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NEW CLASSIFICATION AND DIAGNOSTIC CRITERIA OF DIABETES MELLITUS BY THE JAPAN DIABETES SOCIETY*

Takeshi KUZUYA**

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Abstract: The major points of the report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus by the Japan Diabetes Society (1999) are described. For classification, both etiological classification and the staging of metabolic abnormality are adopted. For diagnosis, cutoff levels of fasting plasma glucose (FPG) and 2-hour plasma glucose (2hPG) after 75g oral glucose load are proposed as follows; diabetic type, FPG≧126mg/dl or 2hPG≧200mg/dl; normal type, FPG<110mg/dl and 2hPG<140mg/dl; borderline type, neither diabetic nor normal type. Diabetes is diagnosed when persistent hyperglycemia of diabetic type is recognized on repeated tests, but if there is either of typical symptoms of diabetes, HbA_{1C}≧6.5%, or diabetic retinopathy, diabetes can be diagnosed by a single plasma glucose of diabetic type. New criteria for gestational diabetes are also presented.

Key words: Diabetes mellitus; Diagnosis of diabetes; Classification of diabetes by etiologies; Staging of diabetes

Introduction

The main purpose of treating diabetes is to prevent the acute complications of diabetes, and to prevent and delay the chronic complications of diabetes. In selecting the diagnostic criteria for diabetes, the most important point is how to identify persons at risk of diabetes-specific complications, early and accurately.

Recently, new classification and diagnostic criteria have been proposed by the American Diabetes Association (ADA),[1] World Health Organization (WHO),[2] and Japan Diabetes Society (JDS).[3] This article describes the major points of the report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus of the Japan Diabetes Society.

The Concept of Diabetes Mellitus

Diabetes mellitus is a group of diseases sharing the following features in com-

* This article is a revised English version of a paper originally published in the Journal of the Japan Medical Association (Vol. 123 No. 3, 2000, pages 331–335).

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Table 1 Etiological Classification of Diabetes Mellitus and Related Disorders of Glucose tolerance

1. Type 1 (caused by destructive lesions of pancreatic beta cells, usually leading to absolute insulin deficiency)
   A. Autoimmune
   B. Idiopathic
2. Type 2 (ranging from predominantly insulin secretory defect, to predominantly insulin resistance with varying degree of insulin secretory defect)
3. Due to other specific mechanisms or diseases
   A. Those in which specific DNA mutations have been identified as a cause of genetic susceptibility
      (1) Genetic abnormalities of pancreatic beta cell function (MODYs, mitochondrial DNA abnormalities etc.)
      (2) Genetic abnormalities of insulin action (insulin receptor abnormalities etc.)
   B. Those associated with other diseases or conditions
      (1) Diseases of exocrine pancreas (chronic pancreatitis etc.)
      (2) Endocrine diseases (Cushing syndrome etc.)
      (3) Liver diseases (liver cirrhosis etc.)
      (4) Drug- or chemical-induced (corticosteroid drug-induced etc.)
      (5) Infections (congenital rubella etc.)
      (6) Rare forms of immune-mediated diabetes (type B insulin resistance syndrome etc.)
      (7) Various genetic syndromes often associating diabetes (Werner syndrome etc.)
4. Gestational diabetes mellitus

mon despite heterogenous etiologies.

(1) Chronic hyperglycemia and other characteristic metabolic abnormalities occur due to the decreased action of insulin, which results from decreased secretion of insulin, and/or decreased insulin sensitivity (insulin resistance). Various mechanisms can cause the deficiency of insulin action.
(2) Symptoms may be absent when metabolic abnormalities are mild, but typical symptoms (i.e., thirst, polydipsia, polyuria, and weight loss) occur with the development of overt hyperglycemia. In severe cases, ketoacidosis or hyperglycemic-hyperosmolar state may occur, sometimes leading to coma.
(3) Patients with diabetes are at risk to develop specific complications (retinopathy, nephropathy, and neuropathy). Arteriosclerosis is also accelerated in patients with diabetes.

Classification of Diabetes Mellitus and Related Glucose Intolerance

The new classification is primarily based on etiologies (Table 1). The staging of patho-physiology by degree of deficiency of insulin is also adopted. The previous terms, insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), are abandoned. Instead, the terms type 1 and type 2 diabetes mellitus are used for etiological classification.

1. Etiological classification

Type 1 diabetes occurs by deficiency of insulin due to the destructive lesions of pancreatic beta cells, which usually leads to absolute insulin deficiency. Auto-

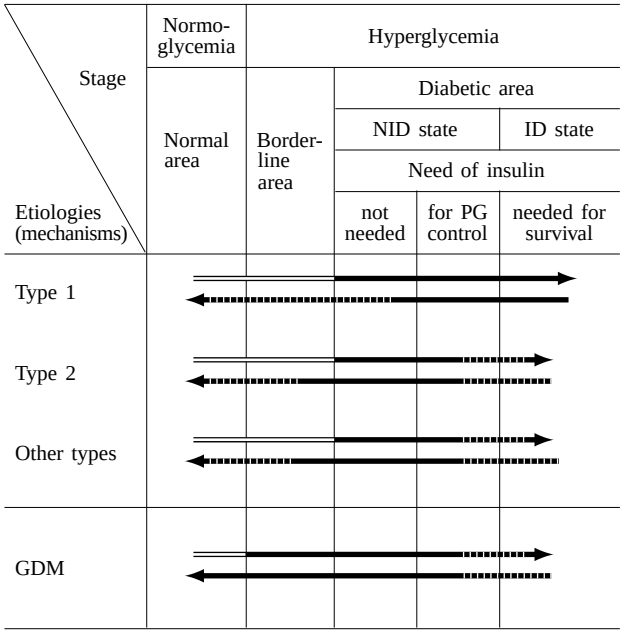

Fig. 1 A scheme of the relationship between etiologies (mechanisms) and stages (pathological states) of diabetes mellitus

The arrows toward the right indicate deterioration of glucose metabolism. The filled portion of solid and broken lines represents the state, regarded as 'diabetes'. The broken lines indicate uncommon phenomena. For example, a patient with type 2 diabetes usually does not need insulin injection for survival, but may develop ketoacidosis in case of severe infection. The arrows toward the left are filled in their full length, meaning that patients who have once developed diabetes, should be regarded to have diabetes, even if he or she improved to have borderline or normal glucose tolerance.

Non-insulin-dependent (NID) state and insulin-dependent (ID) state in the diabetic area correspond to NIDDM and IDDM in the previous classification respectively.

immune process is thought to be the main mechanism to destroy beta cells, but in a few cases the evidence for autoimmune mechanism cannot be obtained. Such cases are classified as a group of idiopathic etiology.

Type 2 diabetes comprises the majority of diabetic patients. This type of diabetes develops by a decrease in insulin secretion and/or a decrease in insulin sensitivity (insulin resistance). The relative contribution of these two factors varies among patients. Obesity is common, and even if the patients are not obese at present, many of them have been obese before the onset of diabetes. Probably, the genetic and precipitating environmental factors of type 2 diabetes are quite heterogenous.

Other types of diabetes and glucose intolerance due to specific causes are divided into two groups. Group A includes diabetes in which specific DNA abnormalities have been identified as a cause of diabetes, and Group B includes diabetes associated with other pathologic conditions or diseases. Group A is further divided into genetic abnormalities of beta cell function, and genetic abnormalities of insu-

lin action mechanisms. Group A(1) includes so-called MODYs (maturity-onset type diabetes of the young), non-insulin-dependent diabetes of autosomal dominant inheritance with onset at young ages. Several different DNA abnormalities have been recently discovered in MODY families. Group A(1) also includes abnormalities of insulin gene and mitochondrial DNA. Group A(2) includes various abnormalities of insulin receptor gene. Diabetes and glucose intolerance associated with other diseases or conditions (Group B) are similar to the previous classification. This group includes so-called 'secondary diabetes' such as pancreatic diseases, endocrine diseases and so on.

Gestational diabetes mellitus is given a special place, because mild degree of glucose intolerance may produce special problems during pregnancy. It will be discussed later.

2. Staging of patho-physiological states by the degree of metabolic abnormality (Fig. 1)

Staging of patho-physiological states includes normal, borderline and diabetic ranges according to the degree of hyperglycemia and deficiency of insulin action. Diabetic range is further divided into 3 stages; (1) insulin is not necessary for treatment, (2) it is necessary for glycemic control, and (3) insulin is indispensable to prevent ketosis and for survival. Stages (1) and (2) correspond to previous NIDDM, the stage (3) to previous IDDM.

In each individual, these stages may vary according to the deterioration and improvement of metabolic state, as expressed by arrows in Fig. 1. The arrow toward the right represents deterioration of metabolism, and the arrow toward the left represents its improvement. The filled portion of arrows is the state which can be called 'diabetes'. The arrows toward the left are expressed by as filled lines for their full length. It is based on the idea that, if diagnosis of diabetes is once established, the patient should be regarded as diabetes and should be followed, even when glucose tolerance is improved to borderline or normal ranges.

The combined use of both etiological classification and staging of metabolic abnormality can better describe the state of each patient.

The Diagnosis of Diabetes Mellitus

Diagnosis of diabetes is an act to judge whether clinical and laboratory features of a patient fits to the concept of diabetes mellitus mentioned above. Confirmation of persistent hyperglycemia is essential for the diagnosis of diabetes. What degree of hyperglycemia is associated with the risk of specific complications will provide the basis to select the cutoff plasma glucose values for diagnosis. Glycemic criteria not only for 'diabetes', but for milder glucose intolerance are needed. Mild glucose intolerance is seldom associated with specific complications of diabetes, but increases the risk for arteriosclerosis and for the development of diabetes mellitus than those with normal glucose tolerance.

1. Cutoff values of plasma glucose

Table 2 shows the cutoff plasma glucose levels for fasting plasma glucose

Table 2 Criteria of Fasting Plasma Glucose and 2-hour Plasma Glucose by 75 g Glucose Tolerance Test (Values are venous plasma glucose)

	Normal range mg/dl (mmol/l)	Diabetic range mg/dl (mmol/l)
Fasting plasma glucose	<110 (6.1)	≧126 (7.0)
2-hour plasma glucose after 75 g glucose	<140 (7.8)	≧200 (11.1)
Evaluation of GTT	Normal type = if both values belong to normal range	Diabetic type = if any of 2 values falls into diabetic range
	Borderline type = neither normal nor diabetic types	

Casual plasma glucose ≧200 mg/dl (11.1 mmol/l) is also regarded as to indicate diabetic type.

Subjects with 1-hour plasma glucose ≧180 mg/dl (10.0 mmol/l) are advised to be followed-up similarly to borderline type, even if they belong to normal type, because such individuals are at higher risk to develop diabetes than those with 1-hour plasma glucose <180 mg/dl.

Table 3 The Procedures of Clinical Diagnosis

1. Diabetes mellitus is diagnosed when hyperglycemia of 'diabetic type' in Table 2 is confirmed on 2 or more occasions examined on separate days. Before confirmation by the second test for plasma glucose, the subject is called simply to have 'diabetic type'.
2. The diagnosis of diabetes can be made by a single plasma glucose test meeting criteria for 'diabetic type', when there is either one of the following three conditions.
   (1) Typical symptoms of diabetes (i.e., thirst, polydipsia, polyuria, weight loss)
   (2) HbA_{1C}≧6.5%
   (3) Unequivocal diabetic retinopathy
3. If the above conditions (1. or 2.) existed in the past and are well documented, the subject is either diagnosed as diabetes or should be suspected of diabetes regardless of the glycemic state at present.
4. If the diagnosis of diabetes cannot be established after repeating plasma glucose tests, clinical informations should be evaluated to assess the probability of developing diabetes. Re-examination of plasma glucose after some interval is recommended.
5. At clinical diagnosis, physicians should assess not only the presence or absence of diabetes, but also its etiology, glycemic stage and the diabetic complications.

(FPG) and 2-hour plasma glucose (2hPG) by 75 g glucose tolerance test (GTT). These cutoff values are the same as in current ADA and WHO criteria, but the term for each category of glucose tolerance is called by adding the word 'type', such as 'diabetic type', 'normal type', and 'borderline type'. Table 2 shows venous plasma glucose values. The values will change when whole blood or capillary blood is used.

The diagnosis of 'diabetes mellitus' is made when persistent hyperglycemia of 'diabetic type' is recognized. To confirm persistent hyperglycemia, repeated tests for plasma glucose are necessary in general.

2. Clinical diagnosis

The procedures of clinical diagnosis are shown in Table 3. The methods to confirm hyperglycemia at the first and second tests need not be the same. Fasting plasma glucose is the value measured before breakfast without meal for more than 10 hours since the last evening. If FPG by the first test is less than 140 mg/d*l*, glucose tolerance test is recommended as the second test. If the first test was done by casual plasma glucose, other methods of plasma glucose test (FPG or GTT) are preferred.

Diabetes mellitus can be diagnosed on a single plasma glucose value of 'diabetic type', if there is one of the following three conditions; (1) typical symptoms of diabetes (thirst, polydipsia, polyuria, and weight loss), (2) $HbA_{1C} \geqq 6.5\%$, or (3) diabetic retinopathy.

HbA_{1C} higher than 6.5% indicates that the patient has had chronic hyperglycemia. The inclusion of HbA_{1C} as an aid for diagnosis of diabetes is unique to the report of JDS. For this purpose, only stable fraction of HbA_{1C} should be measured and the assay value should be corrected by the standard samples of JDS.[4] Very few portions of subjects with normal or borderline type glucose tolerance have HbA_{1C} higher than 6.5%, but a considerable portion of subjects with $HbA_{1C} < 6.5\%$ have diabetic type glucose tolerance. Therefore, the possibility of diabetes cannot be ruled out even if HbA_{1C} is lower than 6.5%.

3. Normal and borderline types

The 'normal type' in the previous JDS report was defined as a group of subjects who were unlikely to progress to diabetes after a follow-up of several years.[5] In the 1982 JDS report, FPG<110 mg/d*l*, and 1hPG<160 mg/d*l* and 2hPG< 120 mg/d*l* were the upper limits of the 'normal type'. In the 1999 JDS report, the cutoff plasma glucose level for 2hPG was raised to 140 mg/d*l* and 1hPG value was omitted from the criteria. Thus, the upper limits of glycemia in 'normal type' are now the same as the lower limits for FPG and 2hPG of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT), respectively. By this change of criteria, the incidence of 'diabetic type' from 'normal type' increases a little, but the annual incidence rate is still less than 1% according to the follow-up data of 4–5 years in Japan.[3]

The 'borderline type' is a group neither of 'normal type' nor 'diabetic type'. The new 'borderline type' corresponds to the sum of IFG and IGT by ADA and WHO. Compared with 'normal type', subjects belonging to borderline type are at higher risk to develop diabetes and arteriosclerosis but at little risk to get microangiopathy.

Table 2 shows cutoff levels only for FPG and 2hPG, but it is advised to measure 30-min and 60-min plasma glucose in clinical situation, and if possible, to measure insulin levels for these samples. Subjects with 1hPG higher than 180 mg/d*l* are at higher risk to develop diabetes than those with lower 1hPG even among people with 'normal type' glucose tolerance.[3] The low insulin response at 30 minutes after 75 g glucose load is a characteristic feature of diabetes. A low insulinogenic index (the ratio of increment of plasma insulin (μU/m*l*) to that of plasma

glucose at 30 min (mg/d*l*) less than 0.4) indicates that the person is very likely to have diabetes. Furthermore, the incidence of diabetes is higher in subjects of borderline type with low insulinogenic index than those with insulinogenic index higher than 0.4.[6]

4. Epidemiology and screening

When the prevalence of diabetes is studied in an epidemiological survey, the 'diabetic type' by a single plasma glucose test may be regarded as 'diabetes'. The use of 2hPG≧200 mg/d*l* by 75 g glucose tolerance test is preferred. If it is difficult, however, FPG≧126 mg/d*l* can be used with description of the criteria in that particular survey.

For screening of diabetes, it is important not to overlook subjects with diabetes. In addition to glycemic parameters, clinical informations such as family history, obesity and the history of body weight changes, diabetic complications should be included to screen subjects for further testing.

5. Gestational diabetes mellitus (GDM)

The traditional concept of GDM has been "mild temporary glucose intolerance which occurs for the first time during pregnancy", which implied that glucose intolerance would become normal after delivery. The reason to give a special consideration to GDM is that even mild glucose intolerance may give adverse effects on the mother and fetus during pregnancy, and it is one of the predictors of future diabetes.

The concept of GDM underwent subsequent modifications, and at the Fourth International Workshop on GDM, it was defined as "any glucose intolerance developed or detected for the first time during pregnancy, without regard to the degree of glucose intolerance and whether it antedated before pregnancy or it persists after delivery".[7] By this definition, diabetes which has its onset before pregnancy but unnoticed and incidentally detected during pregnancy is also included in GDM.

Subjects who have hyperglycemia of diabetic type or diabetic retinopathy already at the first trimester of pregnancy are likely to have had diabetes since before pregnancy. These cases have a greater risk for fetal anomalies, and for perinatal troubles, so that they should be kept under closer supervision than those with GDM of milder glucose intolerance by traditional definition.[8]

There have been no universal criteria for GDM. The JDS Committee adopted the criteria, previously proposed by a Committee of the Japan Society of Gynecology and Obstetrics.[9] Namely, the subject is regarded to have GDM, if either two of venous plasma glucose values exceeded following cutoff levels; FPG≧100 mg/d*l*, 1hPG≧180 mg/d*l*, 2hPG≧150 mg/d*l* by 75 g GTT.

As a screening test during pregnancy, subjects with casual plasma glucose exceeding 100 mg/d*l* should be examined by a 75 g glucose tolerance test and evaluated by the above criteria.[8] For subjects who are diagnosed to have GDM, glucose tolerance state should be re-evaluated at 1–3 months after delivery.

Conclusion

The main points of the new classification and diagnostic criteria of diabetes mellitus by JDS were described. For classification, both etiological classification and the staging of patho-physiology are to be considered. The cutoff levels of plasma glucose to classify diabetic, borderline and normal types are presented. Diabetes is generally diagnosed when persistent hyperglycemia of 'diabetic type' is confirmed, but if there is either (1) typical symptoms of diabetes, (2) $HbA_{1C} \geqq 6.5\%$ or (3) diabetic retinopathy, diabetes can be diagnosed by a single plasma glucose test of 'diabetic type'. Cutoff values for plasma glucose do not give a definition of diabetes, but simply a guideline. The diagnosis of diabetes mellitus should be made not only on plasma glucose levels but clinical symptoms and other findings should also be taken into account.

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GUIDELINES FOR DIET CONTROL IN DIABETES MELLITUS —Importance of Food Exchange Lists and Perspectives for the Future—*

Hiroshi KAJINUMA**

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Abstract: "Food Exchange List for Diet Therapy of Diabetes Mellitus" was proposed by the Japan Diabetes Society to meet the fundamental requirement of diet control in diabetes mellitus. They are (1) appropriate daily caloric intake, (2) diet with good nutritional balance, and, (3) appropriately divided meals taken at designated times. Foods are classified into six tables of four groups and seasonings. A unit, defined as 80 kcal, common to all food groups has been created, and in each table the mean content of nutrients in one unit of the food is indicated. It is recommended, at each caloric intake level, to take definite respective units of food from each table; for example, when taking 1,600 kcal diet (20 units), 11, 1, 4, 1.4, 1, 1, and 0.6 units from Table 1 to 6 and seasonings, respectively. The recommended diets in the Food Exchange List are in good agreement with the composition of the daily diet of the average Japanese people, and are referred to as healthy food. As ready-to-eat food and cooked food have become popular, it may be necessary to revise Food Exchange List, taking them into consideration.

Key words: General rules for diet control;
Characteristics of a food exchange list;
Westernization of dietary habits

Introduction

It is well known that diet control and exercise constitute the basis of the treatment of diabetes mellitus. Diet control, in particular, is an essential approach to the treatment that should be observed by all diabetic patients. It is not rare for cases of non-insulin-dependent diabetes mellitus to improve solely as a result of diet control, without recourse to any medication. Even in cases of insulin-dependent diabetes mellitus, insulin therapy cannot exert its effects fully unless appropriate diet control is also practiced concomitantly.

To maximize the effects of diet control in the treatment of diabetes mellitus, the use of the "Food Exchange List for Diet Therapy of Diabetes Mellitus",[1)]

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** The Institute for Diabetes Care and Research, Asahi Life Foundation

edited by the Japan Diabetes Society, is recommended. This food exchange list is designed based on the following fundamental principles, to facilitate diet control by the patients in daily life:

(1) should be simple and easy to use;
(2) can be used by people with different dietary habits and environments;
(3) should be useful when eating out; and
(4) should be helpful in understanding the basic rules of a proper diet.

The "Handbook for guidance of diet therapy of diabetes mellitus based on the 'Food Exchange List'"[2] edited by the society is expected to be useful for medical staff wishing to instruct their patients on diet control.

This article introduces the contents of the handbook and discusses diet control for the treatment of diabetes mellitus.

Significance of Diet Control

Diet control in diabetes mellitus has the following two roles.

The first role is to supply adequate nutrition for the diabetic patients to lead their daily lives in the same way as healthy people. The amount of nutrition should be limited to the minimum necessary for maintaining the body weight at an appropriate level as well as leading the ordinary daily life. It is important to avoid excessive caloric intake. Since the amount of insulin required is reduced, the metabolism of glucose and other substances occurs smoothly, and the functions of the pancreatic B cells are preserved.

The second role is to supply nutrients in good balance for maintaining a healthy body. The three major types of nutrients, as well as vitamins and minerals, should be supplied in appropriate amounts. This results in smoother metabolism, and risk factors for complications such as hyperlipidemia and hypertension are corrected.

Diet with Appropriate Calorie Level

The appropriate daily caloric intake is that which is necessary for maintaining the body weight at or slightly below the ideal weight, while preventing obesity, and which allows the patients to lead their daily lives without any inconvenience. It is determined individually on the basis of the age, gender, height, body weight, and activity level of the patients. The daily caloric requirement for healthy people is calculated as the sum of that required for basal metabolism, metabolism associated with physical activity (activity metabolism), and specific dynamic action.[3] It remains to be confirmed whether the same equation applies for diabetic patients.

Accordingly, the following caloric intakes are recommended empirically per kg ideal body weight in adults on the basis of their requirement for basal metabolism: 25 to 30 kcal for light labor, 30 to 35 kcal for moderate labor; and 35 kcal or more for heavy labor.

Numerous methods have been recommended for calculation of the ideal body weight. In recent years, the body mass index (BMI; body weight (kg) / body height $(m)^2$) has been proposed as an index for the body constitution. Since a BMI of 22

Table 1 Examples of the Proportion of Each Nutrient According to the Recommended Daily Units Indicated in "Food Exchange List for Diet Therapy of Diabetes Mellitus" Edited by the Japan Diabetes Society and the Ratio of Three Major Nutrients

Recommended daily units (recommended caloric intake)	Recommended daily units (recommended caloric intake)							Caloric ratio of the three major nutrients (%)		
	Table 1	Table 2	Table 3	Table 4	Table 5	Table 6	Seasoning	Carbohydrate	Protein	Fat
In the case of 15 units per day (1,200 kcal)	6	1	4	1.4	1	1	0.6	52	20	28
In the case of 18 units per day (1,400 kcal)	9	1	4	1.4	1	1	0.6	58	18	24
In the case of 20 units per day (1,600 kcal)	11	1	4	1.4	1	1	0.6	61	18	21
In the case of 23 units per day (1,800 kcal)	12	1	5	1.4	2	1	0.6	57	18	25

(Quoted from Reference 2)

is considered to be ideal, the ideal body weight (kg) is calculated as body height $(m)^2 \times 22$.

The recommended caloric intake thus obtained is simply based on paper calculation, and should be reviewed whenever necessary while carefully following the changes in the blood glucose levels, lipid levels, and body weight.

Diet with Good Nutritional Balance

Once the appropriate caloric intake level is determined, attention should be directed to a good balance of nutrients.

1. Appropriate balance of the three major nutrients

Appropriate balance of the three major nutrients (carbohydrate, protein, and lipid) is of primary importance.

Carbohydrates are the source of energy for activities, and should represent 55 to 60% of the daily caloric intake.

Proteins are the raw materials for building the body, and should represent 15 to 20% of the daily caloric intake.

The intake of lipids should be limited to not more than 25% of the daily caloric intake. In recent years, the problem of excessive intake of fat has arisen.[4] Intake of animal fats rich in cholesterol and saturated fatty acids should be restricted.

The recommended diets in the food exchange list are almost perfectly in line with these guidelines (Table 1).[2] They are also in good agreement with the composition of the daily diet of the average Japanese people, that is, they are well-suited to the dietary habits of the Japanese people. Therefore, it allows the patients to naturally take daily diets. This is one of the reasons why diet for dia-

betic patients is often referred to as healthy diet.

2. Supply of vitamins and minerals in appropriate amounts

According to the food exchange list, diets allowing a daily caloric intake of 1,200 kcal contain the minimum necessary levels of vitamins, as well as minerals such as calcium and iron. When the daily calorie intake is lower, these nutrients may become insufficient. Therefore, it is important to ensure that an ideal balance of nutrients is maintained in the daily diet recommended.

3. Supply of dietary fiber

As people have come to eat less rice and more meat, the intake of dietary fiber has become insufficient. Dietary fiber delays the digestion and absorption of food and therefore helps to control the increase in blood glucose levels after meals and reduce the cholesterol levels. It also prevents constipation. Ideally, 20 to 25 g of dietary fiber should be consumed every day.

Characteristics of the "Food Exchange List for Diet Therapy of Diabetes Mellitus" Edited by the Japan Diabetes Society

While the use of this food exchange list often appears daunting, a good understanding of its basic principles would facilitate even complicated nutrition management.

The characteristics of this food exchange list can be summarized as follows:

(1) Foods are classified into six tables of four groups and seasonings depending on the composition of the major nutrients (Table 2). In addition, appendices have been attached.[1)]

(2) A unit common to all food groups has been created. One unit is defined as 80 kcal, and the weight of food equivalent to one unit has been indicated.

(3) In each of the tables of every group, the mean content of nutrients in one unit of the food is indicated.

The "Food Exchange List" based on these characteristics was proposed for the first time by the Japan Diabetes Society.

Type of Diabetes Mellitus and Diet Control

The general rules of diet control are the same for insulin-dependent and non-insulin-dependent diabetes mellitus, however, emphasis is placed on different aspects of diet control in the two conditions.

1. Insulin-dependent diabetes mellitus

Insulin injections are essential in this condition. In order to prevent hypoglycemia and hyperglycemia, it is important to eat meals at designated times and to appropriately divide the daily food intake into several meals. For this purpose, it may be necessary to eat between meals, that is, in addition to breakfast, lunch, and supper. Particular attention is paid to the nutritional content of the meals, such as the amount of carbohydrates.

Table 2 Food Classification Table for Diabetes Mellitus

Food classification	Food type	Mean content of nutrients per unit (80 kcal) Carbohydrate (g)	Protein (g)	Fat (g)
Group I: Foods mainly consisting of carbohydrate				
Table 1	Grain, potatoes, vegetables rich in carbohydrate and fruits, beans and peas (excluding soybeans)	18	2	0
Table 2	Fruits	20	0	0
Group II: Foods mainly consisting of protein				
Table 3	Seafood, meat, eggs and cheese, soybeans and soy products	0	9	5
Table 4	Milk and dairy products (excluding cheese)	6	4	5
Group III: Foods mainly consisting of fat				
Table 5	Lipids, fat-rich foods	0	0	9
Group IV: Foods mainly consisting of vitamins and minerals				
Table 6	Vegetables (excluding some vegetables rich in carbohydrate), seaweed, mushroom, and konnyaku	13	5	1
Seasonings	Miso, sugar, mirin, etc.			

(Quoted from Reference 1)

2. Non-insulin-dependent diabetes mellitus

Non-insulin-dependent diabetes mellitus develops as a result of a hereditary predisposition in association with environmental factors, such as overeating, obesity, and insufficient exercise. These factors not only induce, but also exacerbate this type of diabetes mellitus. Therefore, it is of fundamental importance for patients of non-insulin-dependent diabetes mellitus to avoid overeating and guard against obesity. A good nutritional balance of the diet is also important.

Diet Control in Special Cases

1. Diet control for diabetes mellitus in children

In both children with insulin-dependent and non-insulin-dependent diabetes mellitus, the basic principle of nutritional therapy is the provision of adequate calories and nutrients required for the normal growth of the children. For this purpose, consultation of “Nutritional Requirement for Japanese Boys and Girls” is recommended.

2. Diet control for diabetes mellitus associated with pregnancy

In cases of diabetes mellitus associated with pregnancy, the sum of calories

necessary for the mother and calories necessary for the generation and maintenance of the fetus and placenta, and for lactation, is regarded as the recommended daily caloric intake. The daily caloric intake of pregnant diabetic patients should be 150 kcal higher, 350 kcal higher, and 700 kcal higher during the early stage of pregnancy, late stage of pregnancy, and lactation, respectively, as compared to the daily caloric intake of non-obese, non-pregnant diabetic women.

Monitoring of variations in the body weight is important. The daily caloric intake should be regulated so that the body weight does not increase by more than 6 to 8 kg during the course of pregnancy. For smooth blood glucose control, the total daily caloric intake should be divided in three or more meals.

3. Diet control for patients with diabetic nephropathy

Diabetic nephropathy can be divided into the following stages: the stage before development of nephropathy, early stage of nephropathy, early stage of overt nephropathy, late stage of overt nephropathy, stage of renal failure, and stage of dialysis. In each stage, appropriate restriction of protein, salt, potassium, and phosphorus is necessary.[5] Unlike in renal failure not associated with diabetes mellitus, correction of the abnormality of carbohydrate metabolism is important in patients with diabetes mellitus. Thus, it may be difficult to use the food exchange list designed for ordinary renal diseases, and the use of "Food Exchange List for Diabetic Nephropathy"[6] edited by the Japan Diabetes Society is recommended.

Conclusion — Perspectives for the Future —

Diet control for the treatment of diabetes mellitus is intended not to make the patients eat "special therapeutic diets", but to encourage them to eat "healthy food" that is also recommended for healthy people. For this purpose, it is important to make the patients understand well the importance of appropriate caloric intake and a good nutritional balance.

While evidence-based medicine has often been discussed in recent years, diet control in diabetes mellitus tends to have empirical aspects. Even if restricted diets are useful for controlling blood glucose, diet control for diabetes mellitus needs to be re-examined more scientifically from the global perspective of nutritional balance.

The "Food Exchange List" of the Japan Diabetes Society facilitates the practice of diet control by patients with diabetes mellitus. It is designed such that even patients without sufficient knowledge of nutrition can use it easily, and that patients can be guided in the same manner throughout Japan on the basis of the Food Exchange List. While the Food Exchange List is designed for people who cook meals by themselves, ready-to-eat food and cooked food have become popular in recent years, and have deeply penetrated into the daily dietary lives of the Japanese people. Under such circumstances, it may be necessary to revise the Food Exchange List taking this aspect into consideration.

While diet control established to date for diabetes mellitus has brought about enormous benefits, development of new dietary therapy that meets the contemporary needs is awaited.

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CORRECT TEACHING METHODS OF THERAPEUTIC EXERCISE*
—Guidelines for the Treatment of Diabetes Mellitus—

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Asian Med. J. 44(2): 64–70, 2001

Abstract: The beneficial effects of physical exercise on the maintenance of better health and its promotion are well known.
1. Effects of physical exercise: 1) Physical exercise promotes glucose and lipid utilization in the muscle. 2) High-intensity exercise increases secretion of insulin-counter-regulatory hormones, and impairs glucose metabolism. 3) Continuous mild-intensity physical training, that does not influence the maximal oxygen uptake, improves insulin sensitivity in type-2 diabetic patients. 4) Aerobic exercise has greater beneficial effects on insulin sensitivity than anaerobic exercise. Furthermore, a combination of mild-intensity resistance training and aerobic exercise is effective in the elderly with weakened muscle power and decreased muscle volume. 5) The effect of training, i.e., improvement of insulin sensitivity, wanes within 3 days, and disappears within 1 week.
2. Specific exercise direction: Mild- to moderate-intensity aerobic exercise, including walking and jogging, for 10–30 min, on 3–5 days a week, is recommended. Advocation of an active lifestyle is essential in the management of diabetes mellitus, a major lifestyle-related disease.

Key words: Type-2 diabetes mellitus; Physical training; Insulin sensitivity; Lifestyle

Introduction

Since the end of the 20th century, the demand for evidence-based medicine (EBM) has increased in the medical field. In regard to therapeutic exercise in the management of diabetes mellitus, the mechanisms underlying the effects of exercise have been clarified at the molecular-biological level. Epidemiological long-term follow-up studies on the effects of diet control and therapeutic exercise have been reported, and the effects of therapeutic exercise in the prevention and treatment of diabetes mellitus (especially type-2) have also been clarified.

The Ministry of Health and Welfare, Japan has introduced the concept of "lifestyle-related diseases", including diabetes mellitus and obesity, and proper

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training methods for improvement of lifestyles are desired.[1)] Rapid advances have been made, both in research and clinical practice of therapeutic exercise.

In this paper, the author reviews the outcome of research works and clinical studies on therapeutic exercise, both in Japan and overseas, and introduces correct methods of therapeutic exercise for patients with diabetes mellitus.

Physical Exercise and Diabetes Mellitus—Epidemiological Studies

1. Sedentary lifestyle and insulin resistance

Recently, decrease in the level of physical exercise caused by automation and computerization in daily life, together with western-style meals, have resulted in a shortage of exercise or excessive eating (high-fat diet), and also resulted in an increased incidence of the following diseases, i.e., diabetes mellitus, obesity, hypertension, and hyperlipemia, representing the so-called “syndrome X”, “insulin-resistance syndrome”, “visceral fat syndrome” or “metabolic syndrome”.

As mentioned above, the Ministry of Health and Welfare, Japan has introduced the concept of “lifestyle-related diseases” in the pathogenesis of these diseases. Insulin resistance and the associated compensatory hyperinsulinemia are considered as important common underlying factors in the pathogenesis of these diseases. In addition, each of these diseases and their combinations are risk factors for coronary diseases.[2)]

2. Prevention of type-2 diabetes mellitus by physical training

Many prospective studies have revealed that appropriate diet and continuous physical training are not only useful in preventing and improving type-2 diabetes mellitus via improvement of the insulin sensitivity, but are also useful in preventing and treating all insulin-resistance-related diseases, including hypertension and hyperlipidemia (metabolic syndrome/lifestyle-related diseases).[2,3)]

The results of a prospective study revealed that the incidence of diabetes mellitus decreased by 6%, as the consumptive energy of physical training increased by 500 kcal/week.[2)] Malmö Study (Sweden) reported that patients with impaired glucose tolerance (IGT) showed a high incidence of type-2 diabetes mellitus and a high mortality rate from coronary diseases. The 12-year-prospective study revealed that dietary counseling and physical training decreased the mortality in IGT patients to the level in the ‘normal glucose tolerance’ group.[4)]

Randomized controlled intervention trials (RCT) have also been reported, in which specific populations were randomly assigned to several groups, each receiving dietary education or therapeutic exercise training (intervention), or both, and the outcomes were compared with that in the control group. In DaQing Study (China), for example, the incidence of diabetes mellitus in IGT patients decreased by 31% over 6 years in the ‘diet education alone’ group, 46% in the ‘therapeutic exercise alone’ group, and 42% in the ‘diet education and therapeutic exercise’ group.[2)] Furthermore, a prospective study of the prevention of type-2 diabetes mellitus in IGT patients is under way in Finland.[5)]

Effects of Physical Exercise on Carbohydrate and Lipid Metabolism

1. Acute metabolic effects

(1) Acute exercise and glucose · lipid metabolism

Insulin is a key hormone involved in the acute metabolic effects of exercise. Utilization of glucose and free fatty acids (FFA) in the muscle is promoted by exercise in patients with favorable metabolic regulation. Therefore, if diabetic patients practice physical exercise after meals, the rapid increase of blood glucose is prevented, resulting in favorable control of diabetes mellitus.

Ketotic patients with severe insulin deficiency (fasting blood glucose level ≧250–300 mg/dl; urine positive for ketone bodies) are at increased risk of developing high blood levels of glucose, FFA, and ketone bodies after exercise.[2] Increased ketogenesis is primarily responsible for the occurrence of ketosis after exercise. In addition, increased glucagon levels in the portal vein have also been reported,[6] and a possible relation of this ketosis to the ketone body utilization disturbance in the muscle was suggested based on the results of our studies using microdialysis.[2]

In terms of the exercise intensity in therapeutic exercise, secretion of insulin-counter-regulatory hormones, including glucagon and cathecolamines, may increase, resulting in impaired glucose metabolism during high-intensity exercise. High levels of plasma thiobarbituric acid-reactive substances (TBARS), caused by the increased formation of free radicals, may also occur.

During moderate-intensity exercise, the maximal oxygen uptake (VO_2max) increases by up to 50%, and glucose and FFA are utilized as the source of muscular energy even after short workouts of only a few minutes. The glucose utilization rate may increase if the exercise intensity exceeds the lactate threshold (LT) (i.e., anaerobic metabolism commences and the blood lactic acid levels begin to rise). The source of energy during maximal exercise (anaerobic) depends solely on the glycolytic system, when glucose becomes the only source of energy.[2]

(2) Mechanism underlying the promotion of glucose uptake into the muscle during acute exercise

During exercise, the muscle blood volume increases due to dilation of the capillaries, and since sufficient substrates are thereby supplied to the contracted muscle, glucose incorporation is promoted. At the molecular level, promotion of translocation of the glucose transporter (GLUT 4) from the cytoplasm to the cell membrane by acute exercise plays an important role in glucose incorporation in the contracting muscle.[2] In insulin-resistant states such as type-2 diabetes mellitus, while the total volume of GLUT 4 volume in the skeletal muscle is normal, its translocation from the cytoplasm to the cell membrane is decreased.

Acute exercise has also been reported recently to promote translocation of GLUT 4 to the cell membrane in skeletal muscle cells in type-2 diabetic patients.[7] According to a report from the Joslin Research Institute group, the signal pathways of muscle GLUT 4 translocation promoted by insulin and exercise are different.[8] Another recent reports showed that nitric oxide (NO) is also related to the promotion of glucose incorporation in the muscle.[2]

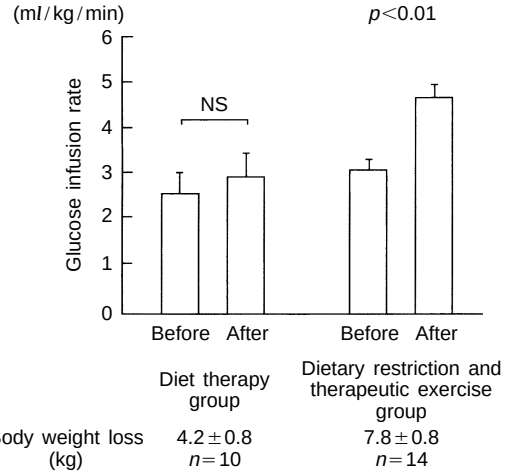

Fig. 1 Changes of insulin sensitivity (glucose infusion rate) in the 'diet therapy alone' group and 'combination of dietary restriction and therapeutic exercise' group

Without therapeutic exercise, the reduced insulin sensitivity in obese type-2 diabetic patients does not improve, even if the body weight was decreased.

2. Training effects

(1) Physical training and insulin sensitivity

1) Continuous long-term mild-intensity physical training, that does not influence the VO_2max, can improve insulin sensitivity.[2,9] Dietary restriction and physical training in obesity and type-2 diabetes mellitus, resulted in a selective decrease of body fat volume and body weight, without a change of the lean body mass (LBM). Thus, combination of therapeutic exercise and dietary control is more useful for the improvement of insulin sensitivity than dietary restriction alone (Fig. 1). In addition, a positive correlation has been reported between improved insulin sensitivity (ΔMCR), and average daily steps determined by the pedometer (Fig. 2).[2,10]

2) Aerobic exercise, such as jogging, is more useful than anaerobic exercise, such as weight lifting, in improving the insulin sensitivity. However, resistance exercise, which is equivalent to moderate-intensity aerobic exercise, is also useful for improving the insulin sensitivity in type-2 diabetic patients and the elderly.

3) Continuous training can prevent deterioration of basal metabolic rate (BMR) that may occur as a result of dietary restriction alone.

4) Training improves physical fitness and lipid metabolism.

5) As previously reported, therapeutic exercise promotes favorable blood glucose control in type-2 diabetic patients. In type-1 diabetics, however, since the metabolic condition changes on a daily basis, the effects of such exercise are not always stable.[2,10]

(2) Mechanism underlying the effects of training

In the appearance of the effects of training, the glucose transporter (GLUT 4)

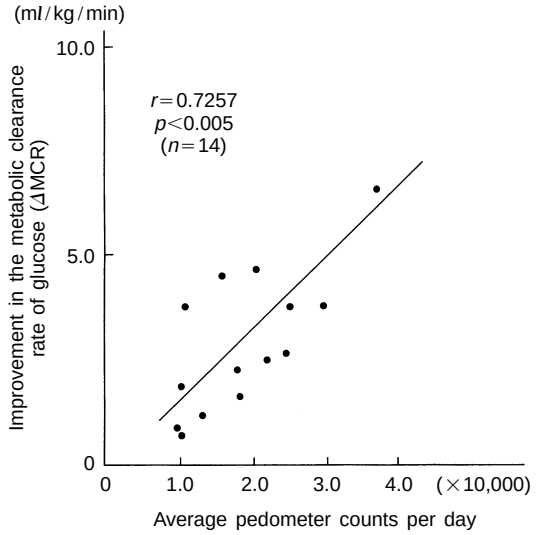

Fig. 2 Correlation between average pedometer counts per day and improvement in the metabolic clearance rate of glucose (ΔMCR)

plays an important role, in addition to muscle weight, glycolytic system in the muscle, and fluctuation of enzymatic activity in the TCA cycle. On the other hand, an important role of adipose-tissue-related factors, including decrease in adipose tissue volume and reduction in size of adipose tissue, have also been implicated, in association with TNF-α and leptin.[2)]

Practice of Therapeutic Exercise

1. Indications for therapeutic exercise and medical examination

Medical examination must be performed before therapeutic exercise is begun, to determine whether diabetes mellitus is well controlled and whether the patient has any progressive complications or not.[10)]

2. Categories of exercise and the exercise intensity

The effects of training, including the improvement of insulin sensitivity, begin to wane within 3 days, and disappear within 1 week. In terms of the exercise intensity, as stated above, moderate LT level exercise is preferable.

The recommended exercise model is moderate-intensity exercise at 50% VO_2max (pulse rate in those 50 years or younger, 120/min; pulse rate in those in their sixties or seventies, 100/min), for 10–30 min (2–3 times/day after meals if possible), on 3–5 days/week. As aerobic exercises involving systemic muscles, walking, jogging, radio exercise, cycling (ergometer), and swimming are recommended. The exercise load should be reduced in the case of resistance exercise.[2,10)]

For patients with diabetes mellitus, which is a prototype of lifestyle-related diseases, exercise in daily life, e.g., getting out of the bus one stop before the

Table 1 Average Energy Consumption of Physical Exercise (per 80 kcal)

Intensity of exercise	Time required per 80 kcal	Categories of exercise (Consumptive volume of energy, kcal / kg / min)
I. Very mild	Consecutive 30 minutes	Walking (0.0464), traveling in vehicles (standing in buses or trains) (0.0375), cooking (0.0481), housework (laundry, cleaning) (0.0471–0.0499), ordinary office work (0.0304), shopping (0.0481), physical exercise (mild) (0.0552)
II. Mild	Consecutive 20 minutes	Walking (70m / min) (0.0623), bathing (0.0606), walking down the stairs (0.0658), radio exercise (0.0552–0.1083), cycling (flat land) (0.0658), golf (men (0.0640), women (0.0500))
III. Moderate	Consecutive 10 minutes	Jogging (mild) (0.1384), going up the stairs (0.1349), cycling (on a sloping road) (0.1472), skiing (flat land) (0.0782–0.1348), ice skating (0.1437), volley ball (0.1437), mountain climbing (0.1048–0.1508), tennis (practice) (0.1437)
IV. High	Consecutive 5 minutes	Marathon (0.2959), jumping rope (0.2667), basketball (0.2588), rugby (forward) (0.2234), swimming (breast stroke) (0.1968), kendo (0.2125)

Note: Indication of taking foods for patients receiving insulin treatment

destination and walking the rest of the distance, is recommended. Pedometer and Calorie Counter® are also useful for controlling the kinetic momentum and motivation of therapeutic exercise. The kinetic momentum should be checked by doctors at the outpatient clinic or during their visits of the patients. The recommendation is more than 10,000 pedometer counts per day (at least 7,500 paces).[10)]

3. Caution in the practice of therapeutic exercise

1) Strict diet control is essential, unless favorable blood glucose control cannot be achieved.

2) Exercise should, in general, be performed after meals.

3) For patients receiving insulin treatment, the insulin dose should be reduced before exercise or something should be eaten before, during, or after exercise, if the exercise is continued for a long time. If hypoglycemia occurs during the exercise, coke or glucose (pet sugar) dissolved in a small volume of hot water should be taken. Appropriate foods that could be given before or after meals for preventing hypoglycemia are cookies, cheese and milk. For further details, refer to Table 1.[2,10)]

4) General instructions should be also given regarding wearing of athletic shoes, warming up, and cooling down.[10)]

Conclusion

Therapeutic exercise in diabetes mellitus is reviewed. Practice of mild- to moderate-intensity physical exercise on 3–5 days per week, is useful for the prevention and treatment of all lifestyle-related diseases, including type-2 diabetes mellitus, hypertension, hyperlipidemia, obesity, and atherosclerosis, via inducing improvement in the insulin sensitivity.

Organization of a medical team, including co-medical staff, and instructions on physical exercise in daily life are important for improving the patient's QOL.

Since April 2000 therapeutic exercise for diabetes mellitus has been approved by social insurance as one of the treatment, therefore quality of physical exercise education for the diabetic patients based on EBM should be improved further.

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GUIDELINES FOR THE TREATMENT OF DIABETIC NEPHROPATHY*

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Abstract: Diabetic nephropathy is the most devastating complication of diabetes and is now the leading cause of end-stage renal failure in many developed countries. How to halt the steady increase in the number of diabetic patients with end-stage renal failure is a pressing issue in Japan. The most important point for the management of diabetic nephropathy is detecting it as early as possible by regular screening for urinary protein or albumin. Microalbuminuria is a reasonably reliable marker for diabetic nephropathy in the early stage, and the blood glucose and blood pressure levels of microalbuminuric patients should be strictly controlled. Once it progresses to overt proteinuria, glycemic control does not appear to be as effective as in the microalbuminuric stage. Blood pressure control seems to be the main therapeutic approach in those proteinuric patients. ACE inhibitors are the antihypertensive agents of first choice in type 1 diabetics. When the disease has progressed to the stage of chronic renal failure, a low-protein diet should be prescribed to prevent the progression of diabetic nephropathy. In conclusion, early detection of diabetic nephropathy and treatment appropriate to each stage is the best strategy for the management of diabetic nephropathy.

Key words: Diabetic nephropathy; Microalbuminuria; Glycemic control; Blood pressure control; Low-protein diet

Introduction

The number of patients who develop end-stage renal failure and are placed on dialysis therapy as a result of diabetic nephropathy has been steadily increasing. In 1998 it finally exceeded 10,000 patients in Japan, and having replaced glomerulonephritis, it now occupies first place and represents an alarming state of affairs.

According to a survey study of the Ministry of Health and Welfare of Japan there are approximately 30,000 to 50,000 patients with diabetic nephropathy in the stage of renal failure one step before the end-stage (plasma creatinine 2 mg/d*l* or more), and it has been estimated on the basis of the results of other surveys that there may be as many as 800,000 to 1,000,000 patients with diabetic nephropathy who manifest proteinuria, and it seems that the number of patients who may

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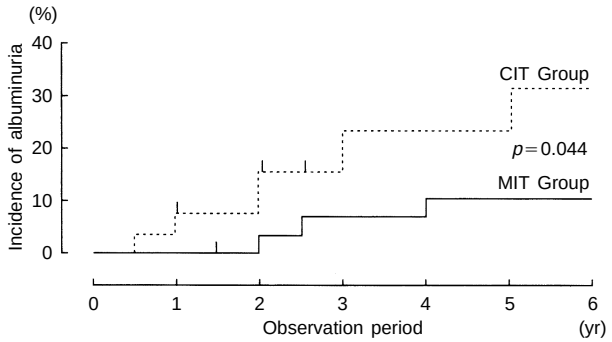

Fig. 1 Secondary prevention of diabetic nephropathy
The incidence of proteinuria was significantly decreased by tight glycemic control (MIT) in comparison with the ordinary treatment group (CIT).
(Results of the Kumamoto study. See Reference 2)

progress to serious stage will probably continue to grow in the future.

How to deal with this continually increasing kidney disease is a major medical problem, and it could hardly be claimed that an adequate system had been put in place to eradicate diabetic nephropathy in our country. In the meantime, the most important measure to deal with this problem would seem to be to have all medical practitioners engaged in the care of nephropathic patients sufficiently understand the gravity of the situation facing us and provide care to their patients with a thorough knowledge of just what appropriate treatment is.

Below I will explain the treatment guidelines based on a rough classification of the stages of nephropathy.

Treatment of Incipient Nephropathy

The stage of nephropathy in which microalbuminuria is observed is referred to as “incipient nephropathy” (stage 2). The most important point is to make every effort to diagnose nephropathy in the incipient stage, and that means regular quantitative urinary albumin testing of all diabetics.

It is not necessary to repeat urine albumin testing monthly in diabetics who have never manifested microalbuminuria (stage 1), once or twice a year is sufficient. More frequent testing is required, however, in incipient nephropathy patients who have already been found to have microalbuminuria, because an increase in urinary albumin excretion is often the sole clinical sign in this stage, and changes in its excretion serve as an indicator for evaluating the pros and cons of treatment. The possibility that measurement of urinary type IV collagen excretion might be useful in the diagnosis of incipient nephropathy and in judging the appropriateness of treatment has also been pointed out.[1)]

As regards methods of treating incipient nephropathy, it has been reported that tight glycemic control is effective in preventing progression to overt nephro-

Table 1 Efficacy of Blood Pressure Control in Preventing the Progression of Nephropathy

	Blood pressure* (mmHg)	Protein-positive patients (%)			Renal failure (Total duration)
		Year 3	Year 6	Year 9	
Ordinary treatment group	154/87	18/317 (5.7)	24/274 (8.6)	11/166 (6.6)	7/390
p value	0.0001	0.073	0.061	0.87	0.29
Tight blood pressure control group	144/82	20/618 (3.2)	29/543 (5.3)	21/299 (7.0)	8/758

Cited from UKPDS 38 (Reference 4)

* Mean blood pressure value during the observation period

pathy manifested by albuminuria and it is now the basic modality of treatment (Fig. 1).[2] HbA_{1C} values less than 7% or less than 6.5% has been proposed as the target for glycemic control, but some are also of the opinion that the lower the HbA_{1C} level, the better. In any event, it is wise to make an effort to evaluate the success of glycemic control on an individual basis while using shifts in urinary albumin values for reference.

Based on the view that angiotensin-converting enzyme (ACE) inhibitors, which are antihypertensive agents, possess renal protective activity, it has been reported that they might be effective in the treatment of incipient nephropathy, and opinions recommending their fairly aggressive use are seen in European countries.[3] Since their use in hypertensive patients is covered by the Japanese national health insurance, it is all right to try them. Nevertheless, since their efficacy has never been compared with other antihypertensive agents, it would be difficult to recommend using them alone. However, there are numerous opinions supporting their efficacy in the management of hypertension, and it seems that aggressive antihypertensive therapy should be carried out in incipient nephropathy patients who have hypertension. There is a strong opinion that the target blood pressure values of the antihypertensive therapy should be less than 130/85 mmHg.

Treatment of Overt Nephropathy

Since it is questionable whether glycemic control is effective in overt nephropathy manifested by proteinuria (stage 3), a treatment policy that emphasizes blood pressure control might be a better approach. The fact that the majority of the nephropathy patients in stage 3 have hypertension also supports the importance of blood pressure control.

Of course, it must be remembered to make an effort to consider the effect of glycemic control on other organ dysfunctions, not just nephropathy, and to strive for as favorable glycemic control as possible.

I wonder if the United Kingdom Prospective Diabetes Study(UKPDS) can be said to have demonstrated that blood pressure control is highly useful in preventing the various complications that occur in diabetics.[4] Unfortunately, no significant

differences were obtained in regard to preventive effect against nephropathy, but that may have been because the number of events was too small, the blood pressure reduction was inadequate, etc.

The mean blood pressure in the tight blood pressure control group in the UKPDS was 144/82 mmHg, and far higher than the systolic blood pressure of less than 130/85 recommended by the American Diabetes Association and the WHO (Table 1). It seems that fairly tight blood pressure control is sought to prevent the progression of overt nephropathy to renal failure. Actually, the extremely strict view that less than 125/75 mmHg is desirable has also been expressed.

Low-protein diet therapy, along with blood pressure control, is cited as a modality of treatment considered to be effective in overt nephropathy. About 1.2 g/kg body weight a day is prescribed in the usual diabetic diet, and the results of several studies have shown that the deterioration of renal function is delayed when protein is restricted to 0.7 g/kg body weight a day or less.[5] However, implementing this level of low-protein diet therapy seems rather difficult, and the Ministry of Health and Welfare's Diabetes Research Group has proposed a slightly milder guideline of 0.8 g/kg body weight a day.[6]

The problem with this treatment is that from the standpoint of evidence-based medicine, which has recently become a topic of considerable discussion, since no results of treatment have been obtained in a multicenter cooperative study, evidence is lacking. In other words, it is viewed with suspicion because it has not been confirmed to be a treatment that yields the same results regardless of the institution where it is conducted. Since this matter should be resolved, a multicenter cooperative study is currently being carried out in Japan, and it is hoped that favorable results will be obtained.

It is also recommended that in addition to making the necessary checks for the differential diagnosis in diabetics who manifest proteinuria, a nephrologist be consulted once.

Treatment of Renal-failure-stage Nephropathy

Treatment of renal failure nephropathy (stage 4) that has reached the point of manifesting an abnormally high serum creatinine, generally 2 mg/d*l* or more, is often difficult. However, since it is at least possible to slow its progression, as great an effort as possible should be made. An effort to develop a close working relationship with a dialysis specialist is also called desirable so that dialysis treatment can be started under the best possible circumstances.

First, it is essential to maintain continuity of blood pressure control. Adverse effects such as hyperkalemia, however, are a problem with ACE inhibitors, and sufficient caution is necessary when using them. Regardless of which antihypertensive agent is used, blood pressure control can rarely be achieved with just one drug, and the physician is often compelled to use a combination of antihypertensive agents, including calcium antagonists, antihypertensive diuretics, etc.

Next, a low-protein diet is considered essential, and there is a report that it is at least definitely effective in lessening the accumulation of nitrogen metabolites in the body and is also useful in maintaining preserved renal function. Protein restric-

tion to about 0.6 g/kg body weight a day is generally considered necessary, and the cooperation of a registered dietitian is indispensable.

There are reports that administration of an erythropoietin preparation for renal anemia is not only useful in maintaining QOL but in maintaining preserved renal function. Please refer to the references in regard to the criteria for placing patients on dialysis.[7)]

Conclusion

The incidence of diabetic nephropathy has been steadily increasing in recent years, and I have explained the modalities of treatment according to the stage of the disease. In regard to incipient nephropathy, I have stated that early diagnosis is necessary and that glycemic control forms the basis of treatment. I have explained in regard to the current approach to the treatment of the overt nephropathy, that blood pressure control is necessary and that in recent years tighter blood pressure control has been called for.

I mentioned the management of the stage of renal failure, which is the stage before end-stage renal failure. Trying nephropathy therapy according to the stage of the disease in this way is indicated in all nephropathic patients, and I hope the number of patient who progress to serious renal dysfunction will decline.

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PRINCIPAL OF MEDICAL MANAGEMENT OF ISCHEMIC HEART DISEASE IN DIABETIC PATIENTS*

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Asian Med. J. 44(2): 76–82, 2001

Abstract: The leading cause of death in patients with diabetes mellitus in the West is ischemic heart disease. Both in Japan and Asian countries, mortality due to ischemic heart diseases is on the rise and is most significant as the cause of death in diabetic patients. Ischemic heart disease seen in diabetic patients is associated with severe coronary artery lesions, with relatively few symptoms; and its discovery is often delayed. Acute myocardial infarction complicated by diabetes mellitus, when compared to a simple myocardial infarction, is associated with high mortality during the acute stage, an unsatisfactory outcome of coronary artery reconstruction, a high rate of recurrence, and poor prognosis. On the other hand, epidemiological surveys have established that diabetes mellitus is a significant risk factor for the development of ischemic heart disease. Recently, the results from a number of extensive clinical studies have been introduced on diabetic patients, in which the development of ischemic heart disease was used as the end point of the evaluation. These studies indicated that the control of blood pressure and lipid metabolism are more important than the management of blood sugar levels. With advances in diagnostic techniques, such as electron-beam computed tomography and transthoracic Doppler echocardiography, non-invasive detection of coronary artery lesions became possible. The principal means for managing ischemic heart diseases in diabetic patients are treatment based on scientific evidences obtained from clinical megatrials and early diagnosis by employing the latest non-invasive diagnostic procedures.

Key words: Megatrial; Insulin resistance; Early detection; Medical network

Introduction

The leading cause of death for patients with diabetes mellitus in the West is ischemic heart disease. Both in Japan and Asian countries, mortality due to ischemic heart diseases is on the rise and is most significant as the cause of death for diabetes mellitus.[1)] Ischemic heart disease seen in diabetic patients is associated with severe coronary artery lesions, with relatively few symptoms; and its discovery is often delayed.[2)]

Acute myocardial infarction complicated by diabetes mellitus, when com-

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pared to a simple myocardial infarction, is associated with high mortality during the acute stage, an unsatisfactory outcome of coronary artery revascularization, a high rate of recurrence, and poor prognosis.[3,4] On the other hand, epidemiological surveys have established that diabetes mellitus is a significant risk factor for the development of ischemic heart disease.[5] To improve the prognosis for diabetic patients and prevent an increase in the incidence of ischemic heart diseases, it is imperative that more precise diabetic control be implemented.

Recently, the results from a number of extensive randomized control trials have been introduced on diabetic patients, in which the development of ischemic heart disease was used as the end point of the evaluation. These studies indicated that the control of blood pressure and lipid metabolism are more important than the management of blood glucose levels. With advances in diagnostic techniques, non-invasive detection of coronary artery lesions became possible.[6,7]

This report outlines the features of ischemic heart diseases in diabetic patients, the key points in diabetic control, and early diagnosis based on large-scale clinical trials.

Characteristics of Ischemic Heart Disease in Patients with Diabetes Mellitus

According to the results of a survey conducted by 1,000 physicians certified by the Japanese Circulation Society and those certified by the Japan Diabetes Society, the clinical features of ischemic heart diseases complicated by diabetes mellitus include the involvement of multiple coronary branches, complex lesions, asymptomatic presentation, rapid progress, and severity.[8]

1. Subjective symptoms

Patients with angina pectoris complicated with diabetes mellitus often do not report typical anginal pain. Some do not experience any symptoms.[2] The involvement of diabetic neuropathy is suspected but details are not known.

2. Coronary angiography

Even when the anginal symptoms are mild, diabetic patients often exhibit advanced stenosis or occlusion on coronary angiography. Coronary lesions are characterized by accentuated calcification, complex morphology, extensive lesions, involvement of multiple coronary branches, and diffuse lesions continuing to the peripheral branches.[9]

3. Treatment and prognosis

(1) β-blockers

Many clinical megatrials proved that β-blockers improve the prognosis for patients with angina pectoris and old myocardial infarction. According to a recent randomized control trial on diabetic patients, the effect of β-blockers was recognized in preventing ischemic heart diseases. It was feared that β-blocker therapy may delay correcting the hypoglycemic state or exacerbate diabetic control due to deterioration of glucose tolerance; but no significant difference was found between

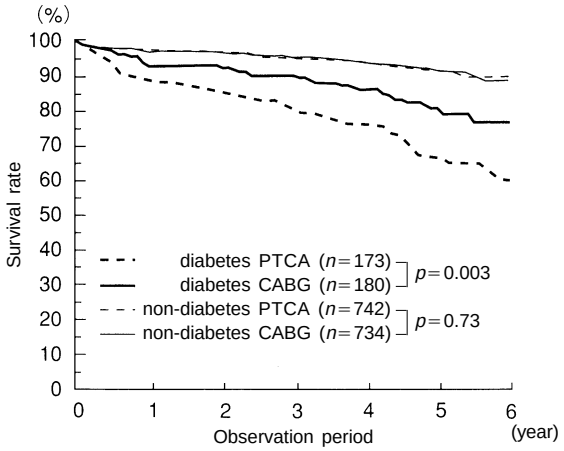

Fig. 1 Survival rate after PTCA and CABG: Comparison of diabetic patients with non-diabetic patients (The Bypass Angioplasty Revascularization Investigation; BARI Study)[4]

the β-blocker treated patients and the control in the management of hypoglycemia or diabetic control.

(2) **Calcium antagonists**

Calcium antagonists are the first choice among the therapeutic agents for the treatment of angina pectoris involving coronary vasospasm. The effect of these agents in preventing the onset of ischemic heart disease has not been established. It has been pointed out that short-acting calcium antagonists may increase the possibility of developing myocardial infarct.

(3) **Angiotensin converting enzyme (ACE) inhibitors**

The results of many clinical studies indicated that ACE inhibitors are effective in improving the prognosis of patients with ischemic heart diseases and compromised cardiac functions. A recent clinical intervention study on diabetic patients proved that ACE inhibitors prevent the onset of ischemic heart disease.

(4) **Aspirin**

In many clinical studies, it has been established that aspirin prevents the onset or recurrence of ischemic heart diseases and improves its prognosis. Diabetic patients are in a hypercoagulable state and it is anticipated that the clinical effects of antiplatelet agents will produce a favorable result. It has not been proven that administering aspirin to diabetic patients will result in the exacerbation of retinopathy. However, there have been no reports of clinical megatrials conducted on diabetic patients and the effects of aspirin in preventing ischemic heart disease in diabetic patients have not been proven.

(5) **Coronary revascularization**

The advances in coronary revascularization, such as percutaneous coronary angioplasty and coronary artery bypass, have markedly improved the quality of life of patients with angina pectoris. However, anginal patients with diabetes mellitus are known to suffer from high restenotic incidence and a poor long-term prognosis[4] (Fig. 1).

Table 1 Interventional Blood Sugar Control Trials on Diabetic Patients

Name of study	Number of subjects (age)	Follow-up period	Outcome (death due to cardiovascular causes)
UGDP	1,027 type 2 DM (40 to 69)	1961–75 (13 years)	No significant difference
VACSDM	153 type 2 DM (males; 40 to 69)	1994–96 (27 months)	No significant difference
DCCT	1,441 type 1 DM (13 to 39)	1983–93 (mean 6.5 years)	No significant difference
UKPDS	3,867 type 2 DM (mean age, 68)	1977–97 (mean 10 years)	16% risk reduction (no significant difference) (The Study is scheduled to continue for 5 more years)
Kumamoto Study	110 type 2 DM (28 to 68)	1988–95 (mean 6 years)	No cardiovascular events

UGDP: University Group Diabetes Program (*JAMA* 240: 37–42, 1978)
VACSDM: Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (*Ann Intern Med* 124: 131–135, 1996)
DCCT: Diabetes Control and Complication Trial (*N Engl J Med* 329: 977–986, 1993)
UKPDS: United Kingdom Prospective Diabetes Study (*Lancet* 352: 837–853, 1998)

(6) **Exercise therapy**

Through an analysis of the results of an interventional blood sugar control trial on diabetic patients, it is intimated that an increase in body weight and a rise in their already high blood insulin level interfere with the preventive effect of blood sugar control on the development of ischemic heart disease. Appropriate exercise therapy is thought to be the best therapeutic modality to reduce body weight and improve insulin resistance. Recently, an improvement in the cardiac function of patients with heart diseases through rehabilitation therapy has been attracting attention. For patients with ischemic heart disease complicated with diabetes mellitus, exercise therapy must be prescribed more actively.

Diabetic Control to Prevent Ischemic Heart Disease

1. Blood sugar control

The results of clinical megatrials, such as UGDP (University Group Diabetes Program) of the 1970s and the more recent UKPDS (United Kingdom Prospective Diabetes Study) proved that blood glucose control is effective in preventing diabetic microangiopathy. However, the effect of blood glucose level reduction on averting ischemic heart diseases has not been substantiated (Table 1).

2. Reduction of blood lipid levels

Clinical application of potent hypolipemic agents that have been developed recently proved that lowering the blood lipid level prevents primary and secondary

Table 2 Interventional Hypolipemic Trials on Diabetic Patients

Name of study	Total number of subjects (males / females)	Number of diabetic patients (males / females)	Period in years (mean observation period)	Effects to suppress the development of coronary disease (relative risk)
WOS	6,595 (6,595 / 0)	79 (79 / 0)	1973–92 (4.9 years)	Primary preventive effect on diabetic patients unknown
4S	4,444 (3,617 / 827)	202 (158 / 44)	1988–94 (5.4 years)	Secondary prevention of cardiovascular events DM group: 0.45 ($p = 0.002$) non-DM group: 0.68 ($p = 0.001$)
CARE	4,159 (3,583 / 576)	586 (471 / 115)	1991–96 (5 years)	Secondary prevention of cardiovascular events DM group: 0.75 ($p = 0.002$) non-DM group: 0.74 ($p = 0.005$)
LIPID	9,014 (7,498 / 1,516)	782	1990–97 (6.1 years)	Secondary prevention of cardiovascular events DM group: 0.81 ($p = 0.002$) non-DM group: 0.75 ($p = 0.005$)

WOS: West of Scotland Coronary Prevention Study (*Am J Cardiol* 79: 756–762, 1997)
4S: Scandinavian Simvastatin Survival Study (*Diabetes Care* 20: 614–620, 1997)
CARE: The Cholesterol and Recurrent Events Study (*Circulation* 98: 2513–2519, 1998)
LIPID: The Long-term Intervention with Pravastatin in Ischemic Disease Study (*N Engl J Med* 339: 1349–1357, 1998)

ischemic heart diseases. The results of many clinical megatrials have established that the effect of hypolipemic therapy on diabetic patients is equal or greater than on non-diabetic patients (Table 2).

3. Hypotensive therapy

It has been noted that antihypertensive therapy for diabetic patients prevents ischemic heart diseases. Among the studies on this topic, the efficacy of ACE inhibitors has been reported by many reports (Table 3). ACE inhibitors, which have vasodilator and anti-arteriosclerotic effects, have been proven to improve the long-term prognosis for patients with heart failure. The use of these agents should be considered as a standard therapeutic modality for patients with ischemic heart diseases combined with diabetes mellitus who suffer from compromised cardiac functions.

Early Diagnosis of Ischemic Heart Disease

A characteristic of ischemic heart disease combined with diabetes mellitus is the presence of severe lesions in the coronary arteries in spite of a relatively asymptomatic state. However, it is hard to believe that these severe lesions existed from the onset: It is most likely that the disease progresses while diabetic patients undergo a long asymptomatic period. If the disease is detected during this stage, treatment will be effective and there will be significant improvement in the prognosis. With the development of ultra-fast CT and Doppler ultrasonic diagnosis with outstanding capacity, non-invasive detection of coronary lesions has become pos-

Table 3 Interventional Antihypertensive Trials on Diabetic Patients

Name of trial	Number of subjects (males / females)	Period in years (mean observation period)	Results
UKPDS	Type 2 DM (blood pressure over 160 / 94 mmHg) 1,148 (637 / 511)	1976–97 (8.4 years)	No significant difference in the incidence of cardiovascular diseases (trial to be continued for 5 more years)
ABCD	Type 2 DM (diastolic pressure over 80 mmHg) 470 (287 / 183)	1993–98 (5 years)	Enalapril reduced the incidence of myocardial infarction: Nisoldipine group, 11%; enalapril group, 2% (relative risk, 5.5)
FACET	Type 2 DM (blood pressure over 160 / 95 mmHg) 380 (152 / 228)	1994–98 (3.5 years)	Fosinopril reduced the incidence of cardiovascular events: Amlodipine group, 14%; fosinopril group, 7.4% (relative risk, 4.9)
HOT	Type 2 DM (diastolic pressure over 100 to 115 mmHg) 1,501	1992–97 (3.8 years)	Incidence of cardiovascular events reduced in the group with greater reduction in diastolic pressure: Significant difference between groups with different target diastolic pressures ($p = 0.005$)

UKPDS: United Kingdom Prospective Diabetes Study, UKPDS 38. (*BMJ* 317: 703–713, 1998)
ABCD: Appropriate Blood Pressure Control in Diabetes Trial (*N Engl J Med* 338: 645–652, 1998)
FACET: Fosinopril Amlodipine Cardiovascular Events Trial (*Diabetes Care* 21: 597–603, 1998)
HOT: Hypertention Optimal Treatment Randamised Trial (*Lancet* 351: 1755–1762, 1998)

Table 4 Comparison of Non-invasive Methods to Detect Coronary Artery Diseases

Methods	Sensitivity / Specificity (%)	Time required	Cost (in yen)
Electrocardiography at rest	20? / ?	10 minutes	1,500
Master's exercise test	28–66 / 70–85	30 minutes	3,500
Treadmill test	70–80 / 82–97	30 minutes	7,000
Holter electrocardiography	30–40? / ?	24 hours	15,000
Ultrafast CT	71–74 / 70–90	10 minutes	13,840
Transthoracic Doppler echo cardiography	93 / 93 (left anterior descending artery)	10 minutes	11,500
Exercise stress myocardial scintigraphy	80–90 / 85–95	5 hours	104,210

sible.[6,7] Because these diagnostic procedures are relatively inexpensive (in Japan) and can be conducted in a short time, they are applicable for routine diagnoses (Table 4).

Treatment at the Acute Stage and Relationship with Diagnosis

It has been reported that patients with acute myocardial infarction complicated with diabetes mellitus had few subjective symptoms. Because they often suffer from asymptomatic myocardial ischemia, hospitalization is delayed, which

results in a poor prognosis.[10] An extended delay before hospital admission means missed opportunities for coronary angioplasty. Rapid diagnosis determines the prognosis. A well-organized medical network is important for rapid diagnosis before the condition becomes serious.

Conclusion

Diabetic patients are liable to develop ischemic heart diseases: yet they present few symptoms until the coronary lesions become severe, thus delaying detection of the condition and resulting in complications with cardiac failure, frequent recurrence of ischemia, and a poor prognosis. The "keys" to improve the prognosis for ischemic heart diseases in diabetic patients, the incidence of which is expected to increase in the future, are more precise and effective control of blood sugar, blood pressure, and blood lipid, early diagnosis during asymptomatic state, and correlation with the accurate determination of the disease condition during the acute stage.

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ANTIHYPERTENSIVE DRUG THERAPY IN CONSIDERATION OF CIRCADIAN BLOOD PRESSURE VARIATION*

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Abstract: J-MUBA was a large-scale clinical study which, for the first time in the world, evaluated the effects of an antihypertensive drug on circadian BP variation in more than 600 patients with hypertension. Although ACE inhibitors reportedly exert equal 24-hour antihypertensive effects on daytime and nighttime BP, α- and β-blockers are reported to have weaker effects on nighttime BP than on daytime BP. However, clinical studies that have investigated the effects of these drugs on circadian BP variation have included only 20–30 subjects and have offered no detailed analyses of circadian BP variation, unlike J-MUBA. An outline of antihypertensive drug therapy in consideration of circadian BP variation has been given in this paper, including the results of J-MUBA. ABPM can provide additional useful information on BP that cannot be obtained by measurement of casual office BP. Increased clinical application of this technique based on further accumulation of study data is expected.

Key words: Circadian blood pressure variation; 24-hour blood pressure; Ambulatory blood pressure monitoring (ABPM); Antihypertensive drug therapy

Introduction

The diagnosis and treatment of hypertension have long been based on casual blood pressure (BP) measurements obtained at outpatient clinics. In contrast, 24-hour ambulatory monitoring of BP, a technique that has become available in recent years, has revealed the time-course of variation in BP and the presence of a circadian rhythm, in that BP is high during the daylight waking hours and low during nighttime sleep.

Thus, it has become apparent that a single BP measurement obtained during a visit to an outpatient clinic does not represent the patient's true BP, a concept that is not tenable since BP is variable. Therefore, it is now generally recom-

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mended that diagnosis and treatment policy be based a comprehensive evaluation of casual BP measurements obtained at multiple visits to an outpatient clinic.

It has been reported that the mean 24-hour BP is more helpful in determining the prognosis of patients with hypertension than casual BP measured at an outpatient clinic.[1)] Additional data analysis from the Syst-Eur (Systolic Hypertension in Europe) trial reported in *JAMA* in 1999 indicated that nighttime BP is a better prognostic factor for the likelihood of developing of cardiovascular disease.[2)]

In this paper, in connection with discussing antihypertensive drug therapy in consideration of circadian BP variation, the author describes the usefulness and clinical significance of 24-hour ambulatory BP monitoring (ABPM), and introduces the results of a large-scale Japanese clinical study focused on ABPM, the Japanese Multicenter Study on Barnidipine with ABPM[3)] (J-MUBA).

Clinical Significance of ABPM

ABPM is useful for evaluating the circadian BP pattern, particularly for determining nighttime and morning BP, for identifying white-coat hypertension, and for evaluating response to antihypertensive drugs.

1. Nighttime blood pressure

Many normotensives and mild or moderate essential hypertensives have nighttime BP 10–20% lower than their daytime BP. Individuals who have this distinct circadian BP profile are called dippers. On the other hand, elderly people or patients who have hypertensive vascular organ damage or complications in the brain, heart, or kidney show lesser or no decreases in nighttime BP. These individuals who have no distinct circadian BP variation are called non-dippers.[4)]

A number of studies have documented that in non-dippers it is important to control high nighttime BP as well as daytime BP to obtain a better prognosis. To this end, medication with long-acting antihypertensive drugs that permit 24-hour control of BP is necessary.

In contrast, in dippers it is necessary to control daytime BP, whereas overreduction of nighttime BP may induce ischemic complications.[5,6)] Therefore, the use of strong antihypertensive drugs that may cause excessive decreases in nighttime BP should be avoided. In particular, recent studies have shown a group of extreme-dippers who have a wide variation in diurnal BP characterized by a large reduction in nighttime BP of 20% or more compared with daytime BP.[7)] In these patients, it is recommended that only daytime BP be lowered, while causing no further reduce in their already low nighttime BP.

2. Morning blood pressure

As research on ABPM advanced, it became apparent that BP increases in the early morning and that the increase, called a morning surge, is particularly steep in certain individuals. It is suspected that hypertension in the early morning or morning surge is involved in complications such as myocardial infarction and cerebral hemorrhage occurring immediately after rising from bed, and much attention is being paid to the investigation of the actual status and treatment of morning

hypertension.[8] In particular, when determining the dosing method for antihypertensive drugs, once-daily administration is used for drugs whose antihypertensive effects last until the early morning of the following day (sustained action), based on measurements of ABPM before and after administration, whereas twice- or three-times-daily administration may be necessary as a natural consequence for drugs that have shorter antihypertensive effects that do not last until the following morning. The definitions of morning hypertension and morning surge and their treatment will be described in greater detail later, in the context of outlining the results of J-MUBA.

3. White-coat hypertension

Some people repeatedly show hypertension when PB is measured at an outpatient clinic, although their BP is normal when measured outside the hospital. This condition, called white-coat hypertension, is a pressor reaction to the doctor's elevated status as represented by his or her white coat, and is considered to be a problem involved in the evaluation of casual BP measured at outpatient clinics. Although the white-coat phenomenon is found in not a few normotensives and general hypertensives, it often diminishes and disappears as they accommodate to visiting the hospital. In contrast, in a certain group of patients, the white-coat phenomenon persists indefinitely. Although white-coat hypertension has been studied extensively, its pathogenesis remains unclarified.

The prognosis of white-coat hypertension, which has been attracting particular attention, is considered to be better than that of true hypertensives[9] and similar to that of normotensives. However, the possibility that white-coat hypertension frequently develops into true hypertension at a later stage has been suggested,[10] and periodic observation is therefore necessary.

Measurement of casual BP at an outpatient clinic does not permit differentiation between white-coat hypertension and true hypertension. White-coat hypertension generally requires no antihypertensive drug therapy. In particular, since the use of potent antihypertensive drugs carries the risk of inducing excessive BP reduction, it is necessary to distinguish true hypertension from white-coat hypertension by ABPM or measurement of BP at home. Whereas it may be difficult for practicing clinicians to employ ABPM for hypertensive patients seen in their daily practice, adequate measurement of BP at home facilitates differentiation between white-coat hypertension and true hypertension.

Automatic cuff-oscillometric devices currently are widely used for home BP measurement in Japan. The reproducibility of the results of ABPM varies according to the pattern of activity on the day of monitoring. In contrast, home BP measurements are highly reproducible; data are consistent and reliable if the BP is measured before breakfast with the patient in the sitting position after gotten up and urinated. It is, however, important to teach the patient how to measure BP correctly. Measuring at the same hour under the same conditions every day is important, and measurement in a cold or hot environment or immediately after eating, drinking alcohol, or smoking should be avoided. Although some of the currently available automatic cuff-oscillometric devices measure BP at the wrist or finger, rather than at the upper arm, these types are more susceptible to error. The

use of automatic devices that measure BP at the upper arm should be encouraged.

Outline of the Results of J-MUBA

A large-scale clinical study, J-MUBA, in which 121 facilities in various parts of Japan participated is described below. This clinical study was designed mainly to study the effects of a long-acting Ca antagonist, barnidipine (Hypoca®) (once-daily administration), on circadian BP variation in Japanese hypertensive patients, using ABPM. All leading ABPM researchers in Japan participated in this clinical study.

1. Purposes and methods of J-MUBA

The purposes of the study were to (1) investigate the influences of patient characteristics on ABPM pattern; (2) compare the clinical significance of ABPM data, home BP measurements, and casual BP data from clinics; (3) examine the action of the antihypertensive drug on white-coat hypertension; (4) determine the action of the drug on nighttime BP, and (5) examine the action of the drug on morning hypertension or morning surge.

The subjects were hypertensive patients aged 30 years or older who had a mean systolic BP of 160 mmHg or more, and/or a mean diastolic BP of 95 mmHg or more in casual office measurements obtained during the observation period. Details of the study were explained to potential participants, and consent to participate was obtained from each patient before the start of treatment.

After obtaining ABPM data during the observation period, a dose of 10–15 mg of the long-acting Ca antagonist barnidipine was given to each patient once daily after breakfast for at least 6 months, and ABPM data obtained during the treatment period were compared with corresponding data obtained during the observation period.

In J-MUBA, the definitions of the terminology of circadian BP variation and processing procedures of ABPM data and their criteria were specifically established prior to data analysis, on the basis of the results of previous clinical studies. These definitions and criteria provide possible standards for future clinical studies on circadian BP variation.

2. Characteristics of registered patients

A total of 612 patients from 121 facilities in various parts of Japan were registered, and 99% of them had essential hypertension (WHO stage I in 45% and stage II in 49%). Most patients were mild hypertensive, without accompanying target organ impairment, with only 4.1%, 2.7%, and 2.2% of patients having impairment in the brain, heart and kidney, respectively. Most subjects were in the age of 40–69 yrs.

Overall, patients' mean 24-hour systolic and diastolic BP were about 20 mmHg and 10 mmHg lower than the mean casual office systolic and diastolic BP, respectively. When the difference between daytime BP and nighttime BP was examined, according to the definitions of daytime BP as BP obtained between 9:00 am and 9:00 pm and nighttime BP as those obtained between 0:00 am and

Table Number of Patients and BP Values (mean ± SD) by the Circadian BP Pattern in J-MUBA

		All	Lower-range hypertensives	Higher-range hypertensives	inverted-dippers	non-dippers	dippers	extreme-dippers
n (%)		502	104 (21)	398 (79)	53 (13)	116 (29)	166 (42)	63 (16)
24-hour BP (mmHg)	SBP	148 ± 15	128 ± 6	153 ± 12	156 ± 12	155 ± 13	152 ± 12	148 ± 10
	DBP	89 ± 11	79 ± 8	91 ± 10	89 ± 9	90 ± 12	93 ± 10	89 ± 9
Daytime BP (mmHg)	SBP	154 ± 15	136 ± 8	159 ± 13	153 ± 12	158 ± 14	160 ± 12	163 ± 11
	DBP	93 ± 12	84 ± 9	95 ± 11	89 ± 10	93 ± 12	98 ± 10	98 ± 10
Nighttime BP (mmHg)	SBP	136 ± 19	114 ± 10	142 ± 17	162 ± 15	150 ± 14	137 ± 11	122 ± 10
	DBP	80 ± 12	70 ± 8	83 ± 11	88 ± 9	86 ± 12	83 ± 9	73 ± 7
Casual office BP (mmHg)	SBP	169 ± 15	163 ± 13	171 ± 15	176 ± 17	172 ± 16	170 ± 14	169 ± 14
	DBP	99 ± 10	98 ± 8	100 ± 10	98 ± 12	98 ± 10	101 ± 9	101 ± 9

5:00 am, the mean nighttime systolic and diastolic BP were generally about 20 mmHg and 10 mmHg lower, respectively, than the corresponding daytime BP.

3. Summary of results

The long-acting Ca antagonist exerted steady antihypertensive effect for 24 hours, regardless of daytime or nighttime, on 24-hour BP in all hypertensive patients, but had no influence on pulse rate. The drug caused a significant decrease in casual office BP, but caused hardly any reduction in 24-hour BP in patients with white-coat hypertension who had high casual office BP and normal 24-hour BP. When circadian BP variation was examined in 398 patients with true hypertension who had both high 24-hour and casual office BP, dippers, in whom nighttime BP was at least 10% lower than daytime BP, accounted for about 60%, with extreme-dippers, in whom nighttime BP was at least 20% lower than daytime BP, accounting for 16%. Non-dippers, who had only slight nighttime decreases, accounted for about 40%, and a little more than 10% of all patients were inverted-dippers, in whom nighttime BP were higher than daytime BP (Table). Whereas non-dippers accounted for a large subgroup (60–70%) among patients of advanced age or with cerebrovascular disorders, 30–40% of younger patients with mild hypertension (30–40 years of age) were also found to have a non-dipper pattern. This is a noteworthy finding that had not been described prior to J-MUBA.

True hypertensive patients were divided into dippers and non-dippers according to circadian BP pattern, and the antihypertensive effects of the long-acting Ca antagonist in these two groups were compared. In non-dippers, who had high BP levels in both day- and nighttime, the drug caused an adequate reduction in nighttime BP as well as in daytime BP, achieving steady 24-hour control. On the other hand, in dippers, who had a nighttime BP decrease, the long-acting Ca antagonist resulted in a sufficient decrease in the high daytime BP, but exerted hardly any effect on the low nighttime BP. In particular, there was no effect on nighttime BP in extreme-dippers, who had normal nighttime BP levels (Fig. 1). Thus, the results

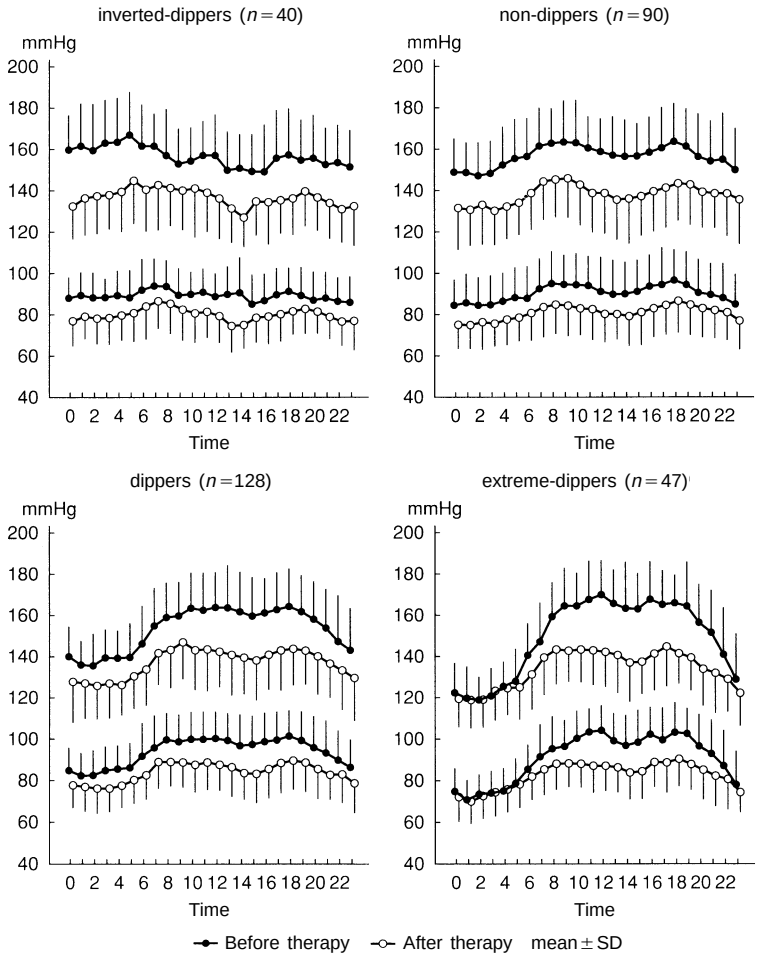

Fig. 1 Changes in 24-hour BP before and after Ca antagonist therapy in relation to the circadian BP pattern (from J-MUBA)

of J-MUBA showed that the long-acting Ca antagonist achieved good 24-hour control of high BP, while it did not reduce low BP, causing no excessive reduction in nighttime BP.

To examine morning hypertension and morning surge, J-MUBA included an analysis of systolic BP over 3 hours before and after awakening. Morning hypertension was defined by at least one measurement of 170 mmHg BP 3 hours after awaking, and under this definition, 37% of all patients had morning hypertension. Morning surge was defined by an abrupt 30 mmHg or higher elevation of mean systolic BP during the 3-hour period after awakening compared with that during the 3-hour period prior to awakening. Twenty-nine percent of patients with morning hypertension exhibited morning surge.

The long-acting Ca antagonist achieved significant control of morning BP in

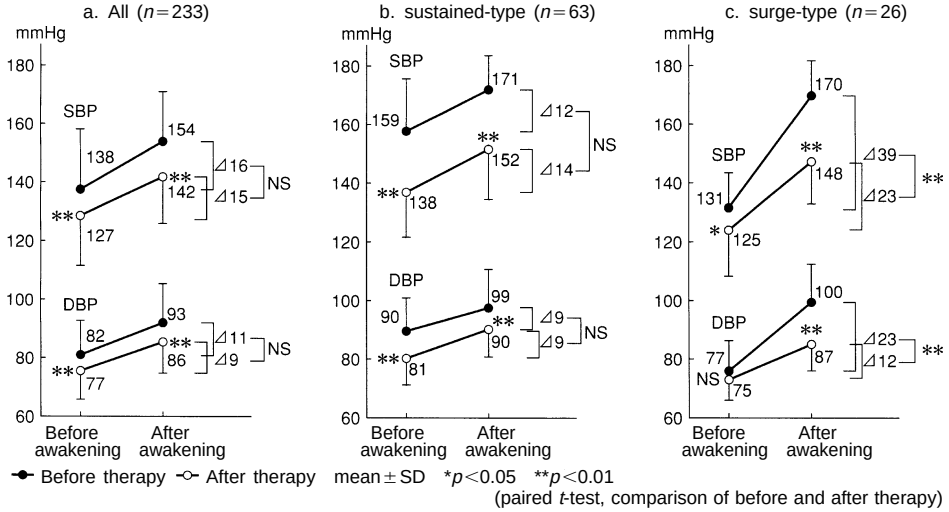

Fig. 2 Changes in morning BP before and after Ca antagonist therapy

all patients during the 3 hours before awakening. In particular, in patients with sustained-type morning hypertension, i.e., those who had high BP even before awakening, the drug decreased the high BP before and after awakening by about 20 mmHg for systolic BP and about 10 mmHg for diastolic BP. In patients with morning surge, the drug exerted a potent reduction on the high BP that occurred after awakening, suppressing the abrupt morning elevation of BP by about 50% (Fig. 2).

These results indicate that the long-acting Ca antagonist was able to achieve good 24-hour control of BP. The trough-peak ratio (T/P ratio) is a known index for evaluating the sustained action of antihypertensive drugs. Although this index was also examined in J-MUBA, it was associated with a number of problems, including the method of calculation. This index is therefore considered to require further refinement before it can be of practical use.

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THE REASON WHY PROSTATIC HYPERPLASIA CAUSES LOWER URINARY TRACT SYMPTOMS*

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Abstract: In benign prostatic hyperplasia (BPH), the lower urinary tract changes both functionally and organically in association with the enlargement of prostate. Thereby, lower urinary tract symptoms (LUTS) are manifested. LUTS are classified into symptoms in the storage phase and in the voiding phase. The former includes urinary frequency, nocturia, urinary urgency, and incontinence. These are caused by detrusor enlargement and increased bladder sensation which occur in association with urethral resistance increased by urethral compression resulting from BPH. The symptoms caused by difficult voiding due to urethral compression by enlarged prostate are called voiding symptoms, which include urinary hesitation, prolongation of micturition time, weakening of stream, and so on. Aging, cerebral disease, vertebral disease, spinal disease, and heart disease present lower urinary tract symptoms very similar to those associated with BPH and these diseases complicate symptoms of BPH.

Key words: Benign prostatic hyperplasia; Lower urinary tract symptoms; Storage symptoms; Voiding symptoms

Introduction

Benign prostatic hyperplasia (BPH) is fundamentally a disease that causes morbidity through the urinary symptoms with which it is associated.[1)] Symptoms related to micturition are called lower urinary tract symptoms (LUTS),[2)] which are classified into those which occur in the storage phase (storage symptoms) and those which occur in the voiding phase (voiding symptoms). The former includes urinary frequency, urinary urgency, nocturia (3 or more times voiding at night), and urinary incontinence. The latter includes micturition pain, hesitation, prolongation of voiding, interruptions of voiding, weak stream, sensation of residing straining for voiding, and terminal dribbling.

Most LUTS are characteristic of various lower urinary tract diseases, espe-

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Table 1 International Prostate Symptom Score (I-PSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	3 times	4 times	5 or more times
	0	1	2	3	4	5

I-PSS = sum of questions 1–7 = ____

Quality of life due to urinary symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	Delighted	Pleased	Mostly satisfied	Mixed (about equally satisfied and dissatisfied)	Mostly dissatisfied	Unhappy	Terrible
	0	1	2	3	4	5	6

Reference: Barry M.J., Fowler, F.J., O'Leary, M.P. *et al.*: the American Urological Association Symptom Index for benign prostatic hyperplasia. *J Urol* 148: 1549, 1992.

cially bladder outlet obstructions. BPH also has several characteristic symptoms. WHO has recommended the use of a standard called "International Prostate Symptom Score (IPSS)", which scores the seven listed symptoms, for severity judgement[3] (Table 1). However, it has already been proven that this scoring standard is not sufficient to estimate or judge the volume of the prostate (benign prostatic enlargement: BPE) or the degree of lower urinary tract obstruction.[4]

In this review we discuss the mechanism by which BPE causes LUTS and the reason why BPH cannot be exactly diagnosed from these symptoms in cases with BPE.

Mechanism Through Which BPE Causes LUTS

An enlarged prostate oppresses the urethra, or obstructs it, and increases urethral resistance and the work of the detrusor for micturition. This results in

Table 2 Mechanism of Urinary Tract Disturbance in BPH

1. Voiding disturbance
A. Organic (BPE)
1) Obstruction
2) Compression of the external urethral sphincter
3) Extension of the prostatic capsule
4) Compression of the bladder base
5) Elongation of the prostatic urethra
B. Functional
1) Increase in α-receptor in the prostate
2) Detrusor bladder neck dyssynergia
3) Inability of the external urethral sphincter
4) Dyscontractility of the detrusor due to bladder distension
2. Storage disturbance
A. Organic (Low compliance bladder)
B. Functional
1) Detrusor overactivity
2) Overdistension of the detrusor

detrusor hypertrophy. As urethral obstruction progresses, the postvoid residual urine volume increases. That is, to whatever extent the detrusor hypertrophies, it cannot void urine sufficiently, and the condition becomes decompensatory (Table 2). LUTS are manifested due to such lower urinary tract changes associated with BPE. Thus the manifested symptoms are considered to be specific urinary symptoms to BPE.

BPE obstructs the urethra, and, thereby, a voiding disturbance occurs. This is also fundamentally important in BPH. The above mentioned voiding symptoms, such as hesitancy, prolongation, weak stream, etc., are found in 60–90% of BPH patients. In our experience, hesitancy is the most important of the voiding symptoms in BPH. We explain the reason below.[5)]

The possible mechanisms of bladder outlet obstruction due to BPE are (1) the enlargement of the prostate resulting in extension of the urethra and prostatic capsule and (2) the increase in tonus of the smooth muscle in the prostate.[6)] As is well known, in the drug therapy of BPH, an anti-androgen is used to reduce the size of the gland and an α-blocker to decrease smooth muscle tone.[7)] Our series of studies have demonstrated that an α-blocker not only decreases smooth muscle tone but also resolves detrusor bladder neck dyssynergia in the voiding phase. When the detrusor contracts, the α-blocker makes the internal urethral orifice open synchronously.

As bladder outlet obstruction progresses due to BPE, the detrusor sensitivity to the stimulus increases and, in this condition, the bladder contracts suddenly even when a small amount of urine, with which no desire to void occurs in normal conditions, accumulates in the bladder. This condition is called detrusor overactivity, or unstable bladder. Unstable bladder causes urinary urgency or urge incontinence. Urinary incontinence is a troublesome condition and the patient frequently goes to the toilet.

Hypertrophy of the detrusor results in bladder wall thickening due to which

Table 3 Other Factors Complicating BPH Symptoms or Causing Similar Symptoms

1. Detrusor hyperactivity with incomplete contraction
2. Cardiac disease
3. Renal failure
4. Cerebral infarction
5. Vertebral or spinal cord disease
6. Bladder neck obstruction
7. Prostatitis
8. Others

the detrusor smooth muscle cannot stretch smoothly in the storage phase. Such a condition is called low-compliance bladder. In this condition, not much urine can be held in the bladder and urinary frequency occurs. It has been reported that benign prostatic enlargement (BPE) causes extension of the urethra and prostatic capsule, and sensory nerves present in the capsule are stimulated. Unstable bladder is thus induced in the filling phase. In our experience, urinary frequency and nocturia are the most important of the storage symptoms in BPH. In the stage of decompensation of the detrusor, intravesical pressure increases due to bladder wall thickening and large postvoid residual urine volume, and urine cannot be transferred to the bladder through the ureter. In this condition, hydroureter and hydronephrosis lead to chronic postrenal failure advance.[8)] As such a condition advances, voiding symptoms increase in severity and large residual urine volume is found in the bladder. Urine cannot be voided without straining. In patients having a lot of postvoid residual urine due to difficulty in voiding, an abdominal pressure by turning over in bed or in standing up sometimes causes urinary incontinence which is a symptom in the storage phase. This is called overflow incontinence. In addition, abdominal distension associated with residual urine and hydronephrosis and edema due to renal failure also occur. As mentioned above, BPH triggers so many urinary symptoms that it is difficult to determine which symptoms are specific to BPH.

Other Factors Complicating BPH Symptoms or Causing Similar Symptoms

The prostate becomes enlarged at the age of 40 years or later. Age-associated urinary disturbance may sometimes change BPH symptoms or cause similar symptoms. Factors complicating BPH symptoms include the aging of lower urinary tract tissue, changes in urine-producing circadian rhythm due to changes in vasopressin secretion, lower limb edema due to cardiac dysfunction, vertebral or spinal diseases, cerebral infarction and so on (Table 3).

The change in urinary symptoms by aging is a significant factor which alters BPH-specific symptoms. A change in the lower urinary tract which arises through aging is the aging of the bladder. The aging of the bladder causes a degeneration of detrusor tissue, resulting in the formation of more junctions between smooth

muscles. Thus, the detrusor becomes overactive (unstable bladder). In this condition, a minimal stimulus to the bladder (small volume of urine) causes detrusor contraction. Unstable bladder is a major cause of urinary frequency, urgency and urinary incontinence. Fibrous tissue deposits between the detrusor muscle and, thereby, the bladder cannot dilate smoothly and it becomes difficult to fill with urine. This condition is low-compliance bladder, which becomes causative of urinary frequency. On the other hand, detrusor degeneration leads to the reduction in bladder contraction and induces voiding symptoms such as prolongation of micturition time, weakening of stream, etc.

Due to the above reasons, detrusor hyperactivity with incomplete contraction (DHIC) is often found in elderly people.[9)] In DHIC, unstable bladder generally coexists with detrusor incomplete contraction. It has been known that the incidence of this phenomenon increases remarkably at the age of 70 years. In DHIC, storage disturbance such as urinary frequency and urinary incontinence is found together with voiding disturbance such as increased postvoid residual urine volume. In the presence of increased residual urine volume, urinary tract infection is often found. This condition is very similar to lower urinary tract symptoms in BPH. In other words, the same lower urinary tract symptoms as those in BPH occur even in BPH-free females aged over 70 years.

It is well known that circadian rhythm of vasopressin secretion changes with aging. The decrease in vasopressin secretion at night leads to nocturnal polyuria, which causes nocturia.

In heart disease with lower limb edema, the volume of circulating blood increases during night sleeping and urine volume increases at night. This causes nocturia.

In vertebral or spinal disease and cerebral infarction, it is likely that voiding-related central nervous system may be damaged. This is called neurogenic bladder. The most common phenomenon is detrusor overactivity (detrusor hyperreflexia) which is caused by supra-nuclear lesion of nerves innervating the detrusor. Like unstable bladder in BPH, this condition causes urinary urgency or urge incontinence. In spinal disease, detrusor-sphincter dyssynergia is often found. In this condition, the external urethral sphincter contracts to close the urethra when the detrusor contracts and, thus, voiding is disturbed. This voiding symptom due to non-synergic contraction of the external urethral sphincter is similar to urethral obstruction due to BPH.

Conclusion

In BPH, the lower urinary tract changes both functionally and organically in association with the enlargement of prostate. Thereby, LUTS are manifested. LUTS are classified into symptoms in the storage phase and those in the voiding phase. The former includes urinary frequency, nocturia, urinary urgency, and incontinence. These symptoms are caused by detrusor enlargement and increased bladder sensation which occur in association with urethral resistance increased by urethral compression resulting from BPH. The symptoms caused by difficult voiding due to urethral compression by enlarged prostate are called voiding symptoms and

include urinary hesitation, prolongation of micturition time, weakening of stream, etc.

In this article, the authors have pointed out that aging, cerebral disease, vertebral disease, spinal disease, and heart disease present lower urinary tract symptoms very similar to those associated with BPH and also that these diseases complicate symptoms of BPH.

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