Treatment Guide for Diabetes
2014-2015
Edited by Japan Diabetes Society
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.

What is diabetes mellitus?

“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.
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 of 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>
<thead>
<tr>
<th>Higher HbA1c values</th>
<th>Lower HbA1c values</th>
<th>Either higher or lower HbA1c values</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapidly improved diabetes</td>
<td>• Sudden onset or exacerbation of diabetes</td>
<td>• Homoglobinopathy</td>
</tr>
<tr>
<td>• Iron deficiency</td>
<td>• Period of recovery from iron deficiency anemia</td>
<td></td>
</tr>
<tr>
<td>• Hemolysis (erythrocyte lifespan ↓)</td>
<td>• After hemorrhage (erythrocyte production ↑), Transfusion</td>
<td></td>
</tr>
<tr>
<td>• Renal anemia during treatment with erythropoietin</td>
<td>• Liver cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

* 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: ≥14.0 μg/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, lower-than-mean 1,5-AG values, which may be seen with the use of the α-glucosidase inhibitor acarbose and SGLT2 inhibitors.
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 (%) × 1.02 + 0.25 (%). JDS value (%) = NGSP value (%) × 0.980 - 0.245 (%). (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 valuesa, 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/).

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*a1 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 ≤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 ≤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%.

*a2 The HbA1c value no longer requires qualifying by adding “(NGSP)” after HbA1c.

Diabetes mellitus is classified from both etiological and pathophysiological standpoints.

### Etiological classification of diabetes

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

* 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.

Etiological classification and pathophysiological stages of diabetes mellitus

Figure 1. A scheme of the relationship between etiology (mechanism) and pathophysiological stages (states) of diabetes mellitus

<table>
<thead>
<tr>
<th>Stage</th>
<th>Normoglycemia</th>
<th>Hyperglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal area</td>
<td>Borderline area</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type 1

Type 2

Other types

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 events of low frequency.

Note: Among patients with type 1 diabetes, there are patients who acutely develop symptoms within 1 week or so of onset of diabetic symptoms similarly to those with fulminant type 1 diabetes and who slowly become insulin-dependent over a period of few years similarly to those with slowly progressing type 1 diabetes, and care needs to be taken to identify these individuals in a timely fashion.

Criteria for screening of fulminant type 1 diabetes mellitus (Cases meeting the standards listed below require careful investigation with hospitalization.)
1. Ketosis or ketoacidosis within a week after the onset of hyperglycemic symptoms
2. Plasma glucose level ≥16.0 mmol/L (≥288 mg/dL) at first visit


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 μg/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

A Diagnostic tests

1 Categories of the state of glycemia and decision criteria

1 Early-morning fasting plasma glucose level:
   ≥ 126 mg/dL
2 Two-hour plasma glucose level after 75 g glucose loading:
   ≥ 200 mg/dL
3 Random (casual) plasma glucose measurements*:
   ≥ 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 Early-morning 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

Glucose levels (in venous plasma)

<table>
<thead>
<tr>
<th></th>
<th>Timing of measurements</th>
<th>Two hours after glucose loading</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before loading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 126 mg/dL or ≥ 200 mg/dL</td>
<td>≥ 200 mg/dL</td>
<td>Diabetic type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Borderline type</td>
</tr>
<tr>
<td></td>
<td>&lt; 110 mg/dL and &lt; 140 mg/dL</td>
<td></td>
<td>Normal type*2</td>
</tr>
</tbody>
</table>

*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)

* Random (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)

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>At 30 min</th>
<th>At 1 hr</th>
<th>At 2 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1: Required for judging 75g OGTT type*2
*1: Required for calculation of insulinogenic index*3
*1: Required for calculation of HOMA-R

The 75g OGTT is not required for the diagnosis of diabetes. When subjective symptoms clearly suggest hyperglycemia, then first, the fasting plasma glucose or the random (casual) plasma glucose should be measured. Performing 75g OGTT upon marked hyperglycemia is detrimental, because raises blood glucose further.

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.

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

* The value for HbA1c (%) is indicated with 0.4% added to HbA1c (JDS) (%).
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. 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.

2. 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.

3. 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.)

4. 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.

5. 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.

6. Since diabetes is not a curable disease, patients are advised not to discontinue hospital visits.
**Figure 3. Flowchart for the clinical diagnosis of diabetes**

<table>
<thead>
<tr>
<th>Diabetic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fasting plasma glucose ≥126 mg/dL; or OGTT 2 hours ≥200 mg/dL; or random (casual) plasma glucose ≥200 mg/dL</td>
</tr>
<tr>
<td>- HbA1c ≥6.5%</td>
</tr>
</tbody>
</table>

![Flowchart Image]

- When diabetes is suspected, the HbA1c should be measured together with the plasma glucose. On the same day, if both the plasma glucose and HbA1c values have indicated the diabetic type, a diagnosis of diabetes can be made based on the initial test results alone.

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

- **Diabetic type**
  - Fasting plasma glucose levels: 110 ~ 125 mg/dL
  - Two-hour plasma glucose levels: less than 140 mg/dL

- **High-normal**
  - Fasting plasma glucose levels: 100 ~ 109 mg/dL

- **Normal type**
  - Fasting plasma glucose levels: less than 100 mg/dL

- **Borderline type**
  - Fasting plasma glucose levels: 110 ~ 125 mg/dL
  - Two-hour plasma glucose levels: 140 ~ 199 mg/dL

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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.
Treatment objectives and control indicators

1 Aims of diabetes treatment

Figure 5. Aims of diabetes treatment

- Maintenance of a quality of life (QOL) no different from that of non-diabetics
- Prevention of onset and deferment of diabetic microvascular complications (retinopathy, nephropathy, neuropathy) and atherosclerotic diseases (ischemic heart disease, cerebrovascular disease, arteriosclerosis obliterans)
- Maintenance of good control of blood glucose, body weight, blood pressure and serum lipid levels

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
readily affected by the amount and type of food taken, as well as by treatment method. The risk of heart disorders needs to be pointed out.

- 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: ≥ 14.0 μg/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 objectives
* This diagram shows NGSP values for HbA1c

<table>
<thead>
<tr>
<th>Objective when aiming for normal glycemia</th>
<th>Objective when aiming to prevent complication</th>
<th>Objective when intensification of therapy considered difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 6.0</td>
<td>&lt; 7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 8.0</td>
</tr>
</tbody>
</table>

Treatment objectives are established individually, in consideration of age, duration of disease, organ damage, risk of hypoglycemia, support structures, etc.

*1 Objective in cases where objectives can be attained by appropriate dietary or exercise therapy, or during pharmacotherapy without the occurrence of side effects such as hypoglycemia.
*2 From the perspective of preventing complication, HbA1c target value is set below 7%. Corresponding glycemic values are set at a target value roughly below 130 mg/dL.
*3 Objective in cases where intensification of treatment is considered difficult due to side effects such as hypoglycemia or for other reasons.
*4 All objective 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*, urine 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.

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**B** Setting up a treatment policy

1. **Non-insulin-dependent state**

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**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 curtail a planned series of 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, and it is necessary that this and other types of compliance 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 so that 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, or if it is possible to achieve it during pharmacotherapy without the occurrence of side effects such as hypoglycemia, the objective 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 complication, 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).
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.

- 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

- Education of patients regarding diet therapy, exercise therapy, improvement of lifestyle
- Treatment with oral hypoglycemic agents (See Fig. 8, next page)
- Insulin treatment
- Treatment with GLP-1 receptor agonist

- Education of patients regarding diet therapy, exercise therapy, improvement of lifestyle
- Treatment with increased dose of oral hypoglycemic agent, or their combination
- Switch to insulin or to an oral hypoglycemic agent in combination treatment with insulin
- Switch to a GLP-1 receptor agonist or an oral hypoglycemic agent or insulin in combination with a GLP-1 receptor agonist

- Education of patients regarding diet therapy, exercise therapy, improvement of lifestyle
- Intensive insulin treatment
Underlying causes of type 2 diabetes

<table>
<thead>
<tr>
<th>MOA</th>
<th>Drug class</th>
<th>Primary effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibiting hepatic glyconeogenesis</td>
<td>Biguanides</td>
<td></td>
</tr>
<tr>
<td>Improving insulin sensitivity in skeletal muscle and liver</td>
<td>Thiazolidinediones</td>
<td></td>
</tr>
<tr>
<td>Promoting insulin secretion</td>
<td>Sulfonylureas (SUs)</td>
<td></td>
</tr>
<tr>
<td>Promoting faster insulin secretion/improving postprandial hyperglycemia</td>
<td>Fast-acting insulin secretagogues (gliptins)</td>
<td></td>
</tr>
<tr>
<td>Glucose-dependently promoting insulin secretion and inhibiting glucagon secretion</td>
<td>DPP-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>Delaying carbohydrate absorption/improving postprandial hyperglycemia</td>
<td>α-Glucosidase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Inhibiting renal reabsorption and promoting glucose excretion in urine</td>
<td>SGLT2 inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

DPP-4, dipeptidyl peptidase-4; MOA, mode of action; SGLT2, sodium glucose cotransporter 2

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

- Diabetic patients 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 (over 65 years of age) diabetic patients 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.
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 pharmacotherapy 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.

Insulin-dependent state

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
Figure 9. Treatment of patients in an 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.

Findings

- Marked hyperglycemia
- Urinary ketone bodies: negative to slightly positive
- Oral ingestion possible. Clear consciousness

Treatment and Management

- Provide ample water supply. Start insulin injections (See p.19: Conducting the first consultation)
- Measure blood glucose, urinary ketones; if possible, measure complete blood count, serum electrolytes, etc.
- Discussion with specialist about further treatment and management

(For cases of children, the basic rule is, consult a specialist)

Findings

- Marked hyperglycemia
- Urinary ketone bodies: strongly positive. Dehydration evident
- Patient’s reactions dull or consciousness clouded

Dehydration evident

- Patient’s reactions dull or consciousness clouded
- Provide intravenous infusion of physiological saline and insulin (See p.39 Diabetic ketoacidosis)

After 36 hours (1.5 days), if urinary ketones are still positive, transport the patient (if necessary) to a specialist.

If patient’s state of consciousness deteriorates, quick transportation to a hospital capable of intensive care. Be aware that other diseases may also be present.

Continued Treatment And Management by General Practitioner

- Basically, maintenance of intensive insulin treatment (4 injections per day, etc.)
- Instruct patient and family about diet, exercise, lifestyle (including care for hypoglycemia).
- For children, consider the school situation
- Continuing cooperation with diabetes specialist

Treatment And Management by Diabetes Specialist

- Initial treatments by diabetes specialist
- If patient’s condition improves, reassess and adjust treatment, diet, exercise plan
- In children with type1 diabetes, have regular consultations, aim at treatment and lifestyle guidance suited to child’s growth and development
- Continuing cooperation with general practitioner

Cooperation
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.

Educating diabetic patients

The principal aim of diabetes education is for patients to obtain both a good understanding of the disease, and the motivation to reach good glycemic control.

Education is not merely a matter of giving information. Through dialogue, information and useful techniques for stimulating desire to take action are developed, and at the same time, the patient is motivated and prepares to make behavioral changes.

The areas covered by this education include diagnosis, pathological states, complications, methods of treatment (diet therapy, exercise, oral agents, and insulin), self-monitoring of blood glucose (SMBG), hypoglycemia, sick days, and hints about everyday living. These should be taught to patients according to their individual needs.

Even after these activities have been successfully started, the proportion of these activities usually falls with time. Together with checks asking, for example, “Which part of the treatment is difficult?” “What hinders continuation of the treatment?” New information on therapeutic methods is also continuously offered to the patients.
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 a Public Interest Incorporated Association linking patient associations from throughout Japan, and now counts not only diabetic patients 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, giving training, giving guidance regarding treatment to diabetic patients 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.

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 membership consisting of 4,996 specialist physicians and over 17,000 non-specialist members.

Looking at the world as a whole, a rapid upsurge of diabetes patients 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 Diabetes 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).
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 1,400 ~ 1,800 kcal, and women, 1,200 ~ 1,600 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.

\[ \text{Energy intake in food} = \text{standard body weight} \times \text{amount of physical activity} \]

Guidelines on energy expended for different degrees of physical activity

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Units: kcal/ kg of standard body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light work (desk workers, housewives, etc.)</td>
<td>25 ~ 30</td>
</tr>
<tr>
<td>Moderate work (mainly standing work)</td>
<td>30 ~ 35</td>
</tr>
<tr>
<td>Heavy work (heavy manual workers)</td>
<td>35 ~</td>
</tr>
</tbody>
</table>

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.
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 300 mg/day).
- The patient must make an effort to eat large amounts of dietary fiber (20 ~ 25 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.

Before the patient receives instruction about exercise therapy, a medical check-up is essential since exercise therapy may need to be forbidden or restricted (See [5] When exercise should be prohibited or restricted).

**Types of exercise**

- There are two types of exercise, aerobic and resistance. 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 (Fig.11).

**Intensity of exercise**

- Generally, intermediate-intensity exercises are recommended. An intermediate-intensity exercise is defined as an exercise involving a maximum oxygen uptake.
Diabetic patients 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.

It is desirable that the patient should include exercise sessions in the daily schedule. The minimum number of sessions should be no less than three times a week.

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.
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 7 should not be used.

1 Sulfonylurea (SU) drugs and related drugs

Table 4

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

* The standard doses are indicated (Table 4-10).
Table 5

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nateglinide</td>
<td>Stasis Fastic</td>
<td>0.8</td>
<td>3</td>
<td>30, 90</td>
<td>90 ~ 270</td>
</tr>
<tr>
<td>mitoglinide calcium hydrate</td>
<td>Glufast</td>
<td>1.2</td>
<td>3</td>
<td>5, 10</td>
<td>15 ~ 30</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Surepost</td>
<td>0.8</td>
<td>4</td>
<td>0.25, 0.5</td>
<td>0.75 ~ 1.5</td>
</tr>
</tbody>
</table>

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

Table 6

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

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

Table 7

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>metformin hydrochloride</td>
<td>Glycoran Medet</td>
<td>1.5 ~ 4.7</td>
<td>6 ~ 14</td>
<td>250</td>
<td>500 ~ 750</td>
</tr>
<tr>
<td></td>
<td>Metgloco*</td>
<td>2.9</td>
<td>6 ~ 14</td>
<td>250, 500</td>
<td>500 ~ 1500</td>
</tr>
<tr>
<td>buformin hydrochloride</td>
<td>Dibetos Dibeton S</td>
<td>1.5 ~ 2.5</td>
<td>6 ~ 14</td>
<td>50</td>
<td>50 ~ 150</td>
</tr>
</tbody>
</table>

* Metgloco 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.

**5 Thiazolidinediones**

Table 8

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pioglitazone hydrochloride*</td>
<td>Actos Actos OD</td>
<td>5</td>
<td>20</td>
<td>15, 30</td>
<td>15 ~ 30</td>
</tr>
</tbody>
</table>

* 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.
6 Pharmacotherapy

6 DPP-4 inhibitors

Table 9

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin phosphatehydrate</td>
<td>Glactiv, Januvia</td>
<td>12</td>
<td>24</td>
<td>12.5, 25, 50, 100</td>
<td>50 ~ 100</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Equa</td>
<td>2.4</td>
<td>12 ~ 24</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Alogliptin benzoate</td>
<td>Nesina</td>
<td>17</td>
<td>24</td>
<td>6.25, 12.5, 25</td>
<td>25</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Tranzenta</td>
<td>105</td>
<td>24</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Teneligliptin hydrobromide hydrate</td>
<td>Tenelia</td>
<td>24.2</td>
<td>24</td>
<td>20</td>
<td>20 ~ 40</td>
</tr>
<tr>
<td>Anagliptin</td>
<td>Suiny</td>
<td>2</td>
<td>12 ~ 24</td>
<td>100</td>
<td>200 ~ 400</td>
</tr>
<tr>
<td>Saxagliptin Hydrate</td>
<td>Onglyza</td>
<td>7</td>
<td>24</td>
<td>2.5, 5</td>
<td>2.5 ~ 5</td>
</tr>
</tbody>
</table>

1 In general, for adults, a daily dose of 50 mg should be administered orally. The maximum daily dose is 100 mg. For the patients with moderate kidney disorder, a daily dose of 25 mg should be administered initially, the maximum dose being 50 mg per day.

2 Usually, for adults, the dosage should be 50 mg, twice per day, each morning and evening, administered orally. Patients with moderate or severe kidney disorder, or patients with end-stage renal failure who are undergoing dialysis should be administered 50 mg once per day, in the morning.

3 The usual dosage in adults is 25 mg once a day. For those with moderate kidney disorder, 12.5 mg is suitable. For the patients with severe kidney disorder or end-stage renal failure, 6.25 mg is suitable.

4 Usually, for adults, the dosage should be 100 mg, twice per day, each morning and evening, administered orally. 200 mg twice per day is the maximum dose. Patients with severe kidney disorder, or patients with end-stage renal failure should be administered only once 100 mg per day.

7 SGLT2 inhibitors

Table 10

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipragliflozin L-Proline</td>
<td>Suglat</td>
<td>15</td>
<td>24</td>
<td>25, 50</td>
<td>50</td>
</tr>
<tr>
<td>Dapagliflozin propylene glycolate hydrate</td>
<td>Forxiga</td>
<td>8 ~ 12</td>
<td>24</td>
<td>5, 10</td>
<td>5 ~ 10</td>
</tr>
<tr>
<td>Luseogliflozin Hydrate</td>
<td>Lusefi</td>
<td>11.2</td>
<td>24</td>
<td>2.5, 5</td>
<td>2.5 ~ 5</td>
</tr>
<tr>
<td>Tofogliflozin Hydrate</td>
<td>Apleway</td>
<td>54</td>
<td>24</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>
### Combination drug treatment

#### Table 11

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Content of 1 tablet (mg)</th>
<th>Daily dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone hydrochloride/Metformin hydrochloride</td>
<td>Metact LD</td>
<td>10.4</td>
<td></td>
<td>15</td>
<td>15/500</td>
</tr>
<tr>
<td></td>
<td>Metact HD</td>
<td>4.4</td>
<td></td>
<td>30</td>
<td>30/500</td>
</tr>
<tr>
<td></td>
<td>Sonias LD</td>
<td>8.9</td>
<td></td>
<td>15</td>
<td>15/1</td>
</tr>
<tr>
<td></td>
<td>Sonias HD</td>
<td>7.5</td>
<td></td>
<td>30</td>
<td>30/3</td>
</tr>
<tr>
<td></td>
<td>Liovel LD</td>
<td>18.3</td>
<td></td>
<td>25</td>
<td>25/15</td>
</tr>
<tr>
<td></td>
<td>Liovel HD</td>
<td>9.2</td>
<td></td>
<td>25</td>
<td>25/30</td>
</tr>
<tr>
<td></td>
<td>Glubes</td>
<td>1.3</td>
<td></td>
<td>10</td>
<td>30/0.6</td>
</tr>
</tbody>
</table>
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, lactic acidosis).
   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.
### B Types of Insulin preparations

**Table 12. Insulin prefilled/kit preparations**

<table>
<thead>
<tr>
<th>Type</th>
<th>Proprietary name</th>
<th>No. of units/volume</th>
<th>Amount of insulin infused (increments)</th>
<th>Time to evident effects</th>
<th>Time to peak effects</th>
<th>Duration of effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NovoRapid FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>10 ~ 20 min</td>
<td>1 ~ 3 hr</td>
<td>3 ~ 5 hr</td>
</tr>
<tr>
<td></td>
<td>NovoRapid FlexTouch</td>
<td>300/3 mL</td>
<td>1 ~ 80 U(IU)</td>
<td>10 ~ 20 min</td>
<td>1 ~ 3 hr</td>
<td>3 ~ 5 hr</td>
</tr>
<tr>
<td></td>
<td>NovoRapid InnoLet</td>
<td>300/3 mL</td>
<td>1 ~ 50 U(IU)</td>
<td>10 ~ 20 min</td>
<td>1 ~ 3 hr</td>
<td>3 ~ 5 hr</td>
</tr>
<tr>
<td></td>
<td>Humalog Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>&lt;15 min</td>
<td>30 min ~ 1.5 hr</td>
<td>3 ~ 5 hr</td>
</tr>
<tr>
<td></td>
<td>Apidra SoloStar</td>
<td>300/3 mL</td>
<td>1 ~ 80 U(IU)</td>
<td>&lt;15 min</td>
<td>30 min ~ 1.5 hr</td>
<td>3 ~ 5 hr</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td>Novolin R FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>about 30 min</td>
<td>1 ~ 3 hr</td>
<td>about 8 hr</td>
</tr>
<tr>
<td></td>
<td>Humulin R Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>30 min ~ 1 hr</td>
<td>1 ~ 3 hr</td>
<td>5 ~ 7 hr</td>
</tr>
<tr>
<td><strong>Premixed</strong></td>
<td>NovoRapid 30 Mix FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>10 ~ 20 min</td>
<td>1 ~ 4 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>NovoRapid 50 Mix FlexPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NovoRapid 70 Mix FlexPen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Novolin 30R FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>about 30 min</td>
<td>2 ~ 8 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Innolet 30R</td>
<td>300/3 mL</td>
<td>1 ~ 50 U(IU)</td>
<td>about 30 min</td>
<td>2 ~ 8 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Humalog Mix 25 Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>&lt;15 min</td>
<td>30 min ~ 6 hr</td>
<td>18 ~ 24 hr</td>
</tr>
<tr>
<td></td>
<td>Humalog Mix 50 Miriopen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Humulin 3/7 Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>30 min ~ 1 hr</td>
<td>2 ~ 12 hr</td>
<td>18 ~ 24 hr</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td>Novolin N FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>about 1.5 hr</td>
<td>4 ~ 12 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Humalog N Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>30 min ~ 1 hr</td>
<td>2 ~ 6 hr</td>
<td>18 ~ 24 hr</td>
</tr>
<tr>
<td></td>
<td>Humulin N Miriopen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>1 ~ 3 hr</td>
<td>8 ~ 10 hr</td>
<td>18 ~ 24 hr</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td>Levmir FlexPen</td>
<td>300/3 mL</td>
<td>1 ~ 60 U(IU)</td>
<td>about 1 hr</td>
<td>3 ~ 14 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Levmir Innolet</td>
<td>300/3 mL</td>
<td>1 ~ 50 U(IU)</td>
<td>about 1 hr</td>
<td>3 ~ 14 hr</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Lantus SoloStar</td>
<td>300/3 mL</td>
<td>1 ~ 80 U(IU)</td>
<td>1 ~ 2 hr</td>
<td>No clear peak</td>
<td>about 24 hr</td>
</tr>
<tr>
<td></td>
<td>Tresiba FlexTouch</td>
<td>300/3 mL</td>
<td>1 ~ 80 U(IU)</td>
<td>--</td>
<td>No clear peak</td>
<td>Over 42 hours*</td>
</tr>
</tbody>
</table>

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

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

- 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

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

* The dark green background indicates an insulin analog preparation, and the others, human insulin.
Injectable drugs other than insulin: GLP-1 receptor agonists

Table 15. GLP-1 receptor agonists

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary names (main)</th>
<th>Blood half-life (hr)</th>
<th>Duration of activity (hr)</th>
<th>Contents of 1 vial</th>
<th>Daily dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide*1 (genetic recombination)</td>
<td>Victoza 18 mg</td>
<td>13 ~ 15</td>
<td>&gt;24</td>
<td>18 mg</td>
<td>0.9 mg</td>
</tr>
<tr>
<td>Exenatide*2</td>
<td>Byetta 5/10 μg Pen 300</td>
<td>1.4 (5 μg)</td>
<td>8</td>
<td>300 μg</td>
<td>10 ~ 20 μg</td>
</tr>
<tr>
<td>Exenatide*3 (Continuous injectable solution)</td>
<td>Bydureon 2 mg</td>
<td>_*1</td>
<td>_*1</td>
<td>2.6 mg</td>
<td>2 mg*2 once per week</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia</td>
<td>2.12 (10 μg)</td>
<td>15</td>
<td>300 μg</td>
<td>10 ~ 20 μg</td>
</tr>
</tbody>
</table>

*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.

Other drug treatments

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 lifestyle intervention.
► The target level of blood pressure is less than 130/80 mmHg.
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.


Diabetes mellitus complicated by dyslipidemia

- When lipid metabolism abnormalities are treated, the table of lipid control target values in diabetic patients (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 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 Probufol should be considered (with kidney functional disorder, the concurrent use of statins and fibrates is contraindicated).
### Table 16. Lipid control target values in diabetic patients

<table>
<thead>
<tr>
<th>Coronary artery disease</th>
<th>Lipid control target values (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDL-C</td>
</tr>
<tr>
<td>Present</td>
<td>&lt; 120</td>
</tr>
<tr>
<td>Absent</td>
<td>&lt; 100</td>
</tr>
</tbody>
</table>

**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:  

\[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \frac{\text{TG}}{5} \]  

(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.

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 (<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 electrolytes 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 passed. 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 (HCO₃⁻) 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 failure results, but no outstanding evidence of acidosis is seen (pH 7.3 ~ 7.4). This syndrome can develop in elderly type 2 diabetes
patients. 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.

### 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 diabetic patients.

1. There are four stages of retinopathy:
   - 1. Normal,
   - 2. Simple retinopathy,
   - 3. Preproliferative retinopathy,
   - 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:
   - From normal to early stage simple retinopathy (microaneurysms, dot hemorrhage) .......... Once a year
   - After the middle stage of simple retinopathy (patchy hemorrhage, small amount of soft exudates) .......... Once every 3 ~ 6 months
• After preproliferative retinopathy, depending on the patient’s condition ............... Once every 1 ~ 2 months

6. Since it is not known when type 2 diabetes started, it is advisable to test the eyes of such patients before treatment is initiated, and then 3 and 6 months later. In addition, if at the first visit there is remarkable hyperglycemia and the patient is suspected to have had a long history of this disorder, it is advisable to conduct another examination of the fundus oculi one month later.

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:

   
   \[
eGFR_{\text{creat}} \ (\text{mL/min/1.73 m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age (years)}^{-0.287}
   \]

   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:** \( \text{eGFR}_{\text{cys}} \ (\text{mL/min/1.73 m}^2) = (104 \times \text{Cys-C}^{-1.019} \times 0.996 \times \text{age (years)} - 8 \)

   **Females:** \( \text{Males: } \text{eGFR}_{\text{cys}} \ (\text{mL/min/1.73 m}^2) = (104 \times \text{Cys-C}^{-1.019} \times 0.996 \times \text{age (years)} \times 0.929) - 8 \)


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 m^2 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 m^2 from early on
Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of type 2 diabetic patients 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.


Table 17 Classification of Diabetic Nephropathy 2014

<table>
<thead>
<tr>
<th>Stage</th>
<th>Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)</th>
<th>GFR (eGFR) (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (pre-nephropathy)</td>
<td>Normoalbuminuria (&lt;30)</td>
<td>≥ 30 *1</td>
</tr>
<tr>
<td>Stage 2 (incipient nephropathy)</td>
<td>Microalbuminuria (30 – 299) *2</td>
<td>≥ 30</td>
</tr>
<tr>
<td>Stage 3 (overt nephropathy)</td>
<td>Macroalbuminuria (≥ 300) or Persistent proteinuria (≥ 0.5)</td>
<td>≥ 30 *3</td>
</tr>
<tr>
<td>Stage 4 (kidney failure)</td>
<td>Any albuminuria/proteinuria status *4</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Stage 5 (dialysis therapy)</td>
<td>Any status on continued dialysis therapy</td>
<td></td>
</tr>
</tbody>
</table>

Diabetic nephropathy does not always progress from one stage to the next. The revised classification takes into account findings on the prognosis of type 2 diabetic patients 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.
Appendix

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

<table>
<thead>
<tr>
<th>Albuminuria category</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative urinary albumin estimation</td>
<td>Normoalbuminuria</td>
<td>Microalbuminuria</td>
<td>Macroalbuminuria ≥300 (or increased proteinuria) ≥0.50</td>
</tr>
<tr>
<td>Urinary albumin/Cr ratio (mg/g Cr)</td>
<td>&lt; 30</td>
<td>30-299</td>
<td>(≥ 0.50)</td>
</tr>
<tr>
<td>(quantitative urinary protein estimation)</td>
<td>(urinary protein/Cr ratio (g/g Cr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR category (mL/min/1.73 m²)</th>
<th>Stage 1 (pre-nephropathy)</th>
<th>Stage 2 (incipient nephropathy)</th>
<th>Stage 3 (overt nephropathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>60-89</td>
<td>45-59</td>
<td>30-44</td>
</tr>
<tr>
<td>15-29</td>
<td>&lt; 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(dialysis therapy)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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.

3. Adequate control of blood pressure (target levels: less than 130/80 mmHg; if urinary protein is at least 1 g/day, the optimum blood pressure is < 125/75 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 proteinuria and the deterioration of renal function.

4. By initiating a low-protein diet (below 0.8 g/kg of body weight) at stage 3A, proteinuria can be reduced, and in its turn, the progression of renal dysfunction can be inhibited.

5. In many diabetic patients 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.
### Table 18. Criteria for lifestyle guidance for patients with diabetic nephropathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Daily living</th>
<th>Dietary intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total energy (kcal/kg BW/day)</td>
</tr>
<tr>
<td>Stage 1 (pre-nephropathy)</td>
<td>Normal life</td>
<td>25-30</td>
</tr>
<tr>
<td>Stage 2 (early nephropathy)</td>
<td>Normal life</td>
<td>25-30</td>
</tr>
<tr>
<td>Stage 3 (overt nephropathy)</td>
<td>Normal life</td>
<td>25-30 &lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stage 4 (renal failure)</td>
<td>Slightly restricted life</td>
<td>25-35</td>
</tr>
<tr>
<td>Stage 5 (dialysis)</td>
<td>Slightly restricted</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> 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.

<sup>2</sup> A patient’s protein intake is to be determined in accordance with the general criteria for diabetic diet.

<sup>3</sup> A patient’s protein intake may be changed to that in stage 4 disease if GFR < 45.

<sup>4</sup> Consider restricting total energy intake to 25-30 kcal/kg BW/day for glycemic and weight control.
<table>
<thead>
<tr>
<th>Exercise*1</th>
<th>Work</th>
<th>Household work</th>
<th>Pregnancy/childbirth</th>
<th>Points to keep in mind</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Exercise therapy for diabetes to be implemented as a rule</td>
<td>- As usual</td>
<td>- As usual</td>
<td>May be an option</td>
<td>- Diabetic diet for glycemic control - Antihypertensive therapy - Lipid control - Smoking cessation</td>
</tr>
<tr>
<td>- Exercise therapy for diabetes to be implemented as a rule</td>
<td>- As usual</td>
<td>- As usual</td>
<td>May be an option but requires careful management</td>
<td>- Diabetic diet for glycemic control - Antihypertensive therapy - Lipid control - Smoking cessation - Excessive protein intake unfavorable</td>
</tr>
<tr>
<td>- Exercise allowed as a rule</td>
<td>- As usual</td>
<td>- As usual</td>
<td>Not recommended</td>
<td>- Appropriate glycemic control - Antihypertensive therapy - Lipid control - Smoking cessation - Protein-restricted diet</td>
</tr>
<tr>
<td>- Exercise restricted</td>
<td>- Work on light to restricted duty</td>
<td>- Restricted</td>
<td>Not recommended</td>
<td>- Appropriate glycemic control - Antihypertensive therapy - Lipid control - Smoking cessation - Protein-restricted diet - Anemia treatment</td>
</tr>
<tr>
<td>- Light exercise as a rule</td>
<td>- Work on light duty as a rule</td>
<td>- Usual work allowed</td>
<td>Not recommended</td>
<td>- Appropriate glycemic control - Antihypertensive therapy - Lipid control - Smoking cessation - Dialysis or renal transplant - Fluid restriction (maximum inter-dialytic BW gain in HD patients, &lt; 6%)</td>
</tr>
</tbody>
</table>

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 pain.

3. For a neuropathy that causes spontaneous pain (such as piercing pain, lancinating pain or urtication), a Ca²⁺ channel α₂δ ligand (pregabalin), a serotonin noradrenaline reuptake inhibitor (duloxetine hydrochloride), an antiarrythmic (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

- The risk of myocardial infarction in diabetic patients is three times higher than in healthy subjects. In Europe and the United States, 40 ~ 50% of deaths in diabetic patients is thought to be directly caused by myocardial infarction; and in Japan, the number of diabetic patients who die directly of ischemic heart disease is growing.
- Acute myocardial infarction in many diabetic patients 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 diabetic patients, 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.
Peripheral arterial disease (PAD)

- Although PAD is not unique to diabetic patients, it is present as a complication in a high percentage of diabetic patients (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 diabetic patients 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 bypass.

Diabetic foot lesions

- Diabetic foot lesions include a wide range of pathologies, from interdigital and onychial trichophytosis, callusities 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, minute circulatory 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.

Diabetic hand lesions

- If a diabetic patient 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).
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.

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.

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 sugar in their school urinalyses, rather than retests for urinary sugar, the blood glucose, HbA1c and urinary ketone bodies take precedence.
- When it is necessary to carry out an oral glucose loading test in order to diagnose diabetes, the patient's current weight in kg × 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 were 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 is not fully developed diabetes (i.e., not reached the range of diabetes). GDM does not include diabetes diagnosed by the clinical diagnosis outlined in Fig. 3, p.11 during pregnancy. The criteria for GDM (Table 19) differ from those for diabetes in a non-pregnant woman.
- Since there is a high risk of diabetes after an interval once the abnormalities of glucose metabolism in the mother show improvement after delivery, it is important to maintain regular observation of glucose tolerance for women who had GDM.
- When glycemic control is poor, and diabetic complications are present, it is advisable to have an introduction to a facility that has a team of specialists in diabetes and in pregnancy.

**Table 19. Gestational diabetes: definition and diagnostic criteria**

<table>
<thead>
<tr>
<th>Definition of gestational diabetes</th>
<th>Glucose metabolism that is abnormal, but less so than in diabetes, and that is first detected, or occurs first, during pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria</td>
<td>In 75g OGTT, gestational diabetes is diagnosed if at least one of the following conditions is met plasma glucose levels:</td>
</tr>
<tr>
<td></td>
<td>FPG: ≥ 92 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose 1 hour after a meal: ≥ 180 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose 2 hours after a meal: ≥ 153 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Those women who had clinically diagnosed diabetes are excluded from the diagnosis of GDM.</td>
</tr>
</tbody>
</table>
In elderly patients, hypoglycemia induced by SU drugs, lactic acidosis due to biguanides, edema and heart failure caused by thiazolidinediones, and ileus resulting from α-glucosidase inhibitors, as well as other side-effects, including some severe cases, frequently occur, and therefore, such drugs must be administered initially in small doses. A careful approach is therefore essential.

In elderly patients, as particular attention should be paid to hypoglycemia and there is a risk of causing long-lasting hypoglycemia, selection of drugs including its dosage administered to elderly patients must be done with circumspection.
If a diabetes specialist is consulted

① Inadequate glycemic control
② Educational hospitalization
③ Acute complications
④ Surgery

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, 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 medical home visits. In connection with these activities, great importance is attached to cooperative medical care. 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 diabetes patients 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.

Diabetic patients 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.

Diabetic patients 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.