Evidence-based practice guideline for the treatment for diabetes in Japan 2013

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Preface

To promote evidence-based diabetes treatment, the Japan Diabetes Society (JDS) published, in February 2002, our first “Evidence-based Practice Guide for the Treatment of Diabetes in Japan” (J Japan Diab. Soc. 45, Supple 1, 2002). Since then, revised editions have been released every 3 years. Evidence-based medicine is a practice of medicine that attempts to integrate individual physician’s clinical

expertise and the best external research evidence, and apply them to solve individual patient’s problems. The physician’s clinical expertise decides whether or not the information obtained from the literature can be applied directly to the individual patient. (Sackett, D.L. et al., BMJ 312: 71, 1996).

Based on this policy, this guideline is formulated with several aims: to gather evidence on diabetes treatment both in Japan and overseas, describe it in forms that are easy to understand and use, subject it to evaluation by diabetes specialists, and offer recommendations for diagnosis and treatment. Although the JDS publishes numerous guidelines related to diabetes, it makes sure that all its books including the “Treatment Guide for Diabetes” comply with the recommendations laid out in this guideline. The guideline won plaudits from the Appraisal of Guidelines for Research and Evaluation (AGREE), an external tool for evaluating various guidelines, for its scope and purpose, rigor of development, and clarity of presentation.

The 2013 Edition of the Evidence-based Practice Guideline for the Treatment of Diabetes in Japan consists of 355 pages and 24 chapters. Each chapter has statements, explanations, abstract-tables, and references. The English-language edition was simplified for publication on our website. It features the entire Statement, plus commentaries that provide explanations of several passages. The tables, figures and references are limited only to those that are necessary. We hope this guideline will be found useful both in Japan and overseas.

- Translated “Statement” of the original Japanese version guideline
- Additional statements abstracted from the “Explanations” of the original Japanese version guideline.

This article is based on a study first reported in the *Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013* (ISBN978-4-524-26996-9), which was published in Japanese by Nankodo Co., Ltd. (© The Japan Diabetes Society, 2013).

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Table 1 Criteria for Assigning Levels of Evidence to Publications of Interest

Level of evidence	Type of evidence
1+	High-quality ^a randomized controlled trials (RCTs) Meta-analysis or systematic review of trials with level 1+
1	RCTs that fail to meet level 1+ evidence Meta-analysis or systematic review of trials with level 1
2	Prospective cohort studies, or meta-analysis or systematic review of them
3	Pre-specified sub-analyses of RCTs Non-randomized controlled trials Self-controlled (before-after) studies Retrospective cohort studies Case-control studies, or meta-analysis or systematic review of them
4	Post-hoc sub-analyses of RCTs Cross-sectional studies Case-series

^a A high-quality RCT was defined as an appropriately designed and conducted trial with a large sample size and a clearly specified randomization scheme, involving double masking and a high rate of follow-up

Methods for developing the “Diabetes Guideline 2013”

The present guideline consists of important statements intended to assist in clinical practice. They are structured as 24 chapters, with the statement also intended as recommendations. These statements were developed on the basis of published clinical evidence as well as expert consensus.

This guideline offers key recommendations in clinical practice as supported by the scientific evidence available from published studies. Any study of interest was systematically searched using the electronic databases of the MEDLINE and Japanese ICHUSHI (<http://www.jamas.or.jp/>), complemented by the authors' own manual searches. The search strategies used were described in detail in the Japanese original version of the guideline. Any study of interest was critically appraised for their strength by the authors to determine their relevance to any particular statement in the guideline and whether they were worth citing. Each study was assigned a level of evidence using the approach described in Table 1. Criteria for assigning a level of evidence were developed in reference to the previously published guidelines [1–4].

Each statement was assigned a grade of recommendation based on the evidences as well as their methodological strength and applicability to the Japanese population.

Table 2 Grading for recommendation

A	Strongly recommend
B	Recommend
C	Insufficient evidence to recommend
D	Not recommend

Criteria for assigning grades of recommendation were shown in Table 2. Statements were graded as A to D, and the grade of recommendation was determined by the scientific evidence and expert consensus currently available. Statements without original literature were designated as “consensus”.

Each chapter involves several statements that were indicated as closed circles. An open circle means a commentary providing with explanations by the authors. Scientific reports supporting a statement were cited as an “References” and additional guidelines or review articles were listed as “Additional reference material”.

All authors of the original Japanese version volunteered to assist in the development of the guideline and disclosed all potential conflicts of interest or relationships with manufacturers of any commercial products discussed in the guideline. External peer review of the guideline content was conducted by a panel of third-party experts not involved in the development of the guideline. The guideline will be reviewed in every 3 year, as there will be considerable advances in clinical research and practice in the meantime requiring a re-evaluation of the scientific evidence becoming available.

1 Guideline for the diagnosis of diabetes mellitus

1. Diagnosis of diabetes mellitus

- The diagnosis of diabetes mellitus should be made as comprehensively as possible, as confirmed by the presence of chronic hyperglycemia, but also by the presence of other factors, such as associated symptoms, clinical laboratory findings, family history of diabetes, and body weight history [1] (grade A; consensus).

2. Classification of hyperglycemia for diagnosis

- Based on combined fasting and 2-h post-75 g oral glucose tolerance test (OGTT) glucose values, patients are classified into diabetic, normal, and borderline types (Table 3). Those with casual blood glucose levels ≥ 200 mg/dL or those with HbA1c ≥ 6.5 % are also classified as diabetic (grade A; consensus).

3. Diagnosis of the diabetic type and diabetes (Fig. 1)

- Patients found to be diabetic on ≥ 2 assessments made on separate days can be diagnosed as having diabetes. Patients must not be diagnosed as having diabetes, based on repeated HbA1c measurements alone. Patients are diagnosed as having diabetes if they are shown to be diabetic on the basis of both their glucose level and HbA1c value in a measurement using the same blood sample [1] (grade A; consensus).
- Of those with either of the following criteria, those whose blood glucose level is shown to be diabetic even in a single measurement are diagnosed as having diabetes [1] (grade A; consensus).
 - ① presence of typical symptoms of diabetes (e.g., dry mouth, polyposia, polyuria, body weight loss)
 - ② presence of diabetic retinopathy

In an epidemiological study aimed to survey the prevalence of diabetes in a population, individuals found to be diabetic and hyperglycemic in a single measurement may be diagnosed as having diabetes [2] (grade A).

4. Patients with a prior history of “diabetes”

- Among patients who fail to meet the diagnosis of the diabetic type, those documented as having met the above criteria and having diabetes are handled similarly to those with diabetes [1] (grade A; consensus).

5. Patients not confirmed to be diabetic on repeated assessments

- Any individual not confirmed to have diabetes on repeated assessments is to be assessed for his/her glucose level, and OGTT performed repeatedly, at intervals of

months, and his/her clinical course is to be observed closely [1] (grade B; consensus).

6. Normal and borderline types

- Annually, less than 1 % of patients with the normal type are shown to progress to the diabetic type [1] (grade B; consensus).
- A large proportion of patients with the borderline type are shown to progress to the diabetic type, and the frequency of atherosclerotic complications is shown to increase in these individuals. Individuals with the borderline type are therefore to receive instructions on lifestyle modification (diet, exercise, and correction of obesity, if present) and be assessed on a regular basis [1] (grade B; consensus).

7. High normal values in fasting glucose measurements

- Of those with normal fasting glucose values, those whose fasting glucose value ranges between 100 and 109 mg/dL are classified as “normal high”. It is recommended that these individuals be assessed with an OGTT in an attempt to establish their diagnosis as either normal, borderline or diabetic type [1] (grade B; consensus).

8. Performing oral glucose tolerance tests (OGTT)

- Patients are to be given an OGTT solution containing 75 g of glucose after fasting 10 h or more and their blood glucose levels are to be measured under fasting conditions at 30- to 60-min intervals following glucose loading. Patients must be assessed for both fasting and 2-h post-OGTT glucose levels and may be assessed for additional glucose levels at a time point in between these two measurements in the clinic. Furthermore, if

Table 3 Criteria of fasting plasma glucose levels and 75 g oral glucose tolerance test (OGTT) 2-h value

	Normal range	Diabetic range
Fasting value	<110 mg/dL (6.1 mmol/L)	≥ 126 mg/dL (7.0 mmol/L)
75 g OGTT 2-h value	<140 mg/dL (7.8 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)
Evaluation of OGTT	Normal type: if both values belong to normal range Borderline type: neither normal nor diabetic types	Diabetic type ^a : if any of the two values falls into diabetic range

Even for normal type, if 1-h value is ≥ 180 mg/dL (10.0 mmol/L), the risk of progression to diabetes mellitus is greater than for <180 mg/dL (10.0 mmol/L) and should be treated as with borderline type (follow up observation, etc.). Fasting plasma glucose level of 100–109 mg/dL (5.5–6.0 mmol/L) is called “high-normal”: within the range of normal fasting plasma glucose. Plasma glucose level after glucose load in OGTT is not included in casual plasma glucose levels

^a Casual plasma glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) and HbA1c ≥ 6.5 % are also regarded as to indicate diabetic type

Fig. 1 Flow chart outlining steps in the clinical diagnosis of diabetes mellitus. *OGTT* Oral Glucose Tolerance Test

Stage Etiology (mechanism)	Normoglycemia		Hyperglycemia		
	Normal area	Borderline area	Diabetic area		
			Non-insulin-dependent state		Insulin-dependent state
			Need of insulin		
			not needed	for glycemic control	for survival
Type 1	←	←	→	→	→
Type 2	←	←	→	→	→
Other types	←	←	→	→	→

Fig. 2 A scheme of the relationship between etiology (mechanism) and patho-physiological stages (states) of diabetes mellitus. *Arrows pointing right* represent worsening of glucose metabolism disorders (including onset of diabetes mellitus). Among the *arrow lines*, indicates the condition classified as “diabetes mellitus”. *Arrows pointing left* represent improvement in the glucose metabolism disorder. The *broken lines* indicate events of low frequency. For

example, in type 2 diabetes mellitus, infection can lead to ketoacidosis and require temporary insulin treatment for survival. Also, once diabetes mellitus has developed, it is treated as diabetes mellitus regardless of improvement in glucose metabolism, therefore, the *arrow lines pointing left are filled in black*. In such cases, a *broken line* is used, because complete normalization of glucose metabolism is rare

feasible at all, patients should have their glucose levels measured under fasting conditions and 30 min after glucose loading to evaluate their initial insulin response, for the following reasons (grade A; consensus).

- ① Even those with the normal type are highly likely to progress to the diabetic type if their 1-h post-load glucose levels are high.
- ② Those with the normal/borderline types are likely to progress to the diabetic type if they have a postprandial 0–30-min insulin increase ($\mu\text{U/mL}$) to postprandial glucose increase (mg/dL) ratio ($\Delta\text{IRI}/\Delta\text{PG}$) of 0.4 or lower [2].

9. Classification of diabetes and its relationship to associated metabolic abnormalities

- An etiological classification of diabetes and associated metabolic abnormalities is given below (Fig. 2). Diabetes is classified into type 1 diabetes, type 2 diabetes, due to other specific mechanisms of onset or diseases, and gestational diabetes. Figure 2 describes the relationship between each type of diabetes and the degree of metabolic abnormality associated with each type of diabetes [1] (grade A; consensus).

10. Establishing the type of diabetes present and its complications

- In making a diagnosis, every effort is to be made not only to establish the presence of diabetes, but also to determine the type of diabetes, the degree of metabolic abnormality present, and the presence of associated complications (grade A; consensus).

2 Goals and strategies for diabetes management

1. Objectives of diabetes management

- The objectives of diabetes management are to reduce symptoms of diabetes, to prevent development or progression of diabetic complications and disease conditions associated with diabetes, and to enable affected individuals to maintain their quality of life (QOL) and life expectancy comparable to those seen in healthy individuals (grade A; consensus).

2. Goals of glycemic control

- Glucose levels in affected individuals should be controlled as close to normal as possible. Achieving and maintaining favorable glycemic control early after initiation of treatment is likely to lead to favorable long-term outcomes. Improving fasting glucose levels and HbA1c values is critically important for prevention of microangiopathy associated with diabetes, and in addition to these, improving postprandial hyperglycemia is key to prevent of macroangiopathy [1, 2] (grade A).
- The goals of glycemic control should be determined individually in light of the patient's age, duration of diabetes, status of complications, risk for hypoglycemia as well as the support system available to address such complications or hypoglycemia. However, the glycemic goal of HbA1c $<7.0\%$ is recommended to ensure prevention of diabetic complications. In this regard, supportive evidence was available from the Kumamoto Study, [3] in which patients with HbA1c $<6.9\%$ were found to be less likely to develop microangiopathy.
- In addition to HbA1c 7% , HbA1c 6 and 8% should also be kept in mind as measures of glycemic control in daily clinical practice. HbA1c 6% represents the best target in ensuring normalization of glucose levels, ideally, with appropriate diet/exercise therapy alone or with drug therapy without causing adverse events, such as hypoglycemia. This target is set for young individuals with a short duration of diabetes without a past history of cardiovascular disease. In contrast, HbA1c 8% serves as a measure of glycemic control that needs at least to be achieved in patients in whom intensive therapy is not feasible due to hypoglycemia or other factors as well as the threshold above which treatment needs to be modified or changed to improve glycemic control.
- Given that radical or too stringent glycemic control may often lead to severe hypoglycemia, aggravation of existing microangiopathy or sudden death in some patients, glycemic goals need to be determined individual depending on the disease condition of each patient [4–6] (grade A).

3. Treatment strategy

- Treatment strategy for patients with diabetes may vary depending on the type of diabetes, disease condition,

Fig. 3 Treatment of patients in a non-insulin-dependent state. This provides a guide to the management of patients without acute metabolic disorder (i.e., those who had a casual blood glucose level of 250–300 mg/dL or less than 250–300 mg/dL and had a negative test for urine ketone). The glycemic goal should be determined individually depending on the disease condition or age of the patient but is generally set at HbA1c <7.0 %

age, extent of metabolic abnormality, and status of diabetic complications (Fig. 3) (grade A; consensus).

- Insulin therapy is to be given not only to patients who are insulin-dependent but also to those in pregnancy, those undergoing surgery which involves whole-body management, or those with severe infection, even if they are not insulin-dependent. In addition, insulin therapy is to be given to those in whom their glycemic goals are not achievable with glucose-lowering agents (grade A; consensus).
- For type 2 diabetes patients in a non-insulin-dependent state, an oral glucose-lowering agent should be initiated if adequate diet/exercise therapy fails to achieve favorable glycemic control within 2–3 months. Depending on the degree of metabolic abnormality,

Table 4 Goals for control of parameters other than glucose

Parameter	Goal
BMI	22 kg/m ²
Serum lipid	
LDL-cholesterol	CAD (–): <120 mg/dL/CAD (+): <100 mg/dL
Triglycerides	<150 mg/dL
HDL-cholesterol	≥40 mg/dL
Non-HDL-cholesterol	CAD (–): <150 mg/dL/CAD (+): <130 mg/dL

CAD Coronary Artery Disease

BMI Body Mass Index

insulin or a glucose-lowering agent should be given in combination with diet/exercise therapy as initial therapy (grade A; consensus).

4. Prevention of chronic complications or their progression (Table 4)

- In people with obesity, not only glycemic and weight control but blood pressure and lipid control are to be implemented to prevent chronic diabetic complications or their progression. Smoking cessation is also to be adhered to (grade A; consensus).

5. Importance of continued treatment/education

- To prevent complications or their progression in diabetes as a chronic disease, continued treatment is essential and patient education by a health care team constitutes the core of diabetes management (grade A; consensus).

3 Diet therapy

1. Diet therapy in general

- Diet therapy is the cornerstone of therapy for all patients with diabetes. Practicing an appropriate diet improves glycemic control [1, 2] (grade A).

2. Individualized diet therapy

- Individualized diet therapy according to the lifestyle of each patient is essential for successful introduction and continuation of the recommended diet therapy and requires, first and foremost, that each patient be interviewed adequately about his/her dietary habits, such as food preferences and diet timetables as well as his/her physical activity level (grade A; consensus).
 - The elderly are often associated with disturbance of taste, smell, and mastication, reduced secretion of saliva and gastric acid, and impaired renal and hepatic function, which leads to malnutrition and sarcopenia. Therefore, it is required that diet therapy for the elderly be so formulated as to avoid the risk of malnutrition.

3. Diet instructions by registered dietitians

- In clinical practice, diet instructions involving a registered dietitian are useful for glycemic control [3] (grade B).

- The Food Exchange Lists, edited by the Japan Diabetes Society, is commonly used for diet instructions. However, if it is difficult for patients to understand the Food Exchange Lists, actual food products or food models may be used to give instructions (grade B; consensus).

4. Determination of the amount of energy intake

- The amount of energy intake is to be determined by a physician, with consideration given to his/her glucose levels, blood pressure, serum lipid levels, height, body weight, age, sex, complications, and energy expenditure (physical activity) as well as the amount of prior food intake. It must be also determined individually to meet disease conditions of each patient (e.g., setting a lower target for energy intake for obese or elderly patients) (grade A; consensus).

Equations used for calculation of energy intake:

Amount of energy intake = ideal body weight × physical activity level

Ideal body weight (kg) = [height (m)]² × 22

Physical activity level (kcal/kg/ideal body weight)

25–30 low-intensity exercise (e.g., jobs involving deskwork)

30–35 moderate-intensity exercise (e.g., jobs involving standing work)

≥35 high-intensity exercise (e.g., jobs involving heavy physical work)

5. Composition of macronutrients

- In formulating a diet for patients with diabetes, it is to be ensured that carbohydrates account for 50–60 % of the total energy [4], while proteins account for 1.0–1.2 g/kg/ideal body weight, with the rest of the energy accounted for by fats (grade A).
 - Carbohydrates: Given that there is a paucity of evidence as to the intake of carbohydrates in Japan and there is no consensus as to the lower normal limits for carbohydrate intake, it is desirable that carbohydrates not more than 60 % of the total energy intake; that the intake of sweets, jams or soft drinks be minimized as they contain a large amount of sucrose that leads to an elevation of triglyceride levels; and that the intake of fruit be limited to up to 1 unit (80 kcal)/day, given that fruits currently on markets often contain a large amount of sugar as a result of selective breeding.

- Proteins: While there is a paucity of evidence for protein intake, it is common practice to recommend 1.0–1.2 g/kg/ideal body weight of proteins. Intake of less animal protein and more plant protein (e.g., soybean products) is recommended to prevent atherosclerosis [5]. Protein-restricted diet is recommended for patients with diabetic nephropathy.
- Saturated and polyunsaturated fats: It is recommended that saturated and polyunsaturated fats account for not more than 7 and 10 % of the total energy intake, respectively (grade B; consensus).
- n-3 polyunsaturated fatty acids (e.g., eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]) which abound in fish are shown to be effective in lowering glucose and triglyceride levels [6, 7].

6. Salt intake

- Excessive salt intake may lead to the onset of vascular diseases through elevation of blood pressure as well as to an increase in appetite. Therefore, salt intake should generally be limited, and restricted to 6 g/day in patients with diabetes and hypertension and in those with overt nephropathy or more severe disease (grade B; consensus).

7. Dietary fiber intake

- Intake of dietary fiber (20–25 g/day) is shown to be effective in improving glycemic control as well as in lowering serum lipid levels (cholesterol and triglycerides) [8] (grade B).
- Daily intake of 350 g or more of vegetables should be targeted. During meals, taking vegetables first helps to reduce postprandial glucose increases, HbA1c values, and body weight [9].

8. Intake of varied foodstuffs

- To avoid vitamin or mineral deficiency, it is to be ensured that patients take as many kinds of food items as possible (grade B; consensus).

4 Exercise therapy

1. Initiation of exercise therapy in patients with diabetes and diabetic complications

- Prior to initiating exercise therapy in a patient with diabetes, the patient must be medically assessed for the presence or absence of cardiovascular disease and chronic complications, such as peripheral neuropathy, dysautonomia, advanced retinopathy or orthopedic diseases (grade A; consensus).
- Even in patients with advanced diabetic complications, every effort is to be made to keep their daily physical activity levels from decreasing (grade A; consensus).

2. Exercise therapy in patients with type 2 diabetes

- Exercise improves cardiopulmonary function, [1, 2] glycemic control, [3–7] and lipid metabolism, [5] lowers blood pressure, [5, 7] and increases insulin sensitivity [9–12] (grade A).
- Both aerobic exercise and resistance exercise [3, 13] as well as their combined use [14] is effective for glycemic control (grade A).
- Exercise therapy is expected to be more effective when combined with diet therapy (grade A; consensus).

3. Exercise therapy in patients with type 1 diabetes

- If glycemic control is favorable and no advanced complications are present in a patient, any sort of exercise is feasible for this patient with only adjustment of the insulin therapy and supplementary foods administered (grade B; consensus).
- As exercise is expected to offer benefits other than glycemic control such as reducing a patient's risk of developing cardiovascular disease and improving his/her QOL, exercise of moderate or higher intensity is recommended [15].
- While the long-term effect of exercise on glycemic control remains unclear, exercise reduces the risk factors for cardiovascular disease, [15] and improves QOL [4] (grade B).

- While exercise of high intensity involving the whole body leads to increased hepatic glucose production, it may also lead to increases in glucose during or after exercise due to impaired glucose utilization in conditions requiring insulin, thus resulting in the onset of ketosis.

4. Exercise therapy for patients with diabetes receiving drug therapy

- Prior to initiating exercise therapy in patients receiving insulin therapy, adjustments are needed such as taking supplementary foods before or during exercise depending on the duration, intensity or amount of exercise involved, based on self-monitoring of blood glucose (SMBG) (grade B; consensus).
- Prior to initiating exercise therapy in patients with glucose lowering agents, particularly sulfonylureas (SU), the drug dose may need to be reduced (grade B; consensus).

5. General precautions for exercise therapy in patients with diabetes

- A close examination of both feet is to be made in every patient to ensure that the shoes chosen for exercise fit their feet perfectly with appropriate cushioning for the entire soles (grade B; consensus).
- When a diabetic patient has poor glycemic control (particularly when both patients with type 1 and type 2 diabetes are found positive for urine ketone body), they are discouraged from doing exercise (grade B; consensus).
- Patients on glucose lowering agents have the risk of developing hypoglycemia during exercise on the day of exercise or the day after exercise. Therefore, it is desirable that these patients, particularly those receiving insulin therapy take 1–2 units of easily absorbable carbohydrates when their glucose levels are less than 100 mg/dL before exercise (grade B; consensus).
- The amount of exercise should be gradually increased as part of activities of daily living. Warm-up and cool-down exercise should be done before and after exercise (grade B; consensus).
- It is recommended that exercise of moderate intensity be done preferably every day, at least 3–5 times a week for 20–60 min [4] (grade A).
- Exercise-induced improvements in glucose metabolism in patients with diabetes are sustained over a period of 12–72 h after exercise.

5 Treatment with glucose-lowering agents (excluding insulin)

1. Indications and non-indications for glucose-lowering agents

- Glucose-lowering agents are indicated for patients with type 2 diabetes failing to achieve favorable glycemic control with adequate diet/exercise therapy of 2–3 months' duration [1–3] (grade A).
- Glucose-lowering agents may be considered for patients whose HbA1c value continues to be 7 % or higher.
- Early use of glucose-lowering agents including insulin is indicated, along with diet/exercise therapy, in patients with type 2 diabetes who require correction of glucotoxicity (grade A; consensus).
- In conditions, such as type 1 diabetes, pregnancy with pre-existing diabetes, diabetic coma, severe infection, surgery requiring whole-body management, in which insulin therapy is an absolute indication, no other glucose-lowering agent should be used for treatment (grade A; consensus).

2. Selection of glucose-lowering agents

- The choice of glucose-lowering agents should be made based on the disease condition of each particular patients with consideration given to the pharmacological and safety profile of each glucose-lowering agent (grade A; consensus).
- The drug dose should be low at first and then increased as required based on monitoring of glycemic control (grade A; consensus).

- Selection of glucose-lowering agents (see Chapter 2, Fig. 3 “Treatment of patients in a non-insulin-dependent state”).

Protective effect of glucose-lowering agents against microangiopathy: It is commonly agreed that this inhibitory effect is strongly correlated with the level of glycemic control does not vary between the glucose-lowering agents.

Protective effect of glucose-lowering agents against macroangiopathy: This effect is considered to be correlated with the level of glycemic control and varies from one agent to another.

Evidence is available to support the use of metformin (biguanides) in obese patients [4,5]. The clinical trials

that generated relevant evidence vary greatly with regard to their historical background and health care environment as well as the level of healthcare involved. Thus, at present, it remains difficult to evaluate the available evidence, which, in turn, does not allow a clear comparison of the glucose-lowering agents used in the trials.

- Dipeptidyl peptidase-4 (DPP-4) inhibitors and Glucagon-like peptide-1 (GLP-1) receptor agonists: No long-term outcome data are available, and their long-term safety remains yet to be established.

3. Approach to patients with insufficient glycemic control

- Favorable glycemic control may not be achieved in patients with diabetes on monotherapy with glucose-lowering agents [6–8] (grade A).
- In such case, every effort should be made to ensure that diet/exercise therapy is administered exactly as planned (grade A; consensus).
- When the HbA1c level continues to be 7 % or higher in a patient despite treatment with a drug of first choice, the drug dose should be increased.
- In addition, every effort should be made to improve glycemic control with the addition of a glucose-lowering agent with a different mechanism of action or by adding, switching to insulin therapy as required (grade A; consensus).

6 Insulin therapy

1. Indications for insulin therapy

- Patients with Type 1 diabetes, diabetic coma (diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome) and pregnancy with pre-existing diabetes must be in insulin therapy. When diet therapy is not effective, insulin therapy is also recommended when patients are in severe infection and at the time of the surgical procedure with whole-body management is needed (grade A; consensus).
- Relative indications for insulin therapy include the following:
 - ① If conspicuous hyperglycemia (e.g., a fasting glucose level of 250 mg/dL or higher or a casual glucose

level of 350 mg/dL or higher) or a tendency toward ketosis (e.g., positive urine ketones) is noted.

- ② If favorable glycemic control is not obtained with glucose-lowering agents (e.g., primary or secondary sulfonylurea failure).
- ③ If adequate glycemic control is not achievable with diet therapy in patients with severe hepatic damage or renal failure.

- Insulin therapy is also used in type 2 diabetic patients when glycemic control is not obtained with diet/exercise therapy and glucose-lowering agents or when glucotoxicity needs to be resolved in these patients (grade A; consensus).

2. Risks associated with insulin therapy

- Insulin therapy may generally be associated with hypoglycemia or aggravation of diabetic retinopathy or neuropathy in some patients [1]. Attention needs also to be given to weight gain as a potential risk associated with long-term insulin therapy [2] (grade A).
- Risk of intensive insulin therapy includes severe hypoglycemia, which is increased as glycemic control improves [3]. To prevent this, appropriate measures against potential hypoglycemia as well as patient education on effective prevention of hypoglycemia based on self-monitoring of blood glucose (SMBG) are required.
- Drastic decline of glycemia may be associated with aggravation of diabetic retinopathy or neuropathy [1].

3. Intensive insulin therapy for type 1 diabetes and its complications

- In type 1 diabetes for which optimal glycemic control is being sought, multiple daily insulin injection (3–4 injections/day) or continuous subcutaneous insulin infusion (CSII) is required [3] (grade A).
- Intensive insulin therapy which combines the above modality with SMBG is shown to be effective in preventing the onset or progression of diabetic microangiopathy (retinopathy, nephropathy, and neuropathy) [3, 4] as well as in preventing the progression of diabetic macroangiopathy (ischemic heart disease, cerebrovascular disease, peripheral vascular disease) [5, 6] (grade A).

4. Type 2 diabetes and insulin therapy

- Rigorous glycemic control is effective for preventing the onset or progression of diabetic microangiopathy in type 2 diabetic patients as well, thus providing the rationale for the use of insulin therapy in type 2 diabetic patients whose glycemic goal cannot be achieved with diet/exercise therapy and glucose-lowering agents [2, 7] (grade A).
- While favorable glycemic control may be achieved with once-daily injection of intermediate or long-acting soluble insulin or twice-daily injection of mixed insulin (morning/evening) in patients with mild diabetes, insulin therapy, including intensive insulin therapy with multiple insulin injections, should be used in patients with moderate or severe diabetes [7, 9, 10] (grade A).

5. Combination therapy with insulin preparations and glucose-lowering agents

- Combination therapy with insulin preparations and glucose-lowering agents (sulfonylureas, [11, 12] biguanides, [13] α -glucosidase inhibitors, [14, 15] thiazolidinediones [16, 17]) is shown to improve glycemic control as well as to reduce the need for insulin. However, its long-term efficacy has not been adequately explored (grade B).

7 Treatment of diabetic retinopathy

1. Diagnosis of retinopathy

- Once the diagnosis of diabetes has been established in a patient, he/she should be referred to an ophthalmologist to be examined for the presence or absence of diabetic retinopathy [1, 2] (grade A).
- Thereafter, the patient should be examined for retinopathy once a year or more frequently if he/she is at high risk of developing retinopathy (grade A; consensus).
- Retinopathy is often classified based on the David classification into four phases: ① no retinopathy; simple retinopathy; ③ non-proliferative retinopathy; and ④ proliferative retinopathy. In recent years, however, a new international classification of retinopathy severity levels has been proposed [3].

2. Risk factors for development and progression of retinopathy

- Patients with diabetes who meet any of the following conditions are at high risk of development or progression of diabetic retinopathy (grade A): ① long duration of diabetes; ② high HbA1c value; ③ severe retinopathy found at initial diagnosis; ④ presence of hypertension as a concurrent disease; and ⑤ pregnancy.

3. Medical treatment of retinopathy

- Stringent glycemic control inhibits the development or progression of diabetic retinopathy in patients with type 1 and 2 diabetes [4–6] (grade A).
- Treatment of hypertension as a complication associated with diabetes is effective in suppressing the progression of diabetic retinopathy [7] (grade A).
- The Kumamoto Study [5] is the only study that has demonstrated a treatment threshold in HbA1c (6.9 %) below which there is nearly no risk of diabetic retinopathy. In contrast, the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) have shown that the nearer to normal the HbA1c value, the greater the inhibition of the development or progression of diabetic retinopathy with treatment.

4. Ophthalmological treatment of retinopathy

- Photocoagulation in patients with non-proliferative and early proliferative retinopathy prevents the development of blindness associated with diabetic retinopathy [8] (grade A).
- Vitrectomy may suppress the progression of severe visual impairment associated with vitreous hemorrhage and retinal detachment and allow normal eyesight to be maintained [9] (grade A).
- Local macular photocoagulation (hereafter macular coagulation), local drug use (steroids, anti-VEGF antibodies) and vitreous surgery are shown to be effective on macular edema [10, 11] (grade A).

5. Pregnancy with pre-existing diabetes

- Diabetic retinopathy may progress drastically in pregnancy complicated by diabetes, irrespective of gly-

cemic control. Therefore, pregnant women should be examined for diabetic retinopathy at least at early, middle and late phases of pregnancy.

8 Treatment of diabetic nephropathy

1. Diagnosis of diabetic nephropathy

- The diagnosis of early nephropathy is made based on the appearance of microalbuminuria. To assist its detection, urine albumin should be measured in patients with diabetes at least once a year by using spot urine samples (Table 5) (grade A; consensus).
- As an assessment of renal function, in addition to glomerular filtration rate (GFR), the use of estimated GFR (eGFR) as calculated based on serum creatinine or cystatin C values is also recommended (grade A; consensus).

2. Principles in the treatment of diabetic nephropathy

- Stringent glycemic control prevents the development or progression of diabetic nephropathy [1–3] (grade A).
- Rigorous blood pressure control (target: <130/80 mmHg) prevents the development or progression of diabetic nephropathy [4–7] (grade A).
- In glycemic and blood pressure control in the elderly, their age needs to be taken into account (grade A; consensus)

3. Prevention of early nephropathy

- Rigorous glycemic control prevents the development of diabetic nephropathy [1–3] (grade A).
- Rigorous blood pressure control prevents the development of diabetic nephropathy [8] (grade A).

4. Treatment of early nephropathy

- Rigorous glycemic control prevents the progression of diabetic nephropathy in patients with type 1 and 2 diabetes [1–3] (grade A).

- The use of angiotensin-converting enzyme (ACE) inhibitors is reported to inhibit the progression to overt nephropathy in patients with type 1 diabetes with microalbuminuria, and the use of ACE inhibitors is recommended for the treatment of early nephropathy [9, 10] (grade A).
- Blood pressure control with antihypertensive agents (particularly ACE inhibitors, angiotensin II receptor blocker [ARB]) prevents the progression to overt nephropathy [4, 5, 11] (grade A).
- ACE inhibitors prevents the progressing to overt nephropathy in normotensive patients with diabetes [9, 12] (grade B).
- Patients with diabetes affected by hypertension should be instructed to restrict their salt intake (grade A; consensus).

5. Treatment of overt nephropathy

- ACE inhibitor- or ARB-based treatment should be administered to patients with overt nephropathy [11, 13] (grade A).
- ACE inhibitors prevent the development of renal dysfunction in patients with type 1 diabetes affected by overt nephropathy [6] (grade A).
- ACE inhibitors and ARBs prevent the development of renal dysfunction in patients with type 2 diabetes and overt nephropathy [7, 13] (grade A).
- In patients with overt nephropathy whose blood pressure cannot achieve to goal with an ACE inhibitor or ARB, other kinds of antihypertensive agents (e.g., long-acting calcium antagonists, diuretics) should be given as add-on (grade A).
- Protein-restricted diets potentially suppress the progression of nephropathy in type 1 diabetes [14] (grade B) Patients with type 2 diabetes and overt nephropathy are recommended to be instructed to use protein-restricted diets (grade B; consensus).
- Patients with diabetes affected by overt nephropathy should be instructed to restrict their salt intake (grade A; consensus).

Table 5 Criteria for diagnosis of diabetic early nephropathy (Joint Committee on Diabetic Nephropathy 2005)

1. Candidates for diagnostic tests: diabetic patients who tested negative or positive (1+) for proteinuria
2. Primary Criteria
Urinary Albumin Creatine Ratio, 30–299 mg/g Cr (spot urine sample) on 2 out of 3 measurements
3. Secondary criteria
Urinary Albumin Excretion Rate, 30–299 mg/24 h (24-h urine collection) or 20–199 µg/min (1-h urine collection)
Urinary type IV collagen, 7–8 µg/g Cr or higher
Kidney size, hypertrophic

- In a cohort study of Japanese patients with type 2 diabetes affected by overt nephropathy followed for about 7 years, urinary protein excretion was identified as a risk factor for end-stage renal failure [15]. A similar finding was reported in a sub-analysis of the reduction in endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) study [16].

9 Treatment of diabetic neuropathy

1. Diagnosis of diabetic neuropathy

- Diabetic neuropathy is among the most common complications affecting patients with diabetes. In examining a diabetic patient, it should be ensured that he/she be assessed for the presence or absence of neuropathy as well as for its stage if present (grade A; consensus).
- In making a diagnosis of diabetic neuropathy in a patients with diabetes, he/she should be assessed comprehensively by not only interviewing him/her about neurological symptoms but examining the patient for pain sensation (using toothpicks or bamboo skewers), vibration perception (with diapason C128), pressure sensation (with a monofilament) as well as for Achilles reflex. Findings of foot dryness, rhagades, callositas, and ulceration are useful as suggestive of the presence of neuropathy (grade A; consensus).
- The heart rate variability test is useful for assessment of autonomic function (grade A; consensus).
- Nerve conduction studies are essential for the definitive diagnosis of diabetic neuropathy as well for the diagnosis of asymptomatic neuropathy (grade A; consensus).
- The examinations mentioned above need to be made on a regular basis to follow up diabetic neuropathy over a period of years (grade A; consensus).

2. Development/progression of diabetic neuropathy

- Risk factors for the development/progression of diabetic neuropathy include ① poor glycemic control, ② duration of diabetes, ③ hypertension, ④ dyslipidemia, ⑤ smoking, and ⑥ drinking, [1–3] but the most significant of these is poor glycemic control, and diabetic neuropathy is seen to develop frequently in patients with poor glycemic control [4] (grade A).
- Stringent glycemic control suppresses the development/progression of diabetic neuropathy [5] Evidence for this benefit is established in type 1 diabetes but less well established in type 2 diabetes [6] (grade A).

- Kumamoto study demonstrated that deterioration of nerve conduction rate and vibration perception threshold was significantly reduced with intensive insulin therapy [7].

3. Basic treatment of diabetic neuropathy

- In treating diabetic neuropathy, not only stringent and maximally useful glycemic control but instructions on lifestyle modification such as abstinence and smoking cessation should be given to patients with diabetes (grade A; consensus).
- In patients in whom hyperglycemia persists over time, neurological symptoms may temporarily appear or worsen with drastic decline of glycemia and need to be watched for (grade A; consensus).
- A majority of these mono-neuropathies resolves spontaneously, however they are often associated with sensory/motor neuropathy. Thus, it is important that patients be given relevant instructions on glycemic control and lifestyle modification.

4. Treatment of painful neuropathy

- Mild painful neuropathy becomes alleviated with glycemic control and lifestyle modification. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in mild painful neuropathy alone. Recommended drugs of first choice for moderate to severe painful neuropathy include tricyclic antidepressants, [8] the $\alpha 2\delta$ ligand pregabalin, [9] and the selective serotonin-noradrenalin reuptake inhibitor (SNRI) duloxetine [10] (grade B).

10 Diabetic foot

1. Regular foot examination in patients with diabetes

- Patients with diabetes should undergo foot examinations on a regular basis for the presence or absence of risk factors for foot ulcers or amputation (grade A; consensus).
- Definition of Diabetic Foot: Internationally, as a working definition, diabetic foot is defined as “infections, ulcers and destructive deep tissue lesions in a patient with diabetes who has diabetic neuropathy and/or peripheral arterial diseases (PAD)”.

- Foot Examination and Risk Assessment of Foot Ulcers: Patients with diabetes should be examined for presence or absence of neuropathy, PAD, foot deformity, skin lesions and other manifestations. As the severity of diabetic neuropathy cannot be assessed on the basis of medical history or symptoms alone, a detailed examination of neuropathy is needed, based on such tests as vibration testing, pin-prick testing, deep tendon reflex and the Semmes–Weinstein 5.07 (10 g) monofilament.

2. Foot care education to patients with diabetes

- To prevent foot ulcers, foot care education should be given to all patients with diabetes (grade A; consensus).

3. Foot care for patients at high risk of foot ulcer

- Patients with diabetes at high risk of foot ulcer (e.g., those with a history of foot ulcer or amputation or those with PAD or neuropathy) should receive foot examinations and foot care more frequently than those at a lower risk (grade A; consensus).

4. Treatment of foot ulcer

- Treatments of foot ulcer include topical therapy, anti-infection therapy, treatment of PAD, off-loading wound care, as well as general care (control of glucose levels, water balance, and nutrition as well as management of heart failure and renal failure) (grade A; consensus).
- Depending on its etiology (e.g., PAD or neuropathy), sites of ulcers, presence or absence of infection, the treatment of foot ulcer varies. Therefore, the treatment of foot ulcer calls for a multidisciplinary team-approach involving physicians and other healthcare professionals from divergent backgrounds (e.g., diabetology, dermatology, orthopedics, plastic surgery, cardiology, vascular surgery, radiology, and physiotherapy).
- Various pharmacological agents and therapeutic modalities are currently available to promote healing of chronic foot ulcer. However, very few of these have been shown to be beneficial in large-scale randomized controlled trials. Of these, negative-pressure wound

therapy has been shown to shorten the time to wound healing in patients undergoing partial foot amputation [1].

5. Lower extremity amputation (LEA)

- Prior to performing LEA, blood flow needs to be evaluated at the site where amputation is to be carried out (grade A; consensus).

6. Multidisciplinary team approach for diabetic foot

- The prevention and treatment of diabetic foot should be based on close collaboration between physicians and other healthcare professionals in relevant specialties [2] (grade A; consensus).
- Care of diabetic foot calls for control of overall health, revascularization in severe lower-limb ischemia, local treatment such as debridement of infected tissue, use of offloading devices and therapeutic shoes, walking rehabilitation, and diabetes education. Therefore, forging a team-approach involving experts across disciplines and responsibilities is essential.

11 Diabetes and periodontitis

1. Relationship between diabetes and periodontitis

- Diabetes and periodontitis adversely affect each other [1–3] Therefore, patients with diabetes should be informed about their relationship, consult dentists regularly to have themselves examined for oral cavity status and undergo dental care as required (grade A; consensus).

2. Periodontitis in patients with diabetes

- Periodontitis is more frequently seen and severer among patients with diabetes (particularly those with poor glycemic control and at risk of disease progression) than among healthy individuals [1–3] (grade A).
- In a Japanese study comparing patients with diabetes and healthy individuals for prevalence of periodontitis,

likewise, periodontitis was shown to be higher in prevalence among both patients with type 1 and type 2 diabetes than among healthy individuals [1].

3. Influence of periodontitis on the onset of diabetes and on its disease condition

- Individuals with periodontitis are more likely to have diabetes [4] and are at a higher risk of developing diabetes than those without [5]. Severe periodontitis may adversely affect glycemic control in diabetes if left untreated [2] (grade B; consensus).
- In the Hisayama cohort study, periodontitis was shown to be higher in frequency among those who developed glucose intolerance over a 10-year period than among those who did not [6].

4. Influence of periodontal care on glycemic control

- Periodontal care in type 2 diabetes may lead to improvements in their HbA1c values [7] (grade B).
- A meta-analysis/systematic review suggests that periodontal care in type 1 diabetes has little or no influence on their glycemic control, while periodontal care in type 2 diabetes is shown to improve their HbA1c values by a mean of 0.66 %, although this is not significant [8].
- Another meta-analysis/systematic review suggests that periodontal care in type 2 diabetes significantly improves HbA1c by a mean of 0.4 % [9].
- In a Japanese study, periodontal care combined with topical antibiotic therapy is shown to significantly improve glycemic control in type 2 diabetes [7].

12 Diabetic macroangiopathy

1. Screening for macroangiopathy

- Screening tests for macroangiopathy include resting electrocardiogram (ECG), chest X-ray, carotid ultrasonography, ankle-brachial index (ABI) and it is desirable that these examinations be performed in patients with diabetes once a year (grade A; consensus).

2. Risk factors for macroangiopathy

- For the prevention of macroangiopathy, it is important that comprehensive control of its risk factors such as diabetes, hypertension, dyslipidemia, obesity and smoking be initiated early and maintained rigorously [1, 2] (grade A).
- The frequency of coronary artery disease is shown to increase by 2- to fourfold among type 1 and type 2 patients with diabetes compared to that among individuals without diabetes.
- Cerebrovascular disease is shown to be higher in incidence among patients with diabetes, with their risk of developing cerebral infarction being 2 times higher than that in non-diabetic individuals [3]. Furthermore, as with coronary artery disease, cerebrovascular disease associated with diabetes has poor prognosis and a high mortality rate [4].
- Likewise, the frequency of PAD is shown to be 4 times higher in patients with diabetes than that in individuals without diabetes as a major cause of gangrene and lower-limb amputation [5].
- The frequency of incidence of macroangiopathy per 1000 persons/year is shown to be 9.6 % coronary artery disease and 6.3 % cerebral infarction in the Japan Diabetes Complications Study (JDCS) [6] and 4.4 % coronary artery disease and 3.1 % cerebral infarction in the Japan Diabetes Clinical Data Management study (JDDM) [7].

3. Lifestyle modification and resolution of obesity

- Diet, exercise and lifestyle modification such as smoking cessation are the cornerstone of therapy for diabetic macroangiopathy [8,9]. Obesity should be resolved, if present in patients with diabetes. (for obesity resolution goals, see chapter 13, “Diabetes Complicated by Obesity”) (grade A).

4. Rigorous Stringent glycemic, blood pressure, and lipid control and drug-based prevention of macroangiopathy

- Stringent glycemic control is effective in inhibiting the development and progression of diabetic macroangiopathy [10] (for glycemic goals, see chapter 2,

“Goals and Strategies for Diabetes Management”) (grade A).

- In glycemic control, the risk of macroangiopathy is shown to be reduced to a greater extent with metformin than with sulfonylurea- or insulin-based therapy [11]. Metformin is shown to be effective in protecting against cardiovascular disease in an observational study which included Japanese patients [12].
- Rigorous Stringent blood pressure control is shown to alleviate the risk of developing diabetic macroangiopathy in patients with diabetes [13, 14] (for blood pressure goals, see chapter 14, “Hypertension Associated with Diabetes”) (grade A).
- Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors or “statins” are shown to be effective for both primary and secondary prevention of coronary artery disease and cerebral infarction [15] (for lipid goals, see chapter 15, “Dyslipidemia Associated with Diabetes”) (grade A).
- However, acute glucose normalization, severe hypoglycemia, and excessive blood pressure lowering may increase mortality or the risk of diabetic macroangiopathy in patients at high risk [16–18] (grade A).

5. Use of antiplatelet agents

- Use of antiplatelet agents is effective for secondary prevention of diabetic macroangiopathy [19, 20] (grade A).

13 Diabetes complicated by obesity

1. Diabetes complicated by obesity

○ Obesity, particularly visceral obesity, is an important risk factor that promotes the development and progression of diabetes. Weight loss should therefore be a priority in the treatment of diabetes complicated by obesity (grade A; consensus).

2. Assessment of obesity

- Obesity as a physical condition is defined as a BMI of 25 kg/m^2 or higher, as distinct from that associated with conditions, such as diabetes, requiring medical measures for weight loss [1] (grade A).
- Visceral obesity is frequently associated with dyslipidemia and hypertension, both of which are risk factors

for atherosclerosis. A BMI of 22 kg/m^2 or less is generally thought to represent a weight loss target which is less likely to be associated with health problems; however, it is desirable that the BMI target as part of diabetic treatment be determined based on each particular patient’s disease condition and lifestyle (grade A; consensus).

3. Causes of obesity

- The most common cause of obesity is simple obesity (excluding secondary obesity, e.g., endocrinologically, neurologically or genetically determined obesity or drug-induced obesity) due to overeating and lack of physical activity (grade B; consensus).
- If the patient is thought likely to have primary obesity after due consideration to secondary obesity as a possibility, the patient should be interviewed about the environmental or psychological factors involved, and every effort should be made to ensure that any lifestyle habit thought to be responsible for obesity is removed or alleviated. The patient should be sufficiently informed about obesity, in particular visceral obesity, which, if it persists and becomes associated with not only hyperglycemia but dyslipidemia and hypertension, places him/her at high risk of developing atherosclerotic diseases, thus motivating the patient for weight loss (grade B; consensus).

4. Treatment of obese type 2 diabetes

- In obese patients with type 2 diabetes, priority should be given to weight loss through diet/exercise therapy. If diet/exercise therapy does not lead to sufficient improvements in glycemic control in the patient, drug therapy should be considered. Treating hyperglycemia with drugs in an obese diabetic patient while leaving obesity untreated may lead to aggravation of obesity in the patient. Thus, every effort should be made to ensure lifestyle modification so that glycemic control can be obtained without causing weight gain in obese patients with diabetes (grade B; consensus).
- The use of insulin or sulfonylureas should be minimized in obese patients with type 2 diabetes (grade C; consensus).
- Uncritical use of these agents may further aggravate the existing obesity in these patients [2, 3] (grade C).
- Surgical therapy for obesity, such as laparoscopic sleeve gastrectomy, laparoscopic Roux-en-Y gastric

Table 6 Recommended clinical laboratory examinations

Urine: albumin or protein, glucose, occult blood, urinary sediment
Blood chemistry: glucose, HbA1c, lipids, liver/renal function
Electrolytes, chest X-ray, electrocardiogram (ECG)

bypass, and laparoscopic adjustable gastric banding are available for use in severe obesity with comorbidity, all of which are, however, not yet covered by insurance, with only laparoscopic sleeve gastrectomy approved as advanced medical care in January 2010 for use in combination with other insurance-covered modalities at designated healthcare institutions.

5. Metabolic syndrome

- Metabolic syndrome, which is diagnosed when 2 or more of such conditions as fasting hyperglycemia, dyslipidemia and elevated blood pressure are present in addition to visceral fat accumulation, has been put forward as a syndrome of interest in the prevention of atherosclerotic diseases, as well as a target for prevention of diabetes since it is frequently associated with insulin resistance or glucose intolerance. Patients with the metabolic syndrome should be encouraged to reduce visceral fat through lifestyle modification (see also chapter 24. “The Metabolic Syndrome”) (grade B; consensus).

14 Hypertension associated with diabetes

1. Treatment of hypertension in diabetes

- Blood pressure control should be initiated from an early stage of diabetes, together with glycemic and lipid control, in patients with diabetes [1, 2] (grade A).
- In treating hypertension in patients with diabetes whose blood pressure is 130/80 mmHg or higher, as a rule, treatment with antihypertensive agents, together with lifestyle modification, should be initiated [2, 3] (grade A).
- Lifestyle modification without medication can be continued up to 3 month. However, treatment with antihypertensive agents should be initiated in these patients if lifestyle modification fails to achieve the blood pressure goals set for these patients [3] (grade B).
- Patients with diabetes should be assessed for diabetic microangiopathy as well as for its severity. Patients with diabetes should also be assessed for other risk factors for hypertension and targeted organ damages, as well as cardiovascular disease.

- Clinical laboratory examinations (Table 6) should be performed in routine clinical practice. Brain MRI, carotid ultrasonography, ultrasonic cardiography (UCG), or ABI may be performed as required to assess the severity of atherosclerosis.

2. Goals for blood pressure lowering

- The blood pressure goal should be set at less than 130/80 mmHg [4, 5] (grade A).
- A meta-analysis of 13 studies evaluating the systolic blood pressure goal of 135 mmHg or less in patients with impaired glucose tolerance (IGT) or diabetes on intensive therapy and 140 mmHg or less in those on standard therapy [5] suggested a 10 % decrease in mortality in those on intensive therapy as well as a continued decrease in incidence of stroke that lasted until a systolic blood pressure of 120 mmHg was achieved. Given the higher incidence of stroke in Japan compared to that in western countries and the evidence demonstrating the effectiveness of blood pressure control to less than 130/80 mmHg in prevention of stroke, the blood pressure goal for patients with diabetes and hypertension has been recommended as less than 130/80 mmHg.
- Adequate blood pressure lowering should be ensured in patients with diabetic nephropathy [1, 4, 6] (grade A).
- In patients with coronary heart disease (CHD), consideration should be given to ensuring that blood pressure lowering is not carried to extremes [4, 5, 7, 8] (grade B).

3. Choice of antihypertensive agents

- ACE inhibitors and ARBs should be used as drugs of first choice [6–10] (grade A).
- The ARBs are shown to reduce the incidence of new-onset diabetes [12]. Similar effects are also suggested for the ACE inhibitors.
- In the Microalbuminuria cardiovascular renal outcomes heart outcomes prevention evaluation (MICRO-HOPE) study in which patients with hypertension accounted for

Table 7 Goals for lipid control by risk category

Treatment policy	Risk category	Goal for lipid control (mg/dL)			
		LDL-C	HDL-C	TG	non-HDL-C
Primary prevention: Consider drug therapy after lifestyle modification	I	<160	≥40	<150	<190
	II	<140			<190
	III	<120			<150
Secondary prevention: Consider drug therapy along with lifestyle modification	With prior CAD	<100			<130

LDL-C LDL-cholesterol, *HDL-C* HDL-cholesterol, *TG* triglycerides, *CAD* coronary artery disease. Adapted from reference [5]

Use the relative risk chart in motivating those with a low absolute risk (e.g., young patients) for lifestyle modification, while at the same time monitoring for changes in absolute risk in these patients. All values given above are intended as goals for lipid control. It is also important to lower LDL-C level by 20–30 %. The goals for non-HDL-C are of secondary interest and are relevant only after achievement of the goals for LDL-C in those with hypertriglyceridemia. Non-HDL-cholesterol should be used when triglycerides are shown to be 400 mg/dL or higher or when postprandial blood was sampled in these patients. In all risk categories, lifestyle modification remains the cornerstone of therapy in achieving the goals for lipid control. In category I, LDL-C 180 mg/dL or higher serves as a basis for considering drug therapy

56 % of the study population, the ACE inhibitors were shown to reduce the incidence of cardiovascular disease by 25 % [6]. Similarly, of the ARBs, losartan has been shown to reduce mortality from cardiovascular disease by 37 % compared to β -blockers.

- In patients with inadequate blood pressure lowering with ACE inhibitors or ARBs, their dose should be increased or a long-acting dihydropyridine calcium channel blockers' (CCBs) or low-dose thiazide diuretics should be added [8, 11, 12] If this proves ineffective, combination therapy with three agents should be given to these patients (grade A).
- The use of diuretics, β -blockers or long-acting dihydropyridine CCBs are shown to reduce the incidence of cardiovascular disease such as stroke or heart disease in patients with diabetes and hypertension [13].

15 Dyslipidemia associated with diabetes

1. Role of anti-dyslipidemic therapy in patients with diabetes

- Dyslipidemia should be aggressively treated in patients with diabetes. Diabetes is a strong, independent risk factor for the development of cardiovascular disease. Dyslipidemia associated with diabetes further increases the risk of cardiovascular disease, whereas, its resolution leads to a decrease in the incidence of cardiovascular disease [1] (grade A).

- Japanese patients with diabetes with LDL-cholesterol 160 mg/dL or higher are placed at 3.7-fold risk of ischemic heart disease (IHD) compared to those with LDL-cholesterol less than 100 mg/dL [2, 3].

2. Goals for lipid control

- Dyslipidemia in patients with diabetes should be treated based on the lipid control goals listed in Table 7 [4] (grade A).

3. Effectiveness of lifestyle modification

- Diet therapy and exercise therapy are expected to improve glycemic and lipid metabolism (grade A; consensus).

4. Drug therapy

- In patients in whom the lipid control goals cannot be achieved even after improvements in lifestyle and glycemic control, drug therapy should be considered (grade A; consensus).
- HMG-CoA reductase inhibitors or “statins” are drugs of first choice for elevated LDL-cholesterol [1, 2, 6] (grade A).
- Fibrates are drugs of first choice for hypertriglyceridemia [6] (grade A).
- Eicosapentaenoic acids (EPA) are also indicated for hypertriglyceridemia [7].

Table 8 Definition and diagnostic criteria of gestational diabetes*Definition of gestational diabetes*

Glucose metabolism that is abnormal, but less so than in diabetes, and that is first detected, or occurs first, during pregnancy

Diagnostic criteria

In 75 g OGTT, gestational diabetes is diagnosed if at least one of the following conditions is met

Fasting plasma glucose	≥92 mg/dL
Plasma glucose 1-h after a meal	≥180 mg/dL
Plasma glucose 2-h after a meal	≥153 mg/dL

Those women who had clinically diagnosed diabetes are excluded from the diagnosis of GDM

Table 9 Management for planned-pregnancy

Achievement and maintenance of HbA1c less than 7.0 %
Comprehensive education on diet therapy, etc. glucose monitoring, and insulin therapy
Assessment and treatment of diabetes retinopathy, nephropathy and neuropathy
Switching from glucose-lowering agents to insulin
Discontinuation of ACE inhibitors, ARBs, statins, and fibrates

16 Impaired glucose metabolism in pregnant women**1. Impaired glucose metabolism in pregnant women**

- Impaired glucose metabolism in pregnancy includes pregnancy in pre-existing diabetes and hyperglycemic disorders in pregnancy. The latter consists of gestational diabetes mellitus (GDM) and overt diabetes in pregnancy (grade A; consensus).
- Definition and diagnostic criteria of GDM in pregnancy are shown in Table 8 (grade A; consensus).
- Fulminant type 1 diabetes may occur as a rare form of impaired glucose metabolism during pregnancy (grade B; consensus).

2. Pre-pregnancy glycemic control

- Poor glycemic control in an early stage of pregnancy is associated with an increase in frequency of congenital anomalies or miscarriage, [1] which, however, can be prevented by tight glycemic control initiated before pregnancy [2] (grade A).
- Advanced chronic diabetic complications in a pregnant woman may affect her delivery outcome and prognosis [3] (grade A).
- Planned pregnancy with adequate pre-pregnancy glycemic control (Table 9) should be performed to prevent congenital anomalies or miscarriage, and not to adversely affect healthy child development and long-term prognosis of the mother.

3. Diabetic retinopathy

- Diabetic retinopathy may be aggravated during pregnancy and therefore needs to be assessed for its presence before pregnancy and closely monitored during pregnancy [4]. Given that proliferative/pre-proliferative retinopathy is particularly highly likely to worsen during pregnancy, a woman who desires to become pregnant should be encouraged to have her retinopathy treated and resolved at an ophthalmologist before becoming pregnant [5] (grade A).

4. Diabetic nephropathy

- Urinary excretion of albumin/protein increases during pregnancy, thus increasing the risk for pregnancy-induced hypertension and premature delivery. Therefore pregnant women with diabetic nephropathy need to be closely monitored [6] (grade A).
- Women with impaired renal function are at risk of further renal impairment during pregnancy and have a poor peripartum prognosis. They should be given careful counseling regarding pregnancy [7] (grade B).

5. Screening for gestational diabetes mellitus (GDM)

- It is desirable that all pregnant women be screened for GDM with a glucose test as a standard procedure, [8] at their initial visit and at gestational 24–28 weeks. A 75 g OGTT should be performed in all women who tested positive at a prior glucose test to establish the diagnosis of GDM (grade A).

6. Glycemic control during pregnancy

- The objective of glycemic control during pregnancy is to prevent the development of peripartum complications and macrosomia. Thus, tight glycemic control is critically important [9] (grade A).
- Required glucose levels should be as close as possible to within the normal diurnal glycemic variation range. In addition, the risk of hypoglycemia should be minimized. The glucose target should be as follows: a fasting glucose level of 70–100 mg/dL, 2-h postprandial glucose level of less than 120 mg/dL (grade A; consensus).
- Frequent SMBG is desirable to ensure tight glycemic control [10] (grade A).

7. Diet therapy

- Diet therapy should be aimed at ensuring providing pregnant women with necessary and sufficient nutrition, thereby promoting healthy child development as well as ensuring tight glycemic control and appropriate weight gain in these women (grade A).

8. Insulin therapy

- Insulin therapy should be given in pregnant women in whom the glycemic goals cannot be achieved with diet therapy alone. As the use of glucose-lowering agents is not recommended,¹¹ they should be switched to insulin therapy (grade A; consensus).
- Intensive insulin therapy with SMBG is preferable in pregnant women to ensure tight glycemic control. Multiple daily insulin injection and CSII are shown to be not different in efficacy [12].
- While it is shown that the use of rapid insulin analogues and regular insulin in pregnant women do not differ significantly in their influence on their fetuses, [13] the safety of insulin glulisine remains yet to be established (grade A).
- The long-acting insulin analogue insulin detemir can be used in pregnant women, [14] but, at present, the safety of insulin glargine in pregnant women remains yet to be established (grade B).

9. Exercise therapy

- There is no evidence that provide the rationale for encouraging exercise therapy among pregnant women with GDM (grade C; consensus).

10. Delivery and post-delivery management

- The term and mode of delivery should follow usual obstetric indications. However, vaginal delivery may be avoided in some patients with advanced proliferative retinopathy (grade B; consensus).
- Neonates from mothers with GDM should be monitored, and if they are found to have complications or to be at high risk of developing complications, they should be transferred to the neonatal intensive care unit (NICU) (grade A; consensus).
- Breastfeeding is recommended (grade A; consensus).

11. Reassessment of mothers with GDM for glucose tolerance

- Women with GDM should be reassessed for glucose tolerance with a 75 g OGTT 6–12 weeks after delivery (grade B; consensus).
- All women with a history of GDM are at high risk of developing diabetes and therefore need to be followed up [15] (grade A).

17 Pediatric/adolescent diabetes

1. Fundamental considerations

- The treatment of pediatric/adolescent diabetes should take into account the age and developmental status of each patient, with due consideration also given to their mental instability or insecurity (grade A; consensus).
- The required energy intake for these patients should be calculated based on Table 10, and in reference to their ideal body weight.

2. Type 1 diabetes in children and adolescents

1) Goals of treatment

- The goals of treatment are to prevent diabetic complications through glycemic control and to maintain socially and mentally healthy status in children and adolescents with type 1 diabetes (grade A; consensus).

2) Insulin therapy

- Insulin injections are indispensable for type 1 diabetes and therefore should be initiated as soon as a patient has been diagnosed with type 1 diabetes (grade A; consensus).

Table 10 Dietary Reference Intakes: Estimated Energy Intakes (kcal/day)

Sex	Male			Female		
	I	II	III	I	II	III
Physical activity level						
Age						
0–5 months	–	550	–	–	500	–
6–8 months	–	650	–	–	600	–
9–11 months	–	700	–	–	650	–
1–2 years	–	1,000	–	–	900	–
3–5 years	–	1,300	–	–	1,250	–
6–7 years	1,350	1,550	1,700	1,250	1,450	1,650
8–9 years	1,600	1,800	2,050	1,500	1,700	1,900
10–11 years	1,950	2,250	2,500	1,750	2,000	2,250
12–14 years	2,200	2,500	2,750	2,000	2,250	2,550
15–17 years	2,450	2,750	3,100	2,000	2,250	2,500
18–29 years	2,250	2,650	3,000	1,700	1,950	2,250
Pregnancy/lactation						
Pregnant women (add)						
Early phase				+50	+50	+50
Middle phase				+250	+250	+250
Late phase				+450	+450	+450
Lactating women (add)				+350	+350	+350

Values for adults were calculated by using the equation: estimated energy intake = basal metabolic rate (kcal/day) $\times$ physical activity level. The physical activity levels for individuals aged 18–29 years are defined as: I = 1.50; II = 1.75; and III = 2.00. Data source: “Dietary Reference Intakes for Japanese” Development Committee. Report of the “Dietary Reference Intakes for Japanese” Development Committee, Ministry of Health, Labour and Welfare, Tokyo, 2009

- The glycemic goals for adults are also used for patients 18 years old or older [1]. As insulin resistance is shown to increase physiologically during puberty, the insulin dose (/kg body weight) for patients is often increased during puberty compared to that before puberty [2].

3) Diet therapy

- The point of diet therapy does not lie in dietary restriction. Rather, diet therapy is aimed at providing patients with necessary and sufficient nutrition for normal development and growth, as adjusted by age and sex (grade A; consensus).

4) Exercise therapy

- In the absence of advanced diabetic complications, and as long as stable glycemic control is obtained in patients, they are encouraged to participate in all kinds of sports available (grade A; consensus).

5) Hypoglycemia

- Hypoglycemia may induce cognitive dysfunction [3, 4]. Patients younger than 7 years old may be unaware of hypoglycemic episodes and develop severe hypoglycemia, and this needs to be kept in mind (grade A).
- From puberty onward, not only hypoglycemia but poor glycemic control and persistent hyperglycemia are associated with the onset of cognitive dysfunction in adolescents [4] (grade B).

3. Type 2 diabetes in children and adolescents

1) Diagnosis

- In a glucose loading test for diagnosis of type 2 diabetes in children and adolescents, the amount of glucose to be loaded is calculated with the equation: measured weight $\times$ 1.75 g (upper limit, 75 g). The hyperglycemic categories and criteria for diabetes for children and adults are the same as those for adults (grade A; consensus).

2) Goals of treatment

- As in pediatric/adolescent type 1 diabetes, the goals of treatment are to prevent diabetic complications through glycemic control and to maintain socially and mentally healthy status in type 2 diabetic children and adolescents (grade A; consensus).
- Prevention of microangiopathy and macroangiopathy in young adults requires initiation of intervention directed at the risk factors responsible for their aggravation [5] (grade A).

3) Diet therapy

- The point of diet therapy does not lie in dietary restriction. Rather, diet therapy is aimed at providing patients with necessary and sufficient energy for normal development and growth, as adjusted by age and sex (grade A; consensus).
- In obese patients, the amount of energy intake should be adjusted to 90–95 % of the energy required for their ideal body weight (grade A; consensus).

4) Exercise therapy

- Every effort should be made to increase physical activity levels and energy expenditure in pediatric/adolescent patients with type 2 diabetes to improve insulin resistance (grade A; consensus).

5) Treatment with glucose-lowering agents

- In patients whose glycemic goals cannot be achieved with diet/exercise therapy alone, glucose-lowering agents should be initiated (grade B; consensus).
- In patients with ketoacidosis or those in whose adequate glycemic control cannot be achieved with glucose-lowering agents, insulin therapy should be used (grade A; consensus).
- Patients with type 2 diabetes should also be treated for hypertension and dyslipidemia if they are found to have these conditions as well (grade B; consensus).

18 Diabetes (and bone metabolism) in the elderly

1. Diabetes in the elderly

- Diabetes increases in frequency with aging [1] (grade A).
- Diabetes in the elderly is a risk factor for diabetic microangiopathy, [2] macroangiopathy, [3] dementia,

[4] depression, [5] and decreased activities of daily living (ADL), [6] and fractures [7] (grade A).

- In the elderly, treatment policy needs to be individually determined with the patient's status in mind. Glycemic control is difficult to achieve in patients with many comorbidities.

2. Diagnosis of diabetes in the elderly

- The same procedures and reference values are used for the diagnosis of diabetes in the elderly. However, elderly patients are frequently diagnosed as having diabetes based on HbA1c, 2-h post-load glucose levels, and hyperglycemia on casual blood glucose measurements, even when they fail to meet the diagnostic criteria for fasting glucose levels [8] (grade A).

3. Diet/exercise therapy in the elderly

- In the elderly as well, both diet therapy [9] and exercise therapy [10, 11] are effective treatments for diabetes [12]. Continued exercise is shown to be useful for prevention of macroangiopathy and dementia, as well as for maintenance and improvement of ADL (grade A).

4. Drug therapy and hypoglycemia in the elderly

- In the elderly as well, drug therapy is an effective treatment for diabetes [13, 14] (grade B).
- Severe hypoglycemia associated with drug therapy is likely to occur in elderly patients, [15] particularly those aged 75 years old or older, [16] and in conjunction with conditions such as multi-drug therapy, immediately after discharge, renal failure, and decreased dietary intake. The elderly tend to be less aware of hypoglycemic episodes as they occur and present with atypical complaints. Severe hypoglycemia increases the risk of dementia [17] (grade B).
- It is accepted that biguanides should be given to elderly patients with caution [18] (grade C).

5. Characteristics of diabetes in the elderly and precautions in treatment

- A high proportion of elderly patients with diabetes are likely to have difficulty being independent and taking care of themselves [6] due to vascular complications, particularly macroangiopathy, [4]

decreased ADL and cognitive function associated with diabetes. The glycemic goal for an elderly patients should be based on his/her disease condition and other physical, mental and social factors rather than based on evidence from randomized controlled trials (RCTs) that established the efficacy of tight glycemic control. On the other hand, it is suggested that the HbA1c goal should be set 1 % higher for frail elderly patients than that for other age groups [19] and that attention should be given to ensuring that glucose lowering is not too drastic for these patients [19] (grade A).

- In elderly patients as well, every effort should be made to optimize glucose, blood pressure and lipid levels, and body weight to prevent the development/progression of micro- and macroangiopathy. In elderly patients for whom maintenance and improvement of their QOL is a priority, attention should be given to ensuring that diabetes treatment does not lead to decreases in their QOL (grade A; consensus)

6. Bone metabolic disorders associated with diabetes

- Bone strength is accounted for by two factors, i.e., bone mass and bone quality. While bone mass is shown to be increased, [20] rather than decreased, in diabetes, diabetic patients are at high risk of developing fractures [7] (grade A).
- The use of thiazolidinediones places female patients at increased risk of developing fractures [21] (grade B).
- The use of alendronate is associated with increases in bone mass, [22] and decreases in fracture risk (grade B).

19 Acute metabolic complications of diabetes

1. Diabetic ketoacidosis (DKA)

1) Diagnosis

- Diabetic ketoacidosis (DKA) is defined as a state in which a severe shortage of insulin and an increase in counter regulatory hormones combine to induce hyperglycemia (≥ 250 mg/dL), hyperketonemia (increased β -hydroxy-butyric acid), and acidosis (pH, < 7.30 ; bicarbonate concentration, < 18 mEq/L) requiring emergency care [1] (grade A; consensus).

2) Treatment

- Patients with DKA are to be given water and sodium supplementation with saline-based infusions [1] (grade A; consensus).
- It is important to ensure appropriate potassium supplementation in patients with DKA [1] (grade A; consensus).
- Acidosis is not to be corrected in patients with DKA [1, 2] (grade A).
- Low-dose insulin (intravenous infusion of regular insulin) is to be given continuously to patients with DKA (grade A; consensus).

3) Complications associated with DKA

- Patients with DKA may be associated with brain edema, hyperchloremic metabolic acidosis, and hypokalemia, and should therefore be monitored for consciousness, vital signs, and electrolytes over time during the course of treatment (grade A; consensus).

2. Hyperosmolar hyperglycemic state (HHS)

1) Diagnosis

- Hyperosmolar hyperglycemic state (HHS) is likely to occur when patients with type 2 diabetes become hyperglycemic due to infection, cerebrovascular disease, surgery, high-calorie infusions, and inappropriate use of diuretics or steroids. While HHS is known to be common in the elderly, it is also drawing attention as an initial symptom of pediatric type 2 diabetes (particularly in African-Americans) (grade A; consensus).
- HHS leads to varying levels of impaired consciousness, polydipsia due to dehydration, polyuria, and general malaise but its onset is slower than DKA with the time to onset of disease being a few days or a week (grade A; consensus).
- Patients with HHS exhibit hyperglycemia (≥ 600 mg/dL) and a hyperosmolar state (≥ 320 mOsm/L) but do not have acidosis (pH, ≥ 7.30 ; bicarbonate concentration, ≥ 18 – 20 mEq/L) (grade A; consensus).

2) Treatment

- Patients with HHS are to be given water and sodium supplementation with saline-based infusions (grade A; consensus).

- As in patients with DKA, patients with HHS are to be treated with intravenous infusion of regular insulin [1] (grade A; consensus).

3) Complications associated with HHS

- Patients with HHS may be associated with brain edema, pneumonitis, gastrointestinal hemorrhage, renal failure, cerebrovascular disease, pulmonary thrombosis, and hypokalemia and should therefore be monitored for consciousness, vital signs, and electrolytes over time during the course of treatment (grade A; consensus).

3. Lactic acidosis

1) Diagnosis

- Lactic acidosis is defined as a state of metabolic acidosis that results from a marked increase in blood lactic acid (>5.0 mmol/L) associated with lactic acid overproduction or impaired lactic acid metabolism that require emergency care (grade A; consensus).
- While lactic acidosis is reported to have developed in patients receiving biguanides, a majority of these patients were those in whom biguanides had been a contraindication or their careful administration had been indicated in the first place (grade A; consensus).

2) Treatment

- In patients presenting with tissue hypoxia, adequate tissue perfusion and oxygenation are to be ensured (grade A; consensus).
- Patients with lactic acidosis are to be treated for any underlying diseases present (grade A; consensus).
- Patients with lactic acidosis are to be treated with oxygen supplementation, artificial respiration, extracellular fluid supplementation or vasopressors drug, depending on their disease condition (grade A; consensus).
- Hemodialysis is reported to be effective in improving lactic acidosis associated with the use of biguanides [3] (grade C).

4. Hypoglycemia

1) Prevention of hypoglycemia

- Given that hypoglycemia remains a major obstacle to diabetes treatment, it is recommended that patients at

risk receive education on its prevention and preventive measures and learn to use self-monitoring of blood glucose (SMBG) (grade A; consensus).

2) Diagnosis of hypoglycemia and treatment

- If a patient presents with palpitation, sweat, faintness or a decreased level of consciousness and has a glucose level of 70 mg/dL or lower, the patient is to be diagnosed as having hypoglycemia and treated accordingly. As a preliminary measure, patients with potential hypoglycemia are encouraged to have their glucose levels measured (e.g., using a SMBG device) (grade A; consensus).
- If a patient has been confirmed to have hypoglycemia, the patient is to be immediately given carbohydrates (equivalent to 5–10 g of glucose) orally, an intravenous infusion of glucose (equivalent to 10–20 g of glucose), or an intramuscular injection of glucagon. Patients with a history of hypoglycemia are at risk of recurrent or prolonged hypoglycemia even after recovery from hypoglycemia and therefore need to be monitored closely with appropriate measures taken against hypoglycemic episodes (grade A; consensus).

3) Asymptomatic hypoglycemia

- Recurrent hypoglycemia may induce a decrease in counter regulatory hormone response as well as asymptomatic hypoglycemia. To prevent this, it is important to take measures to avoid hypoglycemic episodes and maintain favorable glycemic control on a routine basis (grade A; consensus).

4) Drug-induced hypoglycemia

- Of the oral glucose-lowering agents, long-acting sulfonylureas, in particular, are likely to cause hypoglycemia (grade A; consensus).
- Of the insulin preparations, rapid-acting insulin analogues and long-acting soluble insulin analogues are thought less likely to be associated with hypoglycemia than conventional regular insulin and intermediate insulin [4] (grade B).
- Intensive insulin therapy is shown to increase severe hypoglycemia by about threefold in frequency compared to conventional therapy. Therefore, the goal for glycemic control needs to be determined for each patient depending on his/her disease condition [5] (grade A).

20 Diabetes, infectious diseases and sick days

1. Diabetes and susceptibility to infection

- Patients with diabetes showing poor glycemic control are susceptible to bacterial, tuberculous and fungal infection, which, in turn, tend to become severe (grade A; consensus).
- Next to malignant neoplasms and vascular diseases, infectious diseases are the third most common cause of death (14.3 %) in Japanese patients with diabetes, [1] with the age at death from infections shown to be younger in those with poor glycemic control than in those with favorable glycemic control [1].

2. Glycemic control in the presence of infection

- In the presence of infection, glucose levels tend to increase in patients with diabetes, and this increase in glucose makes them less resistant to the infection. Therefore, insulin should be used to maintain favorable glycemic control in these patients during the treatment of infection requiring hospitalization (grade A; consensus).

3. Diabetes and influenza (including that by pandemic influenza [H1N1]2009)

- Patients with diabetes are at high risk of death from influenza and secondary pneumonia. Thus, seasonal influenza vaccination is recommended in patients in whom vaccination is not contraindicated. Patients with diabetes should be instructed to immediately seek medical consultation, undergo relevant examinations and receive appropriate treatment if influenza is suspected because of a high fever or a chill (grade A; consensus).

4. Sick-days

- A sick-day may be defined as a time when patients with diabetes have a fever, diarrhea or vomiting or are unable to eat due to appetite loss. During such sick-days, special measures are required to avoid hyperglycemia or ketoacidosis (grade A; consensus).
- Patients with diabetes should be instructed in daily clinical practice to consult their physicians about how to manage their sick-days and not to act on their own judgment (e.g., discontinue insulin or OHAs or reduce

their dose too much if they are on insulin or glucose-lowering agents).

- During sick-days, glucose levels tend to increase in patients on insulin, despite limited dietary intake, through the influence of insulin-antagonistic hormones. Therefore, it is important to drink water and continue insulin therapy even during sick-days, while adjusting the insulin dose.
- Immediate medical consultation is required when the patient
 - ① has a fever and severe gastrointestinal symptoms
 - ② is unable to eat/is able to eat only a small amount of food for a 24-h period
 - ③ has positive urinary ketones or glucose level ≥ 350 mg/dL
 - ④ has altered mental status

At the time of consultation, the patient should be assessed for urine ketone body.

21 Diabetes and pancreas/islet transplantation

1. Pancreas transplantation

- Pancreas transplantation is indicated for insulin-dependent patients with diabetes in whom glycemic control is extremely difficult. In patients with renal failure undergoing simultaneous pancreas-kidney transplantation (SPK), the proportion of patients discontinuing insulin therapy 5 years later was shown to be high at about 70 %, suggesting the usefulness of SPK [1, 2] (grade B).
- Pancreas transplantation alone has only a limited indication, as it is associated with a poorer graft survival rate than that with SPK [1] (grade C).
- SPK is associated with improved life prognosis and renal graft survival rates, as compared to those with kidney transplantation alone (KTA) [3].
- As with SPK, pancreas transplantation after kidney transplantation (PAK) is associated with improved life prognosis and renal graft survival rates, as compared to those with KTA [4] (grade C).
- Normalization of glycemia with pancreatic transplantation leads not only to improved QOL but reduces micro- and macroangiopathy [5, 6] (grade C).
- Survival rate and pancreatic graft survival rate for 5 years are 95.5 and 71.6 % in Japan, respectively [2].

- In Japan, the Organ Transplant Law went into effect in 1997 and pancreatic transplantation has been included for insurance coverage since April 1, 2006.

2. Islet transplantation

- Islet transplantation is a tissue transplant procedure through which pancreatic islets are isolated and infused into the liver via the portal vein. This procedure is being investigated as a potential therapeutic modality for patients with favorable renal function who experience recurrent episodes of asymptomatic hypoglycemia or severe hypoglycemia and in whom glycemic control is difficult to achieve. While the proportion of patients discontinuing insulin therapy is low, this procedure is shown to improve glycemic control and reduce hypoglycemia [7] (grade C).
- As with SPK and PAK, islet transplantation after renal transplantation is shown to provide renal graft protection [8] (grade C).
- In patients undergoing pancreatic removal for chronic pancreatitis or pancreatic injury, autologous islet transplantation is shown to be useful for post-removal glycemic control [9] (grade C).

22 Diabetes self-management education

1. Diabetes self-management education and its effectiveness

- Diabetes self-management education is effective for achieving/maintaining favorable metabolic control and preventing the development and progression of diabetic complications [1–3] (grade A).

2. Diabetes self-management education by a multidisciplinary team

- A multidisciplinary team approach involving relevant experts enhances outcomes of diabetes self-management education [1, 4] (grade A).
- It is desirable that responsibilities are appropriately divided, and relevant information and goals shared, among the experts involved to allow continued collaboration in various settings (grade A; consensus).
- A multidisciplinary team is to consist of a variety of healthcare professionals, who include nurses, dietitians, pharmacists, clinical laboratory technicians,

physical therapists, clinical psychologists if available, and social workers, in addition to physicians in relevant specialties. While all members are allowed to give an outline of diabetes care, they are to turn to relevant experts for a discussion of details.

3. Involvement of specially trained diabetes educators

- Diabetes education involving specially trained nurses and other healthcare professionals is shown to be effective for improving a patient's knowledge of diabetes, self-care ability, and attitude (e.g., motivation and orientation) as well as for glycemic control, at least, in the short term [5] (grade A).
- Experts participating in a multidisciplinary team may also be expected to play a role as a case manager or coordinator [4] (grade A).
- Certified diabetes educators in Japan are defined as all licensed nurses, dietitians, pharmacists, clinical laboratory technicians, and physical therapists, who qualified for and passed a diabetes educator examination and were certified by the Certification Board for Diabetes Educators in Japan.

4. Standardized curricula meeting a set of specific standards

- Standardized group training programs are shown to be useful when they intend to promote continued patient self-care behavior and meet a set of specific standards [2]. Patient self-care behavior include self-management of diet/exercise therapy, beneficial stress management, drug adherence, self-monitoring, and self-management of acute/chronic diabetic complications (grade A).

5. Importance of self-monitoring of diabetes

- As diabetes remains largely asymptomatic, self-monitoring of diabetes by patients is useful for their self-management. Preferably, instructions aimed at promoting self-monitoring of diabetes should address how they should self-monitor diabetes and determine goals for self-monitoring, as well as how they may translate self-monitoring into self-care behavior [1, 6–8]. Major topics of interest to self-monitoring of diabetes include SMBG, and documentation of body

weight/meals taken, physical activity (pedometer measurement) and blood pressure (grade A).

- SMBG is essential for the maintenance of glycemic control in all patients with type 1 diabetes [1] (grade A).
- SMBG is shown to be effective for improving glycemic control as well as for promoting diabetes self-management education in patients with type 2 diabetes receiving insulin therapy, [6] while this remains to be established in patients with type 2 diabetes not receiving insulin therapy [9] (grade A).
- SMBG is essential for ensuring tight glycemic control in most patients with gestational diabetes as well as in patients with diabetes in pregnancy [7] (grade A).
- SMBG is essential for ensuring the safe treatment of patients with diabetes less or not sensitive to hypoglycemic episodes, and the use of hypoglycemia awareness programs is effective [8] (grade A).

6. Increasing patient potential for diabetes self-management and mental support

- The process of helping patients to explore and exploit their self-managing potential is best defined as empowerment. It is beneficial to appreciate the patients' psychosocial aspects based on mutual trust, to explore opportunities for their initiative and participatory involvement by means of open questions, and to help them solve care-related problems and make informed decisions [10] (grade A).
- In empowering patients, it is required to watch for changes in their behavior and to provide with timely, behaviorally-oriented assistance as well as psychological support [11, 12] (grade A).

7. Need for assessment of diabetes self-management education

- While diabetes self-management education can be assessed for its effects directly by questioning the patients being educated about improvements in their diabetes knowledge/skills, changes in their behavior and their behavioral processes, ultimately, diabetes care education needs to be assessed for outcome in terms of medical records, patient QOL and prognosis as well as medical costs [1, 4] (grade B).
- Multidisciplinary DMSE teams are to be assessed for their effects in terms of their structure, processes, and outcomes (grade B; consensus).

8. Putting treatment guidelines into practice and disseminating their use

- "Treatment Guide for Diabetes" edited by the JDS is a practical guide to putting the evidence-based guidelines compiled by the JDS into clinical practice; and it is thought to be useful in standardizing diabetes care and promoting collaboration within teams and between local healthcare institutions, in that it allows diabetes care to be customized to meet the needs of each team or facility, while at the same allowing delivery of consistently uniform diabetes care (grade B; consensus).
- Timely delivery of DMSE or counseling by telephone or on the Internet is effective in empowering patients and healthcare professionals for diabetes care [13] (grade B).

23 Prevention of type 2 diabetes

1. Screening of at-risk individuals for prevention of type 2 diabetes

- Patients with IGT are at high risk of developing diabetes. Regular examinations are recommended in those aged 45 years old or older as well as in individuals with obesity. Who are physically inactive, or have a family history of diabetes, a history of gestational diabetes or delivery of a macrosomia, a history of hypertension, dyslipidemia, polycystic ovarian syndrome, disease conditions that induce insulin resistance, cardiovascular disease, or IGT even when younger than 45 years old [1] (grade A; consensus).
 - As IGT and diabetes are shown to be present not only in individuals with a fasting glucose level of 110 mg/dL or higher but also in 25–40 % of "normal-high" individuals with a fasting glucose level of 100–109 mg/dL, 75 g OGTTs are recommended in these groups.
 - The risk of developing diabetes is shown to increase by 31.9-fold in Japanese who showed both impaired fasting glucose (IFG) (fasting glucose levels, 100–125 mg/dL) and HbA1c levels 5.7–6.4 %, compared to those with normal glucose tolerance and HbA1c levels [2].

2. Instructions on lifestyle modification

- It is recommended that total energy intake be optimized, and body weight reduced by 5–10 % through lifestyle

modification, in high-risk patients associated with IGT and overweight/obesity [1] (grade A; consensus).

- It is suggested that dietary fiber-rich unrefined grains, low-glycemic index (GI) foods, [3, 4] green leafy vegetables, [5] and fish [6] may be effective in protecting against diabetes (grade A).
- Of the lifestyle intervention studies conducted to date for diabetes prevention, a Japanese intervention study demonstrated that lifestyle intervention reduce the onset of diabetes in an IGT population [7].
- Lifestyle intervention in Japanese subjects with IFG also has been shown to lead to prevention of type 2 diabetes in these individuals [8]

3. Instructions on exercise therapy

- Individuals at risk are recommended to do aerobic exercise such as walking for 150 min/week [9] (grade A).
- Exercise is shown to prevent the development of diabetes, independently of weight loss [9] (grade A).

4. Instructions on preference modification

- Smoking is an independent risk factor for the development of diabetes [10] (grade D).
- While light to moderate drinking is shown to reduce the onset of diabetes, [11] even moderate drinking is reported to be a risk factor for the development of diabetes in Japanese lean adults [12]. It is thus recommended to limit drinking to a moderate amount (25 g of alcohol per day) (grade B).
- While coffee intake is highly likely to be a preventive factor for the development of diabetes, [13] evidence available to support this is not strong enough to include it among the recommendations (grade C).
- Quantity of sleep [14] and depression [15] are also shown to be associated with the development of diabetes (grade B).

5. Clinical research into drug therapy-based prevention

- Some oral glucose-lowering agents (e.g., biguanides, α -glucosidase inhibitors), anti-obesity drugs, antihypertensive agents, lipid-lowering agents, estrogen hormone replacement therapy have been shown to protect against the development of diabetes [16–19]. However, some

of these drugs pose concern over their long-term safety (grade B).

24 Metabolic syndrome

1. Metabolic syndrome: its concept

- The metabolic syndrome is defined as a clustering in individuals of risk factors for the development of atherosclerosis and type 2 diabetes, which include visceral obesity, insulin resistance/hypertension, dyslipidemia (e.g., hypertriglyceridemia, low HDL-cholesterolemia), and elevated blood pressure [1–3] (grade A; consensus).

2. Diagnostic criteria for the metabolic syndrome (Table 11)

- Visceral fat accumulation plays a major role in the metabolic syndrome [2, 3] (grade B; consensus).
- Waist circumference serves as a measure of estimated visceral fat accumulation, and a screening measure based on visceral fat volume estimation for prevention of atherosclerosis [2] (grade B; consensus).
- Japanese diagnostic criteria for metabolic syndrome include increased waist circumference as an essential criterion [4].

3. Clinical implications of the metabolic syndrome

- The risk of developing type 2 diabetes is shown to increase in individuals with the metabolic syndrome by three to sixfold compared to those without the metabolic syndrome [5] (grade A).
- The risk of cardiovascular morbidity and mortality is shown to be 1.5- to 2-fold higher in those with the metabolic syndrome, compared to those in those without the metabolic syndrome [5] (grade B).

4. Treatment of the metabolic syndrome

- The metabolic syndrome is treated to prevent associated cardiovascular disease and type 2 diabetes [2, 3] (grade B).
- The cornerstone of treatment for the metabolic syndrome is lifestyle modification such as diet/exercise therapy and smoking cessation [6] (grade B).

Table 11 Diagnostic criteria for the metabolic syndrome

Component	Joint Statement (2009)	Japanese Criteria (2005)	IDF (2005)	AHA/NHLBI (NCEP-R) (2005)	NCEP ATP III (2001)	WHO (1999)
Essential component		Visceral (intraabdominal) fat accumulation	Central obesity			Insulin resistance
		Waist circumference: Male ≥ 85 cm Female ≥ 90 cm (equivalent in either to a visceral fat area of ≥ 100 cm ²)	Waist circumference Male ≥ 85 cm Female ≥ 90 cm (criteria for Japanese)			Association with IGT or diabetes and/or presence of insulin resistance
Diagnostic criteria		If two or more of the following criteria are met	If two or more of the following criteria are met	If three or more of the following criteria are met	If three or more of the following criteria are met	If two or more of the following criteria are met
Abdominal obesity	Race- and country-specific criteria			Waist circumference Male ≥ 102 cm Female ≥ 88 cm	Waist circumference Male ≥ 102 cm Female ≥ 88 cm	Waist-to-hip ratio Male < 0.9 Female > 0.85 or BMI ≥ 30 kg/m ² or Waist circumference ≥ 94 cm
TG	≥ 150 mg/dL*	≥ 150 mg/dL* and/or	≥ 150 mg/dL*	≥ 150 mg/dL*	≥ 150 mg/dL	≥ 150 mg/dL
HDL-C	Male < 40 mg/dL* Female < 50 mg/dL*	< 40 mg/dL* in either sex	Male < 40 mg/dL* Female < 50 mg/dL*	Male < 40 mg/dL* Female < 50 mg/dL*	Male < 40 mg/dL Female < 50 mg/dL	Male < 35 mg/dL Female < 39 mg/dL
SBP	≥ 130 mmHg	≥ 130 mmHg*	≥ 130 mmHg*	≥ 130 mmHg*	≥ 130 mmHg	≥ 130 mmHg
DBP	≥ 85 mmHg	≥ 85 mmHg*	≥ 85 mmHg*	≥ 85 mmHg*	≥ 85 mmHg	≥ 90 mmHg
FPG	≥ 100 mg/dL	≥ 110 mg/dL*	≥ 100 mg/dL* or prior diabetes	≥ 100 mg/dL*	≥ 110 mg/dL*	
Microalbuminuria						≥ 20 μ g/min or ≥ 30 mg/g $\cdot$ Cr

TG triglycerides, HDL-C HDL-cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure, FPG fasting plasma glucose, IDF International Diabetes Federation, AHA/NHLBI American Heart Association/National Heart, Lung, and Blood Institute, NCEP ATP III National Cholesterol Education Program's Adults Treatment Panel III, WHO World Health Organization

* If the patient is receiving drug therapy for hypertriglyceridemia, low HDL-cholesterolemia, hypertension or diabetes, he/she is to be handled accordingly

- Even a weight loss of 5–10 % is shown to significantly alleviate the metabolic syndrome and reduce the incidence of new-onset diabetes, suggesting that reducing visceral fat leads to reductions in the incidence of cardiovascular events [6] (grade B).

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