entirely clear. However, a recent study utilizing data from the National Health Insurance Service observed 248,000 Korean patients with T2DM aged around 30.90 years over a 9.3-year follow-up period. In this study, it was found that the incidence rate of CVD, defined as myocardial infarction and stroke, increased in diabetic patients without previous CVD when CKD, hypertension, longer duration of disease, and major cardiovascular risk factors were present [480]. Specifically, the risk of CVD increased from an LDL-C level of 1.8 mmol/L (70 mg/dL) in patients with 1.2 major cardiovascular risk factors or a duration of diabetes of over 5 years. Notably, patients with CKD (18.3/1,000 person-years) or three or more major risk factors (14.1/1,000 person-years) showed similar or higher rates of CVD compared to those with previous CVD (14.1/1,000 person-years). It was analyzed that the incidence of CVD was lowest when LDL-C was below 55 mg/dL. Therefore, diabetic patients with a duration of disease of over 10 years or with major cardiovascular risk factors (age [men over 45, women over 55], family history of premature coronary artery disease [men under 55, women under 65], hypertension, smoking, HDL-C below 40 mg/dL), or with target organ damage (albuminuria, eGFR below 60 mL/min/1.73 m², retinopathy, left ventricular hypertrophy) are recommended to control LDL-C to below 70 mg/dL. Additionally, those diabetic patients with target organ damage or three or more major cardiovascular risk factors are selectively advised to consider lowering LDL-C to below 55 mg/dL.

Based on research indicating a decrease in mortality from CVD with an increase in HDL-C levels [492] the 2001 Adult Treatment Panel III (ATP III) guidelines categorized low HDL-C (less than 40 mg/dL) as a risk factor for CVD and included it as a diagnostic criterion for metabolic syndrome. While there is no specific upper limit for the treatment target of HDL-C, attention is directed towards low HDL-C as a risk factor for CVD [493].

Risks

The potential harms of implementing lipid concentration targets for CVD risk groups are unclear, but achieving target LDL-C levels often requires lifestyle modifications and drug therapy, particularly statins. Additionally, when combination therapy with medications other than statins is necessary to reach target concentrations, there may be associated risks of side effects from these medications.

Balancing the risks and benefits

Implementation of lipid control targets for CVD prevention is deemed to outweigh the potential harms associated with lifestyle modifications and medication use, considering the benefits for preventing CVD in diabetic patients.

Alternatives and considerations

In diabetic patients, the primary goal is to control LDL-C when implementing recommendations for lipid management targets. If LDL-C reaches the target but hypertriglyceridemia persists or if blood samples are taken in a non-fasting state, non-HDL-C or apoB can be used as targets [494]. The target level for non-HDL-C is the LDL-C target plus 30 mg/dL, and typically, in diabetic patients without other cardiovascular risk factors, the non-HDL-C target is less than 130 mg/dL, and apoB is less than 100 mg/dL.

Recommendation 13.6 Active lifestyle modification is recommended for lipid management, with adherence monitored. [Randomized controlled trial, general recommendation]

Level of evidence

The analysis included a systematic literature review of RCTs [494] and 11 RCTs described by Franz et al. [144]. The review by Franz et al. [144] 11 RCTs involving T2DM patients, and it appears to have conducted a thorough systematic search using various databases. The selection criteria were pre-specified, although it did not include judgments on the exclusion of individual studies or assessments of bias risks in the included studies. Combining this, the level of evidence was rated as 'RCT,' and since the benefits of the recommendation outweigh the risks, the recommendation grade was evaluated as 'general recommendation.'

Benefits

An RCT investigating the impact of the Mediterranean diet on

cardiovascular risk in individuals with T2DM or CVD risk factors showed that the risk of CVD decreased by 31% compared to the control group [144]. Lifestyle modifications, including dietary adjustments such as the Mediterranean diet and increased physical activity, as well as weight loss in obese patients, can improve lipid levels [495]. Dietary therapy should be individualized considering factors such as age, type of diabetes, medication use, lipid levels, and comorbidities. Consumption of saturated fat, cholesterol, and trans fats should be reduced, while intake of omega-3 fatty acids and fiber should be increased. Strict glycemic control can also improve lipid levels, particularly in cases where triglycerides are very high and glycemic control is inadequate. Additionally, abstaining from alcohol and weight loss are effective in treating high triglyceride levels.

Risks

The potential harms of active lifestyle modification remain unclear. In order to provide systematic education for active lifestyle modifications, it is necessary to secure adequately trained educational personnel, resources, and education time.

Balancing the risks and benefits

While RCTs have demonstrated that active lifestyle modifications improve blood lipid levels and prevent CVD, the risks associated with these interventions are unclear. Therefore, in diabetic patients with dyslipidemia, active lifestyle modifications are considered to clearly outweigh the risks, given their proven benefits in such cases.

Recommendation 13.7 If the LDL-C target level is not achieved, pharmacological therapy is initiated:

Recommendation 13.7-1 Statins should be the first-line therapy. [Randomized controlled trial, general recommendation]

Level of evidence

The analysis included a systemic review of RCTs [477,479,495] and Kearney et al.'s [483] description of 14 RCTs. Kearney et al.'s [483] review included only 14 RCTs involving 1,466 patients with T1DM and 17,220 patients with T2DM. They utilized various databases, suggesting a sufficiently systematic search, and predefined selection criteria. However, their review did not include judgments on the exclusion of individual studies or assessments of bias risks in the studies included. Considering this, the level of evidence was assessed as 'RCT,' and given

that the benefits of the recommendations outweigh the risks, the recommendation grade was evaluated as 'general recommendation.' Lipid management in diabetes is summarized in Fig. 4.

Benefits

In studies targeting diabetic patients, statin therapy showed significant effects in both primary and secondary prevention of CVDs. A prominent example of primary prevention study using statins in T2DM patients is the Collaborative Atorvastatin Diabetes Study (CARDS) [496]. In this study, targeting T2DM patients aged 40 to 75 with one or more cardiovascular risk factors, administration of atorvastatin 10 mg resulted in a 39% reduction in mean LDL-C to 72 mg/dL compared to baseline and a 37% reduction in the risk of cardiovascular events. Representative studies demonstrating the secondary prevention effects of statin therapy in T2DM patients with a history of CVDs include the Treating to New Targets (TNT) and Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT). In these studies, maintaining LDL-C at 57 to 77 mg/dL by administering atorvastatin 80 mg resulted in a significant reduction in cardiovascular events compared to maintaining it at 81 to 99 mg/dL with low-dose statin therapy [477,479]. Meta-analysis also showed that statin therapy in diabetic patients reduced the occurrence of cardiovascular events by up to 23% over 5 years when LDL-C was lowered by 1 mmol/L (38 mg/dL), regardless of baseline LDL-C levels or patient characteristics [483]. The benefits of statin therapy in this meta-analysis were similar in T1DM and T2DM.

Risks

1) Hepatotoxicity

A mild alanine aminotransferase (ALT) elevations occurs in 0.5% to 2.0% of cases, more commonly when using high-intensity or high-dose statins [497]. The use of statins does not worsen liver disease in patients with mild elevation of aminotransferases due to hepatic steatosis [498].

2) Myotoxicity

Among patients taking statins, there are cases where 10% to 15% complain of muscle pain, weakness, etc., and discontinue statin therapy [499]. The frequency of statin-induced muscle damage is reported to be 0.01% higher compared to control groups [500]. The most severe form is rhabdomyolysis, with a reported frequency of 13 per 100,000 person-years [501]. In

cases of rhabdomyolysis, creatine kinase levels typically increase more than 10 times the normal range.

3) Diabetes

Statin use has been linked to hyperglycemia and an increased risk of developing diabetes [500,502]. The new-onset diabetes during statin use is more common among older adults and those with risk factors such as high fasting blood glucose, obesity, or insulin resistance [503]. A meta-analysis of 13 RCTs with 91,140 participants showed a RR of 1.09 for new-onset diabetes during statin use. This means that for every 255 patients treated with statins over 4 years, one additional case of diabetes occurred, but 5.4 cases of vascular events were prevented [502].

4) Contraindication during pregnancy

Statins are categorized as Pregnancy Category X by the U.S. FDA and are contraindicated during pregnancy. A systematic review of 16 clinical studies on statin exposure during pregnancy did not show an increased risk of congenital anomalies in observational studies, although case series have reported congenital abnormalities [503]. However, due to insufficient data, statins should not be used in women who are pregnant or planning pregnancy.

Balancing the risks and benefits

The cardiovascular preventive benefits of statin therapy in diabetic patients have been well demonstrated through RCTs for primary and secondary prevention. While statin-induced diabetes has been reported, the preventive effects of statins are clear in populations at risk of CVDs. Therefore, even if diabetes occurs after statin use, continuing statin therapy while initiating diabetes treatment is beneficial for CVD prevention rather than discontinuing statins.

Alternatives and considerations

During statin use, a significant increase is defined as ALT levels rising to more than three times the upper limit of normal on two consecutive occasions. In such cases, discontinuation of the medication is recommended, and once the levels normalize, restarting with a low dose or trying a different medication is an option. If muscle pain, stiffness, weakness, or general fatigue occur during statin use, measuring muscle enzymes to assess for muscle damage is recommended. If rhabdomyolysis occurs, statin use should be discontinued.

Recommendation 13.7-2) If the target is not achieved with the maximum statin dose, ezetimibe should be added. [Randomized controlled trial, limited recommendation]

Level of evidence

The studies included in the analysis of the effects of statin and ezetimibe combination therapy on CVD in diabetic patients consist of a RCT targeting patients with acute coronary syndrome [484], a subgroup analysis of diabetic patients from this study [504], and a systematic review of seven RCTs [487]. The systematic literature review by Hong et al. [487] included 28,191 participants from seven RCTs, indicating thorough and systematic searches were conducted using various databases. Selection criteria were predefined; however, judgments on the exclusion of individual studies or assessments of bias risks in the included studies were not included. Consequently, the level of evidence for the combination of statin plus ezetimibe is classified as 'RCT', and as the recommendation benefits do not apply to all cases, the recommendation grade is evaluated as 'limited recommendation.'

Benefits

1) Statin and ezetimibe combination

Combining statin with ezetimibe can lower LDL-C by an additional 15.20% compared to statin alone [505,506]. A prominent study demonstrating the reduction in cardiovascular events with statin and ezetimibe combination therapy is IMPROVE-IT. This study targeted 18,144 patients hospitalized with acute coronary syndrome within 10 days of admission. In the group receiving statin and ezetimibe combination therapy, LDL-C was 15.8 mg/dL lower than in the statin alone group, and there was a 6.4% reduction in RR of cardiovascular events [484]. Subgroup analysis showed a 14% reduction in RR of cardiovascular events in diabetic patients, indicating a better preventive effect against cardiovascular events in diabetic patients [504].

There is currently no RCT specifically targeting diabetic patients without CVD to assess the combination effects of statin and ezetimibe. However, in a meta-analysis of seven RCTs targeting patient groups such as stable angina, acute coronary syndrome, CKD, and peripheral vascular disease, the risk of CVD decreased by 11% in the diabetic patient group. The effect was even more favorable compared to non-diabetic groups [487].

2) Combination therapy of statin with omega-3 or fibrate

In addition to ezetimibe, studies have investigated the combination therapy of statin with omega-3 fatty acids or fibrates, but these combination therapies have yet to show clear benefits. Results from studies aiming to assess the preventive effects of omega-3 fatty acids on CVD need to be more consistent. In the Reduction of Cardiovascular Events With EPA Intervention Trial (REDUCE-IT), combination therapy with a statin and eicosapentaenoic acid, one of the omega-3 fatty acids, demonstrated a preventive effect on CVD [202]. In this study, adding 4 g of icosapent ethyl to patients with hypertriglyceridemia already taking a statin resulted in a 25% reduction in CVD risk compared to statin monotherapy. The same effect was observed in the subgroup analysis focusing on diabetic patients. However, in the Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH) study, which included 70% diabetic patients, combination therapy with a statin and 4 g of omega-3 fatty acids did not show efficacy in preventing CVD [507].

There is debate regarding whether combination therapy of statin and fibrate to lower triglycerides and raise HDL-C is beneficial for T2DM patients. In the ACCORD study, combination therapy of statin and fibrate failed to reduce the risk of cardiovascular events compared to statin monotherapy. However, subgroup analysis indicated the potential for CVD prevention in groups with typical diabetic dyslipidemia (triglycerides ≥ 204 mg/dL and HDL-C < 34 mg/dL) [508]. Similar results were observed in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [509,510]. However, in the most recent Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study, treatment with pemafibrate in T2DM patients with dyslipidemia (95.7% were already taking statins) significantly improved lipid profiles, including triglyceride levels, but did not reduce the risk of CVD. This suggests limitations in reducing residual CVD risk with fibrate-induced triglyceride reduction.

Risks

The benefits of combining statin with ezetimibe need to be clarified. In RCTs, there was no difference in adverse reactions such as liver function abnormalities, muscle symptoms, and incidence of diabetes between statin monotherapy and combination therapy of statin and ezetimibe [484,487,504-506]. Combina-

tion therapy of statin and ezetimibe is associated with increased costs compared to statin monotherapy.

Balancing the risks and benefits

In diabetic patients with CVD who have not reached their target levels with statin monotherapy, the preventive benefits of adding ezetimibe have been confirmed through RCTs. It has been demonstrated that adding ezetimibe to statin therapy helps achieve target levels in diabetic patients without CVD who have not reached their goals with statin monotherapy, and this is expected to be beneficial for CVD prevention.

Alternatives and considerations

If the target LDL-C levels are not reached with statin monotherapy, considering the addition of ezetimibe, which incurs minimal cost increase, is prioritized.

Recommendation 13.7-3) In diabetic patients with CVD who do not achieve the target after adding ezetimibe, combination therapy with statins and PCSK9 inhibitors should be considered. [Randomized controlled trial, limited recommendation]

Level of evidence

Studies analyzing the effects of combination therapy with statins and PCSK9 inhibitors on CVD included RCTs targeting patients with CVD [485,486], subgroup analysis results of diabetic patients from these studies [488,489], and a systematic literature review including 39 RCTs [511]. The systematic literature review appears to have been conducted systematically using various databases, with predefined selection criteria; however, it did not include judgments on the exclusion of individual studies or assessments of bias risks in the included studies. Combining these findings, the evidence level is 'RCT,' and as the recommendation benefits do not apply to all cases, the recommendation grade is evaluated as 'limited recommendation.'

Benefits

In patients at high risk of CVD who are already using statins at maximum tolerated doses, or in T2DM patients, adding PCSK9 inhibitors such as evolocumab or alirocumab resulted in an additional reduction of LDL-C by 36% to 59% [512-514]. In the FOURIER study, which included 27,564 patients with CVD, adding evolocumab to statins led to a 59% reduction in LDL-C and a 15% reduction in the RR of CVD over the 2.2-year study period [485]. A subgroup analysis of 11,031 diabetic

patients in this study showed similar results [488]. The ODYSSEY OUTCOMES study, involving 18,924 individuals with a recent acute coronary syndrome, showed that adding alirocumab to statins significantly reduced the risk of CVDs by 15% over 2.8 years [486]. Similar results were also observed in a subgroup analysis targeting diabetic patients [483]. In a systematic literature review of 39 RCTs involving 66,478 participants, the PCSK9 inhibitor group showed no difference in overall mortality compared to the control group, but the risks of myocardial infarction, stroke, and coronary revascularization were significantly lower [511].

Risks

The risks of combination therapy of statin and PCSK9 inhibitor are not clear. In RCTs, there was no difference in adverse reactions such as liver function abnormalities, muscle symptoms, cognitive function, or incidence of diabetes when compared to statin monotherapy [485,486,511]. However, combination therapy with statins and PCSK9 inhibitors is associated with increased costs compared to statin monotherapy, and especially when compared to combination therapy with statins and ezetimibe, the cost increase is much more significant.

Balancing the risks and benefits

In diabetic patients with CVD who have not reached their target levels with statin monotherapy, the CVD prevention benefits of adding PCSK9 inhibitors in therapy have been confirmed through RCTs. While there is an increase in costs with combination therapy with PCSK9 inhibitors, it is judged that the benefits of combination therapy clearly outweigh the risks.

Alternatives and considerations

Currently, if LDL-C targets are not achieved with statins alone, consideration should be given to adding of a PCSK9 inhibitor, but only after an attempt has been made with ezetimibe.

Recommendation 13.8 For severe hypertriglyceridemia (triglyceride levels ≥ 150 mg/dL), primary treatment should focus on lifestyle modification, including abstinence from alcohol, weight loss, and secondary factors such as glycemic control. [Non-randomized controlled trial, general recommendation]

Recommendation 13.9 In cases of severe hypertriglyceridemia (triglyceride levels ≥ 500 mg/dL), pharmacological therapy with fenofibrates, omega-3 fatty acids, etc., is initiated to reduce the risk of acute

pancreatitis. [Non-randomized controlled trial, general recommendation]

Although there is much debate about whether hypertriglyceridemia is a risk factor for CVD, there is consensus that hypertriglyceridemia reflects the number of remnant lipoprotein particles, which are atherogenic factors other than LDL-C and is associated with an increase in small dense LDL particles, so the opinion that triglycerides are one of the risk factors for CVD is dominant [491,515]. Triglycerides are notably elevated in overweight, obese, have metabolic syndrome, or diabetic patients, and the 2001 ATP III guidelines suggested a cutoff of 150 mg/dL for diagnosing metabolic syndrome, recommending it as a target for triglyceride control [493].

In the case of hypertriglyceridemia, it is necessary to check whether there are secondary causes that can increase triglycerides (such as weight gain, alcohol consumption, excessive carbohydrate intake, CKD, diabetes, hypothyroidism, pregnancy, estrogen, tamoxifen, glucocorticoids, etc.) and genetic problems that can cause abnormalities in lipid metabolism. Lifestyle modifications such as weight loss, increased physical ac-

tivity, and MNT including abstinence are effective in treating hypertriglyceridemia and can reduce the risk factors for ASCVD in some patients [516]. If blood sugar is not controlled, hypertriglyceridemia worsens, and strict glycemic control can lower triglycerides. If there are secondary causes, prioritize treatment for the cause.

When triglyceride levels rise above 500 mg/dL, the risk of acute pancreatitis increases, so immediate drug therapy such as fibrates and omega-3 fatty acids may be considered along with a low-fat diet and abstinence to prevent acute pancreatitis. In cases where triglycerides are between 200 and 499 mg/dL, the primary treatment goal is the control of LDL-C according to cardiovascular risk, and lifestyle modifications and statin therapy are recommended as initial treatments to lower LDL-C below the target. Even after achieving the target LDL-C through lifestyle modifications and statin therapy, if triglycerides are still above 200 mg/dL, drug therapy such as fibrates and omega-3 fatty acids may be considered. If single-drug therapy for triglyceride control does not reach the target level, combination therapy may be considered.

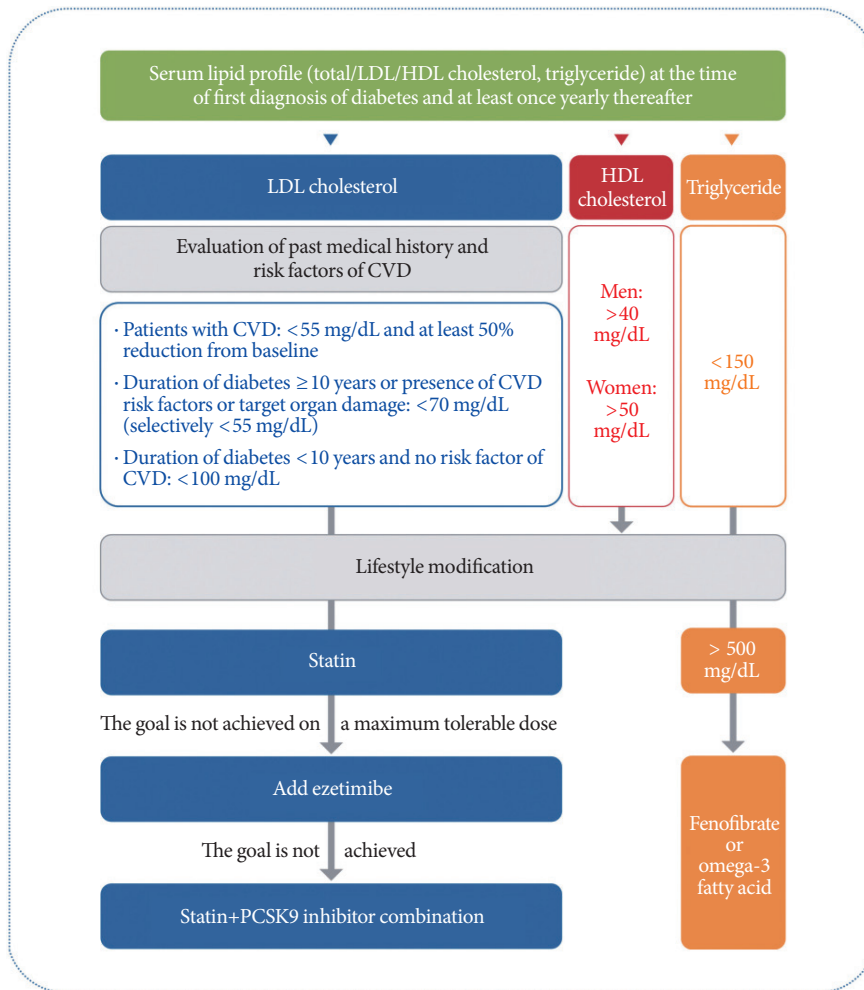


Fig. 4. Lipid management of diabetes. LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin 9.

14. ANTIPLATELET THERAPY

1. Aspirin (100 mg/day) is used for as a secondary prevention in adult diabetic patients with CVD. [Randomized controlled trial, general recommendation]
2. In adult diabetic patients with CVD who are allergic to aspirin, clopidogrel (75 mg/day) should be used. [Randomized controlled trial, limited recommendation]
3. Aspirin (100 mg/day) can be used as a primary prevention strategy for adult diabetic patients with a high risk of CVD, but a low risk of bleeding. [Randomized controlled trial, limited recommendation]

Recommendation 14.1 Aspirin (100 mg/day) is used for as a secondary prevention in adult diabetic patients with with CVD. [Randomized controlled trial, general recommendation]

Level of evidence

Considering the meta-analysis of numerous large-scale RCTs and 16 RCTs, the level of evidence was evaluated as ‘RCT’.

Benefits

The Anti-Thrombotic Trialists’ (ATT) study, which analyzed 16 secondary prevention studies involving over 17,000 individuals, found a significant reduction in serious cardiovascular events in the aspirin group compared to the control group (6.7% vs. 8.2%, $P < 0.0001$), with no difference observed based on gender. Additionally, there were fewer incidences of major coronary events (4.3% vs. 5.3%, $P < 0.0001$) and strokes (2.08% vs. 2.54%, $P = 0.002$) in the aspirin group [517].

Risks

In the ATT study, the occurrence of hemorrhagic strokes was slightly higher in the group using aspirin for secondary prevention but it was not statistically significant [517].

Balancing the risks and benefits

Administering aspirin for secondary prevention purposes yields greater benefits than risks. Therefore, it is recommended to use aspirin for secondary prevention in diabetic patients with a history of CVD.

Alternatives and considerations

The administration of aspirin for secondary prevention purposes is considered to yield more significant benefits than risks; however, caution is necessary regarding the risk of bleeding. Recent studies have been actively exploring the use of oth-

er antiplatelet agents besides aspirin or combination therapy with other antiplatelet agents or anticoagulants. For diabetic patients with acute coronary syndrome, the use of dual therapy combining aspirin with drugs like clopidogrel or ticagrelor targeting the P2Y₁₂ receptor for a certain period has been shown in various studies to increase the risk of major bleeding but can reduce the risk of CVD [518-520]. Recently, in large-scale clinical trials, the combination of aspirin and a non-vitamin K antagonist oral anticoagulant (NOAC) called rivaroxaban is superior in preventing CVD compared to aspirin monotherapy for diabetic patients with coronary artery disease or peripheral artery disease who have a low risk of bleeding [521-524]. However, while reducing overall mortality, this approach significantly increases the risk of bleeding, thus necessitating thorough consultation regarding both CVD prevention and bleeding risk before making a decision.

Recommendation 14.2 In adult diabetic patients with CVD who are allergic to aspirin, clopidogrel (75 mg/day) should be used. [Randomized controlled trial, limited recommendation]

Level of evidence

The level of evidence was evaluated as ‘RCTs’ since multiple RCTs and one meta-analysis study were assessed.

Benefits

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study assessed the efficacy of clopidogrel (75 mg) against aspirin (325 mg) among 19,185 individuals at high risk of recurrent cardiovascular events. The study showed sig-

nificant secondary prevention benefits for both aspirin and clopidogrel. Notably, clopidogrel achieved a RR reduction in myocardial infarction, stroke, and vascular disease-related death by 8.7% more than aspirin (annual incidence rate: 5.32% vs. 5.83%, $P=0.043$) [525]. Furthermore, a additional analysis of 3,866 diabetic patients showed that preventive effect of clopidogrel on CVD was superior to that of aspirin (incidence rate: 15.6% vs. 17.7%, $P=0.042$), indicating its potential as an alternative to aspirin [525]. In 2020, a meta-analysis involving 9,218 diabetic from six studies compared the secondary prevention effects of aspirin and clopidogrel and there were no differences in mortality rates, recurrent strokes, fatal cerebral infarctions, or risks of myocardial infarction between the two drugs [526].

Risks

In the CAPRIE study, the risk of all bleeding was similar between the aspirin and clopidogrel groups. However, incidences of GI bleeding (2.66% vs. 1.99%, $P<0.05$) and non-fatal cerebral hemorrhage (0.53% vs. 0.39%, $P<0.05$) were significantly higher in the aspirin group [525]. A subgroup analysis conducted in diabetic patients also showed a higher risk of bleeding in the aspirin group (2.8% vs. 1.8%, $P=0.031$) [527]. Moreover, a meta-analysis examining the secondary prevention effects of aspirin and clopidogrel in diabetic patients showed no difference in the risk of cerebral hemorrhage between the two drugs, with no analysis conducted for major or GI bleeding [526].

Balancing the risks and benefits

In diabetic patients, the use of aspirin and clopidogrel has been confirmed to have secondary prevention effects for CVDs. Especially, clopidogrel showed similar or better secondary prevention effects for CVDs compared to aspirin, and there was no difference in the risk of bleeding. Therefore, when aspirin is contraindicated or not tolerated, the benefits of using clopidogrel outweigh the potential harms.

Alternatives and considerations

Aspirin resistance can occur due to multiple alternative pathways that act independently of thromboxane A₂ in the platelet activation process, and it is more prevalent among diabetic patients [528]. A study of 1,045 diabetic patients from 11 hospitals in Korea also showed that 9.8% of patients exhibited aspirin resistance [529]. Considering this situation, the administration of other antiplatelet agents, such as clopidogrel, may be

an alternative.

Recommendation 14.3 Aspirin (100 mg/day) can be used as a primary prevention strategy for adult diabetic patients with a high risk of CVD, but a low risk of bleeding. [Randomized controlled trial, limited recommendation]

Level of evidence

Multiple RCTs and meta-analyses evaluating them were assessed, including high-quality, well-planned studies targeting diabetic patients specifically. Therefore, the level of evidence was evaluated as 'RCT'.

Benefits

The ATT study conducted a meta-analysis of six clinical trials examining the primary prevention effects of aspirin, involving approximately 4,000 diabetic patients out of 95,000 participants, and there was no difference in outcomes between diabetics and non-diabetics groups. The use of aspirin (75 to 500 mg) was associated with a 12% reduction in the incidence of overall cardiovascular events and a 23% reduction in non-fatal myocardial infarctions. However, the effects on cardiovascular death and stroke were minimal, with cardiovascular events reduced only in men and strokes reduced only in women [517]. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study aimed to observe the primary prevention effects of aspirin (81 to 100 mg daily) in 2,539 Japanese diabetic patients aged 30 to 85 years. Although no reduction in CVD risk with aspirin use was observed (HR, 0.80; 95% CI, 0.58 to 1.10; $P=0.16$), there was a significant reduction in patients aged 65 and older (HR, 0.68; 95% CI, 0.46 to 0.99) [530]. Recently, a series of large-scale clinical studies on the primary prevention effects of aspirin have been published. The A Study of Cardiovascular Events in Diabetes (ASCEND) study observed the effects of aspirin over 7.4 years in 15,480 diabetic patients aged 40 and older in the United Kingdom. The group using low-dose aspirin (100 mg daily) had a 12% lower incidence of serious vascular events compared to the control group (8.5% vs. 9.6%, $P=0.01$) [531]. In the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) study, which observed the primary prevention effects of aspirin in men aged 55 and older and women aged 60 and older with moderate cardiovascular risk but no history of diabetes or coronary artery disease and not at high risk of bleeding, no significant preventive effects on major cardiovascular events were [532]. Similarly, in the Aspi-

rin in Reducing Events in the Elderly (ASPREE) study, which tracked the effects of low-dose aspirin on primary prevention of cardiovascular events in individuals aged 70 and older residing in the United States and Australia for 4.7 years, aspirin did not significantly reduce cardiovascular events (RR, 0.95; 95% CI, 0.83 to 1.08). Among the participants, 11% had diabetes, and there was no difference in outcomes based on diabetes status [533].

In 2019, a meta-analysis based on 13 clinical trials, including recent large-scale studies such as ASCEND, ARRIVE, and ASPREE, was published. It analyzed 164,225 individuals without a history of CVD, of whom 19% (30,360 individuals) were diabetic patients. In the aspirin group, the risk of all cardiovascular events, myocardial infarction, and ischemic stroke decreased by 11%, 15%, and 19%, respectively, but there was no difference in cardiovascular mortality and overall mortality rates. However, subgroup analysis targeting diabetic patients only showed a 10% reduction in the efficacy variable of cardiovascular risk, with no difference in other risks [534]. Furthermore, another meta-analysis conducted exclusively on diabetic patients analyzed 33,679 individuals from 10 studies. The administration of aspirin did not reduce the risk of major cardiovascular events, overall mortality, mortality associated with antiplatelet use in CVD, myocardial infarction, or stroke [535]. Recent meta-analysis results, focusing on 34,069 diabetic patients from 10 studies and analyzed based on baseline cardiovascular risk, showed no risk reduction in the low-risk group but a 12% reduction in the risk of major cardiovascular events in the moderate/high-risk group [536].

Risks

In the ATT study, the use of aspirin for primary prevention was associated with an increased incidence of hemorrhagic stroke (RR, 1.32; 95% CI, 1.00 to 1.75; $P=0.01$), and although there were also numerous occurrences of major bleeding excluding intracranial hemorrhage (RR, 1.54; 95% CI, 1.30 to 1.82; $P=0.03$), most were non-fatal [517]. In the primary results of the JPAD study, there was no difference in bleeding risk between the low-dose aspirin group and the non-user group [529]. However, in the 10-year follow-up study published in 2017, there was no significant reduction in cardiovascular risk or increase in hemorrhagic stroke in the aspirin group. On the contrary, GI bleeding significantly increased

compared to the non-user group (2% vs. 0.9%, $P=0.03$) [537]. In the ASCEND study targeting diabetic patients, major bleeding events increased by 29% (4.1% vs. 3.2%, $P=0.003$), indicating a higher bleeding risk than the preventive effect on CVD [530]. Furthermore, in the ARRIVE study, the bleeding risk was 2.11 times higher in the aspirin group (95% CI, 1.36 to 3.28; $P=0.0007$), and in the ASPREE study targeting individuals aged 70 and older, the risk of major bleeding increased by 1.38 times (95% CI, 1.18 to 1.62; $P<0.001$) [532]. In a retrospective cohort study based on data from the National Health Insurance Service in Korea from 2005 to 2009, the effect of low-dose aspirin for primary prevention of ischemic stroke in diabetic patients aged 40 and older was analyzed. The use of low-dose aspirin (75 to 162 mg/day) actually increased the risk of hospitalization due to ischemic stroke by 1.73 times, and additional analysis on patients followed for more than 1 year showed a further increase in risk to 1.97 times [538]. A meta-analysis published in 2019 revealed that the use of aspirin increased the risk of major bleeding by 1.43 times, particularly significantly increasing the risk of major GI bleeding by 1.56 times. Subgroup analysis in diabetic patients showed a 1.29 times higher risk of major bleeding and a 1.35 times higher risk of major GI bleeding [534]. Other meta-analysis results, including only diabetic patients, also showed increases in the risk of major bleeding by 1.29 and 1.38 times, respectively [535,536].

Balancing the risks and benefits

The use of aspirin for primary prevention in individuals with diabetes should be carefully considered, balancing the cardiovascular benefits against the risk of bleeding. According to recent studies, aspirin use may lead to more adverse events than benefits in individuals over 70 years of age and those with a low cardiovascular risk. As of 2023, the ADA recommends aspirin for primary prevention in individuals with diabetes aged 50 years and older without a history of vascular disease who have at least one additional risk factor: a family history of premature ASCVD, hypertension, dyslipidemia, smoking, CKD, or albuminuria, and who are not at high risk for bleeding. The decision to use aspirin should be based on a thorough discussion about its potential for CVD prevention and the risk of bleeding [472].

15. HYPOGLYCEMIA MANAGEMENT

1. For individuals who are conscious and have a blood glucose level below 70 mg/dL (<3.9 mmol/L), administer 15 to 20 g of glucose and repeat the glucose intake if the blood glucose level has not returned to average 15 minutes after the treatment. [Expert opinion, general recommendation]
2. If an individual is unconscious or unable to self-treat hypoglycemia, an intravenous infusion of 10 to 25 g of glucose should be administered over 1 to 3 minutes. [Expert opinion, general recommendation]
3. To prevent recurrence of hypoglycemia in patients using insulin or insulin secretion stimulants, it is suggested to measure self-blood sugar periodically even after blood sugar levels return to normal and eat if necessary. Alternatively, it is suggested to educate children to consume additional snacks. [Expert opinion, general recommendation]
4. To facilitate the restoration of impaired hypoglycemia awareness, individuals who have experienced SH should be cautioned to exercise vigilance against hypoglycemic episodes for a duration spanning weeks to months. [Randomized controlled trial, general recommendation]
5. Individuals with recurrent SH, the use of a rtCGM device is recommended. [Randomized controlled trial, limited recommendation]
6. When caring for individuals at high risk for hypoglycemia, it is suggested to carefully identify and regularly assess changes in cognitive function. [Non-randomized controlled trial, general recommendation]
7. During each visit, clinicians should screen individuals for the risk of hypoglycemia and provide comprehensive education on prevention and treatment to those identified as high risk. [Randomized controlled trial, general recommendation]
8. Clinicians should utilize validated tools to assess hypoglycemia unawareness in patients exhibiting indicative symptoms. [Non-randomized controlled trial, general recommendation]

Recommendation 15.1 For individuals who are conscious and have a blood glucose level below 70 mg/dL (<3.9 mmol/L), administer 15 to 20 g of glucose and repeat the glucose intake if the blood glucose level has not returned to average 15 minutes after the treatment. [Expert opinion, general recommendation]

Recommendation 15.2 If an individual is unconscious or unable to self-treat hypoglycemia, an intravenous infusion of 10 to 25 g of glucose should be administered over 1 to 3 minutes. [Expert opinion, general recommendation]

Recommendation 15.3 To prevent recurrence of hypoglycemia in patients using insulin or insulin secretion stimulants, it is suggested to measure self-blood sugar periodically even after blood sugar levels return to normal and eat if necessary. Alternatively, it is suggested to educate children to consume additional snacks. [Expert opinion, general recommendation]

Level of evidence

The recommendation for treating hypoglycemia is based on expert opinion, thereby classifying the level of evidence as an 'expert opinion.' Given that the benefits of this recommendation significantly outweigh the risks, it is categorized as a 'general recommendation.'

Benefits

The goal of treating hypoglycemia is quickly detecting and addressing low blood glucose to alleviate symptoms and prevent

potential damage. Prompt and correct responses to hypoglycemic episodes can help avoid serious complications, such as cardiovascular and cerebrovascular issues. The initial step in responding to a hypoglycemia event is to consume simple sugars, specifically glucose, to elevate blood glucose levels quickly. A dose of 0.3 g of monosaccharide per kilogram of body weight is recommended during such an event. However, for individuals who are overweight, consuming this proportionate amount poses a risk of ingesting excessive carbohydrates. Thus, experts generally advise ingesting a fixed amount of 15 to 20 g of glu-

cose or carbohydrate foods of equivalent glucose content. One gram of glucose can raise blood glucose by about 3 mg/dL, and 15 to 20 g of simple sugars can raise blood glucose by about 45 to 60 mg/dL in 20 minutes, typically relieving symptoms. However, hypoglycemia can occur repeatedly, even after recovery from a previous episode, because hypoglycemic events can lower the body's glucose threshold and weaken the defense system. Additionally, the effects of insulin or insulin secretagogues may persist post-recovery. Continuous blood glucose monitoring and snacking or eating meals are crucial to prevent recurrence. In severe cases of hypoglycemia, where self-treatment is not possible, seeking emergency medical assistance for intravenous glucose administration of 10 to 25 g over a few minutes is necessary.

Risks

Overtreatment of hypoglycemia should be avoided to prevent rebound hyperglycemia and potential weight gain. However, high-level evidence-based clinical studies that examine the potential harms of overtreatment of hypoglycemia are currently lacking.

Balancing the benefits and risks

The recommendations for managing hypoglycemia are suggested by experts and have been used internationally for years among people with diabetes. For SH, particularly when individuals are unconscious or incapable of self-care, the treatment approach is specifically tailored to each stage of hypoglycemia to avoid inappropriate treatment, which could result in more significant harm, such as aspiration or delayed treatment. To diminish the risk of overtreatment and the consequent rebound hyperglycemia, it is essential to frequently monitor blood glucose levels, continuing even after recovery from a hypoglycemic episode.

Alternatives and considerations

Hypoglycemia, defined by low blood glucose levels that can harm an individual, has widely debated thresholds. Conducting high-quality studies on the definition and treatment of hypoglycemia presents ethical challenges, especially involving individuals at high risk for hypoglycemia who are in fragile health states. Historically, hypoglycemia has been defined as blood glucose levels less than 70 mg/dL [539], a threshold based on studies indicating the onset of counter-regulatory hormone secretion below this level. However, the validity of

the 70 mg/dL criterion as a hypoglycemic threshold is contested, as such levels can occur during physiological fasting. Medication-treated individuals might experience a lower threshold due to greater exposure to levels below 70 mg/dL compared to the general population [540]. Significantly, blood glucose levels below 54 mg/dL are unlikely in the absence of impaired hypoglycemic defenses and are associated with an increased risk of ventricular arrhythmias and mortality [541-543]. Consequently, an additional hypoglycemia level, defined as blood glucose below 54 mg/dL, has been recognized, leading to the classification into three levels: 'hypoglycemia alert value,' 'clinically significant hypoglycemia,' and 'SH.'

Symptoms of hypoglycemia can include feelings of thrill, anxiety, confusion, palpitations, and hunger. However, in instances of IAH, symptoms may not be present. Conversely, individuals with consistently high blood glucose levels may experience hypoglycemic symptoms even when their blood glucose is within the normal range. Dysregulation of counter-regulatory hormones or IAH, where the defense against hypoglycemia breaks down, can lead to severe consequences, such as loss of consciousness, seizures, coma, and even death, without warning signs of hypoglycemia. The occurrence of hypoglycemia during activities like driving or operating machinery could lead to severe accidents. Treatments high in fat, like chocolate or ice cream, are unsuitable for correcting hypoglycemia because they are absorbed too slowly to raise blood sugar levels effectively. In Korea, glucagon kits for treating SH are available through the Korea Center for Rare and Essential Drugs. For those experiencing frequent hypoglycemic episodes or at high risk for SH, having a glucagon kit at home for emergency use is advisable, and caregivers should be trained to administer it if necessary.

Recommendation 15.4 To facilitate the restoration of impaired hypoglycemia awareness, individuals who have experienced SH should be cautioned to exercise vigilance against hypoglycemic episodes for a duration spanning weeks to months. [Randomized controlled trial, general recommendation]

Level of evidence

A systematic literature review to identify studies focused on the treatment and prognosis of individuals suffering from IAH or SH was evaluated. The analysis incorporated one meta-analysis [544], three RCTs [260,545,546], and two expert opinions [547,548] regarding recovery from IAH. The majority of

research in this field has been centered on individuals with T1DM, with comparatively fewer studies addressing those with T2DM. This discrepancy is attributed to the elevated risk associated with T2DM due to factors like age, duration of diabetes, and the presence of comorbidities. As a result, there are fewer high-quality clinical studies in this population. The studies we analyzed ranged from moderate to high quality, predominantly RCTs. Hence, the evidence level is classified as a 'RCT.' Given that the benefits of the treatments and interventions discussed outweigh the risks, the recommendation level is considered a 'general recommendation.'

Benefits

After a severe hypoglycemic event, the body's threshold for detecting hypoglycemia decreases, potentially requiring weeks to months of avoiding hypoglycemia to reverse autonomic failure related to hypoglycemia [549]. Various studies have explored the effectiveness of educational, pharmacologic, and technological interventions in reversing IAH. In a follow-up analysis of the DAFNE clinical study, systematic education, including blood glucose monitoring and medication adjustment over 5 days, was conducted for patients with IAH to reduce the risk of hypoglycemia. This intervention decreased the risk of SH over a 12-month follow-up [548]. Additionally, the DAFNEplus study, which incorporated behavioral changes into the traditional educational framework, further enhanced its effectiveness. Moreover, a meta-analysis of eight studies found that structured educational programs significantly reduced the risk of SH in those with IAH. Given the association between SH, IAH, and increased risks of CVD, cognitive dysfunction, and mortality, it is crucial for those with IAH or a history of SH to take proactive measures to prevent further episodes. Healthcare professionals play a vital role in delivering targeted, structured education to aid individuals in recovering from IAH and prevent future hypoglycemic events.

Risks

No studies have been published that evaluate the effectiveness of increasing glycemic targets to prevent recurrent SH, cardiovascular events, and death in individuals with diabetes who have previously experienced SH. As a result, there is no concrete evidence indicating harm from adjusting glycemic targets upwards. However, the potential for harm due to hyperglycemia exists, particularly in individuals with severe glycemic fluctuations when glycemic control targets are elevated.

Balancing the benefits and risks

Individuals with diabetes who suffer from SH are at a heightened risk for CVD and mortality. IAH and recurrent SH are key risk factors for these adverse outcomes, highlighting the importance of preventing such episodes. Given the lack of extensive research on the adverse effects of increasing glycemic targets, the primary focus should be on preventing life-threatening hypoglycemia in those at high risk for IAH and SH. Episodes of SH necessitate medical attention, contributing to higher healthcare costs. Moreover, individuals with significant glycemic fluctuations face a risk of pronounced hyperglycemia if their glycemic targets are elevated for extended periods. Consequently, the decision to adjust glycemic targets upwards should be tailored and closely monitored, considering each individual's specific health profile.

Alternatives and considerations

Individuals who have experienced SH or have IAH are at an increased risk of recurrent hypoglycemic episodes, potentially leading to a compromised hypoglycemic defense mechanism and a cycle of repeated episodes. Recovery from such conditions is achievable, typically necessitating a period of 2 to 3 weeks without any hypoglycemic events, although it may take several months in some cases. This underscores the importance of preventing recurrence during this critical recovery phase. For those with T1DM experiencing IAH, frequent recurrent hypoglycemia, or SH, the use of insulin pumps and CGM systems is advised (refer to section 'Pharmacologic therapy for type 1 diabetes mellitus'). It is important to individualize glycemic control goals, educate individuals and caregivers about hypoglycemia, and actively monitor glycemic levels while adjusting the type and dose of hypoglycemic agents to prevent hypoglycemia. Recently, it has been suggested to raise glycemic targets in individuals at risk for hypoglycemia, even if they have not experienced IAH or SH. For those particularly susceptible to hypoglycemia, such as the elderly, underweight, those with renal dysfunction, or individuals with chronic or severe medical conditions, glycemic targets should be customized, aiming for an HbA1c level between 7.5% and 9.0%.

Recommendation 15.5 Individuals with recurrent SH, the use of a rtCGM device is recommended. [Randomized controlled trial, limited recommendation]

Level of evidence

The analysis encompassed one RCT focusing on the primary outcome of HbA1c reduction in adults with T1DM, two RCTs targeting adults with T2DM [550,551], and one meta-analysis [552]. These studies, comprising systematic reviews and RCTs, were identified as being of moderate to high quality. Consequently, their evidence level was classified as ‘RCTs,’ and the recommendations derived from these studies were categorized as ‘general recommendations,’ given that the anticipated benefits significantly outweighed any associated risks.

Benefits

In 2018, Heinemann et al. [553] conducted a study reporting a significant 72% reduction in hypoglycemia incidence among individuals with T1DM and IAH using rtCGM, without notable device-related adverse events. Similar positive outcomes for glycemic control in T1DM using CGM have been observed in other studies [550]. For individuals with T2DM on multiple insulin regimens, one study highlighted CGM’s role in decreasing SH instances [551]. Conversely, another investigation indicated that while rtCGM improved glycemic control for T2DM, it did not significantly affect hypoglycemia event reduction. These findings underscore the necessity for further investigation into rtCGM’s efficacy for T2DM (refer to section ‘Continuous glucose monitoring and insulin pumps’).

Risks

Aside from insertable continuous glucose monitors, the majority of CGM devices adhere to the skin, potentially causing contact dermatitis. Moreover, employing rtCGM to enhance IAH and mitigate SH risks necessitates extra resources, encompassing both the expenses associated with the devices and the need for trained personnel.

Balancing the benefits and risks

The advantages of using a rtCGM for managing recurrent episodes of SH significantly outweigh the potential risks. Unmanaged episodes can escalate into further cardiovascular and cognitive dysfunction, along with increased medical costs. Hence, the recommendation is to employ CGM for individuals who experience recurrent SH.

Recommendation 15.6 When caring for individuals at high risk for hypoglycemia, it is suggested to carefully identify and regularly

assess changes in cognitive function. [Non-randomized controlled study, general recommendation]

Level of evidence

The analysis encompassed two systematic reviews [554,555], two follow-up analyses of RCTs [556,557], and five observational studies [558-562]. Meta-analyses and RCTs were chosen to explore T1DM, while follow-up analyses of RCTs and observational studies were selected for T2DM due to the lack of high-quality meta-analyses or RCTs for this group. The link between hypoglycemia and cognitive dysfunction is particularly pronounced at both younger and older ages for T1DM and mainly at older ages for T2DM [555]. The studies on T2DM include research conducted in Korea [559]. The resulting recommendations are primarily aimed at elderly individuals with T2DM. Due to the incorporation of studies not deemed high quality for T2DM, the evidence was classified as ‘non-RCTs.’ Furthermore, the recommendation was labeled as a ‘general recommendation’ based on the assessment that the benefits of following it substantially outweigh the risks.

Benefits

The ADVANCE study revealed that individuals with cognitive decline faced over twice the risk of SH (HR, 2.1; 95% CI, 1.14 to 3.87) [556], while a follow-up analysis of the the Memory in Diabetes substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD-MIND) study indicated that cognitive dysfunction was linked to a 13% increased risk of SH [557]. Observational studies, including the Atherosclerosis Risk in Communities (ARIC) cohort study [560] and the Edinburgh Type 2 Diabetes Study [558], have documented that individuals who experience SH in T2DM are at a heightened risk for future cognitive dysfunction and dementia. In contrast, for T1DM, a systematic review of 61 studies demonstrated an association between hypoglycemia and cognitive dysfunction in individuals younger than 10 and older than 55 years [555]. Interestingly, adolescents through to middle-aged individuals in this group appeared more resilient to neuroglycopenia. The DCCT study, focusing on adolescents and middle-aged participants with T1DM, found no cognitive function differences despite more frequent SH in those receiving intensive treatment [563].

In Korea, a retrospective study using Korean National Health Insurance Service data analyzed the risk of Alzheimer’s disease and vascular dementia in individuals with T2DM who experi-

enced hypoglycemia, uncovering an increased risk compared to those without hypoglycemia episodes [559]. In addition, Korean studies have shown an increase in mortality and the incidence of acute cardiovascular events in individuals with diabetes and SH, not only in those with cognitive decline but also in those with cardiac decline, especially in individuals with T2DM [564]. These findings suggest that individuals with diabetes should be more vigilant regarding the occurrence of hypoglycemia and strive to prevent it by periodically evaluating cardiac function.

Risks

In the studies included in the analysis, no adverse effects were reported in relation to the advisories.

Balancing the benefits and risks

From the studies included in the analysis, it can be observed that hypoglycemia and cognitive dysfunction have a bidirectional influence on each other. Cognitive dysfunction weakens the body's defense system against hypoglycemia, increasing the risk of hypoglycemia, while the occurrence of hypoglycemia induces neuroglycopenia in the brain, causing short-term cognitive dysfunction and leading to long-term cognitive decline. In other words, cognitive dysfunction is a strong risk factor for the occurrence of hypoglycemia, making patients with impaired cognitive functions more susceptible to hypoglycemia and increasing the risk of severe cognitive impairments, such as dementia. Given these findings, it is crucial for healthcare providers and caregivers to regularly assess cognitive function in individuals with known or suspected cognitive decline and to educate them on preventing hypoglycemia. In the case of T1DM, particular attention should be paid to younger and older individuals who are more susceptible to cognitive impairments stemming from hypoglycemia. As such, monitoring for changes in cognitive function is especially crucial in these demographics, particularly after episodes of frequent hypoglycemia. This recommendation does not present a specific risk.

Alternatives and considerations

Standardized assessments suitable for clinical use should also be identified. Among the studies analyzed, the Mini-Mental State Examination (MMSE) is one tool that can be utilized in clinical settings to determine cognitive function through simple questions objectively. However, additional evidence and discussion are required to recommend an appropriate tool for

widespread use in assessing cognitive function in older adults with diabetes.

Recommendation 15.7 During each visit, clinicians should screen individuals for the risk of hypoglycemia and provide comprehensive education on prevention and treatment to those identified as high risk. [Randomized controlled trial, general recommendation]

Level of evidence

The analysis encompassed one systematic review and four RCTs. High-quality studies on the effect of systematic education on managing hypoglycemia have primarily been conducted in individuals with T1DM, aiming to improve IAH. Studies in T2DM are limited; however, an RCT was conducted in Korea to investigate the potential benefits of systematic education in improving hypoglycemia management among individuals with T2DM [561]. The studies analyzed were generally well-designed and executed, with a quality ranging from moderate to high. The studies included in this review were generally well-structured and implemented, exhibiting moderate to high quality. The collective evidence was thus categorized under the 'RCT' level, and the recommendation's scope was classified as 'general recommendation' because the benefits of the recommendation outweigh the potential harms.

Benefits

The significance of systematic education in diabetes self-management is widely acknowledged, with research primarily focusing on individuals with T1DM. These structured education programs cover essential aspects of diabetes care, including establishing glycemic targets, medication dosage adjustments, and carbohydrate intake calculations. Among studies evaluating the educational impact, one study on the effect on hypoglycemia was incorporated into the analysis. Programs such as HypoCOMPaSS, DAFNE, and HyPOS have demonstrated success in enhancing hypoglycemia awareness and reducing the occurrence of severe hypoglycemic episodes in individuals with T1DM, with these outcomes being highlighted in prior recommendations [260,548,565]. A systematic review involving 14 studies, including these programs, found that eight studies reported a decrease in hypoglycemic episodes among participants who received systematic education. Moreover, three of these studies highlighted that combining systematic education with medication adjustments and technological interventions could effectively prevent hypoglycemia [566].

Conversely, there are fewer high-evidence-level studies concerning the impact of education on hypoglycemia management in individuals with T2DM. An RCT conducted at a Korean university hospital assessed the effect of systematic education on managing hypoglycemia in individuals with T2DM treated with insulin or sulfonylureas. This study revealed that the intervention group exhibited improved hypoglycemia-related symptoms compared to the control group over 6 months following the education [567].

Risks

There are no harms associated with this recommendation.

Balancing the benefits and risks

Healthcare providers are advised to routinely question individuals with diabetes about any occurrences of hypoglycemia during visits, pinpoint potential risk factors, and proactively identify those at heightened risk. For individuals deemed at high risk, delivering tailored education on hypoglycemia prevention is essential, along with necessary adjustments in glycemic targets and the type and dosage of hypoglycemic medications. High-risk individuals must be informed about hypoglycemia's nature, symptoms, causes, and the steps to take if it happens. Achieving a balance between carbohydrate consumption, physical activity, and medication is crucial for hypoglycemia prevention. Education on managing these elements to avert hypoglycemia should be provided consistently and in a manner that is practical for individuals to implement. This recommendation is not associated with any specific adverse effects.

Recommendation 15.8 Clinicians should utilize validated tools to assess hypoglycemia unawareness in patients exhibiting indicative symptoms. [Non-randomized controlled study, general recommendation]

Level of evidence

The analysis encompassed two non-RCTs [568,569] and two RCTs [570,571]. The randomized trials focused on assessing the effectiveness of questionnaires or visual analog scales in diagnosing IAH, while the non-randomized trials compared these

diagnostic methods directly for IAH. Most of the studies analyzed were of moderate to high quality, well-designed, and well-conducted. Given the nature of the studies, the collective evidence was categorized under 'non-RCTs' for evidence level. Due to the benefits of the diagnostic recommendations surpassing the potential risks, the overall recommendation was given a 'general recommendation' status.

Benefits

Well-validated tools for assessing IAH include the GOLD score [570] and the Clarke score [571]. Both tools employ questionnaires to measure the frequency with which an individual notices symptoms of hypoglycemia and to document the actual blood glucose level at the time these symptoms occur. A score of 4 or higher on either assessment is considered indicative of IAH, with both tools demonstrating similar diagnostic rates for hypoglycemia unawareness [568].

Risks

There are no harms associated with this recommendation.

Balancing the benefits and risks

For individuals with diabetes, particularly those on insulin or medications that may cause hypoglycemia, experiencing hypoglycemia objectively during a clinical visit or through self-monitoring without noticing or reporting subjective autonomic symptoms is not uncommon. If IAH is confirmed, the implementation of education on the prevention and management of hypoglycemia, as discussed earlier, is essential to assist individuals in recovering from hypoglycemia unawareness.

Alternatives and considerations

No notable differences were found in the rates at which hypoglycemia was diagnosed using either the GOLD score or the Clarke score, suggesting both tools are equally effective for clinical use. However, the Clarke score might provide a more precise reflection of an individual's symptoms and hypoglycemia characteristics. Consequently, utilizing both diagnostic tools could enhance the reliability of identifying hypoglycemia compared to depending on a single method [569].

16. DIABETIC NEUROPATHY AND FOOT CARE

1. All people with diabetes should be screened for diabetic peripheral neuropathy (DPN) and autonomic neuropathy, starting at 5 years after diagnosis of T1DM and at the time of diagnosis of T2DM, and annually thereafter. [Expert opinion, general recommendation]
2. Screening for DPN should include the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ) and neurological examination (tests for vibration perception, ankle reflex, 10-g monofilament, pin-prick sensation, and temperature sensation). [Expert opinion, general recommendation]
3. In the presence of symptoms of diabetic autonomic neuropathy (such as resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, voiding dysfunction, urinary incontinence, sweating of the body trunk and face, or anhidrosis of the lower extremities), tests for cardiovascular autonomic neuropathy (CAN), GI autonomic nervous function, urodynamics, and sweating are required. [Expert opinion, limited recommendation]
4. Strict glycemic management is necessary, as adequate glycemic control prevents or delays the development and progression of DPN and CAN in both T1DM and T2DM. [Randomized controlled trial, general recommendation]
5. For individuals with painful diabetic neuropathy, assess the pain and initiate medical treatment to control pain and improve quality of life. [Randomized controlled trial, general recommendation]
6. For all individuals with diabetes, it is recommended to conduct an annual comprehensive assessment for risk factors of ulcers and amputation, and provide education on foot care. [Expert opinion, general recommendation]
7. Perform peripheral angiography in people with severe claudication, weak dorsal artery pulse, or an ankle-brachial index of ≤ 0.9 . [Randomized controlled trial, limited recommendation]
8. A multidisciplinary approach is required for diabetic foot ulcers (DFUs). [Expert opinion, general recommendation]

Recommendation 16.1 All people with diabetes should be screened for DPN and autonomic neuropathy, starting at 5 years after diagnosis of T1DM and at the time of diagnosis of T2DM, and annually thereafter. [Expert opinion, general recommendation]

Recommendation 16.2 Screening for DPN should include the MNSIQ and neurological examination (tests for vibration perception, ankle reflex, 10-g monofilament, pin-prick sensation, and temperature sensation). [Expert opinion, general recommendation]

Background

Diabetic neuropathy is the most common complication of diabetes with a lifetime prevalence of 60% in both T1DM and T2DM, presenting with various symptoms, either locally or systemically [572-574]. The fifth edition of 'Diabetes' by the KDA and the 2023 Standards of Care in Diabetes by the ADA recommend screenings for diabetic neuropathy in people with diabetes and conducting subsequent annual screening tests [572-574]. The prevalence of diabetic neuropathy in Korea was 25% to 53%, according to a multicenter study conducted by the Diabetic Neuropathy Study Group of the KDA and data from the Korean Health Insurance Review and Assessment Service (HIRA) [575-577]. Early diagnosis and management of neu-

ropathy in people with diabetes is essential for the following reasons [572-574]:

- (1) Diabetic neuropathy is a diagnosis of exclusion. Non-diabetic neuropathy may be treatable.
- (2) For symptomatic diabetic neuropathy, medical treatment may be an option.
- (3) About 50% of diabetic neuropathy is asymptomatic, which increases the risk of DFUs due to decreased sensation in the feet.
- (4) Diabetic autonomic neuropathy involves the entire body. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

A neurologic examination includes sensory and motor function tests. In diabetes, sensory nerves, including tactile, pain, temperature, vibration, and joint sensation, are more rapidly and severely damaged than motor nerves; therefore, sensory function tests are more important in diagnosing DPN. Abnormalities in large-myelinated nerve fibers can be assessed by light tactile, vibration, and joint sensations. In contrast, abnormalities in small-myelinated or unmyelinated nerves can be identified by assessing pain and temperature sensations. Of the neurologic tests, the 10-g monofilament test is the simplest and most used method [578].

The Michigan Neuropathy Screening Instrument (MNSI) is a screening tool designed to identify diabetic neuropathy. The MNSI consists of a brief 15-question survey about pain, temperature sensation, and tingling, among other neuropathy symptoms, and a neurological physical examination that includes an assessment of the foot for ulcers or deformities, ankle reflexes, vibrotactile testing with a 128 Hz tuning fork, and a 10-g monofilament test [578]. Therefore, people with diabetes should be screened for distal symmetrical polyneuropathy once a year with a neurologic examination (10-g monofilament test, vibrotactile testing, and ankle reflex test) and small-fiber function testing, such as thermosensory testing, and pin-prick testing [572-574,578,579]. Performing two or more of these tests can increase the diagnostic sensitivity for distal symmetrical polyneuropathy to more than 87% [579].

Neurological tests are likely to be subjective to both the examiner and the subject. Quantitative sensory neurologic testing, measuring vibration, temperature, and pain thresholds, may be used to compensate for this limitation, but these tests may also be subjective to some extent. Nerve conduction study provides the most accurate and objective assessment of peripheral neurologic function but requires skilled examiners and appropriate equipment. This study can be performed when the clinical presentations are atypical and the diagnosis uncertain to exclude other causes [572-574,578,579].

Diabetic autonomic neuropathy affects the sympathetic and parasympathetic neurons of the autonomic nervous system of multiple organs. Therefore, obtaining a detailed history, conducting a comprehensive physical examination and using the Composite Autonomic Symptom Score 31 (COMPASS 31) questionnaire is important in identifying various symptoms and signs of autonomic nervous system abnormalities [572,580].

Benefits

Screening for diabetic peripheral and autonomic neuropathy at the initial diagnosis of diabetes and initiating early treatment can delay and prevent the development of diabetic neuropathy, control neuropathic pain, improve quality of life, prevent diabetic foot disease, prevent and reduce amputations, reduce hospitalizations, and decrease mortality. Half of the people with diabetic neuropathy are asymptomatic, and neuropathic pain negatively affects the physical and psychological quality of life. Therefore, early diagnosis is critical for effective management of diabetic neuropathy.

Risks

As DPN is a diagnosis of exclusion, any signs or symptoms different from the typical presentation of diabetic neuropathy must be examined to exclude other causes [573]. Neurological examinations are likely to be subjective to the examiner and the subject. Quantitative sensory neurologic testing, which measures vibration, temperature, and pain thresholds, can be used to compensate for these limitations, but these methods may also be partly subjective. Nerve conduction study provides the most accurate and objective assessment of peripheral nerve function and can be performed when the clinical presentation is atypical and the diagnosis uncertain, to exclude other causes [573]. Quantitative sensory nerve testing and nerve conduction study can increase healthcare costs.

Balancing the benefits and risks

The benefits of screening for diabetic peripheral and autonomic neuropathy and performing tests, such as quantitative sensory nerve testing and nerve conduction study, to exclude other causes of neuropathy outweigh the harms (increased healthcare costs due to inappropriate diagnosis and testing). These benefits include delaying, preventing, and reducing the development of diabetic neuropathy and DFUs, reducing hospitalizations, and lowering mortality.

Recommendation 16.3 In the presence of symptoms of diabetic autonomic neuropathy (such as resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, voiding dysfunction, urinary incontinence, sweating of the body trunk and face, or anhidrosis of the lower extremities), tests for CAN, GI autonomic nervous function, urodynamics, and sweating are required. [Expert opinion, limited recommendation]

Background

Several clinical studies and meta-analyses have shown that CAN is an independent risk factor for cardiovascular mortality, arrhythmias, silent myocardial ischemia, major cardiovascular events, and myocardial dysfunction. Examination for early diagnosis of CAN should be considered in people with diabetes who experience symptoms of lightheadedness, palpitations, dizziness, or syncope upon standing [581-584]. Hypoglycemia unawareness can be associated with CAN, leading to SH, arrhythmias, and increased cardiovascular mortality [584, 585]. CAN can be diagnosed by symptoms and signs and evaluation of heart rate variability with respiration or Valsalva maneuver, and blood pressure variability upon standing [585-587]. Examinations such as GI autonomic nerve function tests, urodynamic studies, and sweating tests can be conducted to diagnose diabetic autonomic neuropathy, and treatment to improve symptoms and quality of life may be required in patients with diabetes presenting symptoms of diabetic autonomic neuropathy, such as gastroparesis with nausea and vomiting, constipation, diarrhea, fecal incontinence, erectile dysfunction, voiding dysfunction, urinary incontinence, sweating in the body trunk and face, or anhidrosis of the lower extremities [572,574].

Benefits

Early diagnosis of CAN may alleviate symptoms, reduce morbidity and mortality, and improve quality of life in patients with diabetes with symptoms and signs of CAN, such as tachycardia at rest and orthostatic hypotension. Similarly, early diagnosis of diabetic autonomic neuropathy with corresponding tests can improve symptoms and quality of life in patients with diabetes presenting with symptoms of autonomic neuropathy, such as gastroparesis with nausea and vomiting, constipation, diarrhea, fecal incontinence, erectile dysfunction, voiding dysfunction, urinary incontinence, sweating in the body trunk and face, or lower extremity anhidrosis.

Risks

Differential diagnosis is necessary as underlying comorbid conditions or drug effects/interactions may mimic symptoms or signs of CAN and other autonomic neuropathies. Many medications can directly or indirectly affect CAN and other autonomic neuropathies. Testing for CAN and other autonomic neuropathies may increase healthcare costs.

Balancing the benefits and risks

Since CAN is associated with increased morbidity and mortality, decreased quality of life, and limitations in daily activities, the benefits of conducting cardiovascular and other autonomic function testing and taking appropriate measures when symptoms appear outweigh the harms.

Recommendation 16.4 Strict glycemic management is necessary, as adequate glycemic control prevents or delays the development and progression of DPN and CAN in both T1DM and T2DM. [Randomized controlled trial, general recommendation]

Level of evidence

Several RCTs and meta-analyses have highlighted the importance of glycemic control in the treatment of diabetic peripheral and autonomic neuropathy. Many studies have shown that hyperglycemia and the severity of DPN are closely related and that aggressive glycemic control prevents and delays the development of diabetic neuropathy in people with T1DM [99,588-592]. In the DCCT, intensive glycemic control reduced the morbidity of peripheral and autonomic neuropathy to 50% to 60% in people with T1DM [589,590]. On the contrary, in people with T2DM, the effect of intensive glycemic control on neuropathy was reduced in some studies, while others reported no significant effect [99,593,594].

Benefits

For people with T1DM and some with T2DM, intensive glycemic control prevents and delays the development of diabetic peripheral and autonomic neuropathy. Alleviating neuropathic pain and DPN symptoms improves quality of life, aids nerve regeneration by preventing degeneration, and prevents severe complications such as limb loss.

Risks

Strict glycemic control does not prevent or delay the development of diabetic peripheral and autonomic neuropathy in all people with T2DM, and adverse events related to medication use for such intensive glycemic management may occur.

Balancing the benefits and risks

When comparing the benefits and risks of intensive glycemic control, the benefits outweigh the harms. Strict glycemic control is beneficial in the treatment of diabetic neuropathy; therefore, achieving and maintaining the target glucose level is es-

sential in the treatment of diabetic neuropathy.

Recommendation 16.5 For individuals with painful diabetic neuropathy, assess the pain and initiate medical treatment to control pain and improve quality of life. [Randomized controlled trial, general recommendation]

Level of evidence

For the medical treatment of diabetic neuropathy, RCTs on various drugs, such as those based on etiology, mechanism of action, or symptom control, were evaluated.

Benefits

Medical treatment of diabetic neuropathy is based on etiologic and symptomatic medications to reduce pain and improve quality of life by reducing sleep disturbances, depression, and anxiety. Etiologic agents for diabetic neuropathy include antioxidants (alpha-fatty acids, gamma-linolenic acid), vasodilators, benfotiamine, and aldose reductase inhibitors, and may help control neuropathic pain and improve clinical outcomes. Anticonvulsants ($\alpha 2\delta$ ligands), tricyclic antidepressants, and selective serotonin/norepinephrine (noradrenaline) reuptake inhibitors may be administered at the lowest initial dose and titrated afterward. Adding opioids to control neuropathic pain and improve quality of life may also be considered [595-609].

Risks

In some people, medications used for the treatment of diabetic neuropathy may not have any effect on pain control but instead cause adverse drug reactions (such as dizziness, drowsiness, lower extremity edema, weight gain, dry mouth, blurred vision, headache, voiding difficulty, increased intraocular pressure, palpitation, arrhythmia, orthostatic hypotension, and cardiac diseases).

Balancing the benefits and risks

The benefits of medical treatment of diabetic neuropathy outweigh the risks, and medications are beneficial in treating diabetic neuropathy. These medications can improve quality of life by alleviating pain and reducing sleep disturbances, depression, and anxiety.

Alternatives and considerations

Medications for diabetic neuropathic pain should be titrated gradually from the initial dose and monitored until the medi-

cation is effective. If symptoms persist, medications can be substituted or combined with those of different mechanisms of action. Adding opioids or nonpharmacologic therapies for pain control may also be considered.

Recommendation 16.6 For all individuals with diabetes, it is recommended to conduct an annual comprehensive assessment for risk factors of ulcers and amputation, and provide education on foot care. [Expert opinion, general recommendation]

Recommendation 16.7 Perform peripheral angiography in people with severe claudication, weak dorsal artery pulse, or an ankle-brachial index of ≤ 0.9 . [Randomized controlled trial, limited recommendation]

Recommendation 16.8 A multidisciplinary approach is required for DFUs. [Expert opinion, general recommendation]

Background

Several guidelines and meta-analyses have reported that DFUs can be prevented by routine screening, identifying high-risk groups, educating patients, families, and healthcare providers, proper footwear selection, and treatment of non-ulcerative lesions. Therefore, a comprehensive foot evaluation and foot care education are recommended as part of a routine foot examination, and additional angiographic studies, exercise therapy, medical treatment, and interventions may be considered in people with suspected peripheral vascular disease (i.e., severe claudication) [610-618].

All people with diabetes should have their foot inspected at every visit and assessed for risks of diabetic foot disease, including a history of foot ulcers or amputations, neuropathic and peripheral vascular disease symptoms, visual impairment, renal disease, smoking, and foot care routines. The neurologic examination should include a 10-g monofilament test to identify loss of protective sensation rather than to detect early signs of neuropathy. The 10-g monofilament test should be performed in combination with at least one of the following tests: needle-prick, temperature sensation or vibration sensation with a 128 Hz tuning fork, or ankle reflex. DPN, peripheral vascular disease, and abnormal foot weight-bearing can lead to foot ulcers and, eventually, amputation; therefore, early evaluation and diagnosis are essential.

Initial screening for peripheral arterial disease (PAD) includes a history of recently reduced walking speed, leg fatigue, claudication, and assessment of lower extremity pulses. For people with signs or symptoms of PAD, the ankle-brachial in-

dex should be calculated. Any abnormal results require further evaluation with angiographic studies, and exercise therapy, medical treatment, and interventions may be considered. In patients with diabetes, PAD is common and often asymptomatic. Therefore, ankle-brachial indices should be calculated in patients with diabetes over the age of 50 and may be considered for those younger than 50 who have other risk factors of PAD (smoking, hypertension, dyslipidemia, or a period of more than 10 years from the time of diabetes diagnosis) [610,613]. Any abnormal test findings or presence of severe symptoms must be referred for further angiographic studies. Foot ulcers and wounds may require treatment by a podiatrist or an orthopedics, vascular surgery, or rehabilitation medicine specialist experienced in diabetic foot care [610,613]. The standard care for DFUs includes antibiotics treatment, wound debridement, infection control, revascularization if necessary, and off-loading of the plantar ulcerations with total contact casts [615-618]. Adjunctive treatments include advanced wound therapies such as negative pressure wound therapy, hyperbaric oxygen therapy, topical growth factors, bioengineered cellular therapies using fibroblast and keratinocytes, bioengineered dermal replace-

ment therapy, and stem cell therapies [618].

Benefits

Foot ulcers and amputations are the result of diabetic neuropathy or PAD and are common major causes of morbidity and mortality in people with diabetes. Therefore, annual comprehensive foot assessment and foot care education may help the early detection and treatment initiation of diabetic foot disease in people with diabetes, delaying or preventing harmful outcomes and ultimately reducing hospitalization and mortality.

Risks

Additional angiographic studies for diabetic foot disease may lead to increased healthcare costs. Drug-related adverse events may occur, and in some cases, treatment may not be effective.

Balancing the benefits and risks

The benefits of comprehensive evaluation and angiographic studies for diabetic foot disease outweigh the harms; therefore, the aforementioned evaluation and studies should be performed.

17. DIABETIC RETINOPATHY

1. Optimal management of blood glucose levels, blood pressure, and lipids is recommended to reduce the risk or delay the progression of diabetic retinopathy. [Randomized controlled trial, general recommendation]
2. Screening plan:
 - 1) Individuals with T1DM should have an initial comprehensive eye examination, including a dilated peripheral fundus examination, within 5 years of diagnosis. [Expert opinion, general recommendation]
 - 2) People with T2DM should have an initial comprehensive eye examination, including a dilated peripheral fundus examination, at the time of diabetes diagnosis. [Expert opinion, general recommendation]
 - 3) Following the initial examination, annual eye screenings are recommended. However, if there is no evidence of retinopathy and glycemic indicators are within the goal range, screenings may be considered at 1 to 2 year intervals. [Randomized controlled trial, general recommendation]
3. Individuals of child-bearing potential with diabetes who are planning pregnancy should have an eye examination before pregnancy. [Randomized controlled trial, general recommendation]
4. Individuals with preexisting diabetes who are pregnant should have an eye examination within the first 3 months of pregnancy and receive counseling on the risks associated with the development and progression of diabetic retinopathy. Eye examinations should be monitored every 3 months and for 1 year postpartum. [Randomized controlled trial, general recommendation]
5. The use of aspirin for the prevention of CVD does not increase the risk of retinal hemorrhage. [Randomized controlled trial, general recommendation]
6. When retinopathy progresses to proliferative diabetic retinopathy (PDR), an immediate referral to an ophthalmologist for panretinal laser photocoagulation therapy is required. [Expert opinion, general recommendation]
7. Intravitreal injections of anti-vascular endothelial growth factor (VEGF) are an alternative to panretinal laser photocoagulation for some individuals with PDR. [Randomized controlled trial, limited recommendation]
8. For the treatment of diabetic retinopathy with macular edema, intravitreal injections of anti-VEGF or intravitreal dexamethasone implants are indicated. [Randomized controlled trial, general recommendation]

Recommendation 17.1 Optimal management of blood glucose levels, blood pressure, and lipids is recommended to reduce the risk or delay the progression of diabetic retinopathy. [Randomized controlled trial, general recommendation]

Benefits

The prevalence of diabetic retinopathy and PDR are 15.9%–35.4% and 6.1%–7.5%, respectively [619,620]. The duration of diabetes is the strongest predictor of the development and progression of diabetic retinopathy. Inadequate glycemic control constitutes a substantial risk factor. The correlation between the degree of glycemic control and diabetic retinopathy was clearly demonstrated in the DCCT. Additional risk factors include diabetic nephropathy, dyslipidemia, hypertension, and smoking. Furthermore, puberty and pregnancy are also impor-

tant risk factors in people with T1DM. Large-scale prospective RCTs, including the DCCT and the UKPDS, have demonstrated that maintaining nearly normal glucose levels through stringent glycemic control from the time of initial diabetes diagnosis can prevent or delay the onset of diabetic retinopathy [96,621]. Blood pressure control has also been shown to prevent or delay the development of diabetic retinopathy [442], however the ACCORD-eye study did not find additional benefits in lowering SBP to below 120 mm Hg [622]. Dyslipidemia is thought to contribute to the progression of diabetic retinop-

athy, with evidence from two large-scale studies indicating that fenofibrate may prevent or mitigate the progression of this condition [623,624].

Risks

The risks involved in managing blood sugar, blood pressure, and lipids are related to the potential adverse effects of pharmacological treatments.

Recommendation 17.2 Screening plan:

- 1) Individuals with T1DM should have an initial comprehensive eye examination, including a dilated peripheral fundus examination, within 5 years of diagnosis. [Expert opinion, general recommendation]
- 2) People with T2DM should have an initial comprehensive eye examination, including a dilated peripheral fundus examination, at the time of diabetes diagnosis. [Expert opinion, general recommendation]
- 3) Following the initial examination, annual eye screenings are recommended. However, if there is no evidence of retinopathy and glycemic indicators are within the goal range, screenings may be considered at 1 to 2 year intervals. [Randomized controlled trial, general recommendation]

Benefits

Early detection and treatment through routine screening are necessary to prevent vision loss, as people with PDR or macular edema may be asymptomatic. Based on studies showing that retinopathy accompanied by vision loss rarely occurs within 3 to 5 years of T1DM diagnosis, an initial dilated and comprehensive eye examination is recommended within 5 years of diagnosis. Based on research findings that retinopathy accompanied by vision impairment rarely occurs within 3 to 5 years after the onset of hyperglycemia, it is recommended that individuals with T1DM have an initial dilated fundus examination and comprehensive ophthalmic examination within 5 years of their diabetes diagnosis. People with T2DM, who may have had years of undiagnosed diabetes at the time of diagnosis, should have an initial dilated and comprehensive eye examination at the time of diagnosis. Recently, considering cost-effectiveness, there is an opinion that the screening interval can be extended for low-risk groups of diabetic retinopathy. The DCCT/EDIC study, which followed T1DM patients for over 30 years, shows that determining the screening interval based on the current retinal status and HbA1c levels could reduce the number of

screenings while still being efficient for diabetic patients without retinopathy [625]. Nonetheless, evidence supporting the extension of the screening interval beyond 1 year remains limited [626]. Therefore, if you have at least one normal result on an annual test and have good glycemic control, you may want to consider testing every 1 to 2 years [627]. If the screening test shows abnormal results, more frequent testing may be needed depending on the progression of the disease. Per the 2017 International Council of Ophthalmology (ICO) guidelines for diabetic retinopathy management, in countries with well-equipped medical resources like ours, recommended screening intervals include: diabetics without retinopathy every 1 to 2 years; those with mild non-proliferative diabetic retinopathy (NPDR) every 6 to 12 months; moderate NPDR every 3 to 6 months; severe NPDR every 3 months; PDR requiring further treatment should be screened monthly; and treated, stable PDR every 6 to 12 months [628]. When managing macular edema, the follow-up intervals should be adjusted based on the extent of involvement: non-center-involving macular edema warrants follow-ups every 3 to 6 months, while center-involving macular edema requires more frequent monitoring, every 1 to 3 months. For macular edema treated with anti-VEGF, monthly follow-ups may be necessary. It's imperative to tailor the follow-up interval to the individual's specific circumstances, taking into account factors such as the current state of the retina, any concurrent ocular conditions, systemic health issues, and socioeconomic factors.

Risks

Screening for diabetic retinopathy primarily consists of fundus photography, optical coherence tomography, and retinal angiography (fluorescein angiography). These non-invasive tests carry a minimal potential for harm. Although retinal angiography previously entailed a risk of adverse effects due to fluorescein dye injections, advancements in optical coherence tomography for retinal angiography have significantly reduced this risk to almost negligible levels. Thus, the considerations now are the duration and cost of the examination [629].

Recommendation 17.3 Individuals of child-bearing potential with diabetes who are planning pregnancy should have an eye examination before pregnancy. [Randomized controlled trial, general recommendation]

Recommendation 17.4 Individuals with preexisting diabetes who are

pregnant should have an eye examination within the first 3 months of pregnancy and receive counseling on the risks associated with the development and progression of diabetic retinopathy. Eye examinations should be monitored every 3 months and for 1 year postpartum. [Randomized controlled trial, general recommendation]

Benefits

Pregnancy can exacerbate the progression of diabetic retinopathy [630]. Therefore, individuals of child-bearing potential with diabetes who are planning pregnancy should have an eye examination in advance and be counseled about the risk of developing or aggravating diabetic retinopathy. During pregnancy, an eye examination should be received within the first 3 months, and follow-up tests should be conducted at appropriate intervals depending on the severity of retinopathy. The results show that the increased risk of diabetic retinopathy persists up to 12 months postpartum, thus thorough follow-up examinations are conducted for up to 1 year after childbirth [630]. On the other hand, individuals with gestational diabetes do not require eye examinations during pregnancy as they do not appear to be at increased risk of developing retinopathy during pregnancy [631]. The screening schedule may need to be adjusted to occur more frequently or occasionally depending on the patient's retinal status, among other factors. The indications and methods for panretinal photocoagulation are essentially the same as for the general patient population. There is a view that laser photocoagulation can be delayed until after delivery to allow for natural regression, but most still recommend immediate treatment due to the increased likelihood of intraocular hemorrhage during childbirth. Careful consideration is advised in deciding whether to treat diabetic macular edema, as it may improve postpartum, and laser treatment could potentially exacerbate the condition.

Risks

The risk of harm from eye examination in pregnant individuals is similar to that in the general diabetic retinopathy screening protocol and is not increased by pregnancy.

Recommendation 17.5 The use of aspirin for the prevention of CVD does not increase the risk of retinal hemorrhage. [Randomized controlled trial, general recommendation]

Benefits

Although there has been some controversy about whether aspirin use increases the risk of retinal hemorrhage in people with diabetic retinopathy, the Early Treatment Diabetic Retinopathy Study (ETDRS) reported that daily aspirin intake at 650 mg did not increase the risk of retinopathy progression or hemorrhage [632]. Therefore, the presence of diabetic retinopathy does not constitute a contraindication for the use of aspirin in preventing CVD or for other therapeutic purposes.

Risks

The hypothesis suggesting an increased risk of hemorrhage in diabetic retinopathy due to aspirin use is not supported, and the associated risks of aspirin usage align with the conventional risks observed with its medical administration.

Recommendation 17.6 When retinopathy progresses to PDR, an immediate referral to an ophthalmologist for panretinal laser photocoagulation therapy is required. [Expert opinion, general recommendation]

Benefits

The therapeutic effectiveness of panretinal photocoagulation has been proven by two major studies. The Diabetic Retinopathy Study (DRS) findings revealed that panretinal photocoagulation diminished the risk of severe vision impairment by 60% in individuals with PDR 2 years post-treatment [633]. In the ETDRS, although panretinal photocoagulation has not proven effective in mild or moderate non-proliferative retinopathy, it was found to be effective in patients with high-risk proliferative retinopathy, and it also reduced the risk of vision loss by 50% in patients with clinically significant macular edema [634].

Risks

Possible complications from panretinal photocoagulation can include peripheral visual field defects, macular edema, and retinal hemorrhage. Notably, peripheral visual field defects are reported in all instances of panretinal photocoagulation treatment and are irreversible [635].

Recommendation 17.7 Intravitreal injections of anti-VEGF are an alternative to panretinal laser photocoagulation for some individuals with PDR. [Randomized controlled trial, limited recommendation]

Benefits

The therapeutic efficacy of intravitreal anti-VEGF injection for PDR has been proven in two large-scale studies. In the Diabetic Retinopathy Clinical Research Network (DRCRN) study, administering ranibizumab to patients with PDR was not inferior in reducing vision loss compared to those who received laser photocoagulation, and it resulted in less peripheral vision decline, fewer vitrectomy procedures, and reduced occurrence of retinal edema [636]. In the clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy (CLARITY) study, patients with PDR treated with aflibercept showed visual outcomes that were not only not inferior but also superior to those who underwent laser photocoagulation [637].

Risks

Intravitreal injection of anti-VEGF for the treatment of PDR has the disadvantage of increasing the number of treatments and being less cost-effective than laser photocoagulation [638].

Recommendation 17.8 For the treatment of diabetic retinopathy with macular edema, intravitreal injections of anti-VEGF or intravitreal dexamethasone implants is indicated. [Randomized controlled trial, general recommendation]

Benefits

Intravitreal injection treatments of anti-VEGF agents such as bevacizumab, ranibizumab, and aflibercept are being used for the treatment of diabetic retinopathy. In particular, all three drugs have been proven to improve vision in patients with clinically significant macular edema [639]. Additionally, intravitreal injection of dexamethasone implants can be expected to reduce macular edema [640].

Risks

Possible risks of intravitreal injections of anti-VEGF include ocular complications such as endophthalmitis, which are managed with antibiotics and surgical interventions like vitrectomy [641]. There is controversy regarding the hypothesis that intravitreal injections of anti-VEGF increase the risk of CVD. It has been suggested that some of the anti-VEGF injected into the eye may enter the systemic circulation and increase the risk of CVD by inhibiting physiological VEGF, though this has not been proven [642]. Intravitreal injections of dexamethasone implants may have side effects, such as inducing cataracts or increasing the risk of elevated intraocular pressure [640].

18. DIABETES AND PREGNANCY

1. Optimal glycemic control is essential to minimize the risk of perinatal obstetric complications. [Non-randomized controlled trial, general recommendation]
2. During pregnancy, regular SMBG is recommended; glycemic goals are FPG <95 mg/dL, 1-hour postprandial glucose <140 mg/dL, and 2-hour postprandial glucose <120 mg/dL. [Expert opinion, general recommendation]
3. For pregnant women with diabetes, lifestyle correction, including MNT, is recommended. [Expert opinion, general recommendation]
4. Light exercise is recommended if not contraindicated. [Expert opinion, general recommendation]
5. Initiate insulin therapy if medical nutrition and exercise therapy do not achieve glycemic goals. [Randomized controlled trial, general recommendation]
6. For pregnant women with T1DM, rtCGM device is recommended to control blood glucose levels, reduce the risks of hypoglycemia, and improve obstetric outcomes. [Randomized controlled trial, general recommendation]
7. For pregnant women with pre-existing diabetes, starting aspirin therapy of 100 mg from 12 to 16 weeks of pregnancy is considered for the prevention of preeclampsia. [Randomized controlled trial, limited recommendation]
8. Women with gestational diabetes should have the 75 g OGTT at 4 to 12 weeks after delivery and should be screened for the development of diabetes and prediabetes annually thereafter. [Randomized controlled trial, general recommendation]
9. Mothers with gestational diabetes are advised to control their weight and breastfeed after childbirth to improve metabolic risk factors. [Randomized controlled trial, general recommendation]

Recommendation 18.1 Optimal glycemic control is essential to minimize the risk of perinatal obstetric complications. [Non-randomized controlled trial, general recommendation]

Level of evidence

Glycemic control during pregnancy has been reported to reduce the risk of perinatal complications, as evidenced by RCTs in pregnant women with T1DM and observational studies in other pregnant women.

Benefits

Diabetes itself and the degree of hyperglycemia are associated not only with an increase in perinatal complications for the mother and fetus and chronic complications in the pregnant woman but also with the risk of obesity, hypertension, and T2DM in the offspring [23,643-645]. The HAPO study has shown that higher glucose tolerance test values during pregnancy are continuously associated with an increased incidence of perinatal complications [30]. RCTs involving pregnant wom-

en with T1DM have demonstrated that effective glycemic control is associated with a reduced incidence of perinatal complications compared to inadequate control [646,647]. Additionally, observational studies have indicated that good glycemic management reduces the incidence of perinatal complications in pregnant women with both T1DM and T2DM [648].

Risks

This leads to an increase in the number of pregnant women who require treatment, particularly raising the risk of hypoglycemia in patients with T1DM.

Balancing the benefits and risks

Exposure to hyperglycemia during pregnancy is linked with increased short- and long-term complications. Therefore, the

benefits of glycemic control during pregnancy are significant. However, the goals for glycemic control should be carefully adjusted to mitigate the increased risk of hypoglycemia associated with treatment.

Alternatives and considerations

It is difficult to conduct RCTs on glycemic control targets in pregnant women, and since most results are based on observational studies, there is a need to adjust glycemic targets according to the type of diabetes and the individual circumstances of the patient.

Recommendation 18.2 During pregnancy, regular SMBG is recommended; glycemic goals are FPG <95 mg/dL, 1-hour postprandial glucose <140 mg/dL, and 2-hour postprandial glucose <120 mg/dL. [Expert opinion, general recommendation]

Level of evidence

Given the practical difficulties of conducting clinical studies, such as RCTs, recommendations have been made based on expert opinions.

Benefits

In normal pregnancies, FPG typically measures 70 mg/dL, 1-hour postprandial blood glucose is around 110 mg/dL, and 2-hour postprandial blood glucose stands at 100 mg/dL [649]. The approach follows the opinion that lowering the blood glucose levels of pregnant women with diabetes to levels close to those of normal pregnancies aims to reduce perinatal complications due to hyperglycemia [28]. Monitoring postprandial blood glucose levels, compared to monitoring fasting blood glucose levels, resulted in better glycemic control and a lower risk of complications such as preeclampsia [646,647]. SMBG allows for the assessment of glycemic management and the adjustment of insulin dosage.

Risks

There is a lack of large-scale clinical studies comparing the effects of monitoring pre-prandial and postprandial blood glucose. For pregnant women applying insulin pumps or basal insulin, it is necessary to monitor not only postprandial but also pre-prandial blood glucose levels. The uncertainty about the optimal timing of blood glucose measurements and the risk of hypoglycemia increases as insulin therapy is intensified to achieve target blood glucose levels. Therefore, it is necessary to individu-

alize the timing of blood glucose measurements and the range of target blood glucose levels according to the individual circumstances of the pregnant woman.

Balancing the benefits and risks

Failure to self-monitor or maintain glucose levels within the target range can elevate the risk of perinatal complications due to hyperglycemia. However, increasing insulin to achieve glycemic control targets can raise the risk of hypoglycemia. Therefore, the target blood glucose levels may need to be adjusted for pregnant individuals with IAH or those at high risk for hypoglycemia.

Alternatives and considerations

HbA1c can be measured regardless of fasting state and reflects the degree of blood glucose control over a relatively long period, making it a suitable target for glycemic control. However, pregnant individuals may have lower HbA1c values compared to non-pregnant individuals due to the shorter lifespan of red blood cells during pregnancy. Therefore, the interval between HbA1c measurements should be reduced to 1 month, aiming for a target of less than 6% or less than 7% if the risk of hypoglycemia is significant.

Recommendation 18.3 For pregnant women with diabetes, lifestyle correction, including MNT, is recommended. [Expert opinion, general recommendation]

Recommendation 18.4 Light exercise is recommended if not contraindicated. [Expert opinion, general recommendation]

Level of evidence

It is challenging to conduct RCTs on lifestyle modification in pregnant individuals, so the recommendation is based on expert opinion.

Benefits

During pregnancy, specialized medical nutrition education is recommended to ensure that individuals consume the necessary calories to support fetal growth and maternal health and to select the quantity and quality of carbohydrates to achieve glycemic control within the target range [650]. Education in medical nutrition can enhance food literacy, and choosing carbohydrates with a low glycemic index effectively controls postprandial glycemia [651,652]. Exercise can improve blood glucose levels, and moderate-intensity exercise can lower blood glucose

levels and reduce the need for insulin treatment [653]. Beyond glycemic control, exercise enhances the quality of life for pregnant individuals and improves cardiorespiratory fitness [654].

Risks

Carbohydrate restriction may lead to excessive fat intake, increasing insulin resistance, and the potential for fetal growth promotion [655]. It is important to be aware of contraindications to exercise, such as gestational hypertension, preterm rupture of membranes, preterm labor, cervical atony, uterine bleeding, and intrauterine growth restriction.

Balancing the benefits and risks

Personal preferences and culture highly influence food choices. Most clinical studies conducted to date have focused on Western populations, leading to inconsistencies with the situation of pregnant individuals in Korea. Therefore, it is essential to tailor the program to each individual while monitoring glycemia and fetal growth. Assessing contraindications to exercise must precede to prevent adverse effects associated with physical activity. Pregnant women using insulin require education and management strategies to address concerns about hypoglycemia due to exercise.

Alternatives and considerations

Along with MNT, lifestyle modifications such as increased physical activity or light exercise after meals are recommended, and education on weight management is also necessary for obese pregnant women [656]. Large-scale exercise intervention studies in this population are very limited, and general recommendations include 30 minutes of moderate aerobic exercise five times per week, or at least 150 minutes of exercise per week, supplemented by 10 to 15 minutes of brisk walking after each meal [650].

Recommendation 18.5 Initiate insulin therapy if medical nutrition and exercise therapy do not achieve glycemic goals. [Randomized controlled trial, general recommendation]

Level of evidence

In a meta-analysis focusing on gestational diabetes, insulin, and metformin were associated with fewer perinatal complications compared to sulfonylureas. The difference in perinatal complications between insulin and metformin remained unclear, yet insulin is recommended as the first choice since met-

formin crosses the placenta.

Benefits

The Metformin in Gestational Diabetes (MiG) study, which compared metformin to insulin in 751 individuals with gestational diabetes, found no difference in the incidence of perinatal complications. However, 46.3% of the group treated with metformin required insulin treatment, indicating a higher treatment failure rate with metformin [657]. In a meta-analysis, glibenclamide was found to be inferior to insulin or metformin in terms of neonatal weight, the percentage of overweight infants, and the incidence of neonatal hypoglycemia [658]. Insulin therapy is more likely to achieve target glycemia and is associated with a lower incidence of obstetric complications. Its use can be tailored according to the individual's condition, with flexible dosing options.

Risks

Insulin therapy carries a risk of hypoglycemia, necessitates more frequent hospital visits than nonpharmacologic treatments or oral hypoglycemic agents, and may not be favored by some individuals.

Balancing the benefits and risks

In two Cochrane meta-analyses published in 2017, there was no clear evidence that insulin treatment was superior to treatment with metformin or glyburide [659], and oral medications did not demonstrate a clear benefit over placebo [660]. Thus, these analyses did not establish the superiority of insulin treatment over other treatments. However, oral hypoglycemic agents, such as metformin and glyburide, cross the placenta [661] and are not recommended as the first-line treatment due to rates of treatment failure and concerns about infant weight gain during long-term follow-up [662]. Nonetheless, metformin may be considered if insulin is unavailable, but it is contraindicated in individuals at risk for placental insufficiency, preeclampsia, and intrauterine growth retardation [656].

Alternatives and considerations

While studies show effective results for oral hypoglycemic agents aside from insulin therapy, there is uncertainty regarding the long-term safety of oral hypoglycemic agents. In South Korea, the increase in medical costs associated with initiating insulin therapy is not as significant as in other countries, so the issue of limited medical resources for insulin therapy is rela-

tively minor. There is no clear superior result for the type and usage of insulin, indicating a need for individualization [663].

Recommendation 18.6 For pregnant women with T1DM, a rtCGM device is recommended to control blood glucose levels, reduce the risks of hypoglycemia, and improve obstetric outcomes. [Randomized controlled trial, general recommendation]

See section ‘Continuous glucose monitoring and insulin pumps,’ Recommendation 6.

Recommendation 18.7 For pregnant women with pre-existing diabetes, starting aspirin therapy of 100 mg from 12 to 16 weeks of pregnancy is considered for the prevention of preeclampsia. [Randomized controlled trial, limited recommendation]

Level of evidence

Pregnant individuals with diabetes are at increased risk for preeclampsia. The U.S. Preventive Services Task Force (USPSTF) recommends that low-dose aspirin be started at 12 weeks’ gestation in those at high risk for preeclampsia. However, meta-analyses have shown that aspirin doses of less than 100 mg have not been effective in preventing preeclampsia. Consequently, the ADA recommends initiating 100 mg of aspirin at 12 to 16 weeks’ gestation.

The studies included in the analysis comprised one meta-analysis [664], a secondary analysis of one meta-analysis [665], and a secondary analysis of two RCTs [666]. Depending on the study, the aspirin dosage was analyzed as either more than 100 mg per day or less than 100 mg per day in subgroups [664] or varied doses such as 80 mg [665,666]. The timing of aspirin administration was analyzed as before 16 weeks of pregnancy or after 16 weeks [664], or between 13 and 26 weeks [665,666]. The analysis method was a secondary analysis rather than a pre-planned analysis within RCTs, which could introduce the possibility of bias. Study populations identified individuals with diabetes as one of the risk factors for preeclampsia. Although no study focused exclusively on individuals with diabetes, some were specifically limited to those with diabetes and undergoing insulin therapy. Therefore, there is considerable heterogeneity in aspirin dosing and the study populations.

Benefits

Preeclampsia was analyzed as the primary outcome, with one meta-analysis sorting preeclampsia into preterm and term at 37

weeks [664]. Compared with placebo, aspirin treatment significantly reduced the RR of preterm preeclampsia to 0.62 (95% CI, 0.45 to 0.87), and doses of 100 mg or more of aspirin before 16 weeks’ gestation were found to be more protective, with a RR of 0.33 (95% CI, 0.19 to 0.57). Aspirin at a dose of 60 mg was associated with a significant reduction in preeclampsia only in individuals with stage 1 hypertension, with a HR of 0.61 (95% CI, 0.39 to 0.94) [665], and did not show a significant effect in analyses that include all races [666].

Risks

Aspirin crosses the placenta, and there is insufficient data regarding its safety for fetal development. There is a lack of studies involving Korean individuals with pre-existing diabetes, and based on the currently reported results, it is also not possible to determine whether aspirin prevents preeclampsia in mothers with aspirin resistance. Moreover, a secondary analysis of an existing meta-analysis found that aspirin use was associated with increased birth weight [667].

Balancing the benefits and risks

Diabetes before pregnancy is a significant risk factor for preeclampsia, which increases the risk of maternal organ damage, fetal growth issues, and preterm birth. Therefore, efforts should be made to prevent preeclampsia in mothers with pre-existing diabetes before pregnancy. The risk of preeclampsia is especially high in those who require insulin therapy or have high blood pressure. In a meta-analysis of existing studies, 100 mg of aspirin before 16 weeks was associated with a one-third reduction in the risk of preeclampsia in high-risk individuals [664], so aspirin use is recommended for those at high risk. However, there is a lack of data on long-term outcomes for the child, and uncertainty exists about the balance of benefits and harms. Therefore, the potential benefits and harms should be carefully considered in each individual’s condition.

Alternatives and considerations

RCTs of aspirin for the prevention of preeclampsia did not exclusively target individuals with diabetes but included them as part of the high-risk group for preeclampsia. The dosage and timing of aspirin administration varied. In the future, large-scale clinical studies are necessary to confirm the effectiveness and safety of different aspirin regimens in pregnant individuals with diabetes and to examine the long-term prognosis for the infant.

Recommendation 18.8 Women with gestational diabetes should have the 75 g OGTT at 4 to 12 weeks after delivery and should be screened for the development of diabetes and prediabetes annually thereafter. [Randomized controlled trial, general recommendation]

Level of evidence

A meta-analysis revealed a 10-fold increased risk of T2DM after delivery for individuals with gestational diabetes [668]. In a Korean observational study, nearly half of those with gestational diabetes developed T2DM within 10 years of delivery [669]. In a multivariate regression analysis, FPG levels did not predict T2DM development. However, blood glucose levels measured during a 2-hour OGTT were predictive of T2DM, necessitating the performance of the OGTT [670].

Benefits

Since individuals with gestational diabetes are at an increased risk of developing prediabetes and T2DM after childbirth, early diagnosis and treatment can prevent complications.

Risks

The OGTT may cause nausea or vomiting in some individuals and hypoglycemia in those who have undergone GI bypass surgery.

Balancing the benefits and risks

The incidence of T2DM after childbirth in individuals with gestational diabetes increases over time [669,671], making regular blood glucose testing recommended. However, there is a lack of evidence regarding the specific methods and frequency of testing. Fig. 5 is summarized the follow-up and care plan of pregnant women with diabetes.

Alternatives and considerations

The ADA recommends lifelong monitoring at 1 to 3 year intervals for individuals with a history of gestational diabetes. The suggested methods include an annual HbA1c test, an annual FPG test, or a glucose tolerance test every 3 years, tailored to the individual's specific situation [656].

Recommendation 18.9 Mothers with gestational diabetes are advised to control their weight and breastfeed after childbirth to improve metabolic risk factors. [Randomized controlled trial, general recommendation]

Level of evidence

Individuals with gestational diabetes face a 10-fold increased risk of developing T2DM after childbirth [668] and a 2-fold increased risk of CVD [672,673]. Therefore, active efforts to improve cardiovascular risk factors are essential [671]. Weight management [674] and lactation [675,676] have been shown to reduce the risk of developing T2DM. A meta-analysis examining the effectiveness of postpartum lifestyle interventions in preventing T2DM found improvements in glycemic and insulin resistance markers, though a reduction in the incidence of T2DM was reported in only one of 11 studies [677].

Benefits

Individuals who have experienced gestational diabetes are at an increased risk for metabolic diseases and can reduce their risk of T2DM and CVD through lactation and lifestyle modifications. Breastfeeding benefits for fetal immunity, brain development, and the prevention of autoimmune diseases. It also supports maternal health by helping to reduce the risk of postpartum depression, uterine cancer, and breast cancer.

Risks

Mastitis may occur during lactation. The goals for lifestyle and weight management are unclear.

Balancing the benefits and risks

The risks associated with weight management and lactation are small compared to their benefits.

Alternatives and considerations

The benefits of lactation are supported by meta-analyses [676]. Among the 11 RCTs on postpartum lifestyle interventions [677], the intervention period was mostly short, with seven studies lasting less than 6 months, two studies for a year, and two studies for more than a year. Additionally, eight studies did not conduct follow-up observations after the intervention ended. There is a need for additional studies with long-term follow-up to assess the benefits of lifestyle interventions.

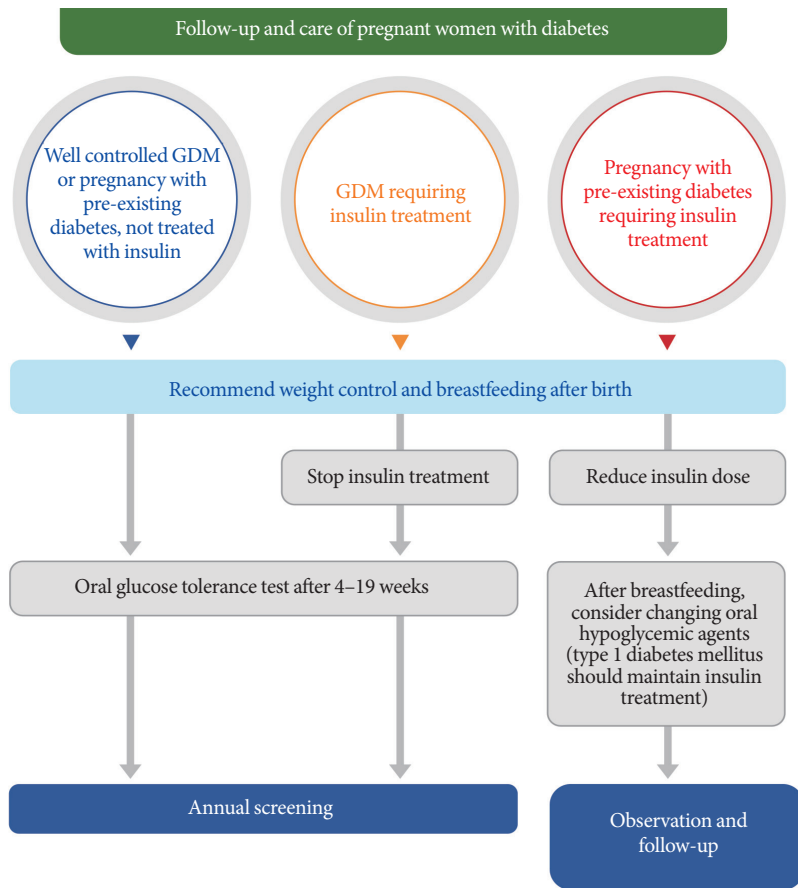


Fig. 5. Follow-up and care of pregnant women with diabetes. GDM, gestational diabetes mellitus.

19. DIABETES IN OLDER ADULTS

1. Complications or comorbidities of diabetes should be evaluated in older adults, and comprehensive geriatric assessment should be performed to check functional autonomy and degree of aging. [Expert opinion, general recommendation]
2. The glycemic goal is an HbA1c <7.5% but should be individualized considering an older adult's health condition or degree of aging. [Expert opinion, general recommendation]
3. Optimal nutrition and protein intake and regular exercise are recommended for older adults because these can help prevent CVD and improve the quality of life and control blood glucose levels. [Randomized controlled trial, general recommendation]
4. Upon determining the therapy, consider the risk of hypoglycemia, and avoid excessive or complicated therapy by checking whether any factors affect adherence to the drugs. [Non-randomized controlled trial, general recommendation]
5. Individualize the screening tests for complications and emphasize the dysfunction evaluation. [Expert opinion, general recommendation]
6. Individualize treatments or drugs for the CVD risks based on general health. [Expert opinion, general recommendation]
7. CGM should be recommended for older adults with T1DM to reduce the risk of hypoglycemia. [Randomized controlled trial, general recommendation]
8. For T2DM patients on a multiple insulin injection regimen, continuous glucose measurements should be considered to improve glycemic control and glycemic variability. [Randomized controlled trial, limited recommendation]

Recommendation 19.1 Complications or comorbidities of diabetes should be evaluated in older adults, and comprehensive geriatric assessment should be performed to check functional autonomy and degree of aging. [Expert opinion, general recommendation]

Although diabetes is a highly prevalent health condition in older adults, it is a highly heterogeneous condition compared to the younger population. Therefore, a comprehensive geriatric assessment should be conducted beyond current glycemic status, comorbidities, and diabetic complications. This includes aspects of the geriatric syndrome such as nutritional status, visual and auditory function, urinary function, basic and instrumental activities of daily living, as well as mental functions like cognitive and emotional health [108]. Environmental factors such as economic and social support systems, living conditions, and polypharmacy should also be considered [678-680].

Of particular importance in the elderly is the assessment of frailty, characterized by a progressive decline in muscle strength, autonomic function, and resilience, leading to an overall decrease in functional performance and a reduced ability to maintain homeostasis, thus increasing the risk of dependency. Frailty cannot be solely defined by overt diseases alone and requires a comprehensive assessment, though its application in clinical

practice can be challenging. No perfect frailty indicator exists to date, however, a three-level categorization of the overall health status adopted by the ADA in 2012 is widely used (in the United States as healthy/complex/very complex, in Europe as good/intermediate/poor, and in Japan as category I/II/III) [680-683]. This guideline also suggests the convenience of utilizing the Korean Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale (normal/pre-frail/frail) and the Clinical Frailty Scale [678], with the understanding that clinical settings require adjustments considering various risk factors [683].

Recommendation 19.2 The glycemic goal is an HbA1c <7.5% but should be individualized considering an older adult's health condition or degree of aging. [Expert opinion, general recommendation]

While reducing the risk of hypoglycemia is paramount in older adults, efforts to lower blood glucose should still be made be-

cause hyperglycemia above 200 mg/dL increases the risk of dehydration, electrolyte imbalance, urinary tract infections, dizziness, falls, and hyperglycemic events (hyperosmolar hyperglycemic state [HHS]/DKA). However, some studies have reported that health benefits may not be as significant as expected and individual satisfaction severely compromised compared to efforts to maintain adequate glycemia, making it difficult to emphasize strict glycemic control [684,685]. In the absence of large-scale clinical studies on appropriate glycemic targets in older adults, countries with advanced aging populations have proposed higher glucose control targets through expert consensus.

Older adults nearing end-of-life may be considered for minimal treatment to manage only symptoms of hyperglycemia. Glycemic control targets based on the degree of frailty and the use of medications with a high risk of hypoglycemia based on international guidelines, but these targets are not based on complete evidence. Glycemic targets for older adults should be individualized based on assessing health status, including life expectancy and degree of frailty, and thoroughly discussing with the individual and caregivers [686,687].

Recommendation 19.3 Optimal nutrition and protein intake and regular exercise are recommended for older adults because these can help prevent CVD and improve the quality of life and control blood glucose levels. [Randomized controlled trial, general recommendation]

Exercise and MNT can help manage glycemia, blood pressure, lipids, and weight goals in older adults. Therefore, it is important to assess physical activity and dietary and nutrition status, provide education to enable appropriate exercise, and facilitate access to MNT [686-688]. For those who are not frail, 150 min/week of moderate-intensity aerobic exercise is recommended. However, the type, intensity, and frequency of exercise should be individualized based on individual health status [688,689].

Education, including MNT, is crucial for diabetes management. Older adults may face challenges in managing their diet due to unfavorable eating habits, dental issues, decreased taste, GI dysfunction, and economic or environmental difficulties. Therefore, healthcare providers must continually educate individuals, taking into account their usual dietary habits, health status, and economic and environmental factors, to enable personalized MNT. It is particularly important to ensure adequate protein intake. MNT is recommended as a fundamental measure for improving quality of life and managing cardiovas-

cular risk [686,689].

Recommendation 19.4 Upon determining the therapy, consider the risk of hypoglycemia, and avoid excessive or complicated therapy by checking whether any factors affect adherence to the drugs. [Non-randomized controlled trial, general recommendation]

Special caution is required when prescribing medications or monitoring their effectiveness in frail individuals. Older adults are more susceptible to hypoglycemia, the symptoms of which can be difficult to recognize promptly, and recovery from hypoglycemia is slower. Therefore, medications with a high risk of hypoglycemia should be avoided, and if the use of sulfonylureas or insulin is necessary, start with a low dose and gradually increase it [686,690].

Metformin can cause anorexia, so it should be started at a low dose, and consider reducing or discontinuing the agent if associated symptoms arise in individuals already taking metformin. Thiazolidinediones should be used with caution as they can exacerbate congestive HF and increase the risk of fractures. DPP-4 inhibitors are commonly recommended for older adults due to their low risk of hypoglycemia and minimal side effects, without increasing major cardiovascular events.

GLP-1RAs are beneficial for people with diabetes with ASCVD, but their side effects significantly increase in people over 60 without ASCVD [691]. SGLT2 inhibitors require caution due to the risk of dehydration and weight loss, yet offer benefits for ASCVD, HF, and CKD, with these benefits also confirmed in the elderly [291,292].

Once-daily basal insulin is appropriate for most people starting insulin therapy. Multiple daily insulin injections can be considered, but the regimen should be simplified as much as possible for frail individuals or those in poor health.

Recommendation 19.5 Individualize the screening tests for complications and emphasize the dysfunction evaluation. [Expert opinion, general recommendation]

Screening for diabetes complications in older adults should be individualized. Older adults may have comorbidities associated with diabetes (hypertension, coronary artery disease, stroke, etc.) as well as various functional impairments associated with geriatric syndromes (polypharmacy, depression, cognitive impairment, incontinence, falls, pain, etc.) [445,551,692,693]. Individuals in the aging population may exhibit a wide range of

clinical or functional characteristics depending on the presence of these conditions or disorders. Particular emphasis should be placed on screening for complications that could develop over a short period or significantly impact functional status [108]. This includes assessing the risk of falls and dental health problems.

Recommendation 19.6 Individualize treatments or drugs for the CVD risks based on general health. [Expert opinion, general recommendation]

For elderly patients with diabetes, controlling other cardiovascular risk factors may be more effective in reducing morbidity and mortality than strict glucose control alone (Table 9) [694, 695]. While managing blood pressure has been relatively emphasized due to its direct effect on reducing major cardiovascular events without a legacy effect, older adults also have a higher risk of adverse effects from blood pressure control, which warrants caution [445]. For older adults with a long life expectancy who are active, motivated, and without cognitive impairments, a similar goal (140/90 mm Hg) as for younger adults should be set, and education and treatment methods should be provided accordingly [692]. On the other hand, for older adults with advanced diabetic complications, limited life expectancy, or severe cognitive and functional impairments, it may be preferable to aim for a higher target (150/90 mm Hg) [292]. ACE inhibitors are sometimes recommended as first-line treatment for people with diabetes over 65.

Management of dyslipidemia becomes more effective as the

absolute risk of CVD increases. Therefore, it should be highly considered in older adults with high absolute risk, though the evidence is not as robust as for blood pressure treatment. Statins have been proven effective and with minimal side effects in people with diabetes over 65 [693,696].

Recommendation 19.7 CGM should be recommended for older adults with T1DM to reduce the risk of hypoglycemia. [Randomized controlled trial, general recommendation]

Level of evidence

One RCT (Wireless Innovation for Seniors With Diabetes Mellitus [WISDM]) involving adults with T1DM aged 60 years [697] and older and another RCT (Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes [DIAMOND]) involving adults aged 60 years and older with T1DM and T2DM taking multiple insulin injections were analyzed [551]. Studies with a mean age of less than 65 were excluded. We excluded studies with a mean age of less than 65 years. Although the number of studies is limited, as the outcomes were similar to those of RCTs in younger adults, the quality of evidence was considered high. The recommendation was rated as a general recommendation because it is considered appropriate to apply the findings broadly.

Benefits

In adults with T1DM aged 65 years and older, several observational studies have indicated the ability of CGM to identify

Table 9. Individualization of glycemic control goals (glycosylated hemoglobin) in the elderly [678]

Categories	I	II	III
Patient characteristics/evaluation methods			
K-FRAIL [694,695]	Robust	Prefrail	Frail
Clinical frailty scale	1–3	4–6	7–9
General characteristics	Cognitively normal and able to live independently	Have mild cognitive impairment or need help with activities of daily living	Moderate dementia, impaired ability to perform activities of daily living, severe medical conditions, or nursing home residency
Use of medications that increase the risk of hypoglycemia			
No	<7.0%	<7.5%	<8.0%
Yes	7.0%–8.0%	7.0%–8.0%	7.5%–8.5%

Adapted from Won et al. [678].

K-FRAIL, the Korean version of fatigue, resistance, ambulation, illnesses, and loss of weight (FRAIL) scale.

those at higher risk of hypoglycemia. The WISDM study randomized adults with T1DM aged 60 years and older 1:1 to CGM or glucose self-monitoring to compare the percentage of time spent below 70 mg/dL over 6 months. The CGM group had a reduction from 5.1% to 2.7%, while the glucose self-monitoring group increased from 4.7% to 4.9%. There was a -1.9% (95% CI, -2.8% to -1.1%) small but significantly lower daily proportion of time with glucose levels less than 70 mg/dL in the CGM group. The glycemic variability was also reduced in the CGM arm, with an 8.8% (95% CI, 6.0% to 11.5%) increase in the proportion of blood glucose levels between 70 and 180 mg/dL [697]. The DIAMOND study compared the effectiveness of rtCGM with glucose self-monitoring in adults with T1DM and T2DM aged 60 years and older on multiple insulin injections. In the CGM group, glycemia improved slightly (HbA1c difference $-0.4\% \pm 0.1\%$, $P < 0.001$) and the glucose variability decreased (CGM group 34%→31%, glucose self-monitoring group 34%→33%; $P = 0.02$). However, no significant difference was seen in the daily proportion below 60 mg/dL between the groups [551].

Considering these studies, CGM is considered beneficial for predicting and reducing hypoglycemia risk in older adults with T1DM, and its use is recommended.

Risks

Potential risks associated with device use include contact dermatitis and discomfort at the attachment site. CGM is more expensive than glucose self-monitoring, and adequate education is required to ensure accurate use and interpretation of results.

Balancing the benefits and risks

While the risks associated with CGM use are minimal, the benefits of reducing hypoglycemia risk and improving glycemic control are substantial.

Alternatives and considerations

If CGM is not available, more frequent glucose self-monitoring can be advised. CGM serves as a means of checking glucose levels and is critical for adjusting insulin doses. However, specialized and structured training is required to maximize these effects. The analyzed studies utilized rtCGM, and the efficacy of intermittently scanned CGM (isCGM) has not been established.

Recommendation 19.8 For T2DM patients on a multiple insulin injection regimen, continuous glucose measurements should be considered to improve glycemic control and glycemic variability. [Randomized controlled trial, limited recommendation]

Level of evidence

A single RCT (DIAMOND) including adults over 60 years of age with T1DM and T2DM who received multiple daily insulin injections was analyzed. Although it was the only study, it showed similar results to RCTs in younger adults, thus the level of the evidence was considered high. However, due to the insufficient research specifically targeting older adults with T2DM and its practical difficulties, a limited recommendation was rated.

Benefits

The DIAMOND study compared the effectiveness of rtCGM with glucose self-monitoring in adults with T1DM and T2DM aged 60 years and older on multiple insulin injections. In the CGM group, glycemia improved slightly (HbA1c difference $-0.4\% \pm 0.1\%$, $P < 0.001$) and the glucose variability decreased (CGM group 34%→31%, glucose self-monitoring group 34%→33%; $P = 0.02$) [551]. However, no significant difference was seen in the daily proportion below 60 mg/dL between the groups. As in T1DM, CGM may be beneficial for glycemic control in older adults with T2DM on multiple daily insulin injections.

Risks

Potential risks associated with device use include contact dermatitis and discomfort at the attachment site. CGM is more expensive than glucose self-monitoring, and adequate education is required to ensure accurate use and interpretation of results.

Balancing the benefits and risks

While the risks associated with CGM use are minimal, the benefits of reducing hypoglycemia risk and improving glycemic control are substantial.

Alternatives and considerations

If CGM is not available, more frequent glucose self-monitoring can be advised. CGM serves as a means of checking glucose levels and is critical for adjusting insulin doses. However, specialized and structured training is required to maximize these effects. The analyzed studies utilized rtCGM, and the efficacy of isCGM has not been established.

20. MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

1. Screening for diabetes should be considered after the onset of puberty or ≥ 10 years of age in overweight or obese children with risk factors for diabetes. [Expert opinion, general recommendation]
2. Children and adolescents diagnosed with T2DM should initiate lifestyle modification and be educated by a team comprising experts, along with their families or caregivers. [Non-randomized controlled trial, general recommendation]
3. The HbA1c goal for children and adolescents with T2DM is $<7.0\%$. [Expert opinion, general recommendation]
4. Initial pharmacologic therapy can be started with metformin monotherapy, insulin monotherapy, or a combination of both. [Expert opinion, general recommendation]
5. Immediate insulin therapy should be considered if ketosis/ketonuria/ketoacidosis is present, the HbA1c is $\geq 8.5\%$, or the blood glucose level is ≥ 250 mg/dL. [Expert opinion, general recommendation]
6. For children and adolescent diabetics without diabetes symptoms and an HbA1c level of $<8.5\%$, treatment can be started with metformin alone. [Expert opinion, general recommendation]
7. If metformin alone does not achieve the glycemic goal, basal insulin should be used concomitantly. [Expert opinion, general recommendation]
8. If metformin and basal insulin treatment do not achieve the glycemic goal, MDIs or insulin pumps should be used. [Expert opinion, general recommendation]
9. Liraglutide can be administered to youth aged ≥ 12 years with T2DM who have a stage II or higher obesity ($\geq 120\%$ of the 95th percentile of BMI). [Randomized controlled trial, limited recommendation]
10. Poor glycemic control or presence of comorbidities in youth with T2DM who have a stage II or higher obesity ($\geq 120\%$ of the 95th percentile of BMI) may require bariatric surgery with considerations to the growth state of the youth. [Non-randomized controlled trial, limited recommendation]
11. For youth with T2DM, routine evaluation of comorbidities and microvascular complications is conducted starting at the time of diagnosis. [Other trial, general recommendation]
12. For youth with T2DM, routine assessments for depression, anxiety, eating disorders, sleep apnea, and sleep disorders should be conducted. [Uncontrolled studies, general recommendation]
13. Youth with T2DM should be transferred to an adult clinic at an appropriate time. [Expert opinion, general recommendation]

Recommendation 20.1 Screening for diabetes should be considered after the onset of puberty or ≥ 10 years of age in overweight or obese children with risk factors for diabetes. [Expert opinion, general recommendation]

Level of evidence

Expert opinion.

Benefits

The incidence of T2DM in children and adolescents has been

increasing recently [698,699]. Overweight or obesity is common, and their onset tends to occur around puberty. Furthermore, signs and symptoms of insulin resistance (such as melanocytosis, hypertension, dyslipidemia, and polycystic ovary syndrome), rapid catch-up growth in infants born small for

gestational age, prenatal exposure to maternal diabetes or gestational diabetes, and a first- or second-degree family history of T2DM are risk factors for developing T2DM [257,700]. Therefore, screening for prediabetes and T2DM is recommended after the onset of puberty or ≥ 10 years of age in children and adolescents with the above risk factors. Screening tests include FPG, 2-hour plasma glucose of an OGTT, and HbA1c [701]. Screening should be conducted at least every 3 years in normal BMI, but more frequently in increased BMI. Given the rise of T2DM in the children and adolescent age groups, rapid progression of β -cell deterioration, and rapid development of complications, screening in at-risk populations is necessary.

Risks

Undiagnosed T2DM in children and adolescents is rare. The diagnostic criteria for prediabetes and diabetes in children and adolescents are the same as in adults, but further research on pediatric diabetes is needed. The USPSTF recently reported that there is insufficient evidence to support screening for prediabetes and T2DM in the general pediatric population [702].

Balancing the benefits and risks

In Japan, it has been reported that about 15% of T2DM occur in individuals who are not obese [703], and in Taiwan, about half of the adolescents diagnosed with T2DM were not obese [704]. According to domestic reports on asymptomatic T2DM newly diagnosed through urine glucose testing during student health examinations, only 38.5% were obese [705]. Therefore, it is common for Korean children and adolescents with T2DM to be non-obese, and differentiation between T1DM and T2DM is essential.

Recommendation 20.2 Children and adolescents diagnosed with T2DM should initiate lifestyle modification and be educated by a team comprising experts, along with their families or caregivers. [Non-randomized controlled trial, general recommendation]

Level of evidence

There are no RCTs on education in youth with T2DM; therefore, this recommendation is based on treatments for T1DM and adult T2DM. Non-RCTs of lifestyle interventions in children and adolescents with T2DM were noted.

Benefits

Intensive lifestyle modification should be initiated at the time

of T2DM diagnosis [700]. The diagnosed youth and their family members should be educated on diabetes self-management. Moreover, weight loss should be achieved through medical nutrition and exercise therapy [706,707]. Since there are no RCTs on lifestyle modification in pediatric T2DM, lifestyle modifications in diabetic youth have been based on treatments for T1DM and adult T2DM. A 7% to 10% reduction of excess body weight is recommended [257]. Children and adolescents with T2DM are recommended to engage in at least 60 minutes of moderate- to vigorous-intensity exercise daily, with muscle- and bone-strengthening exercises three times per week, and to avoid sedentary behaviors. MNT should focus on healthy eating patterns. Obesity and complications of T2DM in children and adolescents increase with age [708,709]; therefore, weight loss through lifestyle modification may improve obesity and delay the development of complications.

Risks

No lifestyle intervention-related adverse effects have been reported in children and adolescents with T2DM. However, an increase in obesity levels has been observed in obese children and adolescents where lifestyle modification was not adequately implemented [710].

Balance the benefits and risks

By participating in lifestyle modification through diabetes education appropriate for their circumstances and environment, both children and adolescents with diabetes and their families can expect good outcomes.

Recommendation 20.3 The HbA1c goal for children and adolescents with T2DM is $< 7.0\%$. [Expert opinion, general recommendation]

Level of evidence

The HbA1c goal for children and adolescents with T2DM is derived from expert opinions and RCTs of pediatric T1DM and adult T2DM.

Benefits

Hypoglycemia is rare in pediatric T2DM [711]. Even though glucose levels may initially be well-regulated, maintaining control tends to become challenging as time progresses [712]. Additionally, there is an increased risk of developing complications related to diabetes [708]. Considering the prolonged nature of the disease in these young individuals, it is crucial to set

stricter goals for glucose control. HbA1c should be measured every 3 months. In children and adolescents with T2DM, the target HbA1c is less than 7.0%. However, a lower target, such as 6.5%, can be set for those without SH and treatment-related side effects. Although no long-term follow-up studies of glycemic control targets in pediatric T2DM have been conducted, lower mean HbA1c has been associated with fewer diabetic complications [708].

Risks

A low HbA1c target may increase the risk for hypoglycemia. However, in children and adolescents with T2DM, the risk of hypoglycemia is low even with insulin use.

Balancing the benefits and risks

A target HbA1c of below 7.0% in pediatric T2DM is reasonable, but this goal should be individualized based on each individual's circumstances. Less stringent HbA1c goals may be considered if there is an increased risk for hypoglycemia.

Recommendation 20.4 Initial pharmacologic therapy can be started with metformin monotherapy, insulin monotherapy, or a combination of both. [Expert opinion, general recommendation]

Recommendation 20.5 Immediate insulin therapy should be considered if ketosis/ketonuria/ketoacidosis is present, the HbA1c is $\geq 8.5\%$, or the blood glucose level is ≥ 250 mg/dL. [Expert opinion, general recommendation]

Recommendation 20.6 For children and adolescent diabetics without diabetes symptoms and an HbA1c level of $< 8.5\%$, treatment can be started with metformin alone. [Expert opinion, general recommendation]

Level of evidence

Expert opinion.

Benefits

Metformin and insulin are the only T2DM medications licensed in Korea for administration in pediatric and adolescent age groups. Initial pharmacologic therapy can be started with metformin monotherapy, insulin monotherapy, or a combination of both, depending on the youth's blood glucose level and metabolic abnormalities, such as ketosis [257,700]. Metformin is the initial pharmacologic treatment of choice in asymptomatic and metabolically stable youth with normal renal function and HbA1c of less than 8.5%. In youth with HbA1c of $\geq 8.5\%$,

a blood glucose level of ≥ 250 mg/dL, or ketosis/ketonuria/ketoacidosis, immediate insulin treatment should be started. The presence of acidosis, ketonuria, ketoacidosis, or HHS warrants treatment with intravenous insulin. In insulin therapy, long-acting insulin is started at 0.25 to 0.5 U/kg daily and adjusted every 2 to 3 days, and metformin may be added after acidosis has been resolved. Initial insulin therapy can usually be discontinued within 2 to 6 weeks and replaced by metformin and lifestyle modification. Metformin can be titrated up to a maximum dose of 2,000 mg daily, depending on blood glucose levels. In marked hyperglycemia, insulin therapy quickly improves the affected individual's medical condition and may increase treatment compliance. In metabolically stable patients, glycemic control can be maintained well with metformin monotherapy [713].

Risks

Metformin may cause GI disturbances and rarely lactic acidosis. Insulin may cause hypoglycemia.

Balancing the benefits and risks

In children and adolescents with T2DM, initial pharmacologic treatment should be decided based on glycemic and metabolic status, with consideration of medication-related side effects.

Recommendation 20.7 If metformin alone does not achieve the glycemic goal, basal insulin should be used concomitantly. [Expert opinion, general recommendation]

Recommendation 20.8 If metformin and basal insulin treatment do not achieve the glycemic goal, MDIs or insulin pumps should be used. [Expert opinion, general recommendation]

Level of evidence

Expert opinion.

Benefits

The addition of basal insulin is considered if HbA1c does not reach 7.0% within 3 to 4 months of metformin monotherapy [257,700]. A stepwise approach can be used in individuals with poor glycemic control, as intensive glycemic control is essential to prevent complication development. A high basal insulin dose of about 1.5 U/kg may be required in children and adolescents with diabetes who exhibit insulin resistance. If the combination of metformin and basal insulin does not achieve treatment goals, ultra-short-acting insulin should be adminis-

tered before meals to achieve an HbA1c level below 7.0%. Currently, several drugs for pediatric diabetes treatment are undergoing clinical trials [714,715]. International guidelines recommend administering other oral antidiabetic drugs, such as GLP-1RAs, when target HbA1c is not reached [257,700]. However, in Korea, GLP-1RA, SGLT2 inhibitors, and DPP-4 inhibitors are not yet approved for pediatric T2DM treatment; it is necessary to continue to take notice of approvals of such drugs. When adding any of the above drugs, it is important to consider factors such as the degree of glycemic reduction, mechanism of action, cost, method of administration, licensure, side effects, and impact on comorbidities of these drugs.

Risks

The challenges associated with adding insulin when glucose control is inadequate include potential decreases in adherence and risks associated with insulin use, such as hypoglycemia and weight gain. The use of other oral antidiabetic drugs require further validation for their effectiveness and safety.

Balancing the benefits and risks

When used alone, metformin is not effective in controlling blood glucose levels in about 50% of cases, necessitating the addition of insulin with evaluation on hypoglycemia and adherence individually. With recent active clinical research on secondary medications in children and adolescents, it is crucial to be well-informed about their approval status in the country.

Recommendation 20.9 Liraglutide can be administered to youth aged ≥ 12 years with T2DM who have a stage II or higher obesity ($\geq 120\%$ of the 95th percentile of BMI). [Randomized controlled trial, limited recommendation]

Recommendation 20.10 Poor glycemic control or presence of comorbidities in youth with T2DM who have a stage II or higher obesity ($\geq 120\%$ of the 95th percentile of BMI) may require bariatric surgery with considerations to the growth state of the youth. [Non-randomized controlled trial, limited recommendation]

Level of evidence

RCTs and non-RCTs demonstrating the effectiveness of liraglutide and bariatric surgery in obese children and adolescents with T2DM were included as evidence.

Benefits

Liraglutide may be used to treat youth with T2DM who are at

least 12 years of age and have stage 2 obesity (BMI > 30 kg/m² or $\geq 120\%$ of the 95th percentile) [716]. Bariatric surgery may be considered if glycemic control is inadequate with pharmacologic therapies or in the presence of severe comorbidities. Experienced surgeons should perform this surgery on selected few individuals who have completed growth spurts in a hospital with a multidisciplinary team capable of pediatric postoperative management. Bariatric surgery in individuals with uncontrolled T2DM has been associated with better glycemic control, more significant weight loss, and better outcomes for other complications, including diabetic nephropathy, compared to pharmacologic therapies [717-719].

Risks

GI side effects are common with liraglutide. A thorough discussion is necessary before deciding on bariatric surgery, as several complications, such as nutrient deficiencies, may occur after the surgery. There are reports that bariatric surgery does not affect growth in individuals who have not completed growth spurts [720], but further studies are needed. Furthermore, data on long-term follow-up of pediatric people undergoing surgery is lacking.

Balancing the benefits and risks

The decision to use liraglutide or to perform bariatric surgery in children and adolescents with T2DM should be made carefully.

Recommendation 20.11 For youth with T2DM, routine evaluation of comorbidities and microvascular complications is conducted starting at the time of diagnosis. [Uncontrolled studies, general recommendation]

Recommendation 20.12 For youth with T2DM, routine assessments for depression, anxiety, eating disorders, sleep apnea, and sleep disorders should be conducted. [Expert opinion, general recommendation]

Level of evidence

Expert opinion.

Benefits

Newly diagnosed T2DM is often accompanied by comorbidities or diabetic complications and should be screened at the time of initial diagnosis [257,700]. Younger-onset T2DM is associated with more severe microvascular and macrovascular complications than later-onset T2DM [708]. Therefore, in in-

dividuals diagnosed with T2DM in childhood or adolescence, screening for microvascular complications (nephropathy, retinopathy, and neuropathy) should be conducted at the time of diagnosis, and routine yearly testing for early detection of complications is recommended.

Blood pressure should be measured every clinic visit, and fasting lipids and liver function tests are recommended yearly. Evaluation for sleep apnea and polycystic ovary syndrome is also necessary, and comorbidities of T2DM should be treated accordingly. Individuals diagnosed with diabetes in childhood and adolescence are at increased risk of developing depression, anxiety, and eating disorders, which can negatively impact diabetes management. Therefore, detailed history-taking and routine evaluation is essential.

Risks

Diagnosis of diabetes complications may be delayed if routine screening is not performed. Comorbidities detected by screening must be treated accordingly, with consideration to medications approved for each age group.

Balancing the benefits and risks

Routine screening for comorbidities and diabetes complications in children and adolescents with T2DM is crucial, and the identified diseases should be treated accordingly.

Recommendation 20.13 Youth with T2DM should be transferred to an adult clinic at an appropriate time. [Expert opinion, general recommendation]

Level of evidence

Expert opinion.

Benefits

Physicians treating children and adolescents with T2DM should begin preparing for the transition from pediatric to adult diabetes care during adolescence, at least 1 year before the transition. This transition period is a high-risk period as interruption of care is likely to occur. Poor glycemic control, increased risk for acute and chronic complications, and psychological and emotional problems may arise during this period [721]. Both pediatric and adult healthcare providers should provide support and resources to young adults transitioning into adult care. The exact timing of transition is decided upon by the healthcare provider and the transitioning individual. When adequately prepared, the transition from pediatric to adult diabetes care is less likely to be challenging and the interruption of care is minimized.

Risks

Recommendations for transitioning from pediatric to adult care for T2DM are similar to those for pediatric T1DM, due to the insufficient studies on this subject.

Balancing the benefits and risks

The transition process of young adults with T2DM is thought to be similar to that of young adults with T1DM, since the course of transition is not influenced by the type of diabetes.

21. CONTINUOUS GLUCOSE MONITORING AND INSULIN PUMPS

1. CGM results should be analyzed using international standardized core metrics and their criteria, as well as the ambulatory glucose profile (AGP). [Non-randomized controlled trial, general recommendation]
2. The clinical benefits of CGM and insulin pumps can only be expected when the user accurately uses these devices and has received education on how to appropriately apply the information obtained to glucose management. For adults who intend to use multiple daily insulin injections or insulin pumps, such education should be provided professionally and systematically through a team of diabetes specialists. [Non-randomized controlled trial, general recommendation]
3. All adults with T1DM should use rtCGM as close to daily as possible to manage blood glucose levels and minimize the risk of hypoglycemia. [Randomized controlled trial, general recommendation]
4. Adults with T2DM on insulin injection regimens may use rtCGM as close to daily as possible to manage blood glucose levels. [Randomized controlled trial, limited recommendation]
5. For adults with diabetes on insulin therapy where constant use of rtCGM is not desired or available, or for adults with T2DM on noninsulin therapy, periodic use of rtCGM can be employed for blood glucose management. [Randomized controlled trial, limited recommendation]
6. Pregnant individuals with T1DM should use rtCGM as close to daily as possible to maintain optimal blood glucose levels, reduce the risk of hypoglycemia, and improve gestational outcomes. [Randomized controlled trial, general recommendation]
7. Automated insulin delivery (AID) systems should be offered to all adults with T1DM who can use the device safely to reduce the risk of hypoglycemia as well as HbA1c levels. [Randomized controlled trial, limited recommendation]
8. For adults with T1DM who are at high risk of hypoglycemia despite constant use of CGM and unable to use AID systems, sensoraugmented pumps with low-glucose suspend (LGS) feature should be used to reduce the risk of hypoglycemia. [Randomized controlled trial, limited recommendation]
9. For adults with T1DM who cannot use an AID system or a sensoraugmented insulin pump, and for adults with poorlycontrolled T2DM with multiple daily insulin injections, multiple daily insulin injections and conventional insulin pumps have similar efficacy. The choice between these two treatment methods should be individualized based on each individual's preferences, and medical and socioeconomic circumstances. [Randomized controlled trial, limited recommendation]

Recommendation 21.1 CGM results should be analyzed using international standardized core metrics and their criteria, as well as the AGP. [Non-randomized controlled trial, general recommendation]

Level of evidence

The studies included in the analysis are three observational studies [722-724]. All are retrospective cohort studies, and the level of evidence is very low. The recommendation range is assessed as a general recommendation.

Benefits

In 2019, international guidelines were published on the use of core metrics for interpreting CGM and the AGP [119]. These guidelines specify the AGP report as the standard template for

interpreting CGM data. The studies on the target values did not include Korean participants; therefore, whether the same criteria can be applied to Koreans can be evaluated based on observational studies conducted in Korea.

In one Korean study, the coefficient of variation was shown to have an inverse correlation with the minimum glucose level recorded by a 3-day CGM in both people with T1DM and T2DM and a coefficient of variation of 36% appeared to be a helpful predictor for minimum glucose level of below 70 mg/dL in Koreans with diabetes [722]. Furthermore, in a study conducted in

Koreans with T1DM, among various core metrics of CGM, the TBR (<54 mg/dL) was most strongly associated with CAN, supporting the international guidelines that categorize hypoglycemia into two stages and define clinically significant hypoglycemia as below 54 mg/dL [723]. In addition, the TIR (70 to 180 mg/dL) was significantly associated with the presence of proteinuria in Korean adults with T2DM, supporting international guidelines based on the association between TIR and microvascular complications [724]. Moreover, the AGP report visually presents glucose levels over time in a standardized format, accumulated for more than 14 days.

Risks

No target CGM metrics are proposed for pregnancy in T2DM, gestational diabetes, and prediabetes due to insufficient evidence from studies, and the benefits and risks of applying the same target range to these individuals have not been evaluated.

Recommendation 21.2 The clinical benefits of CGM and insulin pumps can only be expected when the user accurately uses these devices and has received education on how to appropriately apply the information obtained to glucose management. For adults who intend to use multiple daily insulin injections or insulin pumps, such education should be provided professionally and systematically through a team of diabetes specialists. [Non-randomized controlled trial, general recommendation]

In the cohort study from 2016 to 2018 of the T1D Exchange, a large T1DM cohort in the United States, it was observed that despite the expanded use of CGM and insulin pumps, there was no decrease in HbA1c levels or the incidence of SH compared to the cohort study from 2010 to 2012 [725]. These findings suggest that the consistent benefits of CGM and insulin pumps demonstrated in various clinical trials cannot be replicated in clinical practice by simply increasing the supply of these devices alone, and that the systematic education provided along with the device in these trials is necessary for those benefits to be replicated. In the clinical trials that form the basis for each recommendation, for individuals undergoing intensive insulin therapy such as multiple daily insulin injections or insulin pumps, these educations were provided through a specialized educational system, going beyond the scope of typical diabetes education. It included training on the correct use of devices and the proper interpretation of the information obtained from these devices to apply it to their treatment. The partici-

pants in these studies consistently used CGM on a daily basis, checking the information in real-time. In almost all studies, the percentage of time CGM is active showed a significant correlation with the benefits obtained from the study (refer to each recommendation text).

For those not on intensive insulin therapy, their education did not significantly deviate from the scope of typical diabetes management education, but the subjects retrospectively received help from experts to interpret the information obtained through the devices (professional CGM). Some studies also involved the subjects checking the information obtained from the devices in real-time (real-time feedback). This form of CGM was not continuous but was conducted periodically over a certain period (typically several days to 2 weeks) (refer to each recommendation text).

Recommendation 21.3 All adults with T1DM should use rtCGM as close to daily as possible to manage blood glucose levels and minimize the risk of hypoglycemia. [Randomized controlled trial, general recommendation]

Level of evidence

Eight RCTs with a primary outcome of HbA1c reduction [550, 726-732] and seven RCTs with a primary outcome of reduced hypoglycemia [553, 733-738] in adults with T1DM were included in the analysis. One RCT compared a conventional rtCGM to an isCGM [739]. Blinding was not maintained due to the nature of device-worn studies, which precluded the use of a placebo. However, the risk of bias from other sources was low enough that the same conclusions could be drawn from these studies; therefore, the level of evidence was assessed as high and the recommendation range as a general recommendation.

Benefits

Of the eight RCTs [550, 726-732] with HbA1c reduction as the primary outcome, all but one [728], which provided inadequate education in adults with T1DM from low-income families, showed significant HbA1c reduction. In all seven RCTs [553, 733-738] with hypoglycemia as the primary outcome, the use of CGM with appropriate education significantly reduced the frequency of hypoglycemia in adults with T1DM on multiple insulin injections or insulin pumps. This effect was demonstrated regardless of baseline HbA1c level [738], even in individuals with adequate baseline HbA1c [736, 738]. This was also proven for individuals with hypoglycemia unawareness or fre-

quent SH, where the risk of death from hypoglycemia is increased, regardless of whether they used insulin pumps or multiple daily insulin injections [553,735]. Consistent benefits have also been shown with isCGM, as well as conventional rtCGM [733].

However, in an RCT comparing conventional rtCGM with isCGM, the conventional rtCGM was superior in TBR (<70 mg/dL) and TIR (70 to 180 mg/dL) [739]. Therefore, in T1DM, when isCGM does not provide sufficient benefits, conventional rtCGM is recommended.

Risks

Most CGM devices, except for implantable ones, can cause contact dermatitis as they need to be attached to the skin. To date, no studies have shown an increase in the frequency of hypoglycemia when using scanned CGM instead of SMBG. Given the high morbidity and mortality of T1DM and the increased severe-hypoglycemia-related mortality, the benefits of CGM in reducing HbA1c and reducing hypoglycemia far outweigh the harm. Since there are no side effects other than contact dermatitis, which can be controlled through the identification and removal of allergens in most cases, CGM with proper education can be recommended in all adults with T1DM.

Recommendation 21.4 Adults with T2DM on insulin injection regimens may use rtCGM as close to daily as possible to manage blood glucose levels. [Randomized controlled trial, limited recommendation]

Level of evidence

Six RCTs were analyzed. Due to the nature of studies involving the wearing of devices, the use of a placebo was not possible, and blinding was not maintained in all randomized trials. However, studies with a low risk of bias for other reasons alone were able to draw the same conclusions, leading to the evidence being rated as high quality, but the recommendation range was considered a limited recommendation.

Benefits

The DIAMOND study, an RCT of 158 adults with T2DM using multiple insulin injections, was performed with the change in HbA1c at 24 weeks as the primary outcome. In this study, mean HbA1c was 8.5% at baseline, 7.7% at 24 weeks in the CGM group, and 8.0% at 24 weeks in the control group, with a significant difference in HbA1c reduction between the two groups (adjusted difference in mean change, -0.3%; 95% CI,

-0.5% to 0.0%; $P=0.022$). The groups did not differ in CGM-measured hypoglycemia and quality of life outcomes [740]. This study used CGM as an adjunct to SMBG, not as a stand-alone, due to regulatory status at the time of study, and the control group was also required to measure their blood glucose at least four times per day. In addition to SMBG, the CGM group received individualized recommendations from their physicians to reflect the trends of glucose levels identified by CGM into their glycemic control regimen [740]. A *post hoc* analysis of the study showed significant HbA1c reductions also in individuals over the age 60 [551].

An RCT on 224 adults with T2DM using multiple insulin injections or insulin pumps was conducted to determine whether replacing SMBG with isCGM without specific education improves glycemic control. The primary outcome, HbA1c change at 6 months, did not show a significant difference between the intervention (isCGM) and control groups. However, in participants younger than 65, the isCGM group showed a significantly greater HbA1c change. Of the secondary outcomes, hypoglycemia was reduced in the isCGM group, and treatment satisfaction was higher in the isCGM group than in the control group [741].

An RCT was conducted to determine whether replacing SMBG with isCGM with specific education improves treatment satisfaction in adults with T2DM on multiple insulin injections. The study found no significant difference in treatment satisfaction, the primary outcome, as assessed by the Diabetes Treatment Satisfaction Questionnaire score ($P=0.053$). The secondary outcome, HbA1c reduction, was 0.82% in the isCGM group and 0.33% in the control group, showing a significant difference between the two groups ($P=0.005$) [742].

The Continuous Glucose Monitoring in T2D Basal Insulin Users (MOBILE) study, an RCT of 175 adults with T2DM treated with basal insulin without pre-prandial rapid-acting insulin in primary care practices, was conducted with HbA1c at 8 months as the primary outcome. The mean HbA1c of the CGM group was 9.1% at baseline and 8.0% at 8 months. In the control group, mean HbA1c was 9.0% at baseline and 8.4% at 8 months, showing a significant difference in HbA1c change between the two groups (adjusted difference in mean change, -0.4%; 95% CI, -0.8% to 0.1%; $P=0.02$). The mean CGM-measured TIR of 70 to 180 mg/dL was 59% in the CGM group versus 43% in the control group ($P<0.001$) [743]. In a follow-up study, the 106 individuals initially assigned to the CGM group were reassigned either to continue CGM ($n=53$) or discontin-

ue CGM ($n=53$). In the continued CGM group, the mean TIR increased from 44% at baseline to 56% at 8 months and 57% at 14 months, while the discontinued CGM group lost half of the initial gain in TIR (38% at baseline to 62% at 8 months and 50% at 14 months) [744]. Thus, the MOBILE study demonstrates the need for CGM not only in people with diabetes on multiple insulin injection regimens but also in adults with T2DM treated with only basal insulin.

Although there has not yet been a domestic study exclusively targeting adults with T2DM who use only basal insulin, similar to the MOBILE study, an RCT evaluating the benefits of consistently using isCGM over 3 months among adults with T2DM who do not use multiple daily insulin injection therapy included a subset of such patients on basal insulin only. Of the study participants, 27.5% were on basal insulin, and 19 of the isCGM group (32.8%) and 14 (22.6%) of the control group used insulin. In this study, insulin use was not associated with HbA1c changes, but the increase in TIR and decrease in TBR was more pronounced in insulin users [745].

Risks

Due to their characteristic of being attached to the skin, all CGM devices can cause contact dermatitis. To date, no increase in the frequency of hypoglycemia has been reported when scanned CGM replaces SMBG. As there are no adverse effects other than contact dermatitis, most of which can be controlled by identifying and eliminating the allergen, CGM with proper education can be recommended in adults with T2DM on multiple insulin injection regimens.

Alternatives and considerations

Clinical trials have not tested the independent use of conventional rtCGM devices, without concomitant use of SMBG. The clinical trials on scanned CGM employed devices from a generation that did not yet have real-time alarms features. Current generations of CGM devices, such as rtCGM used without SMBG and isCGM with real-time alarms, may provide additional benefits than those demonstrated in these trials. However, no RCTs have been published to confirm this.

Recommendation 21.5 For adults with diabetes on insulin therapy where constant use of rtCGM is not desired or available, or for adults with T2DM on non-insulin therapy, periodic use of rtCGM can be employed for blood glucose management. [Randomized controlled trial, limited recommendation]

Level of evidence

Four RCTs were included in the analysis. Blinding was not maintained in all four studies due to the nature of the device-worn studies, which precluded the use of a placebo. A 52-week follow-up study had missing values for the primary outcome in 33% of its participants [746,747]. In another study, the dropout rate was 12%, higher than the expected 10%, and the follow-up period was 3 months [748]. The level of evidence was rated as low for long-term outcomes, with limited recommendations.

Benefits

An RCT was conducted to evaluate whether intermittent use of CGM (2 weeks of use followed by a 1-week break) for 12 weeks improves glycemic control in adults with T2DM not using pre-prandial rapid-acting insulin. The primary outcome was reduction in HbA1c at weeks 12 and 52 (weeks 12 through 52 were observed without CGM use). At the time of the study, rtCGM devices were not yet approved for independent use without SMBG, so they were used as an adjunct to SMBG and the CGM group was also required to check SMBG before meals and before bedtime as in the control group. The results showed that rtCGM was significantly better than SMBG in reducing HbA1c at both 12 and 52 weeks [746,747]. An RCT conducted in Korea evaluated whether a monthly 3-day rtCGM for 12 weeks could significantly reduce HbA1c in adults with T2DM [748]. The study included 65 individuals with HbA1c levels of 8% to 10% on insulin or oral antidiabetic medication therapy. The rtCGM group was instructed to increase physical activity and adjust their diet in response to hyperglycemia alerts (>300 mg/dL) and to verify with SMBG followed by correcting hypoglycemia in response to hypoglycemia alerts (<60 mg/dL). Due to the characteristics of the rtCGM device used at the time, participants were required to check SMBG at least 3 days each month for calibration. During CGM-free periods, the number of SMBG was not limited, while the control group was required to measure SMBG at least four times per week. HbA1c decreased from $9.1\% \pm 1.0\%$ to $8.0\% \pm 1.2\%$ in the rtCGM group and from $8.7\% \pm 0.7\%$ to $8.3\% \pm 1.1\%$ in the control group, showing a greater reduction in HbA1c in the rtCGM group ($P=0.004$) [748]. In both studies, there was no significant difference in the frequency of hypoglycemia between the rtCGM and control groups. In a study on Koreans with diabetes, the rtCGM group showed decreased calorie intake, body weight, BMI, and postprandial blood glu-

cose levels and increased physical exercise time [748].

A recent study conducted in Korea assessed the benefits of consistent isCGM use for 3 months in 120 adults with T2DM, not on multiple insulin injections. In this study, the isCGM group was educated to improve their meal content if it consisted of unhealthy food or to reduce the quantity if the meal content was healthy, upon observing postprandial glycemic excursions. The isCGM group showed a greater reduction in HbA1c than the control group (risk-adjusted difference, 20.50%; 95% CI, 20.74% to 20.26%; $P < 0.001$) [745].

In another Korean study, 61 adults with T2DM not on insulin were enrolled in an RCT to evaluate changes in HbA1c with rtCGM use. All participants used blinded CGM for 6 days with lifestyle education based on the 'Pattern Snapshot Report' before randomization. The participants were then assigned to three groups: group 1 with one session of 7-day rtCGM, group 2 with two sessions of 7-day rtCGM with a 3-month interval between sessions, and a control group. Compared to the control group, only group 2 showed significant reduction in HbA1c at 6 months (adjusted difference = -0.68% ; $P = 0.018$). When evaluated based on the number of daily SMBG, participants of group 1 and group 2 who checked SMBG at least 1.5 times per day had significant HbA1c reductions compared to control at 3 and 6 months. However, those with self-measurements of less than 1.5 times per day showed no significant improvement. Compared to the control group, both group 1 (adjusted difference = -0.60% ; $P = 0.044$) and group 2 (adjusted difference = -0.64% ; $P = 0.014$) showed significant reductions in HbA1c at 3 months, but only group 2 showed significant reductions at 6 months. The study was conducted using a rtCGM device that requires calibration with twice-daily SMBG measurements [749].

Risks

All CGM devices that must be attached to the skin can cause contact dermatitis. No increased frequency of hypoglycemia has yet been reported when SMBG is replaced with isCGM. With no side effects other than contact dermatitis, most of which can be controlled by identifying and eliminating the allergen, CGM with structured education can be recommended in adults with T2DM.

Alternatives and considerations

Neither study was conducted with rtCGM alone without concomitant SMBG, as currently practiced. The recent generation

of devices, including rtCGM used without SMBG and isCGM with real-time alarms, may provide additional benefits than those demonstrated in these trials. However, no RCTs have been reported to confirm this.

Recommendation 21.6 Pregnant individuals with T1DM should use rtCGM as close to daily as possible to maintain optimal blood glucose levels, reduce the risk of hypoglycemia, and improve gestational outcomes. [Randomized controlled trial, general recommendation]

Rationale

One RCT was included in the analysis [750]. Blinding was not maintained due to the nature of the device-worn studies, which precluded the use of a placebo, but the risk of bias due to other causes was low; therefore, the level of evidence was assessed as high, and the recommendation range as a general recommendation.

Benefits

The CGM in pregnant women with T1DM (CONCEPTT) study is an international, multicenter RCT to determine whether rtCGM could improve glycemic control and obstetric outcomes in 215 pregnant individuals with T1DM and gestational age of 13 weeks and 6 days or lower on multiple insulin injections or insulin pumps [750]. Both the intervention group (rtCGM plus SMBG) and the control group (SMBG alone) performed at least seven SMBG measurements per day, as independent use of CGM was not approved at that time. The primary outcome was the reduction in HbA1c from baseline to gestational age of 34 weeks; a significantly greater reduction was observed in the intervention group (mean difference, -0.19% ; 95% CI, -0.34% to -0.03% ; $P = 0.0207$). TIR (63 to 140 mg/dL) was 68% in the intervention group and 61% in the control group ($P = 0.0034$). The frequency of SH and TBR did not differ between the two groups. In the intervention group, the number of LGA infant births was reduced by 49%, neonatal intensive care unit admissions were reduced by 52%, neonatal hypoglycemia was reduced by 55%, and duration of hospitalization was reduced by 1 day. The same study design was replicated in individuals with T1DM who were planning pregnancy, but no significant difference was observed between groups [750].

Unlike the benefits of CGM in pregnant individuals with T1DM, the benefits of periodic rtCGM and retrospective CGM in individuals with gestational diabetes or preexisting T1DM or

T2DM during pregnancy are unclear. An RCT of 6-day rtCGM use at the gestational age of 8, 12, 21, 27, and 33 weeks in 123 pregnant individuals with T1DM and 31 pregnant individuals with T2DM, did not show a difference in glycemic and obstetric outcomes, including the number of LGA infant births [751]. Additionally, studies utilizing retrospective CGM, which leverages CGM data during professional consultations at intervals of 1 to 4 weeks either between 24–28 weeks or 28–36 weeks of pregnancy, failed to demonstrate benefits in adults with gestational diabetes during 24–28 weeks of pregnancy [752].

Risks

The most common adverse event reported in the CONCEPTT study was a skin reaction, which occurred in 49 (48%) of the 103 CGM-users and eight (8%) of the 104 in the control group. Since contact dermatitis is often controllable with the identification and removal of the allergen, CGM with proper education can be recommended in adults with T1DM.

Recommendation 21.7 AID systems should be offered to all adults with T1DM who can use the device safely to reduce the risk of hypoglycemia as well as HbA1c levels. [Randomized controlled trial, limited recommendation]

Rationale

The analysis included three RCTs and one observational study with a 1-year follow-up period. Blinding was not maintained in all the RCTs due to the nature of the device-wearing studies, which precluded the use of a placebo, but the same conclusions could be drawn from the studies with a low risk of bias from other causes; therefore, the quality of evidence was assessed as high.

Benefits

The AID system is designed to automatically adjust the basal insulin infusion rate based on glucose levels obtained from CGM, striving for a more physiologic insulin secretion pattern. The system currently used in the clinic has not yet achieved fully automated insulin secretion, and is also referred to as hybrid closed-loop, as it requires the patient to manually input information on meals (carbohydrate counting) for the injection of the mealtime bolus dose. To date, RCTs using various devices and algorithms have shown reductions in HbA1c and increases in time spent in the target range.

In 2018, the results of a multicenter RCT of 86 adults with

uncontrolled T1DM at baseline in the United States and the United Kingdom were reported. The use of a hybrid closed-loop device (CAMAPS FX, CamDiab, Cambridge, UK) significantly improved the primary outcome of TIR (70 to 180 mg/dL) at week 12 at $65\% \pm 8\%$ compared to $54\% \pm 9\%$ in the control group and no SH occurred. The control group used sensor-augmented insulin pumps, and all study participants received training on proper insulin adjustment and device use during a 4-week run-in period [753].

In 2019, the results of the International Diabetes Closed Loop (iDCL) trial, a multicenter RCT comparing the efficacy and safety of sensor-augmented insulin pump and a hybrid closed-loop device (CONTROL-IQ, Tandem Diabetes Care, San Diego, CA, USA) in 168 adults with T1DM, were reported [754]. The hybrid closed-loop device used in the study used a model predictive control algorithm, which releases an automatically calibrated bolus up to 1 hour when blood glucose is expected to rise above 180 mg/dL after 30 minutes with peak basal insulin infusion rate. A separate glycemic goal was established for night-time and exercise. The primary outcome was TIR (70 to 180 mg/dL) at week 26, which was $61\% \pm 17\%$ at baseline, $71\% \pm 12\%$ at week 26 in the hybrid closed-loop group, and $59\% \pm 14\%$ at week 26 in the sensor-augmented insulin pump group, demonstrating significant differences in the outcome (mean adjusted difference, 11% points; 95% CI, 9 to 14; $P < 0.001$). There were no cases of SH in either group. Participants with prior use of insulin pumps or CGM had a run-in period of 2 to 8 weeks before randomization [754]. In a post hoc analysis of the study, the benefit of the hybrid closed-loop device was demonstrated regardless of prior CGM or insulin pump use, and the benefits were greater in those with lower baseline TIR. Additional benefits of a more complete glycemic control were demonstrated in those with excellent baseline HbA1c and TIR [755-757].

In a real-world observational study of Medtronic's Minimed 670G device (Minneapolis, MN, USA), the first commercially available hybrid closed-loop device, a significant correlation between time spent in auto-mode (the mode in which basal insulin infusion dose is automatically adjusted) and HbA1c was observed in the 1-year follow-up period. However, towards the end of the follow-up period, the time spent in auto-mode decreased, and the time spent in manual mode increased, particularly due to the forced shutdown of auto-mode when hyperglycemia above a certain threshold that could not be counteracted by adjusting the basal insulin infusion rate occurred

[758]. In 2021, the Fuzzy Logic Automated Insulin Regulation (FLAIR) study, an RCT that compared the improvement in TIR of two Medtronic Minimed devices, was reported. The two devices were Medtronic's Minimed 780G device, which used an algorithm that delivers small bolus injections every 5 minutes without forcible shutdown of the auto-mode, and the original Minimed 670G device. The Minimed 780G group reduced the primary outcome of time above the target range (>180 mg/dL) from 42% to 34% while maintaining TBR (<54 mg/dL) at 0.46%, a significant improvement compared to the Minimed 670G group (time above the target range of 37% and TBR of 0.50%). The TIR also differed significantly between the two groups, being 57% at the start of the study, 63% for the Minimed 670G, and 67% for the Minimed 780G at the end of the study. In particular, the time spent in auto-mode was 75% for the Minimed 670G and 86% for the Minimed 780G, and the number of forced shutdowns of auto-mode was 5.7 times per week for the Minimed 670G and 1.7 times per week for the Minimed 780G [759]. The Minimed 780G did not show superior results over the Minimed 670G in improving glucose levels within 3 hours of a meal. However, the Minimed 780G proved to better control overnight glucose levels and glucose 3 hours after a meal, with no difference in pre- or post-meal glycemic control [760]. Another RCT also demonstrated significant benefits of hybrid closed-loop device (Minimed 780G) use in individuals with no prior experience with CGM or insulin pump [761], and the benefit of Minimed 670G was significant in adults with T1DM aged 60 years or older [762].

A common finding in all of the above hybrid closed-loop studies was that based on CGM data, when compared to the control, the degree of glycemic improvement was greatest at night. Furthermore, with adequate training, including instructions on manual mode insulin pump use, significant gains were seen in all adults with T1DM. Therefore, the use of AID systems can be recommended for all adults with T1DM, not just in a selected population, given that training by qualified healthcare professionals can be provided and the devices used safely, with consideration to socioeconomic status.

Risks

Sensor-augmented insulin pumps and hybrid closed-loop devices share the same risks as insulin pumps, including the risk of DKA due to infusion set failure. In two separate international multicenter clinical trials of hybrid closed-loop devices, DKA due to infusion set failure occurred in one participant in

the hybrid closed-loop group [753,754].

Individuals with prior education about insulin therapy, CGM, and insulin pumps are thought to have a reduced risk of hypoglycemia without worsening glycemic control (sensor-augmented insulin pumps) or with improved glycemic control (hybrid closed-loop). However, as with any insulin pump, individuals without education on device care and intensive insulin therapy may continue to carry risks, such as DKA.

Alternatives and considerations

Given that the large RCTs that successfully demonstrated the efficacy and safety of AID systems have typically had a run-in period of 4 to 8 weeks to ensure adequate education on device care and insulin management, it is important to explain the practical expectations and safe use of AID systems to uneducated patients.

Recommendation 21.8 For adults with T1DM who are at high risk of hypoglycemia despite constant use of CGM and unable to use AID systems, sensor-augmented pumps with LGS feature should be used to reduce the risk of hypoglycemia. [Randomized controlled trial, limited recommendation]

Level of evidence

The studies included in the analysis were two RCTs and one observational study with a 1-year follow-up period about sensor-augmented insulin pumps and two RCTs and one observational study with a 1-year follow-up period about hybrid closed-loop devices. Blinding was not maintained in all RCTs due to the nature of the device-worn studies, which precluded the use of a placebo, but the same conclusions could be drawn from the studies with a low risk of bias for other causes; therefore, the level of the evidence was assessed as high and the recommendation range as limited.

Benefits

In general, in adults with T1DM who are appropriately educated for CGM use, multiple insulin injections and insulin pumps provide equivalent effects on glycemic control and hypoglycemia risk reduction; therefore, both can be recommended [763]. However, in adults with T1DM who are still at high risk of hypoglycemia despite CGM use, sensor-augmented insulin pumps with algorithms to reduce the risk of hypoglycemia may be considered. One type of such device, a sensor-augmented pump in sync with CGM that discontinues insulin infusion

when blood glucose level falls below a certain threshold (LGS) or is predicted to fall after 30 minutes (predictive low-glucose suspend [PLGS]), was approved by the U.S. FDA in the mid-2010s. PLGS-type sensor-augmented insulin pumps have been approved and are being used in practice in Korea. The Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, which included 247 adults with T1DM with nocturnal hypoglycemia, evaluated whether an LGS-type sensor-augmented insulin pump could reduce nocturnal hypoglycemia. The study showed that the use of sensor-augmented insulin pumps reduced the primary outcome of 3-month nocturnal hypoglycemia without an increase in HbA1c [732,764]. All participants had a 2-week run-in period, and only those who had at least two episodes of nocturnal hypoglycemia (<65 mg/dL) lasting at least 20 minutes during this run-in period were randomized. The PLGS for Reduction Of LOW Glucose (PROLOG) study was a randomized crossover trial comparing the use of sensor-augmented insulin pumps for a total of 6 weeks, in which a PLGS algorithm was used for half of this period. The primary outcome was % of TBR of <70 mg/dL, and PLGS algorithm use reduced the primary outcome by 31% without rebound hyperglycemia [765]. In the analysis of this study, the reduction in hypoglycemia was consistently observed both during the day and at night [48]. In a real-world observational study (median follow-up 12 months [range, 6 to 18]) on the benefits of long-term use of sensor-augmented insulin pumps with PLGS algorithms, the reduction in hypoglycemia was sustained for 12 months [766].

Risks

Sensor-augmented insulin pumps and hybrid closed-loop devices essentially share the same risks as insulin pumps, including the risk of DKA due to infusion set failure. In two separate international multicenter clinical trials of hybrid closed-loop devices, DKA due to infusion set failure occurred in one participant in the hybrid closed-loop group [753,754]. Individuals with prior education about insulin therapy, CGM, and insulin pumps are thought to have a reduced risk of hypoglycemia without worsening glycemic control (sensor-augmented insulin pumps) or with improved glycemic control (hybrid closed-loop). However, as with any insulin pump, individuals without education on device care and intensive insulin therapy may continue to carry risks, such as DKA.

Alternatives and considerations

The expected benefit of a sensor-augmented insulin pump with a basal insulin infusion discontinuation algorithm is hypoglycemia reduction, not HbA1c reduction. Hybrid closed-loop devices have both hypoglycemia and HbA1c reducing effects but are more costly. Thus, sensor-augmented pumps with LGS/PLGS feature may be a viable alternative for adults with T1DM at high risk of hypoglycemia despite CGM use, who do not have the socioeconomic means to use an AID system or do not want to use an AID system due to alarms from the device. As with hybrid closed-loop devices, given that the large RCTs that successfully demonstrated the efficacy and safety of these devices have typically had a run-in period of 4 to 8 weeks to ensure adequate education on device care and insulin management, it is necessary to explain to patients who are not sufficiently educated that they need the ability to manage the device safely with realistic expectations regarding this device.

Recommendation 21.9 For adults T1DM who cannot use an AID system or a sensor-augmented insulin pump, and for adults with poorly-controlled T2DM with multiple daily insulin injections, multiple daily insulin injections and conventional insulin pumps have similar efficacy. The choice between these two treatment methods should be individualized based on each individual's preferences, and medical and socioeconomic circumstances. [Randomized controlled trial, limited recommendation]

Level of evidence

For T1DM, five RCTs were included in the analysis. Due to the nature of the device-wearing studies, which precluded the use of a placebo, blinding was not maintained in all five of these studies. However, the same conclusions could be drawn from the studies with a low risk of bias for other causes; therefore, the level of evidence was assessed as high and the recommendation range as limited.

For T2DM, the analysis included four RCTs with usual education [767-770] and one RCT with intensive education [771]. Blinding was not maintained in all of these trials due to the nature of device-wearing studies, which precluded the use of a placebo. However, the risk of bias due to other causes was low; therefore, the level of evidence was assessed as high, and the recommendation range as limited.

Benefits

A 2012 systematic review and meta-analysis of RCTs compar-

ing insulin pumps to multiple insulin injections in adults with T1DM without CGM were reported [264]. In these studies, insulin pump use was associated with greater HbA1c reduction than multiple insulin injections. However, this result was strongly influenced by one study with a high dropout rate [772], and there was no difference when only the other three studies were analyzed [773-775]. Secondary endpoints of hypoglycemia frequency and weight gain showed similar results, and improvement in quality of life was better in the insulin pump group [772-775]. In 2017, the results of the Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial, including 317 adults with T1DM in the United Kingdom, were reported. This trial compared HbA1c reductions at 2 years after equally providing current insulin dose management education to the MDIs and insulin pump groups. The results did not show a significant difference in HbA1c reduction at 2 years between the two groups, but the insulin pump group showed superior treatment satisfaction [776]. In a meta-analysis that included only studies with ≥ 6 months' duration of insulin pump use and SH frequency greater than 10 episodes per 100 patient-years on MDI, the insulin pump group showed significant reductions in SH, compared to the MDI group (rate ratio, 2.89; 95% CI, 1.45 to 5.76) [777]. Problematic hypoglycemia, defined as two or more episodes per year of SH or one or more episodes of SH associated with hypoglycemia unawareness, extreme glycemic variability, or maladaptive behavior, is likely to exceed the criteria for inclusion in these studies [778], in which case insulin pump use may be recommended independently of CGM.

In general, RCTs in adults with T2DM have shown similar HbA1c-reducing effects and hypoglycemia frequencies with insulin pump use and multiple insulin injections [767-770]. The OpT2mise study was an RCT comparing the effects on glycaemic control of insulin pumps and multiple insulin injections in adults with uncontrolled T2DM despite multiple insulin injection therapies. The study was conducted after a 2-month run-in period to titrate the multiple insulin injection therapy doses. The primary outcome was HbA1c reduction at 6 months, compared to the baseline. HbA1c reduction was 1.1% (standard deviation [SD], 1.2%) in the insulin pump group and 0.4% (SD, 1.1%) in the multiple insulin injection group, showing a significant difference between the groups ($P < 0.0001$). At the end of the study, the total daily insulin requirement was 97 units in the insulin pump group and 122 units in the multiple insulin injection group, demonstrating a more significant reduction in insu-

lin requirement in the insulin pump group. There was no difference in the frequency of DKA or SH [771].

Overall, in adults with T1DM who cannot use AID systems or sensor-augmented insulin pumps and in adults with uncontrolled T2DM despite multiple insulin injection therapy, there was no difference in HbA1c reduction and hypoglycemia frequency reduction between multiple insulin injections and insulin pumps, no one therapy showing superiority over the other. Therefore, in these populations, the choice of which modality to use depends on personal preference, accessibility to healthcare (including healthcare providers who can provide professional education), and socioeconomic status (as insulin pumps are relatively expensive).

Risks

All insulin pumps carry a risk of DKA due to infusion set failure. Studies demonstrating the benefit of independent insulin pump use over multiple insulin injections in adults with T2DM not using CGM were conducted with 8 weeks of intensive training to titrate the multiple insulin injection doses prior to the studies; therefore, these modalities should be used in individuals who have a good understanding of multiple insulin injections and can safely use insulin pumps.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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