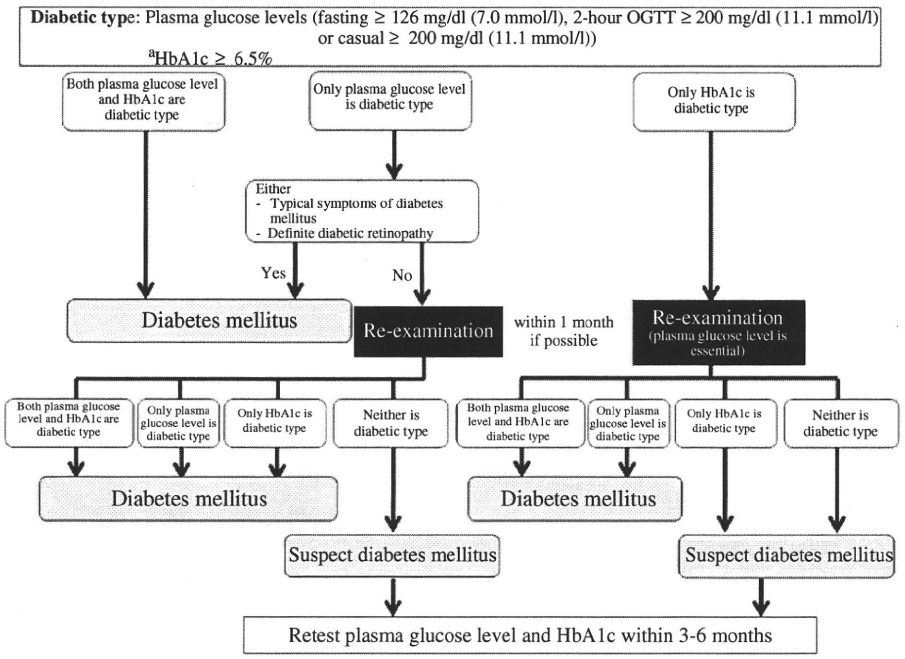

Fig. 2 Flow chart outlining steps in the clinical diagnosis of diabetes mellitus. The value for HbA1c[a] (%) is indicated with 0.4% added to HbA1c (JDS) (%)

practice, OGTT is recommended for confirming glucose tolerance in cases as shown in Table 6, except when overt symptoms of diabetes, marked hyperglycemia or ketosis are present. In fact, extensive analyses in Japan have made it clear that when the fasting plasma glucose level is 100 mg/dl (5.5 mmol/l) or higher, or the HbA1c is 5.6% or higher, these include (i) a group in which diabetes mellitus must be suspected; and (ii) a group in which, if the disease is not present now, is at a high risk for developing diabetes mellitus in the future. OGTT is an important diagnostic tool allowing physicians to avoid the risk of overlooking these patients [5, 33, 34]. In particular, OGTT is strongly recommended in the case of (i) and should be carried out if possible in case of (ii).

When conducting OGTT, the following conditions are necessary to obtain an accurate result. After consuming meals containing at least 150 g of carbohydrates for at least 3 days, patients receive 75 g (as anhydride) of glucose or its equivalent of 250–350 ml carbohydrate solution orally in the morning under fasting conditions. Blood is then sampled over time to measure the plasma glucose levels. The solution should be consumed within 5 min, and evaluation should be timed from the time that the patient starts to drink. The patient should be fasted for 10–14 h from the day before until the test. Nothing, except for water, can be consumed until the test is completed, and the patient should remain as quiet as possible and may not smoke during the test. Measuring urinary glucose at the same time is useful to estimate the urinary glucose excretion threshold. For a diagnosis of diabetes mellitus, at least fasting and 2-h plasma glucose levels are measured. Starvation or low carbohydrate intake may induce glucose intolerance. In patients who have undergone a gastrectomy, the plasma glucose level may rise dramatically soon after the glucose load.

At the least, fasting and 2-h blood samples should be taken. In clinical cases, it is recommended also to measure plasma glucose at 30 and 60 min to enhance the accuracy of diagnosis. The measurement of plasma insulin can help to predict the risk for future development of diabetes.

Table 6 Situations where a 75-g oral glucose tolerance test is recommended

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

[a] The value for HbA1c (%) is indicated with 0.4% added to HbA1c (JDS) (%)

2. Cut-off levels for OGTT

Table 3 shows the criteria for diabetes mellitus according to OGTT. As in past JDS committee reports, the results are classified as normal, borderline and diabetic types [2–4]. The normal range and the diabetic range of fasting plasma glucose levels and OGTT 2-h values are shown in Table 3.

- Diabetic type: Either a fasting plasma glucose level of 126 mg/dl (7.0 mmol/l) or higher, or an OGTT 2-h value of 200 mg/dl (11.1 mmol/l) or higher is called diabetic type.
- Normal type: Normal type is defined as a range of glycemia that is unlikely to develop into diabetes after several years of observation. A fasting plasma glucose level below 110 mg/dl (6.1 mmol/l) and an OGTT 2-h value below 140 mg/dl (7.8 mmol/l) are called normal type. In a previous JDS report, normal type was considered as "patients mostly do not develop diabetes mellitus even after several years of follow up," and the plasma glucose criteria were thus set at lower levels [2, 3]. However, in the 1999 JDS report, the upper limit of normal type was set at the same value as the lower limit of the WHO IGT reference value. This was partly in respect to the international reference value, and partly because the progression rate among the Japanese data from normal type to diabetic type was as low as 0.6–1.0% [4].
- Borderline type: This category is defined when the pattern of OGTT is neither diabetic nor normal type. Borderline type includes heterogeneous conditions: a subject in transition to developing diabetes, diabetes in remission, insulin resistance syndrome and temporary deterioration of glucose tolerance due to stress in an essentially healthy individual. Subjects with borderline type are at little risk of developing diabetes-specific microangiopathy, but at increased risk of progressing to diabetes and to developing macroangiopathy. The fasting plasma glucose level that defines IFG is set at 100–125 mg/dl (5.5–6.9 mmol/l) [10] by the American Diabetes Association and at 110–125 mg/dl (6.1–6.9 mmol/l) [11] by the WHO. The JDS called the range of 100–109 mg/dl (5.5–6.0 mmol/l) "high-normal," because those with a fasting plasma glucose level of 100 mg/dl (5.5 mmol/l) or higher are often borderline type or diabetic type according to OGTT. However, because the judgment of normal type is made in conjunction with the OGTT 2-h value, the fasting plasma glucose criterion below 110 mg/dl (6.1 mmol/l) is retained [5]. The JDS borderline type corresponds to a combination of IGT and a narrowly defined IFG (elevated fasting plasma glucose level only, not IGT). Individually, IGT and IFG are often incongruent [35, 36].

Subjects with a 100 mg/dl (5.5 mmol/l) or higher fasting value and a 1-h value of 180 mg/dl (10.0 mmol/l) or higher (steep hyperglycemia) should be followed similarly to borderline type, even if they belong to normal type, because it is known that such individuals are at higher risk of developing diabetes. Diabetic patients have a decreased early insulin response to glucose with a low insulinogenic index, a 0.4 (μU/ml per mg/dl) or lower ΔIRI/ΔPG (the ratio of increment of plasma insulin to that of glucose at 30 min after oral glucose load), and borderline types showing low insulinogenic index have been reported to have a high risk of progression into diabetes mellitus, and all of these are thought to be fundamental characteristics of diabetes mellitus [37–40].

Epidemiological study

The purpose of epidemiological study is to estimate the prevalence and incidence of diabetes mellitus or glucose metabolism disorders in a population and to examine their risk factors. In this case, repeated examination of plasma glucose is usually difficult. While the reproducibility of fasting plasma glucose level or OGTT results in each individual is not good, for each population, the plasma glucose level distribution and the mean values are reasonably reproducible. Consequently, when estimating the prevalence of diabetes mellitus, the determination of "diabetic type" based on a single test can be considered as representative of "diabetes mellitus" (Table 4). Because it is difficult to verify that the subject actually observed the fasting time for the fasting blood sample, HbA1c ≥6.5% is used as the standard as far as possible. When using the fasting plasma glucose level, OGTT 2-h value or HbA1c, it is always necessary to clarify the diagnostic method in the survey report, because the prevalence of "diabetes mellitus" and individual subjects diagnosed as having "diabetes mellitus" vary according to the methods. When presenting the survey results, it is desirable to include not only the prevalence of "diabetes mellitus" and borderline glucose metabolism disorders, but also the distribution data on plasma glucose levels and HbA1c in the study population.

Health screening

The purpose of health screening is to detect diabetes mellitus and its high risk groups. Therefore, in addition to measuring plasma glucose and HbA1c, information such as family history, bodyweight history, pregnancy and birth

history, present status of obesity, blood pressure, and findings concerning complications is gathered, and subjects at great risk of developing diabetes mellitus should be identified. The diagnosis of subjects thus screened then follows the same procedure as for clinical diagnosis.

Since April 2008 in Japan, national health examinations and health guidance have been conducted for health insurance subscribers aged 40–74 years. The basic idea of the new health screening system is to find those who need healthcare guidance to prevent harmful lifestyle habits, focusing on visceral fat obesity. Subjects who receive healthcare guidance are those with a fasting plasma glucose level of 100 mg/dl (5.5 mmol/l; lower limit of high normal) or higher, which corresponds to an OGTT 2-h value of 140 mg/dl (7.8 mmol/l) (lower limit of borderline type), together with HbA1c ≥5.6%. From the standpoint of diabetes prevention, test data are to be handled as follows, even in those failing to meet the Japanese criteria for waist circumference and body mass index (Table 6).

1. If the fasting plasma glucose level or HbA1c corresponds to the values that recommend further examination (fasting plasma glucose ≥126 mg/dl [7.0 mmol/l] or HbA1c ≥6.5%, the subject is immediately examined at a healthcare facility, because diabetes mellitus is strongly suspected.
2. If the fasting plasma glucose level is 110–125 mg/dl (6.1–6.9 mmol/l) or HbA1c is 6.0–6.4%, OGTT should be performed wherever feasible. If the result is borderline type, follow up or lifestyle guidance is conducted. If the result is diabetic type, the subject should be examined at a healthcare facility.
3. If the fasting plasma glucose level is 100–109 mg/dl (5.5–6.0 mmol/l) or HbA1c is 5.6–5.9%, because the risk of developing diabetes mellitus or arteriosclerosis is probably greater than in those with lower values, other risk factors (family history, obesity, hypertension, dyslipidemia, etc.) are taken into consideration, and provision of information, follow-up observation or OGTT should be carried out.

Elderly people and children

Elderly people

Diagnostic procedures for diabetes mellitus are performed as usual in the elderly with the same reference ranges as described earlier. Because OGTT 2-h plasma glucose levels tend to be more elevated compared to fasting plasma glucose levels in elderly people, it is advisable to confirm an increased HbA1c at diagnosis. In elderly people showing only a slightly higher level above the reference range, even though the condition is diabetic type, it is preferable not to administer pharmacotherapy, but to monitor the progress by providing lifestyle guidance alone as in the borderline cases.

Children

In children, type 1 diabetes usually presents with overt symptoms and with marked hyperglycemia, leaving little problem in diagnosis. However, if type 1 diabetes mellitus is diagnosed in an asymptomatic child at a school health screening, it can be difficult to determine the exact etiology of the disease. Slowly progressive type 1 diabetes mellitus is not rare, even in children, and measurement of autoantibodies, such as GAD antibody or IA-2 antibody, and monitoring of C-peptide are useful to differentiate type 1 diabetes from other types. In Japan, 20–30% of childhood-onset type 2 diabetes mellitus is non-obese, and sometimes differentiating this from slowly progressive type 1 can be difficult. Although those who develop type 1 diabetes mellitus with onset in infancy or childhood quite often show negative results of islet-associated antibodies, endogenous insulin secretion of these patients is usually depleted from an early stage. If an OGTT is needed to diagnose diabetes mellitus, the glucose load should be actual bodyweight (in kilograms) × 1.75 g (maximum 75 g). The classifications of hyperglycemia and the diagnosis of diabetes mellitus are the same as for adults.

Diabetes mellitus with onset in newborns under 6 months of age and infants often has a specific pathogenesis such as a single genetic abnormality, and is classified as neonatal diabetes.

Gestational diabetes mellitus

Glucose metabolism disorders occurring during pregnancy can be classified as pregnancy with pre-existing diabetes and hyperglycemic disorders in pregnancy, with the latter having two forms: GDM and overt diabetes diagnosed or developed during pregnancy.

The diagnosis of GDM is important because of the recognition that excessive fetal growth can occur even with mild glucose metabolism disorders, increasing the perinatal risk. In addition, even if the mother's glucose metabolism disorder improves after birth, she has an increased risk of developing diabetes mellitus in the future. The definition of GDM has undergone many historical changes. In 2008, the results of an international randomized comparative study of the effects of mild hyperglycemia during pregnancy on the child, Hyperglycemia and Adverse Pregnancy Outcome Study (HAPO Study) [41], were reported. The report from this study made recommendations on the definition, diagnostic criteria and screening for GDM based on evidence of an increase in perinatal complications [42]. Based on

Table 7 Definition and diagnostic criteria of gestational diabetes mellitus

Definition of gestational diabetes mellitus
Glucose metabolism disorder with first recognition or onset during pregnancy, but that has not developed into diabetes mellitus
Diagnostic criteria of gestational diabetes mellitus
Diagnosed if one or more of the following criteria is met in a 75 g OGTT
Fasting plasma glucose ≥92 mg/dl (5.1 mmol/l)
1-h value ≥180 mg/dl (10.0 mmol/l)
2-h value ≥153 mg/dl (8.5 mmol/l)
However, diabetes mellitus that is diagnosed according to 'Clinical diagnosis' outlined in Table 4 is excluded from gestational diabetes mellitus

(IADPSG Consensus Panel, Reference 42, partly modified with permission of Diabetes Care)

this, and considering consistency with international guidelines, the definition of GDM excluded overt diabetes and, following the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel, revised the diagnostic criteria for GDM (Table 7). If diabetes mellitus was present before pregnancy, the risk of fetal anomaly is greater than that seen in GDM.

Risk factors for GDM include positive urinary glucose, family history of diabetes mellitus, obesity, excessive weight gain, having previously given birth to a large baby and aging. In order to ensure detection of GDM, a casual plasma glucose test is conducted at the first visit and at mid-term of pregnancy if insulin resistance is elevated, and an OGTT is performed for those patients with a plasma glucose level of 100 mg/dl (5.5 mmol/l) or higher. A diagnosis of GDM is made if one or more of the following criteria is met: fasting plasma glucose ≥92 mg/dl (≥5.1 mmol/l), 1-h value ≥180 mg/dl (≥10.0 mmol/l) or 2-h value ≥153 mg/dl (≥8.5 mmol/l). However, women who are diagnosed with diabetes mellitus according to this clinical diagnosis are precluded from GDM.

Commentary

This committee considered the following points when preparing this report: (i) consistency with recent international reports; (ii) sufficient application of recent data obtained in Japan; (iii) succession of the basic concepts of the 1999 JDS committee report on diabetes mellitus; and (iv) respect for the opinions of the academic council. Points that could not be presented in the main text will be discussed here.

Worsening and improving of stages of diabetes

Figure 1 is a two-dimensional depiction of individual patient positioning, with the etiological classification of diabetes mellitus on the vertical axis and the degree of insulin deficiency on the horizontal axis. The "diabetic area" on the horizontal axis indicates that hyperglycemia has exceeded a certain level or the degree of insulin deficiency has exceeded a certain level. The vertical axis of type 1 and type 2 shows the etiology (mechanisms), although the word "diabetes" is not used here. This is because even if disease procession that can lead to diabetes mellitus is proceeding, it is not called "diabetes" until hyperglycemia has reached a certain stage or degree.

The arrows in Figure 1 point in both directions, and the arrows pointing to the left indicate improvement in the diabetic condition, either naturally or due to treatment. In the figures of the American Diabetes Association [14] and WHO [11], the left and right arrows are depicted by a single line, but in Figure 1, the line pointing left is a separate and partially broken line. Improvement of definite diabetes mellitus to the point of normal glucose metabolism is not common, except in special cases, such as pheochromocytoma resection or soft drink ketosis [43]. The arrow pointing left can be said to represent the goal of diabetes mellitus treatment.

Even if diabetes mellitus diagnosed in a patient improves with treatment from diabetic type glucose tolerance to a borderline or normal type, unless the underlying disease process has definitely been eliminated, the patient must still be considered and treated as having diabetes and the subsequent course should be observed.

Diagnostic criteria and relevant matters

The position of HbA1c in the diagnosis of diabetes mellitus

It is clinically useful to use HbA1c for making a diagnosis for the following reasons. The use of this parameter is scientifically relevant in that elevation of HbA1c serves as an indicator reflecting chronic hyperglycemia. Furthermore, HbA1c is specified as an indicator of glycemic control in the treatment guide for diabetes mellitus. Its use enhances continuity of diagnosis and treatment of diabetes, because day-to-day variations are less conspicuous and not affected by dietary conditions, and its use enables diagnosis of diabetes by one test even on a single occasion. However, because the distribution of HbA1c in diabetic types is broad, diabetes mellitus cannot be diagnosed by HbA1c alone (Figure 3), and HbA1c is affected by red blood cell turnover in addition to plasma glucose levels (Table 5) [4, 13].

In contrast, fasting plasma glucose and OGTT 2-h values have long been used in the diagnosis of diabetes

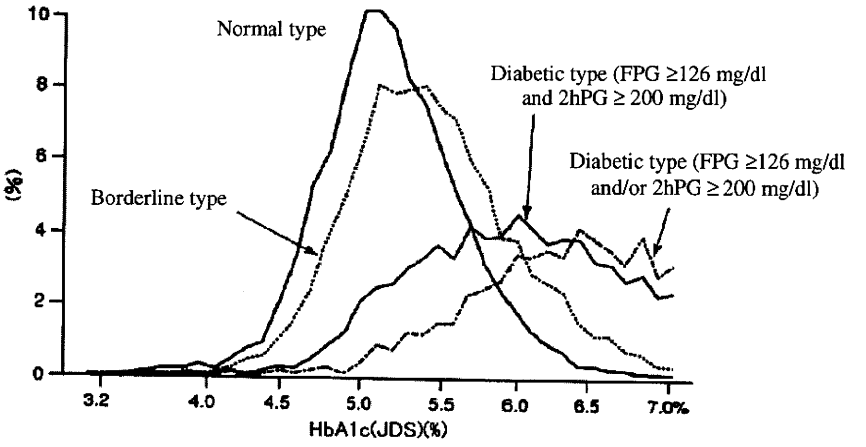

Fig. 3 Distribution of HbA1c in groups with varying degree of glucose intolerance. Distribution of HbA1c (JDS) in 6720 normal types, 6296 borderline types and 5040 diabetic types. Among diabetic types, 2950 cases that had fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/l) and 2-h oral glucose tolerance test (OGTT) (2hPG) ≥200 mg/dl (11.1 mmol/l) are shown separately (Chikako Ito, Reference 4, with the author's permission)

mellitus, and there is ample evidence that they reflect chronic hyperglycemia and that they are related to retinopathy, which is considered highly characteristic of diabetes mellitus [8, 44]. In addition, these have come to be regarded at the most important findings for a diagnosis of diabetes mellitus. Therefore, this committee examined the relationship between fasting plasma glucose level and OGTT 2-h value to HbA1c in Japanese people, and the relationship between HbA1c and retinopathy. Retinopathy was recorded by fundus camera photography and the findings were judged by an ophthalmologist.

When 6658 OGTT examinees aged under 60 years were reviewed, a very high correlation between fasting plasma glucose level and HbA1c was seen ($r = 0.854$), with a fasting plasma glucose level of 126 mg/dl (7.0 mmol/l) corresponding to a HbA1c (JDS) of 6.1%, calculated from the regression equation HbA1c (JDS) = $1.869 + 0.0333x$ (fasting plasma glucose level in mg/dl) (Figure 4a). In the same manner, a correlation was identified between OGTT 2-h value and HbA1c, ($r = 0.809$), with an OGTT 2-h value of 200 mg/dl (11.1 mmol/l) corresponding to a HbA1c (JDS) of 6.0%, calculated from the regression equation HbA1c (JDS) = $3.553 + 0.0122x$ (OGTT 2-h value) (Figure 4b). Conversely, when the fasting plasma glucose level and OGTT 2-h value corresponding to a HbA1c of 6.1% were sought from the regression equations, fasting plasma glucose level = $-9.2 + 21.9x$ (HbA1c [JDS]) and the OGTT 2-h value = $-127.1 + 53.5x$ (HbA1c [JDS]), a fasting plasma glucose level of 124.4 mg/dl (6.91 mmol/l) and an OGTT 2-h value of 199.3 mg/dl (11.07 mmol/l) corresponded to a HbA1c (JDS) of 6.1% (Figure 4c, d). These results indicate that a HbA1c (JDS) of 6.1% corresponds to the criteria for a diabetic range from the fasting plasma glucose level and OGTT 2-h value [45].

Second, based on data covering 36267 examinees, the prevalence of diabetic retinopathy (except for capillary microaneurysm alone) was compared by HbA1c and was found to be 0.06% for HbA1c (JDS) ≤4.5%. The prevalence of diabetic retinopathy increased with increasing HbA1c to become as high as 0.59% for HbA1c (JDS) between 6.1 and 6.5%; hence, it was considered relevant to set the cut-off value of HbA1c (JDS) at 6.1% (Figure 5) [44].

The relationship between HbA1c and diabetic retinopathy (moderate non-proliferative diabetic retinopathy and worse) is being studied in the USA with an extensive amount of epidemiological data. Specifically, a HbA1c (NGSP) ≥6.5% is being advocated as diagnostic for diabetes mellitus based on the high frequency of retinopathy at this level [13]. It has been pointed out in individual cases that there is a possibility of overlooking the disease if the diagnosis is made based on HbA1c alone [46]. A recent report regarding diagnostic exploration for the risk of diabetes indicates that, compared to the fasting plasma glucose level, HbA1c shows an equivalent relationship to the risk of developing diabetes mellitus and a stronger relationship with cardiovascular diseases and death [47].

Concerning HbA1c [15]

1. Definition of HbA1c
   HbA1c was originally named as one of the chromatography peaks in the hemoglobin of healthy people as a trace component, but the IFCC redefined the substance as hemoglobin that is non-enzymatically and stably bound to glucose, a valine on the hemoglobin's β-chain N-terminal being glycosylated to form β-N1-deoxyfructosyl Hb [48, 49, 50].
2. HbA1c measurement and precision control
   Presently, the exact separation of the stable form β-N1-mono-deoxyfructosyl Hb by high performance liquid chromatography using cation-exchange resin is established as the standard method of HbA1c measurement. Other methods of measurement include

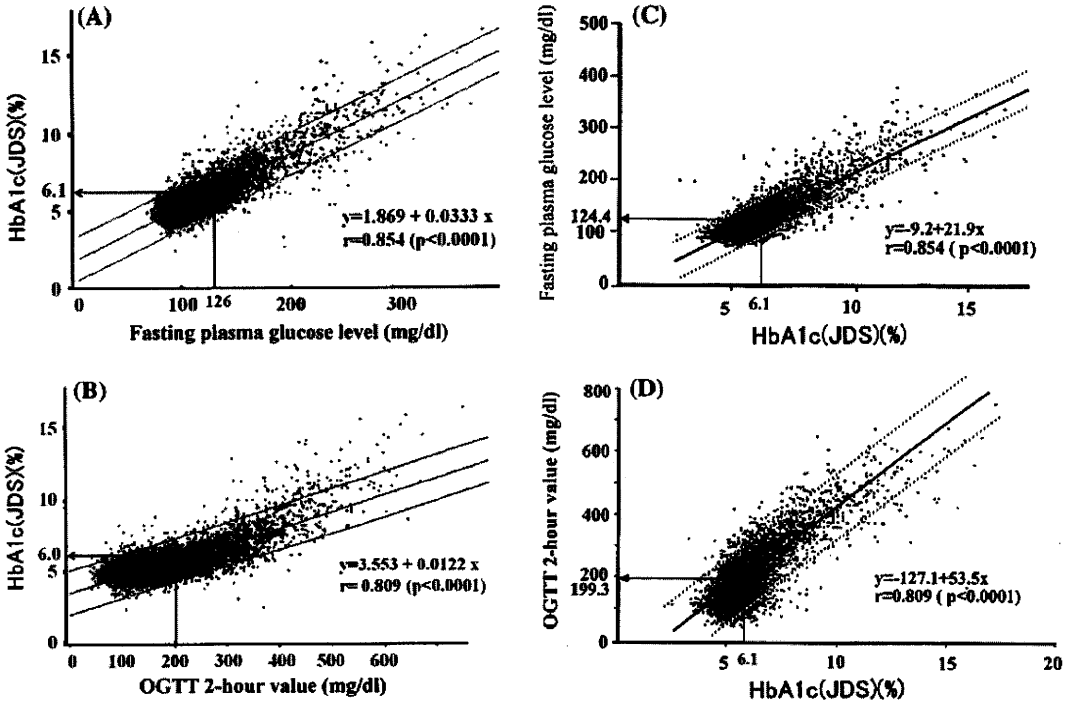

Fig. 4 Relationship between HbA1c and fasting plasma glucose level and OGTT 2-h values. **a** Relationship between fasting plasma glucose and HbA1c (JDS) (n = 6658). Fasting plasma glucose level (mg/dl). **b** Relationship between OGTT 2-h value and HbA1c (JDS) (n = 6658) OGTT 2-h value (mg/dl). **c** Relationship between HbA1c (JDS) and fasting plasma glucose (n = 6658). Fasting plasma glucose level (mg/dl). **d** Relationship between HbA1c (JDS) and OGTT 2-h value (n = 6658) OGTT 2-h value (mg/dl) (Chikako Ito, unpublished data and Reference 45, with permission from Diabetes Res Clin Pract)

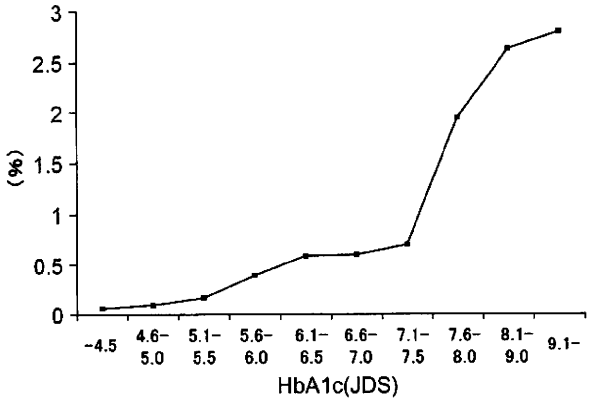

Fig. 5 HbA1c (JDS) and frequency of diabetic retinopathy (n = 36267). Excluding those with capillary microaneurysms alone (Chikako Ito, unpublished data)

immunological methods (latex agglutination immunoassay [inhibition assay], agglutination immunoassay [blocking assay] and turbidimetric immunoinhibition) and an enzymatic method. Each of these can accurately measure the stable form β-N1- deoxyfructosyl Hb. However, to maintain the precision and stability of the measured values, nationwide surveillance of differences in measured values between facilities and test methods, facility certification, and disclosure of information on assay reagents are necessary. Especially in some Point of Care (POC) devices for simplified HbA1c measurement, standardization is seen as insufficient and the use of such devices for diagnosis of diabetes mellitus cannot be recommended at this time.

3. Notation for the international standardization of HbA1c

HbA1c described in the JDS values that are used in Japan, despite its leading position in the world in precision control and progressive standardization [12, 15], has the problem that it is approximately 0.4% lower than the HbA1c described in the NGSP values that are used by almost every other country. International standardization using a new notation with numeric values very different from the previous ones is being studied by the IFCC, including Japan, to solve the various problems facing HbA1c measurement. This notation (IFCC value), which exactly indicates the currently defined β-N1-deoxyfructosyl Hb, is approximately 1.5% lower than HbA1c (JDS) (%) and 1.9% lower than HbA1c (NGSP) (%), and mistakes and

confusion in clinical diagnosis might occur if it were immediately adopted in general medical practice. Therefore, the IFCC recommends use of the System International (SI) unit (mmol/mol) to indicate the IFCC value. However, shifting to that notation will probably take considerable time, and the JDS has decided that a notation that does not differ from HbA1c (NGSP) should be used in the current revision from the standpoint of emphasizing international standardization, as follows. The HbA1c (%) is estimated as a NGSP equivalent value (%) calculated by the formula HbA1c (%) = HbA1c (JDS) (%) + 0.4%, considering the relational expression of HbA1c (JDS; %) measured by the previous Japanese standard materials and measurement methods and HbA1c (NGSP) (NGSP[%] = 1.019 × JDS[%] + 0.30) and the coefficient of variance of 2–3% in the measurement of HbA1c.

Evidence for setting reference values for diabetic type

Complications characteristic of diabetes mellitus are closely related to hyperglycemia. The degree of hyperglycemia at which complications will occur is the basis for setting plasma glucose reference standards to determine diabetes mellitus [51]. Fasting plasma glucose level, OGTT 2-h value or HbA1c all show a relationship with retinopathy [52].

The fasting plasma glucose level and OGTT 2-h value that determine the "diabetic type" in the 1999 JDS report are the same as the reference values that decide "diabetes mellitus" in the reports of the ADA and the WHO. This was due to the importance of international consistency and, in the Japanese data, the mean fasting plasma glucose level corresponding to a 75 g OGTT 2-h value of 200 mg/dl (11.1 mmol/l) is approximately 125 mg/dl (6.9 mmol/l) in patients under the age of 60 years [45, 53].

When viewed with reference to domestic and overseas cross-sectional survey decile method data, in contrast, the risk of retinopathy apparently increases with a fasting plasma glucose level of 140 mg/dl (7.8 mmol/l), an OGTT 2-h value of 230–240 mg/dl (12.8–13.3 mmol/l) or a HbA1c of 6.9%, and some studies claim that these levels should be used as the reference values for determining the diabetic type [8, 54]. That is, the current reference values of fasting plasma glucose level ≥126 mg/dl (≥7.0 mmol/l) and OGTT 2-h value ≥200 mg/dl (≥11.1 mmol/l) may be set too low from the point of view of apparent retinopathy risk. However, these reference standards have been adopted because: (i) reference values to determine diabetic type need to conform to international reference values as far as possible; and (ii) the aforementioned data by decile method are from a cross-sectional survey, and it seems preferable to begin treatment before the risk of retinopathy markedly increases and to prevent hyperglycemia from reaching that level.

Casual plasma glucose level ≥200 mg/dl (≥11.1 mmol/l) was added to the determination of diabetic type. This is because plasma glucose measured 1.5–3 h after eating exceeding 200 mg/dl (11.1 mmol/l) usually reflects a more severe degree of glucose metabolism disorder than a 75 g OGTT 2-h value of 200 mg/dl (11.1 mmol/l), or higher, and casual plasma glucose levels often do not reach 200 mg/dl (11.1 mmol/l), even if the OGTT indicates a diabetic type [4, 5]. For these reasons, the combined use of HbA1c measurement and another method other than casual plasma glucose level is recommended for diabetes mellitus screening and early diagnosis.

Diagnosis of "diabetes" by fasting plasma glucose level and oral glucose tolerance test

Diabetic type can be determined by fasting plasma glucose level or OGTT 2-h value or HbA1c. In the Japanese health screening data, determining the diabetic type from OGTT 2-h value alone results in a greater frequency of diabetic type than by determination using the fasting plasma glucose level alone. However, the reverse can also be true depending on the country. Assessment results according to these two reference values in each individual are frequently discordant [55]. From a pathophysiological viewpoint, fasting plasma glucose level is primarily determined by glucose output from the liver, while OGTT 2-h value is affected by the absorption rate of glucose from the gut, the utilization rate of glucose by muscle and other peripheral tissues, and changes in glucose handling by the liver. It is thus conceivable that fasting plasma glucose level and OGTT 2-h value do not increase in parallel in some patients.

In the Japanese population, it is common for an increase in the OGTT 2-h value to precede an increase in the fasting plasma glucose level. Therefore, to actively detect mild glucose metabolism disorders, a fasting plasma glucose level alone is insufficient, and performing the OGTT is important. Measuring insulin levels at the same time is very useful to understand the clinical condition and predict future onset of diabetes mellitus, and is strongly recommended.

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Predictors of coronary heart disease in Japanese patients with type 2 diabetes: Screening for coronary artery stenosis using multidetector computed tomography

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ABSTRACT

Aims/Introduction: Multidetector computed tomography (MDCT) coronary angiography has been applied as a tool for non-invasive evaluation of the coronary arteries. The purpose of the present study was to evaluate the effectiveness of MDCT in screening for coronary artery disease (CAD), and to identify the indications for screening in diabetes patients with CAD.

Materials and Methods: The study population consisted of 52 Japanese type 2 diabetes patients who underwent examination with a 64-slice MDCT scanner, electrocardiogram (ECG), echocardiography and ultrasonographic scanning of the carotid arteries. Regression analysis was carried out to assess the correlation between MDCT results and CAD risk factors.

Results: Stenosis of the coronary artery was detected in 19/52 patients. Of the 19 patients, 7 patients had no symptoms, including chest pain, and no ischemic changes in ECG. Significant differences between patients with stenosis and those without stenosis were detected by mean IMT (1.21 *vs* 0.95 mm), and duration of diabetes (20 *vs* 13 years). Two-tailed χ^2-test showed that a duration of diabetes of more than 20 years (odds ratio 6.222) and more than 1.1 mm of mean-IMT (odds ratio 4.600) significantly correlated with the stenosis.

Conclusions: It was shown that MDCT is useful in detecting coronary artery stenosis in diabetic patients without symptoms of CAD or ECG abnormality, and the predictors of CAD are mean IMT and duration of diabetes. It is recommended that patients with more than 1.1 mm mean IMT at the carotid artery and/or more than 20 years duration of diabetes should be screened for CAD by carrying out MDCT. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2009.00003.x, 2010)

KEY WORDS: Cronary artery disease, Multidetector computed tomography, Silent myocardial ischemia

INTRODUCTION

In 2007, 246 million people had diabetes worldwide, and its prevalence is expected to continue increasing. A close relationship between type 2 diabetes and the development of atherosclerosis exists, and type 2 diabetes is associated with a two to fourfold increase in coronary artery disease (CAD)[1]. In fact, cardiovascular disease is the leading cause of death in this patient population. Myocardial ischemia in patients with diabetes is often asymptomatic and frequently in an advanced stage when it becomes clinically manifest. Once CAD is symptomatic in patients with diabetes, morbidity and mortality are high and significantly worse than those in patients without diabetes. Therefore, early identification of CAD is of paramount importance in patients with diabetes[2–4].

Non-invasive tests, including electrocardiogram (ECG), echocardiography and myocardial perfusion scintigraphy, have been used to detect CAD in diabetic patients. Nonetheless, after normal findings of the tests, elevated event rates are still observed in diabetic patients compared with non-diabetic individuals. Furthermore, direct visualization of the coronary arteries is preferred because patients with diabetes frequently have diffuse, multivessel CAD. Although conventional angiography is carried out to evaluate the presence and extent of CAD, this is an invasive approach associated with a minimal but definitive risk of complications. Therefore, non-invasive techniques, which are capable of directly visualizing the coronary arteries, are required for further refinement of prognostication in diabetes patients[2].

Recently, contrast-enhanced multidetector computed tomography (MDCT) coronary angiography has been shown to be a

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tool for non-invasive visualization of the coronary arteries. MDCT permits the detection of coronary lesions with high sensitivity and specificity, which could be valuable for preventing risk during examination[5–9]. Furthermore, MDCT is useful for the evaluation of coronary plaque characteristics[10]. The purpose of the present study was to evaluate the indication of MDCT for the screening of CAD, especially asymptomatic CAD, and to identify the predictors of CAD in Japanese patients with type 2 diabetes.

MATERIALS AND METHODS

Subjects

Between June 2006 and December 2007, 56 patients with type 2 diabetes were enrolled for the present study. The inclusion criteria were: (i) diabetes was diagnosed according to the American Diabetes Association criteria[11]; (ii) absence of a history of myocardial infarction; (iii) absence of renal failure (serum creatinine >1.5 mg/dL [114 mol/L]); and (iv) absence of an allergic history to iodinated contrast media. The enrolled patients satisfied all criteria ($n = 56$). Four patients were excluded because they manifested arrhythmia or tachycardia of more than 75 b.p.m. ($n = 3$), and severe calcification of coronary arteries that caused blooming artifacts and obscured over 75% of the entire vessel lumen in the proximal segment of the coronary artery ($n = 1$). Consequently, 52 patients were available for the assessment, they were 37 men and 15 women ranging in age from 34 to 81 years (mean 66.2 ± 11.8 years). The present study was approved by the ethical committee of Kumamoto University School of Medicine. Informed consent was obtained from each patient.

Physical examinations were carried, and blood and urine samples were obtained from patients for laboratory testing. A resting 12-lead ECG was recorded, and we determined Q-wave myocardial infarction, ischemic ST-segment change (horizontal and downsloping ST-segment depression of over 0.3 mV or ST-segment elevations of more than 0.1 mV) or T-wave change were determined to be 'ischemic change positive'. Ankle-brachial blood pressure index (ABI) and pulse wave velocity (PWV) were measured using an automatic waveform analyzer (BP-203RPEII, Colin, Komaki, Japan). Ultrasonographic scanning of the carotid arteries was carried out using an echotomographic system (SDU-2200, Shimadzu, Kyoto, Japan) and carotid intima-media thickness (IMT) was measured as described previously[12]. Echocardiography (Vivid-7, GE-Vingmed, Milwaukee, WI, USA and SSA-770A, Toshiba Medical Systems, Tokyo, Japan) was also carried out. Wall motion was analyzed using the 17-segment model and evaluated by a four-point scale according to the guideline[13].

MDCT Data Acquisition and Analysis

Each patient received an additional oral beta-blocker (metoprolol, 20 mg, single dose) 2–3 h before examination and 0.3 mg of nitroglycerin (Nitropen, Nippon Kayaku, Tokyo, Japan) sublingually 5 min before scanning. All patients were scanned in the supine position during a single breath-hold with inspiration during scanning on a 64-detector computed tomography (CT) scanner (Brilliance-64, Philips Medical Systems, Cleveland, OH, USA). In all patients, Iohexol-350 (Omnipaque-350, Daiichi-Sankyo, Tokyo, Japan) was delivered through a 20-gauge catheter inserted into an antecubital vein and a power injector (Autoenhance A-250, Nemoto Kyorindo, Tokyo, Japan).

We used the test-bolus technique to synchronize the arrival of contrast media (CM). This technique is based on the intravenous injection of a small amount (10 mL) of contrast material during the acquisition of a series of dynamic low-dose (120 kV, 20 mAs) monitoring scans at the level of the ascending aorta. The time interval between each monitoring scan acquisition was 1 s. Acquisition of the dynamic monitoring scans started 5 s after the beginning of the injection of intravenous contrast material (10 mL of CM injected at 5 mL/s). A region of interest (ROI) was drawn inside the ascending aorta to generate an enhancement curve (generated by Test Injection Bolus Timing Application, Philips Medical Systems), which showed the time needed to reach the peak of maximum enhancement for the test-bolus. We selected the delay applied for angiographic scanning as 3 s after the time of peak enhancement at the test-bolus in the ascending aorta. Our contrast injection protocol was a patient bodyweight (BW)-tailored small contrast dose protocol, 0.7 mL/kg BW of CM at a fixed injection duration of 9 s.

The scan parameters were as follows: detector collimation 64 × 0.625 mm, 11.9 mm/s table feed, 0.20 helical pitch (beam pitch), 420 msec tube rotation time, 120 kV tube voltage, 900 mAs tube current time-product. Depending on the cardiac dimensions, the scanning time varied from 6 to 8 s. Image reconstruction was in a 16.5–20.0-cm display field-of-view depending on the patient's physique. All scans started at the upper end of the coronary sinus in a craniocaudal direction. We reconstructed axial images with a section thickness of 0.67 mm, a section interval of 0.33 mm, and a 16.5–20.0-cm display field-of-view depending on the patient's physique using a medium cardiac kernel (XCB) with ECG gating. Initially, a single data set was reconstructed during the mid-diastolic phase (75% of the R-wave to R-wave interval). In cases with unsatisfactory image quality, image reconstruction of the raw data was carried out at 0, 10, 20, 30, 40, 50, 60, 70, 80 and 90% of the R-wave to R-wave interval to improve the image quality of all available coronary segments.

Together, two board-certified radiologists (TN and KA) with 5 and 7 years of experience interpreting cardiac CT analyzed the generated images on the same workstation (ZAIO. M900®, ZAIO Software, Tokyo, Japan). Both were blinded to the patients' clinical information. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification[14]. The presence of coronary lesions was evaluated visually using a volume rendering view, angiographic view, curved multiplanar reconstructions and a cross-sectional image. Plaques were classified as stenosis and no stenosis using a 75% threshold of luminal narrowing, and one coronary plaque was

assigned per coronary segment. Interobserver disagreement was solved by consensus of the two radiologists.

Statistical Analysis

Continuous variables are described as means and standard error. Categorical data are presented with absolute frequencies and percentages. Unpaired *t*-tests were carried out to evaluate differences between patient groups or samples. Values of $P < 0.05$ were considered to show statistically relevant differences.

A forward stepwise logistic-regression procedure was then carried out to adjust CAD risk factors with the use of covariates that were found to be significant predictors of MDCT detecting stenosis. Furthermore, to identify the threshold value of each significant predictor, two-tailed χ^2-test was used for each variable and the odds ratios were calculated by cross-tabulation. We carried out further receiver operating characteristics (ROC) curve analyses to evaluate the sensitivity and specificity of IMT and the duration of diabetes on MDCT detecting stenosis. Statistical analyses were carried out using computer software (SigmaStat for Windows version 3.5, Systat Software, Chicago, IL, USA).

RESULTS

The patient characteristics are summarized in Table 1. The study group consisted of 52 patients with type 2 diabetes (age 66.2 ± 11.8 years; 37 men; BMI 24.7 ± 4.2; glycated hemoglobin [HbA1c] 7.9 ± 1.7%). The average duration of diabetes was 15.9 ± 10.8 years at the time of MDCT. A total of 36 patients received oral hypoglycemic medication and 17 patients received insulin.

In MDCT, stenosis of coronary arteries was detected in 19/52 patients (36.5%). Of the 19 patients, one-vessel disease was identified in 12 patients, two-vessel disease in four patients, and three-vessel disease in three patients. Accidents during MDCT or side-effects as a result of contrast material were not detected in the present study.

Table 1 | Patient characteristics

Age (years)	66.2 ± 11.8
Male/female	37/15
Body mass index (kg/m^2)	24.7 ± 4.2
Duration of diabetes (years)	15.9 ± 10.8
Smoking (+/–)	26/26
Diabetes therapy (insulin/oral agents)	17/36
Glycated hemoglobin (%)	7.9 ± 1.7
Systolic blood pressure (mmHg)	132 ± 21
Diastolic blood pressure (mmHg)	72 ± 12
LDL-cholesterol (mg/dL)	124 ± 39
HDL-cholesterol (mg/dL)	52 ± 15
Triglyceride (mg/dL)	133 ± 94
Oral agents for hypertension (+/–)	34/18
Statins (+/–)	19/33

Data are mean ± SE or *n*.
HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2 | Correlation between multidetector computed tomography results and electrocardiogram or echocardiography

	n	Echocardiography LV dysfunction (+) (*n* = 3)		Echocardiography LV dysfunction (–) (*n* = 49)	
		ECG positive (*n* = 2)	ECG negative (*n* = 1)	ECG positive (*n* = 19)	ECG negative (*n* = 30)
MDCT stenosis	19	2	1	8	8
MDCT No stenosis	33	0	0	11	22

ECG, electrocardiogram; LV, left ventricular; MDCT, multidetector computed tomography results.

The correlation between MDCT and symptoms, ECG, and echocardiography are provided in Tables 2 and 3. Of the 19 patients who had stenosis detected by MDCT, eight patients (42%) were identified with neither a positive ischemic change in ECG nor a wall motion abnormality in echocardiography (Table 2). Thirteen patients (25% of 52 patients) who had no symptoms of ischemic heart disease (IHD) had coronary artery stenosis detected by MDCT, indicating the presence of silent myocardial ischemia. More importantly, of the 19 patients with stenosis, seven patients (37%) had no symptoms, including chest pain, nor ischemic changes in ECG (Table 3). These data indicate the high prevalence of asymptomatic ischemia in diabetes patients and the usefulness of MDCT for the screening of silent ischemic heart disease in diabetes patients.

The comparison of the patient characteristics and clinical variables between MDCT stenosis detection and no MDCT stenosis detection are presented in Table 4. Interestingly, there were no significant differences in age (69 ± 8 years in stenosis *vs* 64 ± 13 years in no stenosis, $P = 0.061$), blood pressure (131 ± 22/72 ± 13 mmHg *vs* 133 ± 20/72 ± 11 mmHg), serum low density lipoprotein (LDL)-cholesterol (123 ± 44 mg/dL *vs*

Table 3 | Correlation between multidetector computed tomography results and electrocardiogram or presence of symptoms

	n	Symptomatic (*n* = 11)		Asymptomatic (*n* = 41)	
		ECG positive (*n* = 6)	ECG negative (*n* = 5)	ECG positive (*n* = 15)	ECG negative (*n* = 26)
MDCT stenosis	19	4	2	6	7
MDCT No stenosis	33	2	3	9	19

ECG, electrocardiogram; MDCT, multidetector computed tomography.

Table 4 | Comparisons between patients with multidetector computed tomography detected stenosis and those without stenosis

	MDCT stenosis	MDCT no stenosis	*P*-value
n	19	34	–
Age (years)	69 ± 8	64 ± 13	0.061
Duration of diabetes (years)	20 ± 11	13 ± 10	0.008*
Glycated hemoglobin (%)	8.1 ± 1.8	7.7 ± 1.7	0.240
Blood glucose (2 h, mg/dL)	257 ± 89	256 ± 108	0.482
eGFR (mL/min/1.73 m^2)	64.9 ± 25.3	74.8 ± 20.6	0.066
Systolic blood pressure (mmHg)	131 ± 22	133 ± 20	0.379
Diastolic blood pressure (mmHg)	72 ± 13	72 ± 11	0.483
LDL-cholesterol (mg/dL)	123 ± 44	126 ± 37	0.388
HDL-cholesterol (mg/dL)	55 ± 14	51 ± 15	0.195
Triglyceride (mg/dL)	115 ± 63	144 ± 109	0.144
Urinary albumin excretion (mg/gCre)	80.7 ± 149.6	83.1 ± 167.2	0.481
ABI	1.10 ± 0.15	1.12 ± 0.10	0.311
PWV (cm/s)	1917 ± 323	1899 ± 433	0.411
Mean IMT (mm)	1.21 ± 0.44	0.95 ± 0.26	0.007*

Data are mean ± SE and *n*. * $P < 0.05$ by unpaired *t*-test and Mann–Whitney *U*-test.
ABI, ankle brachial index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; IMT, intima-media thickness; LDL, low density lipoprotein; MDCT, multidetector computed tomography; PWV, pulse wave velocity.

126 ± 37 mg/dL, $P = 0.388$), serum high density lipoprotein (HDL)-cholesterol (55 ± 14 mg/dL *vs* 51 ± 15 mg/dL, $P = 0.195$), urinary albumin excretion (80.7 ± 149.6 mg/g creatinin *vs* 83.1 ± 167.2 mg/g creatinin, $P = 0.481$), estimated glomerular filtration rate (eGFR) (64.9 ± 25.3 mL/min/1.73m^2 *vs* 74.8 ± 20.6 mL/min/1.73m^2, $P = 0.066$) and PWV (1917 ± 323 cm/s *vs* 1899 ± 433 cm/s, $P = 0.411$) between the patients with stenosis and those with no stenosis. Significant differences were detected in mean IMT (1.21 ± 0.44 mm in stenosis *vs* 0.95 ± 0.26 mm in no stenosis, $P = 0.007$) and duration of diabetes (20 ± 11 years *vs* 13 ± 10 years, $P = 0.008$).

To identify the correlation between the presence of stenosis of coronary arteries on MDCT and CAD risk factors, we carried out forward stepwise logistic regression analysis (Table 5).

Table 5 | Independent predictors of coronary artery stenosis by multiple logistic regression analysis

	Odds ratio	95% CI	*P*-value
Duration of diabetes (per year)	1.157	1.034–1.294	0.011
Statin (yes *vs* no)	9.867	1.655–58.882	0.012
Mean IMT (per 0.1 mm)	1.359	1.018–1.814	0.038

IMT, intima-media thickness.

Although a significant correlation was not found between MDCT detecting stenosis and age, BMI, HbA1c, eGFR, diastolic blood pressure, serum LDL- and HDL- cholesterol concentrations, triglyceride, urine-microalbumine, ABI or PWV, the correlation of MDCT detecting stenosis and duration of diabetes, medication of statin and mean-IMT of carotid artery remained statistically significant after correction for baseline characteristics. The dependent variable of MDCT detecting stenosis can be predicted from a linear combination of the independent variables as follows: (i) duration of diabetes ($P = 0.004$), (ii) treatment with statin ($P = 0.029$); and (iii) mean IMT ($P = 0.023$). The odds ratio of these predictors were 1.157 (95% CI 1.034–1.294, $P = 0.011$) in duration of diabetes (per year), 9.867 (95% CI 1.655–58.882, $P = 0.012$) in treatment with statin, 1.359 (95% CI 1.018–1.814, $P = 0.038$) in mean IMT (per 0.1 mm) by multiple logistic regression analysis.

DISCUSSION

In the present study, it was shown that symptomatic or asymptomatic CAD in type 2 diabetes patients can be diagnosed non-invasively by the use of MDCT. The population of the present study group was considered to be representative of Japanese diabetic patients,[15] although the BMI had a tendency to be lower compared with other studies of Caucasian patients[3,16]. The patients in the present study were receiving contemporary medical treatment and were under almost reasonable metabolic control (blood pressure 132 ± 21/72 ± 12 mmHg, LDL-cholesterol 124 ± 39 mg/dL, HDL-cholesterol 52 ± 15 mg/dL, triglyceride 133 ± 94 mg/dL), although HbA1c (7.9 ± 1.7%) was considered to be higher.

Previous studies reported that both sensitivity and specificity of MDCT were high enough for the diagnosis of coronary artery stenosis to be made[5,7,8]. Continuous modification of hardware, scan protocol and renewing scanner generation has led to a significant stabilization and improvement of image quality[17]. Recently, studies using 64-slice scanners have been reported, showing a more accurate assessment for the diagnosis of CAD and characteristics of plaque[10,18,19]. However, several general limitations of MDCT, including the administration of an iodinated contrast agent and elevated radiation dose, should be mentioned. In the present study, we generated a protocol to carry out MDCT with less iodinated agent and lower radiation exposure.

In the present study group, 13 patients (25.0% of 52 patients) who had no symptoms of IHD had coronary artery stenosis detected by MDCT. Wackers *et al.* indicated that 133/522 patients with diabetes (25.5%) were diagnosed with silent myocardial ischemia using adenosine technetium-99m sestamibi single photon emission-computed tomography myocardial perfusion imaging[3]. The prevalence of MDCT detecting stenosis detection without IHD symptoms in the present study was similar to those of previous reports, suggesting that MDCT is useful in screening for silent ischemia in patients with diabetes. Furthermore, of 19 patients who had coronary artery stenosis

detected by MDCT, seven patients had neither positive ischemic change in rest ECG nor symptoms of IHD. For diagnosis of CAD, exercise ECG is the most commonly applied non-invasive test. However, Dewey *et al.* reported that both sensitivity and specificity of MDCT were significantly higher than those of exerciseECG[8]. It was also reported that exercise ECG had a certain risk, the most relevant being myocardial infarction or death which have been confirmed in multiple surveys to occur in approximately 10/10 000 tests[20]. Taken together, it is suggested that the MDCT is effective for the screening of CAD, especially silent myocardial ischemia.

It was reported that the incidences of coronary heart disease (CHD), per 1000 patients per year, among Japanese diabetes patients were 9.8 in men and 5.5 in women,[21] although that of CHD among Caucasian diabetes patients was 17.4[22]. The prevalence of CAD in type 2 diabetes in the Caucasian population has been reported to be 30–40%[4,10]. In the present study, even the incidence of CHD in Japanese type 2 diabetes patients was much lower than that of Caucasian patients, as 19/52 patients (36.5%) had coronary artery stenosis detected by MDCT. Therefore, it is thought that MDCT might detect more CAD in type 2 diabetes patients in the Caucasian population.

Another important finding of the present study is the assessment of the predictors of MDCT detecting stenosis in diabetes patients. In the guidelines for early detection of CHD in asymptomatic patients with diabetes from the American Diabetes Association (ADA), the presence of multiple cardiovascular risk factors including LDL-cholesterol, HDL-cholesterol, blood pressure, micro-/macroalbuminuria is mentioned[2]. In the analysis of risk factors that contribute to CHD risk in diabetic patients in the United Kingdom Prospective Diabetes Study, LDL-cholesterol, HDL-cholesterol, blood pressure and HbA1c were reported to be important[22,23]. However, in the present study, significant differences were not detected in blood pressure, LDL-cholesterol, HDL-cholesterol, triglyceride, blood glucose, HbA1c, microalbuminuria, ABI or PWV between the MDCT detected stenosis and MDCT detecting no stenosis groups. The reason why there is no significant difference in these markers between MDCT detecting stenosis and MDCT detecting no stenosis groups might be a result of the limited number of subjects in our study group. With regard to blood pressure, it was also possible that aggressive blood pressure control using calcium channel blockers, angiotensin II receptor inhibitors, etc. in both MDCT detecting stenosis and MDCT detecting no stenosis groups led to no significant difference. We could not find a significant correlation between oral agents for hypertension and MDCT detecting stenosis. In addition, there was no significant difference in the presence/absence of diabetic retinopathy between the MDCT detecting stenosis and MDCT detecting no stenosis groups (data not shown). In contrast, significant differences were detected in mean IMT and duration of diabetes between MDCT detecting stenosis and MDCT no stenosis groups in the present study. The data of multiple logistic regression analysis indicated that the predictors of MDCT detecting stenosis were mean IMT, treatment with statin and duration of diabetes. This multiple regression analysis showed that the administration of statin is a predictor of MDCT detecting stenosis although the LDL-cholesterol is not. These results indicate that the subjects with diabetes and dyslipidemia, who were given statin and had relatively lower LDL-cholesterol levels, still were at risk of having coronary artery stenosis. Furthermore, to determine the threshold value of the duration of diabetes and mean IMT at the carotid artery for the prediction of MDCT detecting stenosis, two-tailed χ^2-test was used for each variable and the odds ratios were calculated by cross-tabulation, with a 95% CI. More than 20 years of duration of diabetes significantly correlated with the detection of stenosis of coronary arteries by MDCT (odds ratio 6.222 [95% CI 1.679–23.064, $P = 0.011$], sensitivity 0.474, specificity 0.805), and more than 1.1 mm of mean IMT in carotid arteries significantly correlated with MDCT detecting stenosis (odds ratio 4.600 [95% CI 1.207–17.525, $P = 0.047$], sensitivity 0.500, specificity 0.833). Recently, the American Heart Association reported that routine surveillance with MDCT in asymptomatic patients at low risk for IHD was not recommended[24]. The results of this study indicated that the type 2 diabetic patients with longer duration of diabetes or increased thickness of mean IMT in carotid arteries have a high risk of IHD. Thus, it is recommended that diabetic patients with more than 1.1 mm mean IMT in the carotid arteries and/or more than 20 years duration of diabetes should receive MDCT for screening of CAD even though they are in good control of blood pressure and lipid metabolism.

Several limitations of the present study should be mentioned. In the present study, 52 patients were included, and examinations were carried out at a single time-point and were not repeated over time. Prospective studies with larger patient cohorts are required.

In summary, it was shown that MDCT detects coronary artery stenosis in diabetic patients without symptoms of IHD or ECG abnormality. From the data of the present study, the predictors of CAD in Japanese type 2 diabetes patients were mean IMT and duration of diabetes. Thus, MDCT is a non-invasive, effective method to detect or rule out CAD, especially silent myocardial ischemia in patients with diabetes, and it is recommended that patients with more than 1.1 mm mean IMT at the carotid artery and/or more than 20 years duration of diabetes should be screened for CAD.

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Optimal cut-off point of waist circumference for the diagnosis of metabolic syndrome in Japanese subjects

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ABSTRACT

Metabolic syndrome (MetS) has been redefined by a new criterion in Japan, in which waist circumference cut-off points, that is 85 cm for men and 90 cm for women, are used; however, objections are rising against this criterion. The present study examined the criterion for waist circumference to predict the accumulation of the components of MetS. In the present study, we used data for 5972 Japanese people who received annual health examinations, and 621 men (16.3%) and 51 women (2.4%) were diagnosed as having MetS. A cut-off point as a predictor for two or more components of MetS was evaluated by the sensitivity/specificity and a receiver operating characteristic analysis. The optimal point of waist circumference was estimated as being approximately 84 cm for men and 80 cm for women. We therefore recommend revising the cut-off value for the criterion of MetS in women according to our results and studies from other investigators. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00020.x, 2010)

KEY WORDS: Metabolic syndrome, Waist circumference, Cut-off point

INTRODUCTION

Metabolic syndrome (MetS), which is defined by multiple risk factors, including central obesity, high blood pressure, dyslipidemia, and high fasting blood glucose; and persons with MetS have an elevated risk of developing cardiovascular disease (CVD), which is correlated with all-cause mortality[1]. Because the morbidity and mortality of CVD is rapidly increasing worldwide[2], establishing appropriate screening for MetS is essential to prevent the initiation and progression of CVD.

To date, internationally recognized definitions of MetS have been released, namely the criteria of the World Health Organization (WHO)[3], the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III)[4], and the International Diabetes Federation (IDF)[5]. In Japan, a criterion for MetS has been defined as the presence of central obesity (85 cm for men and 90 cm for women) plus any two of the following three factors; (i) dyslipidemia; (ii) high blood pressure; and (iii) impaired fasting glucose[6]. In contrast, the IDF recommended cut-off levels of 90 cm for men and 80 cm for women for central obesity in Asian individuals[5]. There has been controversy as to which of these cut-off points of waist circumference is better for diagnosing central obesity in Japanese men and women. The aim of the present article is to re-evaluate the waist circumference for detecting the risk factor accumulation of MetS in Japanese subjects.

SUBJECTS AND METHODS

The total number of participants in the present study was 5972 (3811 men and 2161 women), aged 20–79 years, who received annual health examinations at Okayama Red Cross General Hospital with informed consent. We measured waist circumference at the umbilical level. MetS was defined among men and women as waist circumferences in excess of 85 cm and 90 cm[6], respectively, in addition to having two or more of the following components: (i) dyslipidemia: triglycerides ≥ 150 mg/dL and/or HDL cholesterol <40 mg/dL; (ii) high blood pressure: blood pressure ≥ 130/85 mmHg; and (iii) impaired fasting glucose: fasting plasma glucose ≥ 110 mg/dL[6]. If an individual was receiving drug therapy for hypertriglyceridemia, low HDL cholesterol, high blood pressure or diabetes mellitus, each item was recorded as a positive finding regardless of the data. To identify the optimal cut-off point of waist circumference as a predictor of the presence of at least two components comprising the MetS, we carried out receiver operating characteristic (ROC) analysis. The statistical software SPSS for Windows (version 8.0; SPSS, Chicago, IL, USA) was used for the analysis.

RESULTS

The mean age of the study subjects was 49.9 ± 10.1 years for men and 48.6 ± 9.4 years for women. Among the 5972 Japanese subjects, 1744 men (45.8%) had a waist circumference in excess of 85 cm and 216 women (10.0%) had a waist circumference

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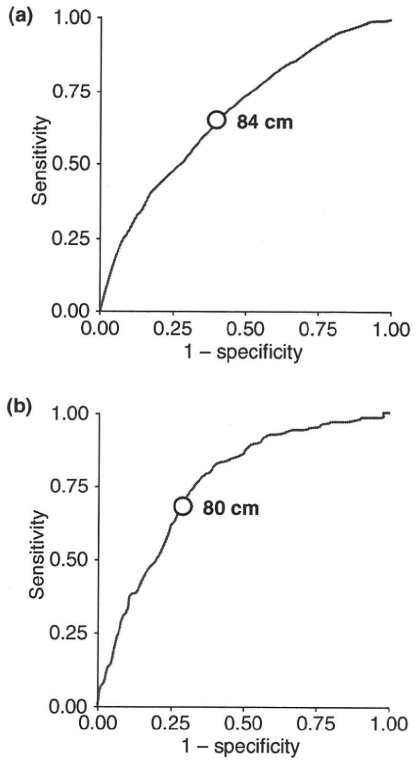

Figure 1 | Receiver operating characteristic (ROC) curve of waist circumference for detecting two or more risk factors of the metabolic syndrome in (a) men and (b) women. O, Cut-off waist circumference yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors.

exceeding 90 cm. In addition, the prevalence of MetS according to the Japanese diagnostic criteria was 621 (16.3%) for men and 51 (2.4%) for women.

We investigated the sensitivity and specificity of waist circumference in predicting the association with two or more metabolic risk factors; that is dyslipidemia, high blood pressure and impaired fasting glucose. In men, the sensitivity and specificity of the waist circumference criterion, that is 85 cm, were 64.2% and 60.2%, respectively. However, in women, the sensitivity and specificity of waist circumference criterion, that is 90 cm, were found to be 29.3% and 91.5%, respectively. A cut-off point as a predictor for two or more components of MetS was evaluated by sensitivity/specificity curves, as well as a ROC curve. The optimal point yielding the maximal sensitivity plus specificity for predicting two or more risk factors was estimated to be approximately 84 cm (sensitivity: 66.3%, specificity: 59.4%) of waist circumference for men and 80 cm (sensitivity: 69.0%, specificity: 65.4%) for women (Figure 1). Based on these findings, 1966 men (51.6%) and 718 women (33.2%) had a waist circumference exceeding 84 cm and 80 cm, respectively. In addition, 675 men (17.7%) and 119 women (5.5%) were diagnosed as having MetS by using 84 cm for men and 80 cm for women as the waist circumference criterion.

DISCUSSION

The IDF has used a waist circumference cut-off value of 90 cm for men and 80 cm for women as its diagnostic criteria of MetS for Asians[5]. In contrast, the waist circumference cut-off value for Japanese was 85 cm for men and 90 cm for women, which correspond to 100 cm^2 of intraperitoneal visceral fat in a cross-section at the height of the navel as shown by computed tomography (CT) both for men and women[6]. To address this controversial point, we re-evaluated the cut-off points of waist circumference for the diagnosis of MetS using ROC analysis. We proposed that the optimal cut-off points are 84 cm for men and 80 cm for women for predicting the clustering of the components of MetS. In men, the criterion of waist circumference deduced from the present study was matched to that of the criterion of MetS in Japan. However, in women, the cut-off value of waist circumference in the present study was lower than that of the criterion.

The first report that estimated the waist circumference cut-off value for diagnosis of MetS in Japan was a study of 3574 employees of a telephone company and their family members (2947 men and 627 women). It estimated the optimal cut-off value for the intraperitoneal visceral fat area at the height of the navel, as determined by CT, to be 100 cm^2 for men and 65 cm^2 for women. Based on these findings, the corresponding cut-off value for waist circumference is 86 cm for men and 77 cm for women[7]. Hara *et al.* also calculated the optimal cut-off point of waist circumference among 692 healthy subjects (408 men and 284 women). and the value of 85 cm for men and 78 cm for women yielded the maximal sensitivity plus specificity for predicting the presence of multiple risk factors[8]. Other studies also reported that the optimal cut-off point for men ranges from approximately 85 to 90 cm; however, in women it ranges from 77 to 83 cm, approximately 80 cm overall (Table 1)[9–15].

Table 1 | Reports on optimal cutoff point of waist circumference for the diagnosis of metabolic syndrome in Japan

Author (reference number)	No. subjects	Cut-off point for men (cm)	Cut-off point for women (cm)
Miyawaki T *et al.*[7]	3574	86	77
Hara K *et al.*[8]	692	85	78
Miyatake N *et al.*[9]	3185	85	80
Nishimura R *et al.*[10]	2113	85	81
Eguchi M *et al.*[11]	420	83	78
Narisawa S *et al.*[12]	12,725	87	83
Oka R *et al.*[13]	1870	89	82
Sato A *et al.*[14]	395	87	80
Doi Y *et al.*[15]	2452	90	80
Present study	5972	84	80

Table 2 | Reports on optimal cut-off point of waist circumference for the diagnosis of metabolic syndrome in Asian countries

Country (reference number)	No. subjects	Cut-off point for men (cm)	Cut-off point for women (cm)
Singapore[16]	4723	90	80
India[17]	640	90	80
Korea[18]	6561	85	80
China[19]	1140	90	85
Korea[20]	31,076	83	76
Korea[21]	4677	84–86	78–80

The cut-off points of waist circumference for MetS suggested by the NCEP-ATP III (102 cm for men and 88 cm for women) are accepted in Western countries and there are no studies that consider whether the optimal cut-off value should be revised. In contrast, several studies that were carried out in Asian countries show that the cut-off values should be lower than those of the NCEP-ATP III (Table 2)[16–21]. Although the cut-off values are defined by the IDF for Asian populations as 90 cm for men and 80 cm for women, several studies from Korea[18,20,21] and China[19] suggest that the optimal cut-off points are different from those of the IDF. Taking these findings together with those of the studies from Japan (Table 1) and Asian countries (Table 2), ethnic differences are likely to exist between populations across Asia, and the criteria for defining MetS in Japan needs to be revised.

The present study has potential limitations. First, the subjects enrolled in our study chose to undergo annual health examinations; they were therefore more health-conscious than average, which might have caused some bias in the current study. Second, the cross-sectional study design makes it difficult to infer causality between waist circumference and metabolic risk factors. Finally, it is still controversial whether or not the waist circumference cut-off values of MetS are significant predictors of cardiovascular events. McNeil *et al.* assessed the association between MetS, using the NCEP III definition, and CVD with an 11-year follow-up period, and they reported that waist circumference is not a significant predictor for CVD[22]. Therefore, our findings are not fully applicable to clinical and public health practice settings. Further studies are needed to prospectively relate the accumulation of visceral fat to the presence of risk factors of CVD.

In conclusion, although follow-up studies are required to prove the feasibility of the definition of MetS to predict the development of CVD, the cut-off value of waist circumference as a criterion for MetS in Japan should be 80 cm for women based on the present results and a review of the literature.

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Association of resistin polymorphism, its serum levels and prevalence of stroke in Japanese type 2 diabetic patients

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ABSTRACT

Aims/Introduction: Resistin, an inflammatory cytokine, might be involved in the development of atherosclerosis. In a recent paper, we showed that resistin polymorphism might be a risk marker for stroke susceptibility in Japanese type 2 diabetic patients. We tested whether the serum resistin levels might be also a risk marker of stroke independently from *RETN* polymorphism.

Materials and Methods: Type 2 diabetic outpatients from our hospitals were enrolled. Patients (n = 89) with a history of coronary heart disease and stroke, and randomly selected controls (n = 178) matched for sex and age, but without a history of coronary heart disease and stroke, were examined for polymorphism -420 (C>G) and cytokines levels.

Results: Serum resistin levels were significantly higher in patients with cardiovascular diseases (CVD) than in those without CVD (P = 0.024), and were highest in patients with stroke among the CVD. In multiple logistic regression analysis, serum resistin levels was an independent risk marker of stroke even after adjusted by *RETN* polymorphism, age, sex, body mass index, HbA_{1c}, systolic and diastolic blood pressure, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, creatinine, history of coronary heart disease, treatment of insulin, sulfonylurea and aspirin (odds ratio 1.33, 95% confidence interval [CI] 1.02–1.73, P = 0.039). The enrolled patients were divided by their serum resistin levels (high or low group) and their genotypes (CC, CG, GG at -420) into six groups. Patients with the GG genotype and high resistin levels showed the highest odds ratio, 5.69 (95% CI 1.24–26.1), compared with the group with CC and low levels.

Conclusions: The results suggest that serum resistin levels might be a good marker of susceptibility to stroke as well as *RETN* polymorphism. (J Diabetes Invest, doi: 10.1111/j.2040-1124.00040.x, 2010)

KEY WORDS: Resistin, Type 2 diabetes, Stroke

INTRODUCTION

Resistin, an inflammatory cytokine expressed in human macrophages[1], has been reported to be elevated in subjects with obesity and inflammation[2,3]. It has direct action on the arterial wall[4,5] and might be involved in the development of atherosclerosis. Previously, the specific recognition of the -420G allele in the resistin gene (*RETN*) by Sp1/3 transcription factor was shown to increase its promoter activity[6]. The present authors and others have reported that serum resistin levels are increased in a genotype-dependent manner based on the *RETN* polymorphism at -420 (C>G)[7–9]. In a recent paper, the present authors have also shown that the genotyping of this polymorphism might provide a good risk marker for stroke susceptibility in Japanese type 2 diabetic patients[9]. However, there have been some conflicting reports that don't support a relationship between the blood resistin levels and susceptibility to cardiovascular diseases (CVD)[10–13]. In addition, not only genetic factors, but also systemic inflammation was suggested to affect the blood levels of resistin[14]. The aim of the present case–control study was thus to investigate, at first, the association between the serum resistin levels, inflammatory status and the prevalence of CVD, including coronary heart disease (CHD) and stroke, in Japanese type 2 diabetes patients. Therefore, we tested the serum resistin levels and *RETN* polymorphism at position -420 (C>G) as a risk marker of CVD.

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METHODS

Subjects

A total of 267 type 2 diabetic outpatients (89 cases, 179 controls) who were consecutive visitors to Nagoya University Hospital and Chubu Rosai Hospital were enrolled. Cases were defined as all participants who had previously suffered from CVD (CHD and stroke). Controls were defined as participants with no record of CVD. Controls were randomly selected 2:1 from the enrolled