

Treatment Guide for Diabetes

2016-2017 Edited by Japan Diabetes Society

A

What is diabetes mellitus?

- ▶ **Diabetes mellitus (DM) is a group of diseases characterized by chronic hyperglycemia due to deficiency of insulin action*.**

In type 1 diabetes, deficiency of insulin action is mainly caused by the destruction and loss of β cells in the islets of Langerhans in the pancreas, which produce and secrete insulin (See p.5 : Table 2, Etiological classification of diabetes mellitus and glucose metabolism disorders).

Type 2 diabetes arises as a result of genetic factors including those causing reduced insulin secretion and insulin resistance, and a number of environmental factors such as overeating (especially a high fat diet), lack of exercise, obesity and stress, to which may be added the factor of advancing age.

* Insulin is produced and secreted by the β cells of the pancreatic islets of Langerhans. After passing through the portal vein, insulin reaches the liver, and is carried via the hepatic vein to all the tissues of the body. It binds to the insulin receptors in the cell membrane of the liver, muscles, adipose tissue and other tissues that are insulin-sensitive, and promotes the uptake of glucose into the cells, energy usage and storage, protein synthesis, and cell proliferation.

- ▶ **“Insulin action”** is used to refer to the metabolic regulatory function exhibited by insulin in the tissues of the body. If a balance between the supply of insulin and the insulin requirement of the body is maintained, the metabolism as a whole remains normal, including the plasma glucose level. Decreased insulin secretion, or increased insulin resistance results in insufficient insulin action, and the plasma glucose level rises.
- ▶ **Sustained hyperglycemia** indicates insufficient insulin action. At the minimum degree of plasma glucose increase necessary for a case to be judged as “diabetic type” the patient experiences only mild subjective symptoms, and is frequently not aware of having the disease at all. If a moderately high level of hyperglycemia persists, characteristic symptoms (thirst, polydipsia, polyuria, weight loss and an easy fatigability) appear.
- ▶ **Sudden and marked deficiency of insulin action** causes a sharp increase in the plasma glucose level, ketoacidosis, severe dehydration, and may cause diabetic coma.
- ▶ **Chronic hyperglycemia and other metabolic abnormalities** develop and aggravate microangiopathy of the retina and the kidney, as well as systemic atherosclerosis. In addition, they cause neuropathy and cataracts, and have a very deleterious effect on the patient’s quality of life (QOL).
- ▶ **Even when diabetes develops as a result of pancreatitis and endocrine disorders of well-defined etiology**, complications emerge in the same way as in ordinary diabetes. Consequently, diagnosis and treatment are approached in the same way as in ordinary diabetes.

B

Indicators related to diabetes

1 Indicators of mean blood glucose level

- ▶ **HbA1c** (hemoglobin A1c, glycohemoglobin, GHb), which is produced by glycation of hemoglobin A0: The HbA1c value reflects the mean blood glucose level during one to two months before the time when the blood sample was taken, and is used in the diagnosis of diabetes (See p.10 : [Diagnosis of diabetes mellitus](#)). Moreover, it is an indicator of the status of glycemic control (See p.13 : [Indicators of glycemic control](#)). The standard HbA1c value of subjects with normal glucose tolerance is between 4.6 and 6.2%*. It is related to the lifespan of erythrocytes, and is low during the period of recovery from hemorrhage and iron deficiency anemia, and in hemolytic diseases and advanced liver cirrhosis; and caution is necessary in its evaluation in various hemoglobinopathies because the mean blood glucose level is dissociated from it.

Table 1. Conditions present during dissociation of HbA1c values and blood glucose levels

Higher HbA1c values	Lower HbA1c values	Either higher or lower HbA1c values
<ul style="list-style-type: none">• Rapidly improved diabetes• Iron deficiency	<ul style="list-style-type: none">• Sudden onset or exacerbation of diabetes• Period of recovery from iron deficiency anemia• Hemolysis (erythrocyte lifespan ↓)• After hemorrhage (erythrocyte production ↑), Transfusion• Renal anemia during treatment with erythropoietin• Liver cirrhosis	<ul style="list-style-type: none">• Hemoglobinopathy

* The distribution of HbA1c shows a large overlap between the normal type and the borderline and diabetic types, and around 6.2% for HbA1c (NGSP), the normal type, the borderline type and the diabetic type exist.

- ▶ **Glycoalbumin (GA)**: Glycoalbumin (standard value: 11 ~ 16%) reflects the mean blood glucose level during the previous two weeks. This falls to low values and become dissociated from the mean blood glucose value in conditions such as nephrotic syndrome in diabetic nephropathy, in which the blood protein half-life shortens due to protein loss, and becomes dissociated from the mean blood glucose value.
- ▶ **1,5-AG** (1,5-anhydroglucitol: 1,5-AG (standard value: $\geq 14.0 \mu\text{g/mL}$) is useful as an indicator of sudden change in glucose metabolism. It falls when the amount of glucose excreted in the urine is increased. Consequently, in contrast with the other indicators, 1,5-AG falls as the condition of glucose metabolism worsens. Watch for abnormal 1,5-AG values, lower-than-mean glucose levels, which may be seen with the use of the α -glucosidase inhibitor acarbose and SGLT2 inhibitors.

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COLUMN

Changes in the system of notation accompanying the international standardization of HbA1c— for now, the written use of both HbA1c (NGSP) and HbA1c (JDS)

HbA1c is widely used internationally as an important index in the treatment of diabetes. However, a problem arose in Japan: HbA1c as it has been expressed in Japan using the Japan Diabetes Society (JDS) system gives values that are approximately 0.4% lower than the National Glycohemoglobin Standardization Program (NGSP) values. Therefore, it was decided by the Japan Diabetes Society to augment by 0.4% the JDS values in use until then for HbA1c (JDS values), in order to give a new expression of HbA1c values, so that, from then on, these values would be termed “International Standard Values”. (these “International Standard Values” were not the NGSP values themselves, but were stubbornly made to correspond to the NGSP values.)

Afterwards, however, on October 1, 2011, an organization known as the Reference Material Institute for Clinical Chemistry Standards (ReCCS) obtained certification as the Secondary Reference Laboratory (SRL) in the Asian region, a facility carrying out NGSP standards measurement as well as regulation and optimization of testing for the purpose of international standardization, and aiming, through consultations with associated organizations, to fix the value of NGSP (%) at $JDS (\%) \times 1.02 + 0.25 (\%)$, $JDS \text{ value } (\%) = NGSP \text{ value } (\%) \times 0.980 - 0.245 (\%)*1$. (See footnote* for further details related to this formula.) As a result, instead of the “International Standard Value” (the NGSP equivalent), it can now formally be called the “NGSP value”. Consequently, since April 1, 2012, the label and the directions for use for HbA1c are changed as indicated in the following:

1. For clinical practice also, the NGSP value is used, and the label is marked HbA1c (NGSP). The former JDS value appears as HbA1c (JDS), but as of April 1 2014, HbA1c labeling will feature only the NGSP values*2, with no JDS value shown.
2. To avoid problems with changes in the system related to specific health checkups and to specific health guidance, during the period from April 1, 2012 to March 31, 2013, notification of the patients examined as to their results, and provision of reports of the results to the medical insurers were carried out as usual using only JDS values. As of April 1, 2013, however, notification of results and provision of reports of results are being done using only the NGSP values.

For further details, please refer to the web page of the Japan Diabetes Society (<http://www.jds.or.jp/>).

*1 When this conversion formula is used for calculation, the following results are obtained (rounded down to one place of decimals): (1) For JDS values of $\leq 4.9\%$, NGSP values (%) = JDS values (%) + 0.3%. (2) For JDS values of 5.0~9.9%, NGSP values (%) = JDS values (%) + 0.4%. (3) For JDS values of 10.0~9.9%, NGSP values (%) = JDS values (%) + 0.5%. Whereas, [1] for NGSP values of $\leq 5.2\%$, JDS values (%) = NGSP values (%) - 0.3%. [2] For NGSP values of 5.3~10.2%, JDS values (%) = NGSP values (%) - 0.4%. [3] For NGSP values of 10.3~15.2%, JDS values (%) = NGSP values (%) - 0.5%.

*2 The HbA1c value no longer requires qualifying by adding “(NGSP)” after HbA1c.

see Journal of Diabetes Investigation Volume 3, Issue 1, p39–40, 2012

C

Classifications of diabetes

► Diabetes mellitus is classified from both etiological and pathophysiological standpoints.

1 Etiological classification of diabetes

Table 2. Etiological classification of diabetes mellitus and glucose metabolism disorders*

<p>I. Type 1</p>	<p>Destruction of pancreatic β cells, usually leading to absolute insulin deficiency</p> <p>A. Autoimmune</p> <p>B. Idiopathic</p>
<p>II. Type 2</p>	<p>Ranging from predominantly insulin secretory defect, to predominantly insulin resistance with varying degrees of insulin secretory defect</p>
<p>III. Due to other specific mechanisms or diseases</p>	<p>A. Those in which specific mutations have been identified as a cause of genetic susceptibility</p> <p>① Genetic abnormalities of pancreatic β cell function</p> <p>② Genetic abnormalities of insulin action</p> <p>B. Those associated with other diseases or conditions</p> <p>① Diseases of exocrine pancreas</p> <p>② Endocrine diseases</p> <p>③ Liver disease</p> <p>④ Drug- or chemical-induced</p> <p>⑤ Infection</p> <p>⑥ Rare forms of immune-mediated diabetes</p> <p>⑦ Various genetic syndromes often associated with diabetes</p>
<p>IV. Gestational diabetes mellitus</p>	

* The occurrence of diabetes-specific complications has not been confirmed in some of these conditions. Those that cannot at present be classified as any of the above are called unclassifiable.

Excerpted with slight modification from the Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus : report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetology International.1(1):7,2010

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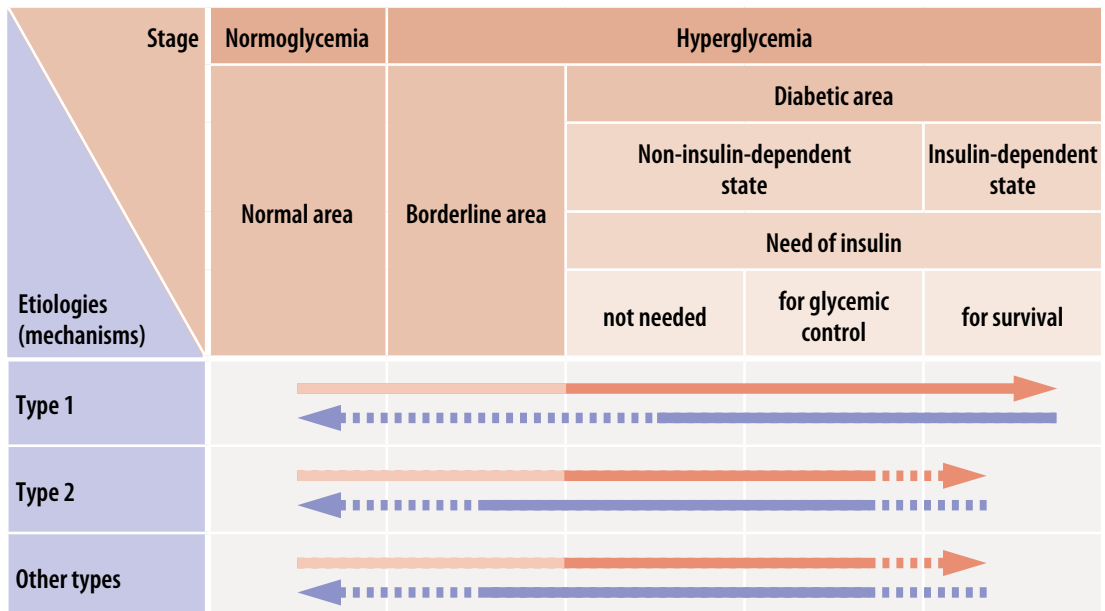
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1 Diabetes mellitus: The disease itself

2 Etiological classification and pathophysiological stages of diabetes mellitus

Figure 1. 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, — and — indicate the condition classified as “diabetes mellitus”. Arrows pointing left represent improvement in the glucose metabolism disorder. The broken lines indicate stage of low frequency.

Excerpted with slight modification from the Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus : report of the committee on the classification and diagnostic criteria of diabetes mellitus. Diabetology International.1(1):6,2010

- ▶ Patients with acute-onset type 1 diabetes are likely to develop ketosis or ketoacidosis, generally, within 3 months of onset of symptoms of hyperglycemia, thus requiring insulin therapy immediately. In contrast, those with slowly-progressive type 1 diabetes are not likely to develop ketosis or ketoacidosis even after diagnosis, thus not requiring insulin therapy immediately. Again, those with fulminant type 1 diabetes are likely to develop ketosis or ketoacidosis within 1 week of onset of symptoms of hyperglycemia with the hallmark being their relatively low HbA1c values versus their glucose values, thus requiring insulin therapy immediately.

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Criteria for definite diagnosis of fulminant type 1 diabetes mellitus (Fulminant type 1 diabetes mellitus is confirmed when all the following three findings are present)

1. Occurrence of diabetic ketosis or ketoacidosis soon (around 7 days) after the onset of hyperglycemic symptoms (elevation of urinary and/or serum ketone bodies at first visit)
2. Plasma glucose level ≥ 16.0 mmol/L (≥ 288 mg/dL) and glycated hemoglobin level $< 8.7\%$ * at first visit
* This value does not apply to patients in whom impaired glucose tolerance was shown to be present prior to onset of fulminant type 1 diabetes.
3. Urinary C-peptide excretion < 10 $\mu\text{g/day}$ or fasting serum C-peptide level < 0.3 ng/mL (< 0.10 nmol/L) and < 0.5 ng/mL (< 0.17 nmol/L) after intravenous glucagon (or after meal) load at onset

Excerpted with slight modification from Imagawa A, et al : report of the committee of the Japan diabetes society on the research of fulminant and acute-onset type 1 diabetes mellitus: new diagnostic criteria of fulminant type 1 diabetes mellitus. Diabetology International.3(4):181,2012

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Diagnostic tests

1 Categories of the state of glycemia and decision criteria

① Fasting plasma glucose level:

≥ 126 mg/dL

② Two-hour plasma glucose level after 75 g glucose loading:

≥ 200 mg/dL

③ Casual plasma glucose level*:

≥ 200 mg/dL

④ HbA1c : ≥ 6.5%

Category “**Diabetic type**” is indicated when any of ① to ④ are confirmed. Please refer to “B Diagnosis of Diabetes mellitus (p. 10)” on the following page in regard to diabetes diagnosis.

⑤ Fasting plasma glucose level:

< 110 mg/dL

⑥ Two-hour plasma glucose level after 75 g glucose loading:

< 140 mg/dL

Category “**Normal type**” is indicated when ⑤ and ⑥ are both confirmed.

▶ “Borderline type” is indicated when plasma glucose levels do not meet the criteria for either “**diabetic type**” or “**normal type**”.

Figure 2. Categories of state of glycemia as indicated by fasting plasma glucose levels*¹ and 75g OGTT, with reference values

	Before loading	Timing of measurements	Two hours after glucose loading	Category
	Glucose levels (in venous plasma)	≥ 126 mg/dL	◀ or ▶	≥ 200 mg/dL
Neither diabetic type nor normal type			Borderline type	
< 110 mg/dL		◀ and ▶	< 140 mg/dL	Normal type* ²

*¹ Plasma glucose levels are expressed as those in venous plasma, unless otherwise stated.

*² Even if 75g OGTT is judged to be the “normal type”, the same care as is given to those with borderline type (such as follow-up observation) is necessary if the one-hour plasma glucose levels are 180 mg/dL or higher. This is because diabetes is more likely to develop in such patients than in those with lower one-hour levels. Also, the fasting plasma glucose level of 100~109 mg/dL is within normal limits, but is considered to be “high-normal”. Because those with the high-normal glucose level are at the risk of developing diabetes and include those with various degree of impaired glucose tolerance are included, OGTT is desirable. (See “Situations where a 75g oral glucose tolerance test is recommended” on the next page.)

Excerpted with slight modification from the report of the Japan Diabetes Society Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetology International.1(1):12,2010 (extracted and revised)

* Casual plasma glucose level: the level of glucose in the plasma when blood is collected without regard for the timing of meals. The plasma glucose level after glucose loading is excluded.

2 75g OGTT (75g oral glucose tolerance test) *1

- ▶ Test procedure
 - 1) Instruct the patient to arrive at the hospital without having breakfast, after fasting for at least 10 hours. It is desirable to start the test around 9 a.m.
 - 2) Take a blood sample from the (fasting) patient, and measure plasma glucose levels (Table 3).
 - 3) Administer glucose to the patient orally (75 g anhydrous glucose dissolved in water or the equivalent amount of starch hydrolysate such as Trelan G).
 - 4) Take blood samples at 30 minutes, 1 hour, and 2 hours after glucose loading, and measure plasma glucose levels.
 - 5) According to reference values for 75g OGTT (Fig. 2), the case is allocated to the “diabetic type”, “normal type”, or “borderline type” category.
- ▶ No smoking and no exercising should be permitted until the end of the test. Also, the test should not be performed after an upper GI series or endoscopy.
- ▶ For OGTT in children, refer to “Diabetes of childhood and adolescent” [p.50].
- ▶ For OGTT during pregnancy, refer to “Pregnancy and diabetes mellitus” [p.50].

Table 3. Blood sampling necessary for 75g OGTT*1 (depending on purpose)

	Fasting	At 30 min	At 1 hr	At 2 hr
Plasma glucose	75 I R	I	(75)	75
Insulin level	I R	I		

75 : Required for judging 75g OGTT type*2

I : Required for calculation of insulinogenic index*3

R : Required for calculation of HOMA-R

- *1 When subjective symptoms clearly suggest hyperglycemia, the 75g OGTT is not required for the diagnosis of diabetes, and the fasting plasma glucose or the casual plasma glucose should be measured. Performing 75g OGTT upon marked hyperglycemia is detrimental, because raises blood glucose further.
- *2 In 75g OGTT, although it is not always necessary for the diagnosis of diabetes to measure plasma glucose levels 30 minutes and 1 hour after loading, these levels are useful for finding patients at a high risk of diabetes.
- *3 Take a sample for insulin measurement before and 30 minutes after loading, in order to check the insulin response during 75g OGTT.

Situations where a 75g oral glucose tolerance test is recommended

1. Strongly recommended (suspicion of present diabetes mellitus cannot be ruled out)
 - Fasting plasma glucose level is 110 ~ 125 mg/dL (6.1 ~ 6.9 mmol/L)
 - Casual plasma glucose level is 140 ~ 199 mg/dL (7.8 ~ 11.0 mmol/L)
 - *HbA1c is 6.0 ~ 6.4% (excluding those having overt symptoms of diabetes mellitus)
2. Testing is desirable (high risk of developing diabetes mellitus in the future; Testing is especially advisable for patients with risk factors for arteriosclerosis such as hypertension, dyslipidemia and obesity.)
 - Fasting plasma glucose level is 100 ~ 109 mg/dL (5.5 ~ 6.0 mmol/L)
 - *HbA1c is 5.6 ~ 5.9%
 - Strong family history of diabetes mellitus or present obesity regardLess of above criteria

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B Diagnosis of diabetes mellitus

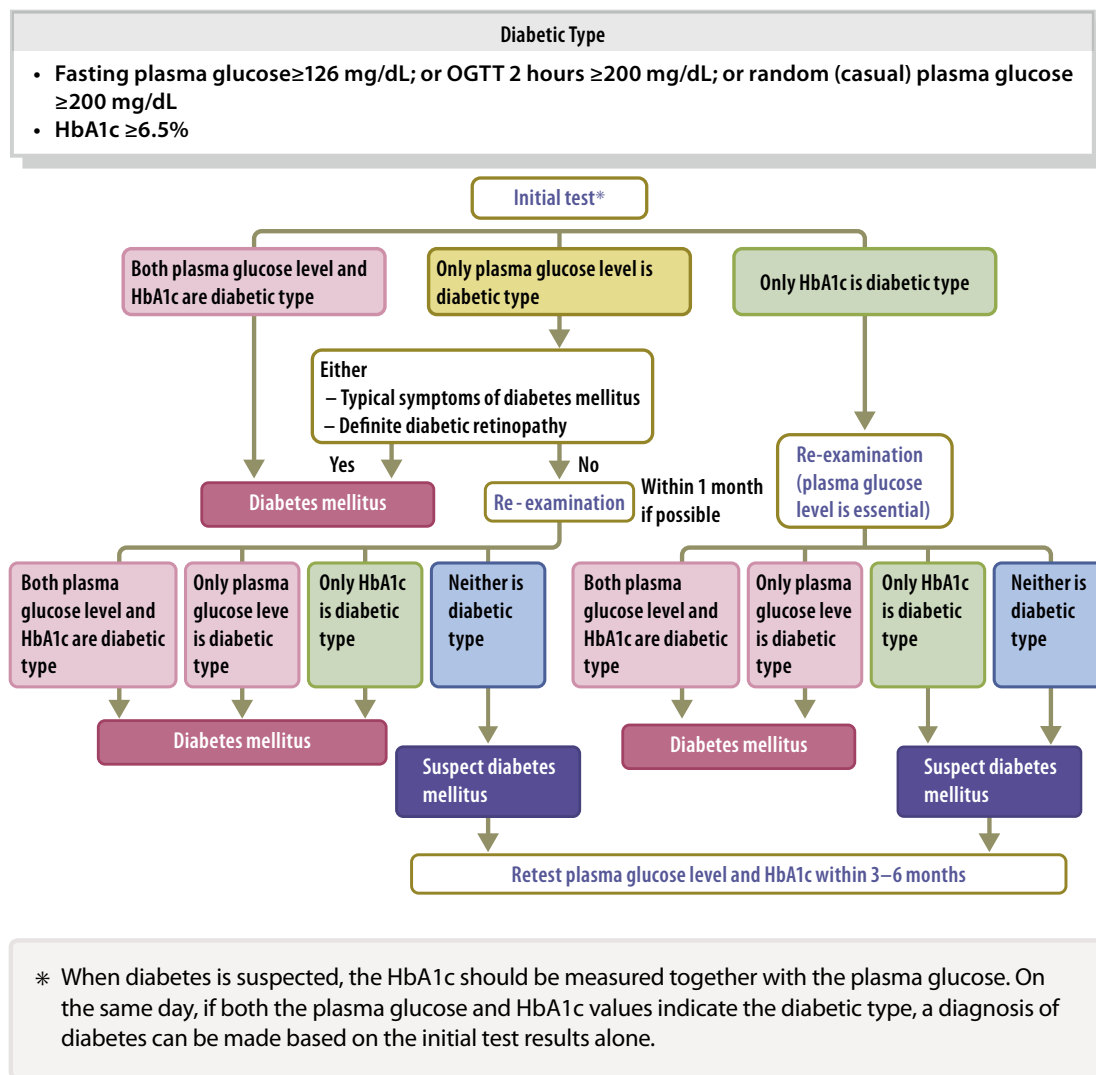
- ▶ A diagnosis of diabetes mellitus is achieved by proving the chronic continuation of a hyperglycemic state.
- ▶ A diagnosis of diabetes is made if the results of a second test performed on another day confirm a judgment of “diabetic type” (See p.8). However, in at least one of the two tests—either the initial or the repeated test—it is essential that the plasma glucose level must be reached to the “diabetic type”, and a diagnosis based on repeated HbA1c tests alone is not acceptable (Fig. 3).
- ▶ If plasma glucose and HbA1c are measured at the same time and both confirm a diabetic state, it is possible to diagnose diabetes at the initial examination.
- ▶ The plasma glucose level indicates “diabetic type”, and if any one of the subsequent items is recognized, a diagnosis of diabetes can be made.
 - 1) When there are typical symptoms of diabetes, such as thirst, polydipsia, polyuria, and weight loss.
 - 2) When there is definite evidence of diabetic retinopathy.
- ▶ Even if the plasma glucose and HbA1c levels obtained do not exceed the reference values for diabetes, the existence of a past record (in test data) of the diabetic type, or of any record of the above conditions 1) and 2) raises suspicion of diabetes. Therefore the care should be taken as such.
- ▶ For diagnosis during pregnancy (including gestational diabetes), refer to “Pregnancy and diabetes mellitus” [p.50].

Points requiring attention in the diagnosis of diabetes

1. HbA1c alone is not a sufficient measure for diagnosis of diabetes. Definitive diagnosis of diabetes must necessarily entail blood glucose testing.
2. It should be kept in mind that there may be a discordance between the HbA1c value and the mean blood glucose value in a variety of disease states (see Table 1 on page 3).
3. As a criterion for the diagnosis of diabetes, HbA1c is to be measured by using a National Glycohemoglobin Standardization Program (NGSP)-certified device, with the caveat that discretion should be exercised in the interpretation of measured HbA1c values, given that they are reported to vary depending on the measurement method and device used.
4. Urine glucose tests are not used for diagnosis of diabetes, because the results are affected by the renal glucose threshold and the patient’s current medication. Blood glucose tests are essential for making a diagnosis.
5. In many cases of type 1 diabetes mellitus, the time of the onset can be correctly estimated because of the appearance of distinct diabetic symptoms.
6. It should be taken into consideration that cold-like symptoms and gastrointestinal symptoms are seen in 70% of the patients with fulminant type 1 diabetes mellitus. Fulminant type 1 diabetes mellitus is also characterized by disproportionately low HbA1c levels despite the presence of hyperglycemia. (See p.7 for Criteria for definite diagnosis of fulminant type 1 diabetes mellitus.)
7. In cases of type 2 diabetes mellitus, the existence of typical complications of diabetes (retinopathy, nephropathy, and neuropathy) is common by the time diabetes is diagnosed, because symptoms of diabetes are usually absent or mild in its early stage.

8. The presence and severity of these complications have to be evaluated when the diagnosis is made, because these complications, depending on their stages, can to some degree influence the choices of treatment.
9. Since diabetes is not a curable disease, patients are advised not to discontinue hospital visits.

Figure 3. Flowchart for the clinical diagnosis of diabetes

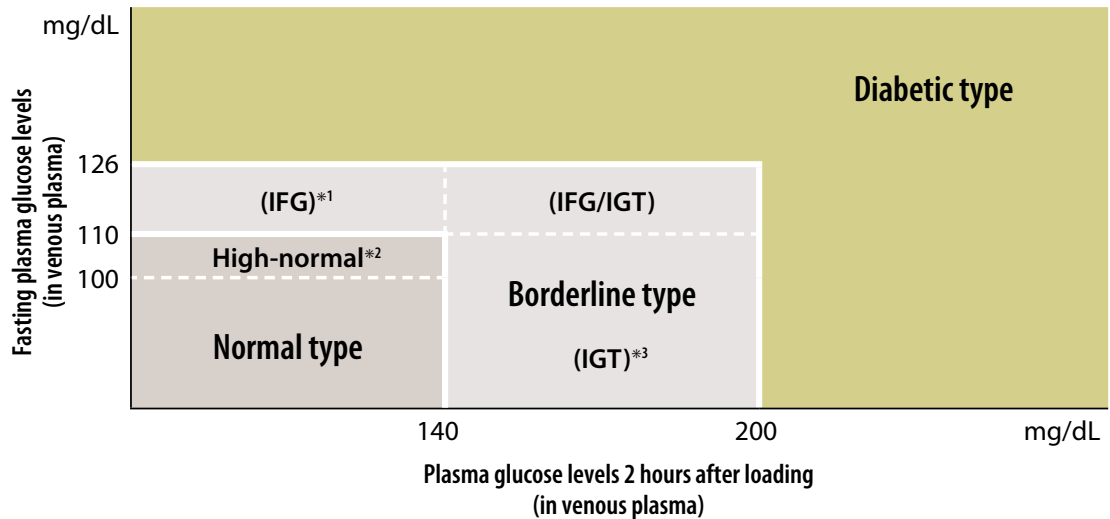


Excerpted with slight modification from the report of the Japan Diabetes Society Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetology International.1(1):12,2010 (extracted and revised)



Borderline type glycemic state and metabolic syndrome (“obesity syndrome”)

Figure 4. Categories of the state of glycemia as indicated by fasting plasma glucose levels and 75g OGTT



- *1 The category IFG (Impaired Fasting Glucose) represents cases of fasting plasma glucose levels of 110 ~ 125 mg/dL and two-hour plasma glucose levels of less than 140 mg/dL in 75g OGTT (WHO). However, in the ADA criteria, IFG is defined as fasting plasma glucose levels falling in the range 100 ~ 125 mg/dL, and only FPG is used for the determination of IFG.
- *2 Fasting plasma glucose levels of 100 ~ 109 mg/dL are within normal limits, but are considered to be “high-normal”. Because those with the high-normal glucose level are at the risk of developing diabetes and include those with various degree of impaired glucose tolerance, OGTT is desirable.
- *3 The category IGT was adopted by the WHO in the diagnostic criteria of diabetes mellitus, and represents cases of fasting plasma glucose levels of less than 126 mg/dL and two-hour plasma glucose levels of 140 ~ 199 mg/dL in 75g OGTT.

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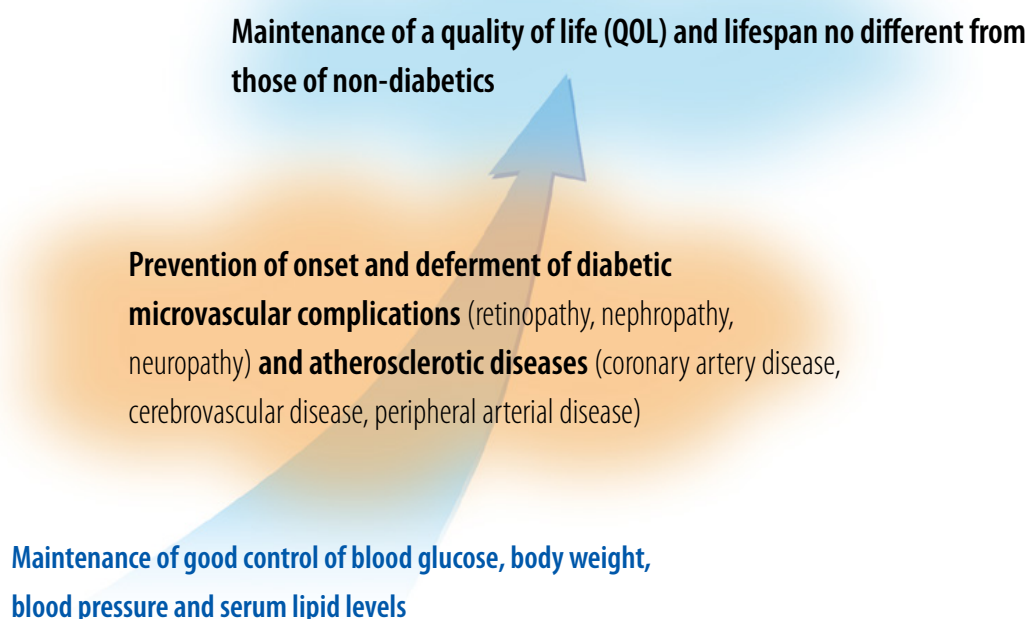
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Treatment objectives and control indicators

1 Aims of diabetes treatment

Figure 5. Aims of diabetes treatment



2 Control indicators

1. In preventing the onset of microangiopathy and inhibiting its progress, the aim is to achieve an HbA1c (NGSP) level below 7.0% (Fig. 5).
2. Establish suitable current treatment aims according to age and complications on a case-by-case basis.

A Indicators of glycemic control

- ▶ Among the indicators of glycemic control, HbA1c is very important and influences the main decisions about treatment. HbA1c is an indicator that reflects the patient's mean blood glucose level of 1 ~ 2 months before. In the individual patient, this value shows little daily variation and therefore is the most important indicator of overall glycemic control. On the other hand, HbA1c does not give any information of the daily fluctuations of blood glucose. Moreover, there are a number of factors other than blood glucose that affect the level of HbA1c.
- ▶ The blood glucose level is an important metabolic indicator that complements the HbA1c value. The fasting plasma glucose, because it is relatively stable, is an indicator of metabolic state. On the other hand, the plasma glucose level 2 hours after a meal is

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readily affected by the amount and type of food taken, as well as by treatment method. It is pointed out to be associated with the risk of cardiovascular disease

- ▶ It is desirable, in comprehensively assessing the metabolic state of a patient, to take the HbA1c value, fasting plasma glucose, plasma glucose level 2 hours after a meal, casual plasma glucose, etc., into consideration.
- ▶ Other indicators of glycemic control include glycoalbumin (GA) (standard values: 11~16%), and 1,5-anhydroglucitol (1,5-AG) (standard value: $\geq 14.0 \mu\text{g/mL}$).
- ▶ If it is not possible to sufficiently improve control of a patient's condition by giving both guidance on lifestyle and the appropriate pharmacotherapy, and if, furthermore, there is a need to review the treatment methods, the patient should be referred to a diabetes specialist, or such a person's advice should be sought.

Figure 6. Glycemic control target (See precautions for elderly patients aged 65 years old or older on pages 52.)

Control target values *4			
Target	Target when aiming for normal glycemia *1	Target when aiming to prevent complication *2	Target when intensification of therapy considered difficult *3
HbA1c (%)	< 6.0	< 7.0	< 8.0

Control targets are established individually, in consideration of age, duration of disease, organ damage, risk of hypoglycemia, patient support, etc.

- *1 In case, targets can be attained by appropriate dietary or exercise therapy, alone or by pharmacotherapy without the occurrence of side effects such as hypoglycemia.
- *2 From the perspective of preventing complications, HbA1c target value is set below 7%. A fasting plasma glucose level <130 mg/dL and a 2-hour postprandial plasma glucose level < 180 mg/dL were used as an approximate estimate for the corresponding plasma glucose levels.
- *3 Target in cases where intensification of treatment is considered difficult due to side effects such as hypoglycemia or for other reasons.
- *4 All target values are for adults, not including pregnant women.

B Other control indicators

1. Body weight

Standard body weight (kg) = height (m) × height (m) × 22

Body mass index (BMI) = Body weight (kg) / height (m) / height (m)

In both Japan and the USA a BMI of approximately 22 is reportedly associated with a long life and little illness. The standard body weight given above is the aim, but even if the BMI is less than 22, it is not necessary to actively try to put on weight. A BMI of 25 and above is considered to indicate obesity. The immediate objective for obese individuals is to reduce their present weight by 5%.

2. Blood pressure

Systolic blood pressure < 130 mmHg

Diastolic blood pressure < 80 mmHg

3. Serum lipids (See p.37: Diabetes mellitus complicated by dyslipidemia)

LDL cholesterol < 120 mg/dL (if coronary artery disease is present, < 100 mg/dL)

HDL cholesterol ≥ 40 mg/dL

Triglycerides < 150 mg/dL

Non-HDL cholesterol < 150 mg/dL (If coronary artery disease is present, < 130 mg/dL)

4. Testing for complications

The fundus of the eye*, urinary albumin, proteinuria, creatinine, blood urea nitrogen (BUN), creatinine clearance (Ccr), Achilles tendon reflex, pallesthesia, serum lipids, uric acid, liver function, complete blood count, chest X-ray, electrocardiogram, blood pressure (in standing and supine positions), etc.

* An ophthalmologist should be asked to examine the fundus oculi.

B

Setting up a treatment policy

1 Non-insulin-dependent state

A Type 2 diabetes mellitus

- ▶ In type 2 diabetes, by the time of the first consultation, retinopathy, nephropathy, neuropathy, or atherosclerotic disorders may already have come to light. Together with the control of diabetes, it is necessary to check for and treat such complications.
- ▶ In cases of non-insulin-dependent state, since there are few subjective symptoms, the patient may be apt to stop hospital or clinic visits. A clearer understanding of the nature of the disease may be achieved by showing patient his or her own test results and other data, and it is essential that an appointment be made for the patient's next visit. If they do not attend their follow-up visit, then they should be contacted and urged to do so,

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and it is necessary the patient's adherence for the treatment be improved. The influence of the family may also be brought to bear.

1. Diet therapy and exercise therapy

- ▶ Educate patients about how diabetes develops and progresses and how they can carry out diet therapy and exercise therapy appropriately on their own. HbA1c as well as plasma glucose levels and other metabolic indicators are measured and followed in the context of this treatment and discuss results (improvement of metabolism) with the patient. According to need, give the patient guidance for the reinforcement of either or both types of treatment.
- ▶ If, despite continuation of these treatments for 2 or 3 months, the target value for glycemic control is not achieved, use drug treatment (See Fig. 7: Treatment of patients in a non-insulin-dependent state). This target value differs from patient to patient, but should generally be HbA1c of below 7.0%. If it is possible for the patient to achieve this through appropriate dietary or exercise therapy alone, or if it is possible to achieve it by pharmacotherapy without the occurrence of side effects such as hypoglycemia, the target is set at HbA1c of below 6.0%. Moreover, in a pregnant diabetic woman and in a woman desiring a child, stricter glycemic control is necessary.

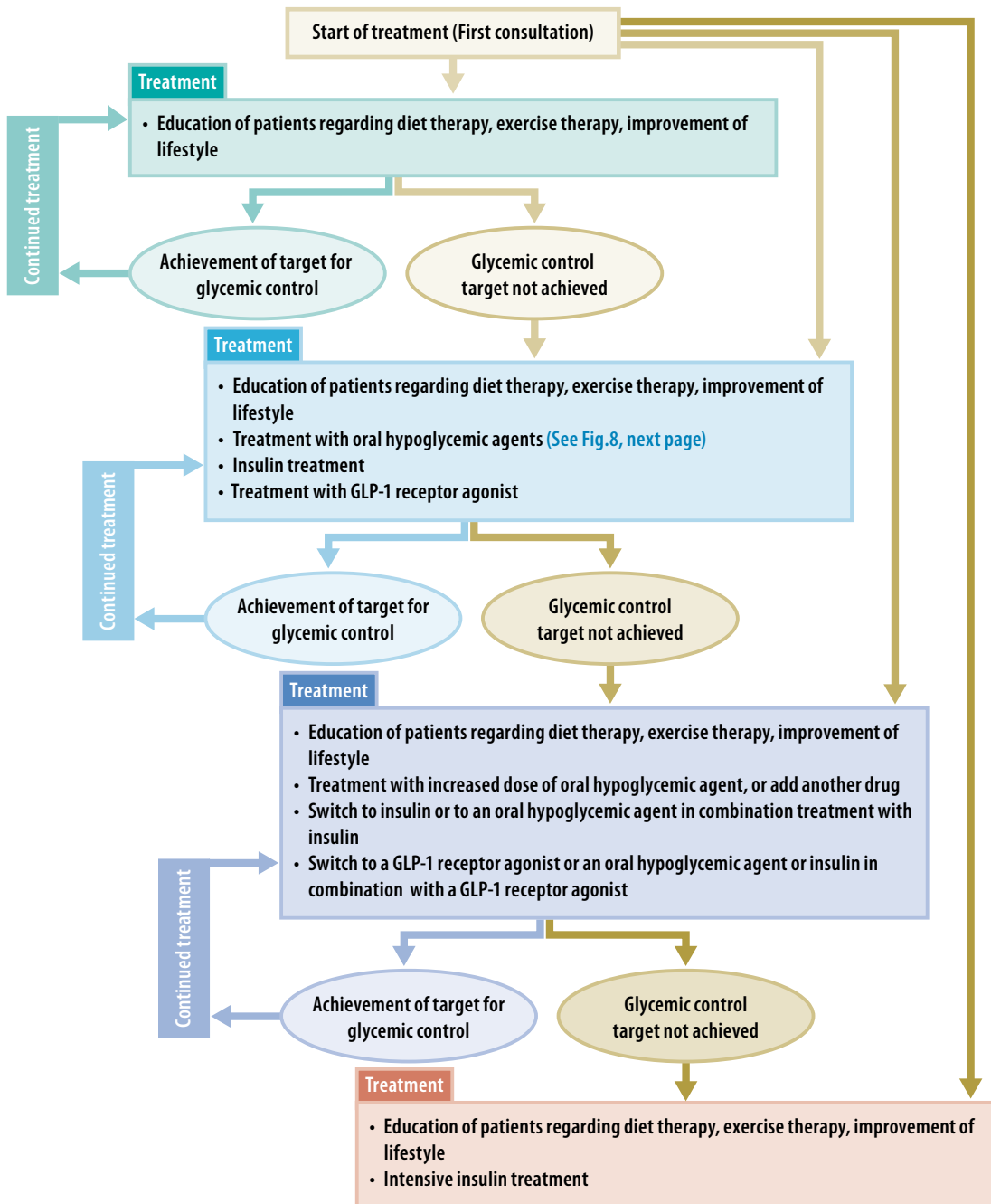
2. Pharmacotherapy

- ▶ Oral hypoglycemic agents and insulin are initially administered in small doses, but these doses are gradually increased with an attentive eye on the control of the blood glucose level. Weight reduction, improvement of lifestyle and improvement of the blood glucose level, with consequent elimination of glucose toxicity, may make possible the reduction and ultimate cessation of oral hypoglycemic agents and insulin. The drugs should always be given with a careful watching glycemic control, bearing in mind the possibilities of both dose reduction and cessation.
- ▶ It must be decided whether to use oral hypoglycemic agents or insulin preparations, after determining not only the degree of metabolic abnormality, but also the patient's age and level of obesity, the degree of any chronic complications, the state of liver and kidney function, together with the insulin secretory capacity and the degree of insulin resistance. If good control cannot be achieved with one type of oral hypoglycemic agent, combination therapy with another drug having a different mode of action should be carried out (Fig. 8).

Figure 7. Treatment of patients in a non-insulin-dependent state

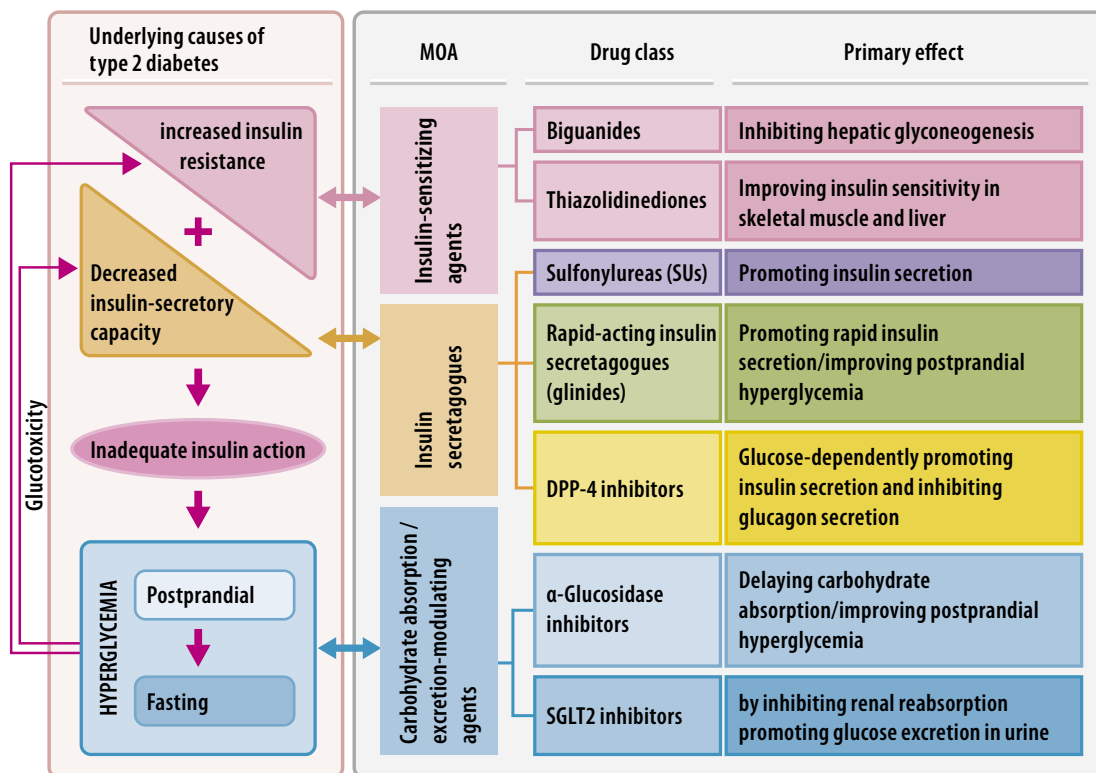
- Applicable to most cases of type 2 diabetes
- Without acute metabolic disorder
- Casual plasma glucose levels approximately 250 ~ 300 mg/dL or lower
- Negative urinary ketone bodies

The target for glycemic control is established for each patient by the physician-in-charge, taking into account the patient's age and the condition.



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Figure 8. JDS Treatment Guide for Diabetes 2014-2015: Updates and revisions Page 29



Combined use of 2 or more oral drugs should be applied only in cases in which the combination of improvement of lifestyle including diet and exercise, together with administration of one type of oral drug, is not efficacious. Although the combined use of drugs with different modes of action may be considered to be efficacious, there are some drug combinations whose efficacy and safety have not been established. For detailed information on such matters, always refer to the package insert for each drug.

3. Other points of importance

- ▶ Patients with diabetes frequently suffer from obesity, hypertension, and disorders of lipid metabolism, and these conditions may be accompanied by abnormalities of the blood coagulation-fibrinolysis system. Smoking is a factor contributing to atherosclerosis and renal impairment in individuals with this habit. To prevent the onset and progression of complications, it is necessary to improve not only glycemic control, but also body weight, blood pressure, and serum lipid levels, as well as improvement of lifestyle by the cessation of smoking and the reduction of alcohol consumption, and by instituting an appropriate amount of exercise.
- ▶ Elderly (65 years old or older) patients with diabetes may be considered to include two groups: those in whom the onset of diabetes is after 65, and those who developed diabetes in youth or middle age. The target for glycemic control can then be decided, after considering the patient's age, the duration of the disease, and the length of time needed for a chronic complication to arise.

B Non-insulin-dependent type 1 diabetes mellitus

- ▶ There are cases of type 1 diabetes that show relatively slow onset and progression, and in which some insulin secretion is preserved (slowly progressive type 1 diabetes mellitus).
- ▶ In patients in whom type 2 diabetes is diagnosed, blood glucose is controlled, with diet therapy and oral hypoglycemic agents alone, slowly progressive type 1 diabetes may be present, with continuous positive reactions for autoantibodies related to the islets of Langerhans (GAD antibodies, etc.).
- ▶ Since some insulin-secretory capacity is more or less preserved at this time, such patients present in a non-insulin-dependent state, but in many cases, there is a gradual transition to an insulin-dependent state. Insulin treatment is desirable in these patients.

2 Insulin-dependent state

A Type 1 diabetes mellitus

1. Conducting the first consultation

- ▶ When type 1 diabetes mellitus is suspected, immediately start insulin treatment (See Fig. 9, Treatment of patients in a insulin-dependent state).
- ▶ In ketosis or ketoacidosis, particularly when patients have slightly dull reactions or their consciousness is clouded, emergency treatment (See p.39 : Diabetic ketoacidosis) is administered even if oral ingestion is possible, and without delay such patients should be taken immediately to a diabetes specialist.
- ▶ Even if the blood glucose level is high, if a state of ketosis allows oral ingestion and the patient is fully conscious, the patient should drink large amounts of water or Japanese tea (approximately 2 liters per day). A diabetes specialist is contacted as soon as possible and subsequent treatment and other measures are discussed. The patient is then sent to the specialist with a referral note.
- ▶ If the diabetes specialist cannot see the patient on the same day, a course of subcutaneous injections of approximately 4 ~ 6 units of short-acting insulin or rapid acting insulin analogue is generally initiated. The blood glucose is checked four times a day (for example, before each meal and at bedtime), and the amount of insulin is adjusted accordingly. For the time being, the blood glucose at these time points is maintained below 200 mg/dL.
- ▶ After 36 hours, if the urinary ketone bodies continue to give a positive reaction, or the patient's condition does not improve, the patient is quickly referred to a diabetes specialist.
- ▶ If the patient's consciousness level falls, the presence of another disease should be considered, and the patient should be transported to a hospital where intensive care can be given.

2. Continuous treatment

- ▶ In order to maintain good glycemic control for a long time in a patient with type 1 diabetes, intensive insulin treatment is needed. The cooperation of a diabetes specialist is desirable (2 or 3 consultations per year, for example). However, a regimen of two daily injections or of three daily injections may be selected, taking into consideration the patient's age, the nature of his or her daily work, and the times of meals. Thus, the

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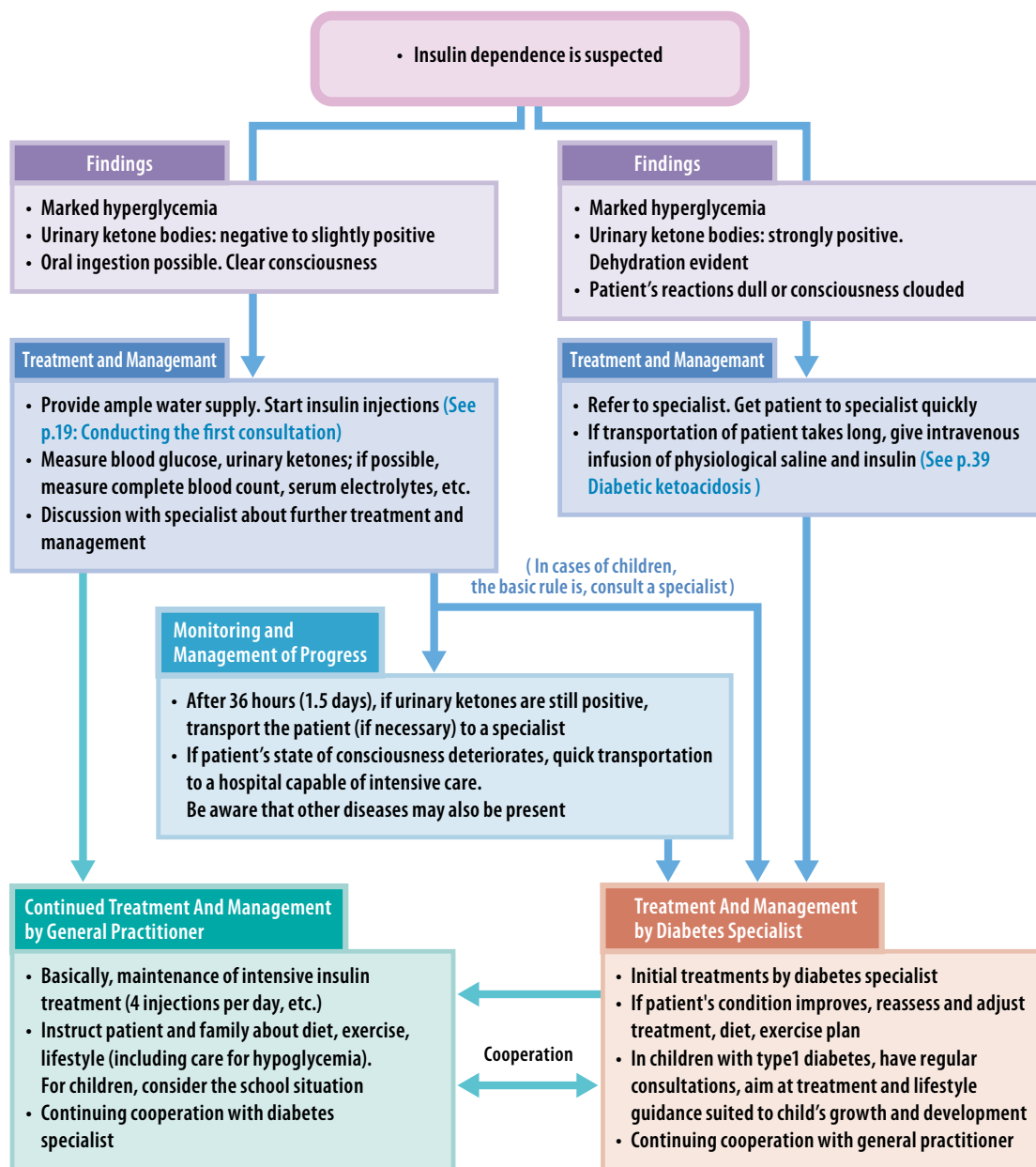
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3 Treatment

Figure 9. Treatment of patients in a insulin-dependent state

- It is preferable that the cooperation of a diabetes specialist be obtained for the purposes of consultation and continuous treatment of type 1 diabetes.
- The treatment of type 1 diabetes in children should be carried out by a childhood diabetes specialist.



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method and doses vary according to the requirements of the individual patient.

- ▶ When the patient's condition stabilizes and ketosis disappears, give following essential instructions to the patients; the relationship between the doses of insulin given and the blood glucose level (that is, which insulin injection affected which blood glucose level), between meals and the blood glucose level (diet therapy), between exercise and the blood glucose level (exercise therapy), etc.
- ▶ In some patients with type 1 diabetes mellitus who are treated immediately after onset with an intensive regimen of insulin, the normalization of blood glucose that this causes may bring about a period of remission (a period when insulin may reduce the blood glucose level to an extreme degree). However, in order to prolong the remission, it is important not to terminate the insulin injections, but to continue the treatment at lower doses since the required amount of insulin will ultimately increase.

B Type 2 diabetes mellitus in the insulin-dependent state

- ▶ The state of insulin dependence in type 2 diabetes can occur under the following conditions
 - ① Ketoacidosis resulting from poor glycemic control due to a secondary failure of a sulfonylurea drug (SU drug)
 - ② Temporary insulin dependence due to causes such as severe infection and injury
 - ③ Soft drink ketosis common in young, obese males (transient insulin dependence)
- ▶ When these occur, measure the blood glucose rapidly by a simple blood glucose measuring device, start urgent treatment (p.39: Acute complications), and quickly transport the patient to a hospital where intensive care can be carried out.
- ▶ In these states, glucose toxicity is usually relieved by insulin treatment, so that many patients return to the non-insulin-dependent state, but insulin treatment must be continued as needed.

C

Diabetes education

- ▶ Diabetes education is to be implemented on a routine daily basis with the target audience being patients with diabetes themselves. The goals of diabetes education are to promote an understanding of diabetes among patients with diabetes; to help patients with diabetes cultivate a willingness to achieve their respective treatment goals; and to promote their confidence in their ability to continue diabetes care.
- ▶ Thus, education is not merely provision of knowledge but provision of relevant knowledge or information on procedures required to achieve the above treatment goals, according to his/her motivation toward diabetes treatment and readiness for behavioral change (from utter unwillingness to willingness to start) through continued dialogues with each patient.
- ▶ Diabetes education addresses such topics of interest to diabetes as its diagnosis and pathophysiology, complications and treatment (diet/exercise therapy, oral hypoglycemic agents and injectable agents), self-monitoring of blood glucose (SMBG), hypoglycemia, sick days, and conduct of everyday life.
- ▶ Adherence to any treatment initiated, even when it is desirable, decreases over time,

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which points to the need to examine which part of the treatment has made it difficult to continue treatment, what obstacles may have been involved, the quality of life (QOL) and mental (psychological) status of the patient being treated, as well as to provide information on novel therapeutic options as required.

COLUMN

The Public Interest Incorporated Association Japan Association for Diabetes Education and Care (JADEC, <http://www.nittokyo.or.jp/>)

The Association was established in 1961 as an unincorporated Association linking patient associations from throughout Japan, and now counts not only patients with diabetes and their families, but also many health professionals engaged in the treatment of diabetes among its members. It aims to contribute to promoting the health of the Japanese people, through sharing correct knowledge about diabetes, offering training, giving guidance regarding treatment to patients with diabetes and their families, and conducting surveys and research into diabetes. The Association partners with regional diabetes associations in various prefectures to offer educational activities. Nationwide, it has around 105,000 members, and about 1,600 patient societies in 2014.

Japan Diabetes Society (<http://www.jds.or.jp/>)

In April 1958, an organisation was formed with the aim of bringing about advances and growth in the field of diabetology. It in 1985 became a private incorporated body, the Japan Diabetes Society, whose aim was to make contributions within its field to the nation.

The Society currently (April 2014) has seven branches spread over the country, with a total of over 17,000 members including 4,996 specialist physicians.

Looking at the world as a whole, a rapid upsurge of patients with diabetes is predicted, especially in Asia, and it is expected Japan will play an important role in this field.

Japanese Certification Board for Diabetes Educators (JCBDE, <http://www.cdej.gr.jp/>)

In February 2000, this Board was inaugurated as a voluntary organization under three parent bodies: the Japan Diabetes Society, the Japan Academy of Diabetes Education and Nursing and the Japan Society of Metabolism and Clinical Nutrition.

The qualification of Japanese Board-Certified Diabetes Educator is awarded to nurses, senior dietitians, pharmacists, clinical laboratory technicians and physical therapists fulfilling the standard criteria.

Currently, in March 2014, there are 17,651 members with the CDEJ qualification.

Japan Promotion Council for Diabetes Prevention and Countermeasures (<http://www.med.or.jp/jma/diabetes/>)

Three organisations, the Japan Medical Association, the Japan Diabetes Society and The Japan for Diabetes Care and Education Association, recognizing the need for more positive measures to cope with the problem of diabetes, organized the Japan Promotion Council for Diabetes Prevention and Countermeasures in February 2005. Later, the Japan Dental Association (JDA) joined the Council, thus making the four societies the Council's organizing bodies. Additionally, a total of 11 organizations showed their willingness to support the Council's activities and subsequently joined the Council as member organizations, which led to the Council's activities for diabetes awareness building being extended. Member organizations include the National Federation of Health Insurance Societies, All-Japan Federation of Health Insurance Organizations, Japanese Society of Nephrology, Japanese Ophthalmological Society, Japanese Nursing Association, Japan Society of Metabolism and Clinical Nutrition, Japan Health Promotion & Fitness Foundation, Japan Health Fitness Programmers' Association, Japan Academy of Diabetes Education and Nursing, Japan Society of Health Evaluation and Promotion, and Japan Dietetic Association (as of April 2014).

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How to promote diet therapy

1

Guidance on appropriate energy intake

- ▶ Determine energy intake by taking into consideration the subject's sex, age, degree of obesity, amount of physical activity, blood glucose level, and any complications. Usually, men should consume between 1,600 ~ 2,000 kcal, and women, 1,400 ~ 1,800 kcal, but it is also necessary to consider the patient's standard body weight.
- ▶ Aim for a balance between the energy expended in physical exercise and energy intake (in food); and keep in mind the presence of any other diseases and the patient's general condition.
- ▶ Method of calculating appropriate energy intake.

Energy intake in food = standard body weight × amount of physical activity

Guidelines on energy expended for different degrees of physical activity

(Units: kcal/ kg of standard body weight)

Light work (desk workers, housewives, etc.)	25 ~ 30
Moderate work (those doing mainly standing work)	30 ~ 35
Heavy work (heavy manual workers)	35 ~

B

Diet therapy in practice — Food Exchange Lists

- ▶ The Food Exchange Lists classify foods into four groups and six lists (Fig. 10) by means of the main nutrients contained in them. One unit of energy (contained in the foodstuff) is set at 80 kcal, and the Food Exchange Lists are designed so that foodstuffs on the same list can be interchanged and consumed to give the same amount of energy.

Figure 10. Food classification table

Food classification table		Average amount of nutrients per unit (80 kcal)		
Food class	Food type	Carbohydrates (g) 4kcal/gr	Protein (g) 4kcal/gr	Lipid (g) 9kcal/gr
Foods which mainly contain carbohydrates (Group I)				
List 1	• Cereals • Potatoes • Vegetables high in carbohydrates, nuts and seeds • Beans (not including soybeans)	18	2	0
List 2	• Fruits	19	1	0
Foods which mainly contain protein (Group II)				
List 3	• Seafood • Soybeans and soybean products • Eggs, cheeses • Meats	1	8	5
List 4	• Milk and dairy products (not including cheeses)	7	4	4
Foods which mainly contain lipid (Group III)				
List 5	• Oils and fats • Oily and fatty foods	0	0	9
Foods which mainly contain vitamins and minerals (Group IV)				
List 6	• Vegetables (not including some vegetables high in carbohydrates) • Sea weed • Mushrooms • Konnyaku	14	4	1
Seasonings	• Miso, sweet sake, sugar, etc.	12	3	2

Excerpted from: Japan Diabetes Society, ed.: Food Exchange Lists, Dietary Guidance for Persons with Diabetes, 13, Bunkodo, 2013.

C To prevent complications

- ▶ In cases of hypertriglyceridemia, keep to an absolute minimum the intake of saturated fatty acids, sucrose and fructose.
- ▶ In case of hypercholesterolemia, foods rich in cholesterol should be restricted (up to 200 mg/day).
- ▶ The patient must make an effort to eat large amounts of dietary fiber (20 g/day). Dietary fiber has the properties of inhibiting postprandial rises in blood glucose, preventing the increase of serum cholesterol, and improving defecation.
- ▶ In cases complicated by hypertension, a salt intake of 6 g/day or less is recommended. For patients with nephropathy, the limit for salt varies with the stage of the disease (See p.44, Table 18, Standard guidance criteria for living with diabetic nephropathy).
- ▶ If patients are shown to have urinary albumin excretion (UAE) 300 mg/g-Cr or continuous proteinuria (0.5 g/g-Cr), i.e., overt nephropathy stage 3, their protein intake should be restricted to 0.8 to 1.0 g/kg of body weight.

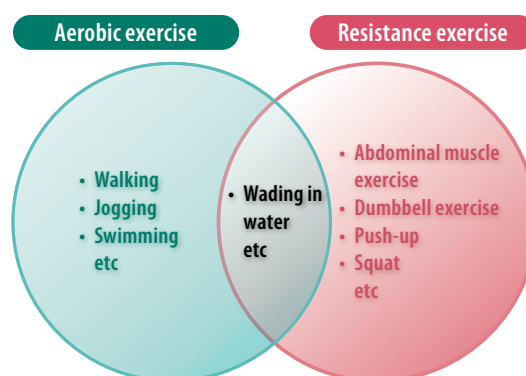
Effects of exercise

1. An immediate effect of exercise is to increase utilization of glucose and fatty acids and lower blood glucose.
2. A long-term effect of exercise is the improvement of insulin resistance.
3. The improved balance between energy intake and expenditure is effective for the reduction of body weight.
4. Muscular atrophy and osteoporosis caused by aging and insufficient exercise can be prevented.
5. Exercise can improve hypertension and dyslipidemia.
6. Cardiopulmonary function is improved.
7. Exercise capacity increases.
8. Exercise can improve QOL, accompanied by feelings of exhilaration and increased energy.

1 Types of exercise

- ▶ There are two types of exercise, aerobic and resistance (Fig.11). The former consists of exercise whose intensity is proportional to the consumption of oxygen, and which, if performed regularly, increases insulin sensitivity. Exercise involving the whole body, such as brisk walking and jogging belong in this category. Resistance exercise, on the other hand, if performed intensively, is anaerobic exercise against a force or resistance. If practiced effectively, this form of exercise can be expected to increase the mass and strength of the muscles.
- ▶ Not much energy is expended in exercise therapy. It is a mistake to think, “The amount of energy I used for exercising today makes it OK for me to eat that much more today”. The main effect that exercise has on glucose metabolism is the improvement of insulin sensitivity.

Figure 11 Aerobic and resistance exercises



2 Intensity of exercise

- ▶ Generally, intermediate-intensity exercises are recommended. An intermediate-intensity exercise is defined as an exercise involving a maximum oxygen uptake ($\dot{V}O_2\text{max}$) of more or less 50%, the intensity of which is determined by the heart rate registered during exercise. The heart rate during exercise is to be maintained within 100 to 120 beats per minute in those aged < 50 years old and within 100 per minute in those aged 50 years old. In those for whom these recommended rates do not apply

due to any concomitant condition such as arrhythmia, the exercise intensity should be determined as one involving an exercise felt to be “effortless” or “slightly arduous”. Exercises felt to be “arduous” are to be avoided as too intense.

3 Frequency and intensity of exercise

- ▶ Generally, it is recommended, if possible at all, that intermediate-intensity exercise be implemented for 20 to 60 minutes on a daily basis or 3 to 5 times a week for a total of 150 minutes or longer per week. It is also recommended that resistance exercise be implemented simultaneously 2 to 3 times a week.
- ▶ Patients with diabetes should spend 15 ~ 30 min, twice a day, for walking. The amount of walking should be approximately 10,000 steps in a day, and the amount of energy expended, between 160 ~ 240 kcal.

4 When exercise should be prohibited or restricted*1

- ① When metabolic control is extremely poor (fasting plasma glucose level over 250 mg/dL; or urinary ketone bodies moderately positive or above).
- ② New hemorrhaging in the ocular fundus caused by proliferative retinopathy (consult an ophthalmologist).
- ③ Renal failure (serum creatinine in men over 2.5 mg/dL and in women over 2.0 mg/dL).
- ④ Ischemic heart disease*2 and cardiopulmonary disorders (seek a specialist’s advice).
- ⑤ Presence of bone or joint disease (seek a specialist’s advice).
- ⑥ Acute infectious disease.
- ⑦ Diabetic gangrene.
- ⑧ Severe autonomic neuropathy.

*1 In these cases, it is seldom necessary to restrict movement in everyday life, and complete rest is never necessary.

*2 In diabetes, attention must be paid for an asymptomatic myocardial ischemia.

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Oral drug treatment

- ▶ The drug to be used is selected after consideration of the patient's pathophysiological state, the presence of any complications, the particular properties of the drugs, etc., (See p.16 : Pharmacotherapy). Diet treatment and exercise therapy are also used, but when glycemic control is still inadequate, oral drug treatment is started.
- ▶ When oral drug treatment is initiated, a small dose is given first while the patient's condition is monitored. Then, the dose is increased while the plasma glucose and HbA1c levels are carefully watched. It is necessary, especially when sulfonylureas (SU) are used, to give the patient firm and definite instructions on how to deal with hypoglycemia.
- ▶ When the condition of a patient after oral ingestion of a drug is unstable, efforts are made, not only through physical findings and test results, but also through conversation with the patient, to understand the cause and to come to a conclusion about the instability. This is essential to choosing the best medicine for the individual patient. At this point, if there are problems about the choice of medication, or anxiety about the progress of complications, consultation with a specialist is recommended.
- ▶ If the goals for a patient are not reached 3 months after initiation of the oral drug, another form of treatment should be considered, including the concurrent use of other drugs.
- ▶ **When a female patient is pregnant, likely to be pregnant, or lactating, the oral drugs ① to ⑧ should not be used.**

1

Biguanides

Table4

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
metformin hydrochloride	Glycoran Medet	3.6	6 ~ 14	250	500 ~ 750
	Metgluco*	2.9	6 ~ 14	250, 500	500 ~ 1500
buformin hydrochloride	Dibetos Dibeton S	1.5 ~ 2.5	6 ~ 14	50	50 ~ 150

* Metgluco differs from the existing Metformin hydrochloride. It can be used with caution in elderly patients, those with mild kidney disorders, mild to moderate liver disorders.

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2 Thiazolidinediones

Table 5

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
pioglitazone hydrochloride*	Actos Actos OD	5	20	15, 30	15 ~ 30

* Administered orally in doses of 30 mg (or maximum 45 mg) once daily before or after breakfast. Where insulin is being administered at the same time, the maximum dose should be 30 mg. In female or elderly patients, start the course with 15 mg once a day, with careful monitoring for edema.

3 Sulfonylurea (SU) drugs and related drugs

Table 6

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
glibenclamide	Euglucon Daonil	2.7	12 ~ 24	1.25, 2.5	1.25 ~ 7.5
gliclazide	Glimicron Glimicron HA	12.3	12 ~ 24	40 20	20 ~ 120
glimepiride	Amaryl Amaryl OD	1.5	12 ~ 24	0.5, 1, 3	0.5 ~ 4

4 Rapid-acting insulin secretagogues

Table 7

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
nateglinide	Stasis Fastic	1.1~1.3	3	30, 90	180 ~ 270
mitiglinide calcium hydrate	Glufast	1.2	3	5, 10	15 ~ 30
Repaglinide	Surepost	0.8	4	0.25, 0.5	0.75 ~ 1.5

* To be taken 3 times a day, immediately before meals.

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5 DPP-4 inhibitors

Table 8

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
▼ Once-twice a day					
Sitagliptin phosphatehydrate* ¹	Glactiv Januvia	12	24	12.5, 25, 50, 100	50 ~ 100
Vildagliptin* ²	Equa	2.4	12 ~ 24	50	100
Alogliptin benzoate* ³	Nesina	17	24	6.25, 12.5, 25	25
Linagliptin	Tranzenta	105	24	5	5
Teneligliptin hydrobromide hydrate	Tenelia	24.2	24	20	20 ~ 40
Anagliptin* ⁴	Suiny	2	12 ~ 24	100	200 ~ 400
Saxagliptin Hydrate	Onglyza	7	24	2.5, 5	2.5 ~ 5
▼ Once a week					
Trelagliptin Succinate	Zafatek	54.3	168	50, 100	100 Once a week
Omarigliptin	Marizev	82.5	168	12.5, 25	25 Once a week

6 α-Glucosidase inhibitors

Table 9

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
acarbose	Glucobay Glucobay OD	–	2 ~ 3	50, 100	150 ~ 300
voglibose	Basen Basen OD	–	2 ~ 3	0.2, 0.3	0.6 ~ 0.9
miglitol	Seibule Seibule OD	2*	1 ~ 3	25, 50, 75 50, 75	150 ~ 225

* Miglitol is absorbed from the upper portion of the small intestine, but there is no evidence of the absorbed drug exhibiting any pharmacological effect.

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7 SGLT2 inhibitors

Table 10

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
Ipragliflozin L-Proline	Suglat	15	24	25, 50	50 ~ 100
Dapagliflozin propylene glycolate hydrate	Forxiga	8 ~ 12	24	5, 10	5 ~ 10
Luseogliflozin Hydrate	Lusefi	11	24	2.5, 5	2.5 ~ 5
Tofogliflozin Hydrate	Apleway Deberza	5.4	24	20	20
Canagliflozin Hydrate	Canaglu	10.2	24	100	100
Empagliflozin	Jardiance	14 ~ 18	24	10, 25	10 ~ 25

8 Combination drug treatment

Table 11

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Content of 1 tablet (mg)	Daily dosage (mg)
Pioglitazone hydrochloride/ Metformin hydrochloride	Metact LD	10.4 4.4		15 500	15/500
	Metact HD			30 500	30/500
Pioglitazone hydrochloride/ Glimepiride	Sonias LD	8.9 7.5		15 1	15/1
	Sonias HD			30 3	30/3
Alogliptin benzoate/ Pioglitazone	Liovel LD	18.3 9.2		25 15	25/15
	Liovel HD			25 30	25/30
Mitiglinide calcium hydrate/ Voglibose	Glubes	1.3 –		10 0.2	30/0.6
Vildagliptin Metformin Hydrochloride	EquMet LD	1.8 3.6		50 250	100/500
	EquMet HD	1.9 4.0		50 500	100/1,000

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B Treatment by injection

1 Insulin treatment.....●

A Indications for insulin treatment

1. Absolute indications for insulin treatment

- ① Insulin-dependent state.
- ② Diabetic coma (diabetic ketoacidosis, hyperglycemic hyperosmolar coma).
- ③ When a hyperglycemic condition is complicated by a severe liver or kidney disease.
- ④ Serious infection, trauma, major surgery (cases requiring general anesthesia, etc.).
- ⑤ Pregnant women with diabetes (including cases of gestational diabetes in which good glycemic control cannot be obtained with diet therapy alone).
- ⑥ Glycemic control with intravenous alimentation.

2. Relative indications for insulin treatment

- ① In the non-insulin-dependent state, when marked hyperglycemia (for example, a fasting plasma glucose level of 250 mg/dL or above, and a casual plasma glucose of 350 mg/dL or above) is found.
- ② When good glycemic control cannot be achieved by treatment with oral hypoglycemic agents (for instance, primary and secondary failure with SU drugs).
- ③ When the nutritional status of a thin patient is deteriorating.
- ④ When hyperglycemia is observed during steroid treatment.
- ⑤ When elimination of glucose toxicity is actively needed.

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B Types of Insulin preparations

Table 12. Insulin prefilled/kit preparations

Type	Proprietary name	No. of units/volume	Amount of insulin infused (increments)	Time to evident effects	Time to peak effects	Duration of effects
Rapid-acting	Humalog Miriopen	300/3 mL	1 ~ 60 U(1U)	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
	NovoRapid FlexPen	300/3 mL	1 ~ 60 U(1U)	10 ~ 20 min	1 ~ 3 hr	3 ~ 5 hr
	NovoRapid FlexTouch	300/3 mL	1 ~ 80 U(1U)	10 ~ 20 min	1 ~ 3 hr	3 ~ 5 hr
	NovoRapid InnoLet	300/3 mL	1 ~ 50 U(1U)	10 ~ 20 min	1 ~ 3 hr	3 ~ 5 hr
	Apidra SoloStar	300/3 mL	1 ~ 80 U(1U)	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
Short-acting	Humulin R Miriopen	300/3 mL	1 ~ 60 U(1U)	30 min ~ 1 hr	1 ~ 3 hr	5 ~ 7 hr
	Novolin R FlexPen	300/3 mL	1 ~ 60 U(1U)	about 30 min	1 ~ 3 hr	about 8 hr
Premixed	Humalog Mix 25 Miriopen Humalog Mix 50 Miriopen	300/3 mL	1 ~ 60 U(1U)	<15 min	30 min ~ 6 hr 30 min ~ 4 hr	18 ~ 24 hr
	Humulin 3/7 Miriopen	300/3 mL	1 ~ 60 U(1U)	30 min ~ 1 hr	2 ~ 12 hr	18 ~ 24 hr
	NovoRapid 30 Mix FlexPen NovoRapid 50 Mix FlexPen NovoRapid 70 Mix FlexPen	300/3 mL	1 ~ 60 U(1U)	10 ~ 20 min	1 ~ 4 hr	about 24 hr
	Novolin 30R FlexPen	300/3 mL	1 ~ 60 U(1U)	about 30 min	2 ~ 8 hr	about 24 hr
	Innolet 30R	300/3 mL	1 ~ 50 U(1U)	about 30 min	2 ~ 8 hr	about 24 hr
	Combination-acting	Ryzodeg Flex Touch	300/3 mL	1 ~ 80 U(1U)	10 ~ 20 min	1 ~ 3 hr
Intermediate-acting	Humalog N Miriopen	300/3 mL	1 ~ 60 U(1U)	30 min ~ 1 hr	2 ~ 6 hr	18 ~ 24 hr
	Humulin N Miriopen	300/3 mL	1 ~ 60 U(1U)	1 ~ 3 hr	8 ~ 10 hr	18 ~ 24 hr
	Novolin N FlexPen	300/3 mL	1 ~ 60 U(1U)	about 1.5 hr	4 ~ 12 hr	about 24 hr
Long-acting	Levemir FlexPen	300/3 mL	1 ~ 60 U(1U)	about 1 hr	3 ~ 14 hr	about 24 hr
	Levemir Innolet	300/3 mL	1 ~ 50 U(1U)	about 1 hr	3 ~ 14 hr	about 24 hr
	Tresiba FlexTouch	300/3 mL	1 ~ 80 U(1U)	–	No clear peak	Over 42 hours*
	Lantus SoloStar		1 ~ 80 U(1U)			
	Insulin Glargine Miriopen "Lilly"	300/3 mL	1 ~ 60 U(1U)	1 ~ 2 hr	No clear peak	about 24 hr
	Lantus XR Solostar	450/1.5 mL	1 ~ 80 U(1U)	1 ~ 2 hr	No clear peak	Over 42 hours

- The dark green background indicates an insulin analog preparation, and the others, human insulin.

* Duration of effects after continuous daily injection.

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Table 13. Insulin cartridge preparation

Type	Proprietary name	No. of units/volume	Time to evident effects	Time to peak effects	Duration of effects
Rapid-acting	Humalog cart	300/3 mL	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
	NovoRapid Penfill	300/3 mL	10 ~ 20 min	1 ~ 3 hr	3 ~ 5 hr
	Apidra cart	300/3 mL	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
Short-acting	Humulin R cart	300/3 mL	30 min ~ 1 hr	1 ~ 3 hr	5 ~ 7 hr
Premixed	Humalog Mix 25/50 cart	300/3 mL	<15 min	30 min ~ 6 hr 30 min ~ 4 hr	18 ~ 24 hr
	Humulin 3/7 cart	300/3 mL	30 min ~ 1 hr	2 ~ 12 hr	18 ~ 24 hr
	NovoRapid 30 Mix Penfill	300/3 mL	10 ~ 20 min	1 ~ 4 hr	about 24 hr
Intermediate-acting	Humalog N cart	300/3 mL	30 min ~ 1 hr	2 ~ 6 hr	18 ~ 24 hr
	Humulin N cart	300/3 mL	1 ~ 3 hr	8 ~ 10 hr	18 ~ 24 hr
Long-acting	Levemir Penfill	300/3 mL	about 1 hr	3 ~ 14 hr	about 24 hr
	Tresiba Penfill	300/3 mL	–	No clear peak	Over 42 hours*
	Lantus cart	300/3 mL	1 ~ 2 hr	No clear peak	about 24 hr

• The dark green background indicates an insulin analog preparation, and the others, human insulin.

* Duration of effects after continuous daily injection.

Table 14. Insulin vial preparations

Type	Proprietary name	No. of units/volume	Time to evident effects	Time to peak effects	Duration of effects
Rapid-acting	Humalog 100 units/mL	1,000/10 mL	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
	NovoRapid 100 units/mL	1,000/10 mL	10 ~ 20 min	1 ~ 3 hr	3 ~ 5 hr
	Apidra 100 units/mL	1,000/10 mL	<15 min	30 min ~ 1.5 hr	3 ~ 5 hr
Short-acting	Humulin R 100 units/mL	1,000/10 mL	30 min ~ 1 hr	1 ~ 3 hr	5 ~ 7 hr
	Novolin R 100 units/mL	1,000/10 mL	about 30 min	1 ~ 3 hr	about 8 hr
Premixed*	Humulin 3/7 100 units/mL	1,000/10 mL	30 min ~ 1 hr	2 ~ 12 hr	18 ~ 24 hr
Intermediate-acting	Humulin N 100 units/mL	1,000/10 mL	1 ~ 3 hr	8 ~ 10 hr	18 ~ 24 hr
Long-acting	Lantus 100 units/mL	1,000/10 mL	1 ~ 2 hr	No clear peak	about 24 hr

- The dark green background indicates an insulin analog preparation, and the others, human insulin.

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2 Injectable drugs other than insulin: GLP-1 receptor agonists

Table 15. GLP-1 receptor agonists

Generic name	Proprietary names (main)	Blood half-life (hr)	Duration of activity (hr)	Contents of 1 vial	Daily dosage
▼ Once-twice a day					
Liraglutide* ¹ (genetic recombination)	Victoza 18 mg	13 ~ 15	>24	18 mg	0.9 mg
Exenatide* ²	Byetta 5/10 µg Pen 300	1.4 (5 µg) 1.3 (10 µg)	8	300 µg	10 ~ 20 µg
Lixisenatide	Lyxumia	2.12 (10 µg) 2.45 (20 µg)	15	300 µg	10 ~ 20 µg
▼ Once a week					
Exenatide* ³ (Continuous injectable solution)	Bydureon 2 mg	—* ¹	—* ¹	2.6 mg	2 mg* ² Once a week
Exenatide (Continuous injectable solution)	Bydureon 2 mg Pen	—* ¹	—* ¹	2.76 mg	2 mg* ³ Once a week
Dulaglutide (Genetical Recombination)	Trulicity 0.75 Ateos	108	—* ⁴	0.75 mg	0.75 mg Once a week

*¹ No applicable data available, since it is a sustained release preparation.

*² Where a pharmaceutical suspension is administered of one vial of this preparation (2.6 mg) added to additive suspension liquid, the drug solution administered will contain 2 mg of Exenatide.

*³ Where one kit of this preparation is administered, the drug solution administered will contain 2 mg of Exenatide.

*⁴ No applicable data available, since it is a prolonged action preparation.

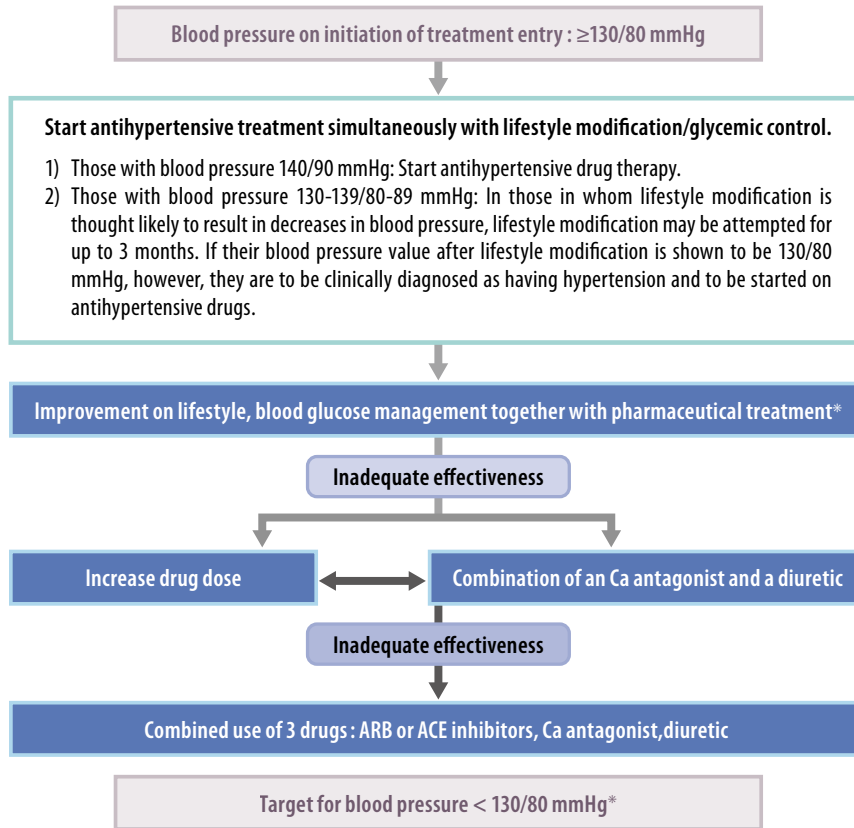
C Other drug treatments

1 Diabetes mellitus complicated by hypertension

- ▶ When a patient has diabetes complicated by hypertension and the blood pressure is over 130 ~ 139/80 ~ 89 mmHg, advice should be given to make lifestyle improvements within three months, but if the outcome of this is inadequate, antihypertensive drugs should be initiated (Fig. 12). Diet and exercise therapy have beneficial effects, especially in obese patients, in whom losing weight can lower blood pressure. It is important to advise reduction of salt intake to less than 6 g/day.
- ▶ When the blood pressure is over 140/90 mmHg, antihypertensive drugs should be

- initiated with life style intervention.
- ▶ The target level of blood pressure is less than 130/80 mmHg.

Figure 12. Treatment of hypertension complicating diabetes mellitus



* However, care needs to be taken to closely monitor patients with coronary atherosclerosis, peripheral arterial disease or elderly patients for any decrease in organ blood flow.

Excerpted from: The Japanese Society of Hypertension, Guidelines for the Treatment of Hypertension, 2014

2 Diabetes mellitus complicated by dyslipidemia

- ▶ When lipid metabolism abnormalities are treated, the table of lipid control target values in patients with diabetes (Table 16) should be consulted.
- ▶ Improvement of lifestyle is the foundation of treatment for a lipid metabolism disorder, and improvement of glucose and lipid metabolism can be expected as a result of diet and exercise therapies.
- ▶ If the targets of lipid management cannot be achieved, despite the improvement of glycemic control and the control of lifestyle factors, pharmacotherapy must be considered.
- ▶ If the LDL cholesterol level is elevated, the first-choice drugs are statins (HMG-CoA reductase inhibitors).
- ▶ To cope with hypertriglyceridemia and HDL hypocholesterolemia, use fibrate drugs.
- ▶ When statins or fibrates are used, be aware of rhabdomyolysis. When renal function is

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poor, the use of these drugs is sometimes contraindicated. In such cases, the possibility of using negative ion-exchange resins, Ezetimibe, nicotinic acid preparations and Probucol should be considered (with kidney functional disorder, the concurrent use of statins and fibrates is contraindicated).

Table 16. Lipid control target values in patients with diabetes

Coronary artery disease	Lipid control target values (mg/dL)			
	LDL-C	HDL-C	TG	Non-HDL-C
Present	< 120	≥ 40	< 150	< 150
Absent	< 100			< 130

LDL-C: LDL cholesterol

HDL-C: HDL cholesterol

TG: triglycerides (in fasting early morning blood)

Non-HDL-C: non-HDL cholesterol

When TG is less than 400 mg/dL, Friedewald's equation, below, should be used to calculate LDL-C:

$LDL-C = TC - HDL-C - TG/5$ (TC: total cholesterol)

When the level of TG is 400 mg/dL or more, and/or the postprandial blood is drawn, non-HDL-C (TC-HDL-C) value should be used as a therapeutic target

Edited by Japan Atherosclerosis Society: Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, published 2012, p. 42.

A

Complications of diabetes

- ▶ Some of the complications of diabetes are acute, and occur when the action of the insulin is seriously inadequate; and some, which result from long-term hyperglycemia, are chronic. They cause deterioration of both the patient's QOL and his prognosis. Prevention of both the occurrence and the deterioration of such complications is the aim of diabetes treatment.

B

Acute complications

- ▶ The lack of marked effectiveness by insulin causes acute metabolic failure. There are two types: diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome. The latter is accompanied with relatively little ketone body production. Both cause various degrees of impaired consciousness, which, when severe, constitutes coma.

1

Diabetic ketoacidosis.....●

- ▶ As a result of marked insulin deficiency and increases of the insulin-counter-regulatory hormones cortisol, and adrenalin, high levels of plasma glucose (≥ 300 mg/dL), hyperketonemia (increase of β -hydroxybutyric acid) and acidosis ($< \text{pH} 7.3$) occur together, and this condition is known as ketoacidosis. Initial treatment should be started immediately, and arrangements should be simultaneously made to transport the patient to a hospital, adequately having a diabetes specialist.
 - ▶ Initial treatment entails a major infusion of saline and appropriate insulin administration.
- ① The degree of hydration is estimated from the change in body weight, and a drip infusion of physiological saline is initiated at a rate of 500 to 1,000 mL per hour. For the first few hours, 200 to 500 mL per hour of fluid infusion (the amount depending on the amount of water deficiency) is administered, and the infusion rate is regulated according to the amount of urine volume. When the serum potassium level is ≤ 5.0 mEq/L, the amount removed needs to be replaced, since its concentration in the blood must be maintained. The correction of acidosis with bicarbonate (HCO_3^-) is as a rule not carried out above pH 7.0.
 - ② It is a principle to maintain a continuous intravenous infusion of a small amount of insulin. After the intravenous infusion of short-acting insulin at a dose of 0.1 unit per kg body weight, then 0.1 unit per kg body weight per hour using a constant infusion pump is infused.

2

Hyperosmolar hyperglycemic syndrome.....●

- ▶ Because of severe hyperglycemia (≥ 600 mg/dL) and hyperosmolarity due to a high degree of dehydration, circulation shock often occurs, but no outstanding evidence of acidosis is seen (pH 7.3 ~ 7.4). This syndrome can develop in elderly patients with

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type 2 diabetes. When a patient has an infectious disease or a cerebrovascular accident, undergoes surgery or is receiving high-calorie infusions, diuretics or steroid hormones, a high plasma glucose can follow, and may result, after several days, in hyperosmolar hyperglycemic syndrome .

- ▶ The basis of treatment is the correction of dehydration and of the electrolyte balance, and the proper administration of insulin. As soon as an intravenous line has been secured, the patient should be transported to a hospital with a specialist in diabetes.

C

Chronic complications

- ▶ These complications arise through long-standing metabolic disorders including hyperglycemia, lipid disorders, and factors contributing to blood vessel injury, such as hypertension. Retinopathy, nephropathy and neuropathy are classified as microangiopathies, and coronary arteriopathy, cerebrovascular disease, and peripheral arterial disease are forms of macroangiopathy. Diabetic foot lesions are also included in chronic complications.

1 Diabetic retinopathy

- ▶ As a result of degeneration of the retinal vessel wall cells, circulatory disturbance due to thickening of the basement membrane and transudation of blood components, early-stage lesions such as hemorrhage, exudates and retinal edema can arise. If these conditions become severe, maculopathy results, and preretinal and vitreous neovascularization takes place, causing vitreous hemorrhage, retinal detachment and further visual impairment. Neovascular glaucoma is a terminal complication which frequently leads to blindness. Cataract may also cause visual impairment in patients with diabetes.

1. There are four stages of retinopathy:

① Normal, ② Simple retinopathy, ③ Proliferative retinopathy, and ④ Proliferative retinopathy

2. Management of early retinopathy: For cases ① and ②, prescribe non-surgical treatment such as glycemic control and control of hypertension in order to prevent or delay progression to stages ③ and ④.

3. Management of advanced retinopathy: At stages ③ and ④, treatment by an ophthalmologist is essential. To prevent blindness, the advance of retinopathy can be halted or delayed by photocoagulation in preproliferative retinopathy and early proliferative retinopathy. Hemorrhage in the vitreous body and retinal detachment are dealt with by surgery to the vitreous body.

4. Edema in the macula of the retina results in marked deterioration of visual acuity. It may occur during the stage of simple retinopathy or at later stages.

5. The figures below are a guideline to the intervals between consultations to the ophthalmologist:

- Normal Once every 6 ~ 12 months
- Simple retinopathy Once every 3 ~ 6 months
- Proliferative retinopathy Once every 1 ~ 2 months
- Proliferative retinopathy Once every 2 weeks ~ 1 month

6. Given that the time of onset of disease remains unclear in patients with type 2 diabetes, these patients are to undergo fundus examinations before, 3 months and 6 months after initiation of treatment. Again, all patients who present with marked hyperglycemia at initial consultation and whose disease is thought to be long-standing require to be monitored and closely examined every 2 to 3 months at least for one year after initial consultation.

2 Diabetic nephropathy

- ▶ Changes similar to those of diabetic retinopathy are seen in the blood vessels of the renal glomeruli. There is increased growth of the connective tissue around the vessels, known as mesangium, and the glomerular structure is destroyed and its function is impaired.
1. Indicators for progression of nephropathy and staging of nephropathy
Clinically, glomerular filtration rate (GFR, now substituted by eGFR) and urinary albumin excretion (UAE) or urinary protein excretion are to be used to assess the presence of nephropathy. eGFR is to be calculated from serum creatinine values (Cr mg/dL) using the following formula:

$$\text{eGFR}_{\text{creat}} (\text{mL}/\text{min}/1.73 \text{ m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age} (\text{years})^{-0.287}$$

Value for females: the value obtained by the above formula $\times 0.739$

Cf. Alternative eGFR formula using serum cystatin C values

As serum cystatin C values are less affected by skeletal muscle mass, diet or exercise, this formula may prove useful when nephropathy may be difficult to assess using the eGFR formula based on serum creatinine values.

Males: eGFR_{cys} (mL/min/1.73 m²) = (104 × Cys-C^{-1.019} × 0.996^{age [years]}) – 8

Females: Males: eGFR_{cys} (mL/min/1.73 m²) = (104 × Cys-C^{-1.019} × 0.996^{age [years]} × 0.929) – 8

Both formulas drawn from: Evidence-based Clinical Practice Guidelines for CKD, edited by the Japanese Society of Nephrology, Tokyo, Tokyo Igakusha, 2013.

Generally, structural changes in renal glomerulus can be captured as increases in urinary albumin excretion (UAE). UAE < 30 mg/g creatinine as assessed using casual urine samples is defined as stage 1 (pre-nephropathy phase); any UAE value above this, which is thought to be associated with structural renal changes, is defined as stage 2 (early nephropathy phase); and UAE 300 mg/g creatinine, which represents a continuous proteinuria-positive status in qualitative assessments (equivalent to urinary protein excretion 0.5 g/g creatinine) is defined as stage 3 (overt nephropathy phase) (Table 17). Some patients may be found to have high-degree proteinuria and present with the nephrotic state. Of these, patients with eGFR < 30 mL/min/1.73 m² are associated with increased serum creatinine values and are defined as stage 4 (renal failure phase), irrespective of their urinary albumin or protein values. Those with advanced renal failure requiring dialysis therapy are defined as stage 5 (dialysis therapy phase). It is to be noted, however, that not all patients may follow this clinical course, with some patients exhibiting inconsistent eGFR and urinary albumin values. Of note here is that those found to have eGFR < 60 mL/min/1.73 m² from early on are to be construed as meeting the definition of chronic kidney disease (CKD) and to

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be examined for the presence or absence of retinopathy, with some other diagnosis than nephropathy e.g., renal sclerosis, in mind. In addition to correction of obesity and smoking cessation, tight glycemic, blood pressure, and lipid control represent the most important of measures to prevent nephropathy from progressing, where early intervention may lead to disease resolution. All patients with stage 3 or more advanced disease are to be instructed to restrict protein intake (0.8 to 1.0 g/kg of body weight/day) and salt intake (< 6.0 g/day) and may be considered as candidates for a low-protein diet (0.6 to 0.8 g/kg of body weight/day) based on evidence of their declining renal function (Table 18).

Table 17 Classification of Diabetic Nephropathy 2014

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m ²)
Stage 1 (pre-nephropathy)	Normoalbuminuria (<30)	≥ 30 * ¹
Stage 2 (incipient nephropathy)	Microalbuminuria (30 – 299) * ²	≥ 30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥ 300) or Persistent proteinuria (≥ 0.5)	≥ 30 * ³
Stage 4 (kidney failure)	Any albuminuria/proteinuria status * ⁴	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	

Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of patients with type 2 diabetes from a "historical cohort study" conducted as part of the MHLW-subsidized Project on Kidney Disease, entitled "Diabetic Nephropathy Research, from the Ministry of Health, Labour and Welfare of Japan"

*¹ While a GFR of less than 60 mL/min/1.73 m² is consistent with the diagnosis of CKD, underlying causes other than diabetic nephropathy may be involved in patients with a GFR below 60 mL/min/1.73 m² thus calling for the differential diagnosis between diabetic nephropathy and any other potential non-diabetic kidney diseases

*² Patients with microalbuminuria are to be diagnosed as incipient nephropathy after the differential diagnosis based on the criteria for an early diagnosis of diabetic nephropathy

*³ Precautions are required in patients with macroalbuminuria, in whom renal events (e.g., a decrease in eGFR to half its baseline value, the need for dialysis) have been shown to increase as the GFR decreases below 60 mL/min/1.73 m²

*⁴ All patients with a GFR of less than 30 mL/min/1.73 m² are classified as exhibiting kidney failure, regardless of their urinary albumin/protein values. However, in those with normoalbuminuria and microalbuminuria, the differential diagnosis is required between diabetic nephropathy and any other potential non-diabetic kidney diseases

Key Precautions in View of Drug Use: this table is intended, first and foremost, as a classification of diabetic nephropathy and not as a guide to drug use. All drugs, including anti-diabetic drugs, particularly renally metabolized agents, are to be used in accordance with their prescribing information, with due consideration to relevant factors, such as GFR, in each patient

Excerpted with slight modification from the report from Joint Committee on Diabetic Nephropathy: A new classification of Diabetic Nephropathy 2014. *Diabetology International*.5(4):209,2014

Appendix

Relationship between the 2014 categories for diabetic nephropathy stages and the CKD severity categories

Albuminuria category		A1	A2	A3
Quantitative urinary albumin estimation Urinary albumin/Cr ratio (mg/g Cr) (quantitative urinary protein estimation) (urinary protein/Cr ratio (g/g Cr)		Normoalbuminuria < 30	Microalbuminuria 30-299	Macroalbuminuria ≥300 (or increased proteinuria) (≥ 0.50)
GFR category (mL/min/1.73 m ²)	≥90 60-89 45-59 30-44	Stage 1 (pre-nephropathy)	Stage 2 (incipient nephropathy)	Stage 3 (overt nephropathy)
	15-29 < 15	Stage 4 (kidney failure)		
	(dialysis therapy)	Stage 5 (dialysis therapy)		

Excerpted with slight modification from the report from Joint Committee on Diabetic Nephropathy: A new classification of Diabetic Nephropathy 2014. *Diabetology International*.5(4):211,2014

2. Measurement of urinary albumin excretion (UAE)

Measurement of albumin (mg) and creatinine levels (g) in spot urine should be carried out regularly once every 3 ~ 6 months. By doing so, changes in the kidney become detectable before urine protein appears. The Ccr level should be checked once a year. The standard values for albumin in the urine expressed in ACR are defined as follows: normal, < 30 mg/g of creatinine; microalbuminuria, 30 ~ 299 mg/g of creatinine; and proteinuria, ≥ 300 mg/g of creatinine. If microalbuminuria is found at least twice out of three measures, incipient nephropathy is detected.

- Adequate control of blood pressure (target levels: less than 130/80 mmHg); in order to delay the progression of nephropathy. The first-choice antihypertensive drugs, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs), inhibit the increase of GFR during the first stage of the disease, and inhibit the increase of albuminuria/proteinuria and the deterioration of renal function.
- In many patients with diabetes with renal failure, it is common to find systemic edema, heart failure and other disorders concurrently, and in individual patients, dialysis is performed at a suitable time.

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Table 18. Criteria for lifestyle guidance for patients with diabetic nephropathy

Stage	Daily living	Dietary intake			
		Total energy ^{*1} (kcal/kg BW/day)	Proteins	Salt (g/day)	Potassium (g/day)
Stage 1 (pre-nephropathy)	· Normal life	25-30	≤20% energy	< 6 if also hypertensive	Not restricted
Stage 2 (early nephropathy)	· Normal life	25-30	≤20% energy ^{*3}	< 6 if also hypertensive	Not restricted
Stage 3 (overt nephropathy)	· Normal life	25-30 ^{*4}	0.8-1.0 ^{*4} g/kg BW/day	< 6	· Not restricted (< 2.0 if hyperkalemic)
Stage 4 (renal failure)	· Daily living unlilely associated with fatigue	25-35	0.6-0.8 g/kg BW/day	< 6	< 1.5
Stage 5 (dialysis)	· Slightly restricted · Daily living not associated with fatigue	Hemodialysis (HD) ^{*5} : 30-35	0.9-1.2 g/kg BW/day	< 6 ^{*6}	<2.0
		Peritoneal dialysis (PD) ^{*5} : 30-35	0.9-1.2 g/kg BW/day	PD-removed water (L) × 7.5 × urine (L) × 5	· Not restricted as a rule

*1 This illustrates a case of patients implementing low-intensity exercise.

*2 The amount of exercise needs to be carefully determined depending on the extent/severity of urinary protein excretion, hypertension, and macroangiopathy present. However, excessive exercise is to be avoided in patients with proliferative retinopathy, irrespective of their nephropathy stage.

*3 A patient's protein intake is to be determined in accordance with the general criteria for diabetic diet.

*4 A patient's protein intake may be changed to that in stage 4 disease if GFR < 45.

*5 Consider restricting total energy intake to 25-30 kcal/kg BW/day for glycemic and weight control.

*6 Values are to be adjusted according to the urine output, physical activity, physique, and nutritional status of each patient, as well as his/her inter-hemodialysis body weight increase.

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	Exercise *2	Work	Household work	Pregnancy/ childbirth	Points to keep in mind
	· Exercise therapy for diabetes to be implemented as a rule	· As usual	· As usual	May be an option	· Diabetic diet for glycemic control · Antihypertensive therapy · Lipid control · Smoking cessation
	· Exercise therapy for diabetes to be implemented as a rule	· As usual	· As usual	May be an option but requires careful management	· Diabetic diet for glycemic control · Antihypertensive therapy · Lipid control · Smoking cessation · Excessive protein intake unfavorable
	· Exercise allowed as a rule · Exercise to be modified as per disease condition	· As usual	· As usual	Not recommended	· Appropriate glycemic control · Antihypertensive therapy · Lipid control · Smoking cessation · Protein-restricted diet
	· Exercise allowed as a rule · Exercise to be modified as per disease condition	· As usual, but modified as per disease condition	· Restricted · Light work felt to be not fatiguing	Not recommended	· Appropriate glycemic control · Antihypertensive therapy · Lipid control · Smoking cessation · Protein-restricted diet · Anemia treatment
	· Exercise allowed as a rule · Exercise to be modified as per disease condition	· As usual, but modified as per disease condition	· Usual work allowed · light work felt to be not fatiguing	Not recommended	· Appropriate glycemic control · Antihypertensive therapy · Lipid control · Smoking cessation · Dialysis or renal transplant · Fluid restriction (maximum inter-dialytic BW gain in HD patients, < 6%)

Created based on the Report of the Joint Committee on Diabetic Nephropathy, "On the Revised Staging of Diabetic Nephropathy" (in Japanese) (<http://www.jds.or.jp/modules/important/index.php?page=article&storyid=46>)

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3 Diabetic neuropathy

- ▶ There are two types of diabetic neuropathy: polyneuropathy (symmetrical diffuse neuropathy) and mononeuropathy, and polyneuropathy is most frequently seen in clinical practice. However, it is necessary to differentiate between these and other neuropathies that have causes other than diabetes.
 - ▶ **Polyneuropathy:** The onset and development of polyneuropathy occur as a result of prolonged hyperglycemia, and present symptoms of both sensori-motor and autonomic neuropathy. By means of rigorous control of the blood glucose level, both the onset and the progression of polyneuropathy can be kept at bay. If the progression continues, it causes the level of the patient's sensory perception to drop, resulting in foot ulcers and gangrene (See p.48)
1. The presence of sensation disorder (numbness, pain, hypesthesia, and dysesthesia), of many abnormalities of the Achilles tendon reflex in both lower extremities, or of vibration and tactile perception (as judged by the use of monofilaments) in both legs suggests polyneuropathy. If nerve conduction testing and examinations for heart rate variability are performed, an objective diagnosis can be made.
 2. Prevention and treatment of polyneuropathy is good for maintaining control of the blood glucose level. It is reported that aldose reductase inhibitors (such as epalrestat) improve the subjective symptoms of neuropathy, and also prevent deterioration of nerve function. In some cases in which blood glucose control has been poorly maintained for prolonged periods, rapid improvement of the blood glucose level may cause post-treatment neuropathy, and consequent painful neuropathy.
 3. For a neuropathy that causes spontaneous pain (such as piercing pain, lancinating pain or urtication), a Ca^{2+} channel $\alpha\delta$ ligand (pregabalin), a serotonin noradrenaline reuptake inhibitor (duloxetine hydrochloride), an antiarrhythmic (mexiletine hydrochloride), an anticonvulsant (carbamazepine), a tricyclic antidepressant, and so on, may be prescribed alone or in combination, but if side effects occur the medication must be changed or terminated. Chronic cases are likely to be difficult to treat; and psychological support is also important.
 4. Let us consider the clinical symptoms resulting from autonomic neuropathy and their modes of handling
 - Treatment is given in consideration of the hypoglycemia unawareness that results from deficiency in reflexes of the sympathetic nervous system.
 - A vasoconstrictor is used if the patient becomes dizzy and faints (orthostatic hypotension) as a result of hypofunctioning of the vasomotor nerves.
 - Painless myocardial ischemia and severe arrhythmia result from depression of the function of the vagus and sympathetic nerves of the heart, and recognition of this arrhythmia and heart failure leads to suspicion of myocardial infarction.
 - For nausea, vomiting, constipation, diarrhea and glycemic instability due to motor dysfunction of the digestive tract, mosapride citrate hydrate can be used for treatment.
 - Urinary retention and atonia due to bladder dysfunction ultimately cause infection of the urinary tract.
 - Erectile dysfunction (ED) is treated with sildenafil citrate, vardenafil hydrochloride or tadalafil. (None of these drugs should be used in conjunction with nitrite products.)
- ▶ **Mononeuropathy:** Sudden paralysis of a single nerve can occur. Paralysis of the

extraocular muscles (disorders of the oculomotor, trochlear and abducent nerves) and facial nerve paralysis are common. There is no interrelation between this paralysis and the duration of the illness or glycemic control. In 95% of cases spontaneous remission of these disorders takes place within 3 months.

4 Atherosclerotic disorders

- ▶ Diabetes is one of the risk factors in conditions involving atherosclerosis, and the risk rises even when the hyperglycemia is mildly in the borderline range. Atherosclerotic disorders are more likely to occur in the condition known as metabolic syndrome (See p.12), in which abdominal obesity, dyslipidemia, hypertension and glucose intolerance are concurrent, and the risk is increased by cigarette smoking. Comprehensive control of these risk factors is important for the prevention of disorders arising from arteriosclerosis. It is reported that anti-platelet medication is effective in the secondary prevention of these disorders.

A Coronary arteriosclerosis

- ▶ Patients with diabetes are at high risk of developing coronary artery disease (CAD), with myocardial infarction being a direct cause of death in 40 to 50% of these patients in Western countries. In Japan as well, there is an increase in the number of patients with diabetes in whom CAD is likely to become a direct cause of mortality.
- ▶ Acute myocardial infarction in many patients with diabetes does not present a clear clinical picture (such cases being asymptomatic or atypical). At onset, the coronary arteries may already have lesions in many branches, and in many cases, these lesions are advanced, so heart failure and arrhythmia can readily occur.
- ▶ When glycemic control deteriorates or ketosis develops without apparent cause, when edema of the lower leg or the lung, atypical arrhythmia, or abnormalities in the electrocardiogram are present, CPK, AST, ALT and WBC should be examined, since acute myocardial infarction should be suspected. If it is possible to take a simple measurement of myocardial troponin T, this is an advisable precaution.

B Cerebrovascular disease

- ▶ Cerebral infarction is more common than cerebrovascular hemorrhage. Diabetes is an independent risk factor for cerebral infarction, which is 2 ~ 4 × more frequent compared with non-diabetic subjects. Diabetes is associated with atherothrombotic cerebral infarction in the cortical branches, but since hypertension is present in about 50% of patients with diabetes, lacunar infarctions in the perforating branch region are also common. Overall, small infarctions tend to be more common. As transient ischemic attacks and mild paralysis occur repeatedly, cerebrovascular dementia gradually develops.
- ▶ As a general rule, during the initial treatment of acute-phase cerebral infarction, the blood pressure should not be lowered for 2 weeks following infarction. Attention should be given to preventing a low plasma glucose level; this should be maintained at about 150 ~ 200 mg/dL, and strict glycemic management should gradually be instituted.

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C Peripheral arterial disease (PAD)

- ▶ Although PAD is not unique to patients with diabetes, it is present as a complication in a high percentage of patients with diabetes (10 ~15%). The Fontaine classification is usually employed for diagnosing stage (Grade I, Cold; numbness; Grade II, Intermittent claudication; Grade III, Rest pain; Grade IV, Skin ulcers). Lowering of the skin temperature of the lower limb, weakening and disappearance of the pulse of the dorsal artery and posterior tibial artery, and a difference between left and right pulses are all important signs for diagnosis.
- ▶ Intermittent claudication: This should be distinguished from spinal cord disorders, including stenosis of the vertebral canal. A ratio between the systolic blood pressure measured in the leg (ankle) and in the arm (brachial), ankle-brachial index, or ABI equal to or below 0.9 suggests the presence of this disorder. A characteristic of PAD in patients with diabetes is that the lesion lies mostly at or below the knee.
- ▶ Foot ulcers and gangrene of patients with PAD often resist medical treatment and therefore require surgical treatment. The preferred treatments for severe ischemia in the legs are: ① EVT (endovascular therapy) and ② surgical vascular bypass.

5 Diabetic foot lesions

- ▶ Diabetic foot lesions include a wide range of pathologies, from interdigital and onychial trichophytosis, callosities and deformities of the foot and toes, as far as ulcers and gangrene of the foot. In order to achieve an early diagnosis of these conditions, detailed examination is essential: through external observation, identification of pulsation in the arteries on the dorsum of the foot, and appraisal of any disturbance of the blood flow or of any neurological disorders.
- ▶ Diabetic polyneuropathy, microcirculatory impairments, PAD (peripheral arterial disease), traumata, infections and other conditions can all play a part in the complex onset of severe lesions of the foot (ulcers and gangrene). Gangrene due to blood vessel occlusion caused by PAD accounts for fewer than half of them. Hyperglycemia retards the healing of lesions.
- ▶ The direct causes of ulcers or gangrene are a failure to notice a burn or an external lesion due to hypesthesia, leading to tardy treatment of that injury; dermal hypertrophy and calluses with cracks; and pressure and blisters on the feet due to their deformation.
- ▶ **Foot care:** Patients having a high risk of foot lesions—that is, those with a history of foot ulcers and gangrene, of nerve impairment or PAD as a complication, of kidney failure and dialysis, and those who are unable to feel monofilaments 5.07 (10 g) during sensory testing—are instructed to carefully observe their bare feet every day, and to consult their chief physician if there is any abnormality such as infection, sores, deformation of their nails, trichophytosis, or calluses. Instruction is given on the choice of shoes and protective equipments, and on the manner in which the nails should be clipped (straight cut), and the use of foot warmers and hot water bottles is forbidden.

6 Bone lesions

- ▶ Decreased bone quality is shown to be associated with an increased risk of bone fracture in both patients with type 1 diabetes and patients with type 2 diabetes, while bone mineral density (BMD) is shown to be decreased in patients with type 1 diabetes

but rather increased in patients with type 2 diabetes.

- ▶ Persistently poor glycemic control is shown to be associated with an increased risk of bone fracture.
- ▶ While the thiazolidinediones (TZDs) are shown to be associated with an increased risk of bone fracture in women (particularly elderly women), no consensus has been reached on the relationship between other classes of drug and the risk of bone fracture.

7 Diabetic hand lesions

- ▶ If a patient with diabetes complains of stiffness of the hands, limitation of finger movement or pain in the fingers, these symptoms may be judged to be complications of the diabetes that result from constrictive flexor tendon tendinitis, carpal tunnel syndrome, Dupuytren contracture or limited joint mobility (LJM).

8 Periodontal disease

- ▶ Periodontal disease is a chronic infection of the periodontal tissues by periodontal anaerobic bacteria such as *Porphyromonas gingivalis*, a pathogenic Gram-negative bacterium. It is one of the major complications of diabetes.
- ▶ This disease becomes a serious illness in diabetic subjects.
- ▶ Poor glycemic control results in aggravation of periodontal disease, especially in the elderly, smokers, the obese, and those whose immune function is poor, and all of these subjects have high infection rates.
- ▶ The more serious the periodontal disease, the worse the glycemic control. Moreover, it was reported that, the treatment of the patient's periodontal condition lessened the insulin resistance and improved glycemic control.

9 Dementia

- ▶ Dementia in elderly diabetics causes impairment of diabetes control, and even when care is available, major difficulties arise.
- ▶ The risk involved in an elderly diabetic with dementia is two to four times as great as it is in a patient with both Alzheimer-type dementia and cerebrovascular dementia, but no diabetes.
- ▶ In the MMSE (Mini Mental State Examination)-type or Hasegawa-type Simplified Intelligence Scale, the cognitive function is evaluated, and the cause of the decline of the cognitive function is sought using an MRI (CT) of the brain.

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COLUMN

Diabetes and malignancy

The Joint Japan Diabetes Society/Japanese Cancer Association Committee on Cancer reports on the association between diabetes and cancer as follows. Epidemiological data currently available in Japan underpins the association of diabetes with colorectal cancer, hepatic cancer and pancreatic cancer in the Japanese population. Assumed mechanisms of oncogenesis through diabetes include insulin resistance and associated hyperinsulinemia, hyperglycemia, and inflammation. Common risk factors for both diabetes and malignancy include aging, male sex, obesity, low physical activity, inappropriate diet (e.g., excess intake of red/processed meat, inadequate intake of vegetable, fruit, and dietary fiber), excessive drinking and smoking. Diet/exercise therapy, smoking cessation, and temperance may be associated with decreased risk for malignancy. There is only limited evidence as to whether any particular anti-diabetic drug given to a patient may affect the risk of onset of malignancy in the patient.

A

Diabetes of childhood and adolescent

- ▶ In the case of children with positive findings for urinary sugar in their school checkup, the blood glucose, HbA1c and urinary ketone bodies are preferred to retests for urinary sugar.
- ▶ When it is necessary to carry out an oral glucose loading test in order to diagnose diabetes, the patient's current weight in kg \times 1.75 g (but no more than 75 g) of glucose is used for the loading. The categorization of high blood glucose levels and the diagnostic categories of diabetes are the same as for the adults (See p.11, Fig. 3).

B

Pregnancy and diabetes mellitus

- ▶ Gestational diabetes mellitus (GDM) refers to abnormal glucose tolerance that arises or is first noticed during pregnancy, but does not meet the diagnostic criteria of fully developed diabetes (*i.e.*, not reach the range of diabetes). GDM does not include overt diabetes diagnosed (by the clinical diagnosis outlined in Fig. 3, p.11) in pregnancy. The criteria for GDM (Table 19) differ from those for diabetes in a non-pregnant woman.
- ▶ Since there is a high risk of later diabetes even if the impaired glucose metabolism in the mother improves after delivery, it is important to maintain regular observation of glucose tolerance for women who had GDM.
- ▶ When glycemic control is poor, or diabetic complications are present in a patient, it is advisable to introduce him to a facility that has team of specialists in diabetes and in pregnancy.

Table 19. Gestational diabetes: definition and diagnostic criteria

Definition of gestational diabetes	Impaired glucose metabolism not meeting the diagnostic criteria of diabetes that is first detected, or occurs, during pregnancy.
Diagnostic criteria	<p>In 75g OGTT, gestational diabetes is diagnosed if plasma glucose levels meet at least one of the following conditions:</p> <p>FPG: ≥ 92 mg/dL Plasma glucose 1 hour after a meal: ≥ 180 mg/dL Plasma glucose 2 hours after a meal: ≥ 153 mg/dL</p> <p>Those women who had clinically diagnosed diabetes are excluded from the diagnosis of GDM.</p>

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Diabetes in the elderly

- ▶ Elderly patients with diabetes are likely to be associated with drug-related adverse effects, including severe ones (i.e., hypoglycemia associated with sulfonylureas, lactic acidosis associated with biguanides, edema, cardiac failure and fracture associated with thiazolidinediones, ileus associated with α -glucosidase inhibitors and dehydration associated with SGLT2 inhibitors). It is necessary to ensure their safety by taking measures, such as initiating any drug of interest at a low dose.
- ▶ In elderly patients with diabetes, in particular, attention should be paid to hypoglycemia and it is desirable that they do not take a bath on an empty stomach. Again, given that they are at risk of developing delayed hypoglycemia, the dose and class of any drug given to these patients should be carefully considered.

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Figure 13. Glycemic targets (HbA1c values) for elderly patients with diabetes

Patient background/health status <small>Note 1</small>	Category I		Category II		Category III	
	1. Intact cognitive function and 2. No impairment of ADL		1. Mild cognitive impairment to mild dementia or 2. Impairment(s) of instrumental ADL, no impairment of basic ADL		1. Moderate or severe dementia or 2. Impairment(s) of basic ADL or 3. Presence of multiple comorbidities or functional impairments	
Use of drugs potentially associated with severe hypoglycemia (e.g. insulin or sulfonylureas, glinides)	No <small>Note 2</small>	< 7.0 %		< 7.0 %		< 8.0 %
	Yes <small>Note 3</small>	65 ≤ age < 75 years < 7.5 % (Lower limit, 6.5 %)	≥ 75 years < 8.0 % (Lower limit, 7.0 %)	< 8.0 % (Lower limit, 7.0 %)		< 8.5 % (Lower limit, 7.5 %)

The glycemic target is to be determined for each patient by taking into account his/her age, duration of diabetes, risk for hypoglycemia, and any support available to the patient, as well as the patient's cognitive function, basic/instrumental ADL, and comorbidities/functional impairments. It should be noted that the potential risk of hypoglycemia increases with age in each patient.

ADL activities of daily living; *Note 1* Refer to the Japan Geriatrics Society website [<http://www.jpn-geriat-soc.or.jp/tool/index.html>], for the evaluation of the cognitive function, basic ADL (e.g. self-care abilities such as dressing, transferring, bathing, and toileting), and instrumental ADL (e.g. abilities to maintain an independent household such as shopping, meal preparation, taking medication, and handling finances.). In end-of-life care, priority is to be given to preventing significant hyperglycemia and subsequent dehydration and acute complications through appropriate therapeutic measures; *Note 2* As in other age groups, the glycemic target is set at <7.0% in the elderly for preventing diabetic complications. However, this could be set at <6.0% for those thought likely to achieve glycemic control through diet and exercise therapy alone or those likely to achieve glycemic control with drug therapy without adverse reactions, or 8.0% for those in whom intensifying therapy may prove difficult. In either case, no lower limit is specified for the glycemic target. A glycemic target of <8.5% may be allowed in patients thought to be in category III and therefore at risk of developing adverse reactions to multi-drug combination therapy or in those with serious comorbidities or poor social support; *Note 3* In patients in whom priority should be given to preventing the onset/progression of diabetic complications due to their duration of disease, the glycemic target or its lower limit may be set for each elderly patient with appropriate measures to prevent severe hypoglycemia. Current treatments are to be continued in those less than 65 years of age despite their HbA1c values falling below their glycemic target or lower limit while on therapy, but attention should be paid to potential severe hypoglycemia. Glinides may be classified as drugs unlikely to be associated with severe hypoglycemia, depending on the type and amount of glinide used in a particular patient relative to the patient's glucose level.

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When consultation is required to a specialist

- ① Inadequate glycemic control
- ② Educational hospitalization
- ③ Chronic complications
- ④ Acute complications
- ⑤ Perioperative care

B

Regional and inter-hospital collaboration

- ▶ According to the laws governing medical practice, in each of the 47 prefectures of Japan, regional medical care planning is necessary to cover five diseases (diabetes mellitus, cancer, stroke, acute myocardial infarction and psychiatric illness) and five special fields of difficulty (emergencies, disasters, remote locations, perinatal illness and pediatric care including the emergency pediatric service) as well as home medical care. In connection with these activities, great importance is attached to regional medical liaison. As part of these considerations, and in response to the circumstances in each of the areas of the country, the introduction of a regional diabetes clinical pathway has been carried out, or is planned.
- ▶ This regional clinical pathway provides standard blood test results (such as HbA1c), conditions (metabolic disorders, complications) and other findings for referral from general physicians to diabetes specialists or, in turn, from diabetes specialists to general physicians.
- ▶ It is necessary to continuously promote cooperation between diabetes specialists and general physicians and between clinics and hospitals using this standard. This will enable information regarding diabetes treatment to be shared, thereby creating a smoothly running clinical system for all patients.
- ▶ Although the number of patients is continuously growing, the number of diabetes specialists is limited. In diabetes treatment, everyday health care is important. It is desirable that patients with diabetes should be cared for with the cooperation of diabetes specialists and general practitioners, together with medical staff such as Certificated Diabetes Educators of Japan (CDEJs), visiting nurses, registered dietitians, pharmacists, and also dentists.
- ▶ Patients with diabetes are susceptible to periodontal disease; conversely, those with severe periodontal disease may be suspected of having diabetes, even when they remain asymptomatic. Again, as it is suggested that the poorer the glycemic control in a patient, the more severe the existing periodontal disease is likely to become, collaborative efforts are required to identify those at risk of either by encouraging them to consult internists and dentists.
- ▶ Patients with diabetes are in need of assistance in continuing to work while remaining on treatment, where their follow-up (e.g., recommendations for consultation, confirmation of continued treatment) by occupational physicians is crucial and close collaboration between their attending physicians and occupational physicians such as sharing of patient information is required.

- ▶ There must be a common understanding of the need for inter-regional and hospital-clinic collaboration in diabetes care among all those immediately concerned including patients themselves. Again, it is urgently required that all healthcare practitioners involved in diabetes care actively engage in activities by the local Promotion Council for Diabetes Prevention and Countermeasures, thus building a local collaborative network for diabetes care.

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