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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REFERENCES

1. Luscher TF, Creager MA, Beckman JA, *et al.* Diabetes and vascular disease: pathophysiology, clinical consequences,

and medical therapy: Part II. *Circulation* 2003; 108: 1655–1661.
2. American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes: 10–11 February 1998, Miami, Florida. *Diabetes Care* 1998; 21: 1551–1559.
3. Wackers FJ, Young LH, Inzucchi SE, *et al.* Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care* 2004; 27: 1954–1961.
4. Kharlip J, Naglieri R, Mitchell BD, *et al.* Screening for silent coronary heart disease in type 2 diabetes: clinical application of American Diabetes Association guidelines. *Diabetes Care* 2006; 29: 692–694.
5. Bax JJ, Young LH, Frye RL, *et al.* Screening for coronary artery disease in patients with diabetes. *Diabetes Care* 2007; 30: 2729–2736.
6. Bax JJ, Inzucchi SE, Bonow RO, *et al.* Cardiac imaging for risk stratification in diabetes. *Diabetes Care* 2007; 30: 1295–1304.
7. Burgstahler C, Beck T, Reimann A, *et al.* Diagnostic accuracy of multislice computed tomography for the detection of coronary artery disease in diabetic patients. *J Diabetes Complications* 2007; 21: 69–74.
8. Dewey M, Dubel HP, Schink T, *et al.* Head-to-head comparison of multislice computed tomography and exercise electrocardiography for diagnosis of coronary artery disease. *Eur Heart J* 2007; 28: 2485–2490.
9. Raff GL, Gallagher MJ, O'Neill WW, *et al.* Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005; 46: 552–557.
10. Pundziute G, Schuijf JD, Jukema JW, *et al.* Noninvasive assessment of plaque characteristics with multislice computed tomography coronary angiography in symptomatic diabetic patients. *Diabetes Care* 2007; 30: 1113–1119.
11. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; 27: S5–S10.
12. Mitsuhashi N, Onuma T, Kubo S, *et al.* Coronary artery disease and carotid artery intima-media thickness in Japanese type 2 diabetic patients. *Diabetes Care* 2002; 25: 1308–1312.
13. Lang RM, Bierig M, Devereux RB, *et al.* Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440–1463.
14. Austen WG, Edwards JE, Frye RL,*et al.* A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; 51: 5–40.
15. Sone H, Yoshimura Y, Tanaka S, *et al.* Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes. Analysis from the Japan Diabetes Complications Study. *Diabetes Res Clin Pract* 2007; 77: S23–S29.
16. Wong ND, Rozanski A, Gransar H, *et al.* Metabolic syndrome and diabetes are associated with an increased likelihood of inducible myocardial ischemia among patients with subclinical atherosclerosis. *Diabetes Care* 2005; 28: 1445–1450.
17. Nieman K, Cademartiri F, Lemos PA, *et al.* Reliable noninvasive coronary angiography with fast submillimeter multislice spiral computed tomography. *Circulation* 2002; 106: 2051–2054.
18. Leschka S, Alkadhi H, Plass A, *et al.* Accuracy of MSCT coronary angiography with 64-slice technology: first experience. *Eur Heart J* 2005; 26: 1482–1487.
19. Hacker M, Jakobs T, Hack N, *et al.* Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenoses in patients with stable angina. *Eur J Nucl Med Mol Imaging* 2007; 34: 4–10.
20. Fletcher GF, Balady GJ, Amsterdam EA, *et al.* Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001; 104: 1694–1740.
21. Sone H, Mizuno S, Fujii H, *et al.* Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study. *Diabetes Care* 2005; 28: 1463–1471.
22. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837–853.
23. Turner RC, Millns H, Neil HA, *et al.* Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; 316: 823–828.
24. Gerber TC, Carr JJ, Arai AE, *et al.* Ionizing radiation in cardiac imaging. A science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation* 2009; 119: 1056–1065.

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.

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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

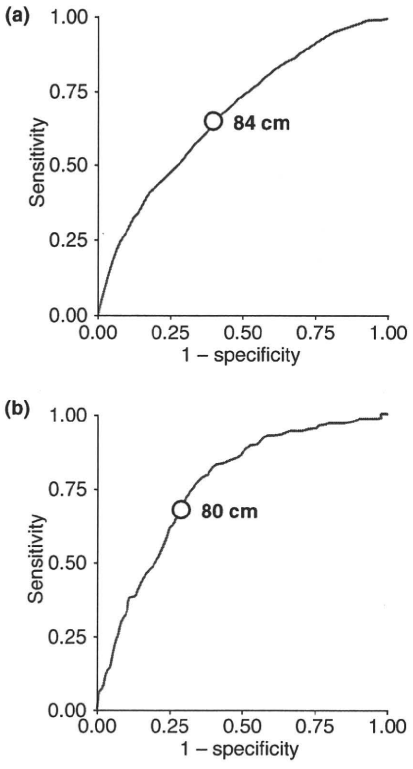

Figure 1 | Receiver operating characteristic (ROC) curve of waist circumference for detecting two or more risk factors of the metabolic syndrome in (a) men and (b) women. O, Cut-off waist circumference yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors.

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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REFERENCES

1. Lakka HM, Laaksonen DE, Lakka TA, *et al.* The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288: 2709–2716.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415–1428.
3. World Health Organization. *Definition, Diagnosis and Classification of Diabetes and its Complications: Report of a WHO Consultation*. WHO, Geneva, 1999.
4. Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). *JAMA* 2001; 285: 2486–2497.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469–480.
6. An examination committee for criterion of metabolic syndrome. Definition and criteria of metabolic syndrome. *Nippon Naika Gakkai Zasshi (in Japanese)* 2005; 94: 794–809.
7. Miyawaki T, Hirata M, Moriyama K, *et al.* Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad* 2005; 81 (Ser. B): 471–479.
8. Hara K, Matsushita Y, Horikoshi M, *et al.* A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; 29: 1123–1124.
9. Miyatake N, Wada J, Matsumoto S, Nishikawa H, Makino H, Numata T. Re-evaluation of waist circumference in metabolic syndrome: a comparison between Japanese men and women. *Acta Med Okayama* 2007; 61: 167–169.
10. Nishimura R, Nakagami T, Tominaga M, Yoshiike N, Tajima N. Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan. *Diabetes Res Clin Pract* 2007; 78: 77–84.
11. Eguchi M, Tsuchihashi K, Saitoh S, *et al.* Visceral obesity in Japanese patients with metabolic syndrome: reappraisal of diagnostic criteria by CT scan. *Hypertens Res* 2007; 30: 315–323.
12. Narisawa S, Nakamura K, Kato K, Yamada K, Sasaki J, Yamamoto M. Appropriate waist circumference cutoff values for persons with multiple cardiovascular risk factors in Japan: a large cross-sectional study. *J Epidemiol* 2008; 18: 37–42.
13. Oka R, Kobayashi J, Yagi K, *et al.* Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. *Diabetes Res Clin Pract* 2008; 79: 474–481.
14. Sato A, Asayama K, Ohkubo T, *et al.* Optimal cutoff point of waist circumference and use of home blood pressure as a definition of metabolic syndrome: the Ohasama study. *Am J Hypertens* 2008; 21: 514–520.

15. Doi Y, Ninomiya T, Hata J, *et al.* Proposed criteria for metabolic syndrome in Japanese based on prospective evidence: the Hisayama study. *Stroke* 2009; 40: 1187–1194.
16. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; 27: 1182–1186.
17. Misra A, Wasir JS, Pandey RM. An evaluation of candidate definitions of the metabolic syndrome in adult Asian Indians. *Diabetes Care* 2005; 28: 398–403.
18. Lee SY, Park HS, Kim DJ, *et al.* Appropriate waist circumference cutoff points for central obesity in Korean adults. *Diabetes Res Clin Pract* 2007; 75: 72–80.
19. Bao Y, Lu J, Wang C, *et al.* Optimal waist circumference cutoffs for abdominal obesity in Chinese. *Atherosclerosis* 2008; 201: 378–384.
20. Kim HK, Kim CH, Park JY, Lee KU. Lower waist-circumference cutoff point for the assessment of cardiometabolic risk in Koreans. *Diabetes Res Clin Pract* 2009; 85: 35–39.
21. Baik I. Optimal cutoff points of waist circumference for the criteria of abdominal obesity: comparison with the criteria of the International Diabetes Federation. *Circ J* 2009; 73: 2068–2075.
22. McNeill AM, Rosamond WD, Girman CJ, *et al.* The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 2005; 28: 385–390.

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

cohort in our hospitals after matching for sex and age. The assessment and definition of CVD were based on the following criteria. CHD was defined according to histories of physician-diagnosed ischemic heart disease. Strokes (ischemic cerebrovascular diseases) were diagnosed by means of neurological signs and symptoms, together with computed tomography or magnetic resonance imaging by neurologists. Only patients with a history of large vessel diseases and carotid stroke were enrolled, and patients with a history of cardioembolic and lacunar strokes were excluded. The study protocol and informed consent procedure were approved by the Ethics Committee of Nagoya University Graduate School of Medicine and Chubu Rosai Hospital and carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000.

Evaluated Parameters

Body mass index (BMI) and blood pressure (BP) were measured. Fasting blood samples were obtained, and sera were stored at −80°C. Blood glucose, HbA_{1c}, insulin, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), triglycerides (TG) and creatinine were measured in our hospital laboratory. Adipocytokines and C-reactive protein (CRP) were also analyzed by an enzyme-linked immunoassay (ELISA) kit (R&D, Minneapolis, MN, USA or American Research Products, Belmont, MA, USA).

Genotyping of Polymorphisms

DNA-fragments of the single nucleotide polymorphism (SNP)-420 were amplified from genomic DNA using polymerase chain reaction with a previously described procedure[9].

Statistical Analyses

Statistical analyses were carried out using the program SPSS (SPSS, Chicago, IL, USA). The normally distributed parameters were expressed as means ± standard deviations and evaluated by Student's *t*-test. The parameters that were not normally distributed were expressed as median and interquartile range, and evaluated by Mann–Whitney *U*-test. Correlations were sought

Table 1 | Baseline clinical characteristics in patients with or without cardiovascular diseases

	Control	Case	*P*
n	178	89	
No. females	65	31	
Age (years)	65.5 ± 9.4	67.0 ± 10.0	0.86
Duration of diabetes (years)	13.7 ± 9.4	17.3 ± 9.9	0.47
Body mass index (kg/m^2)	23.0 ± 3.5	23.4 ± 3.5	0.41
HbA_{1c} (%)	7.2 ± 1.2	7.5 ± 1.2	0.45
FBG (mmol/L)	8.2 ± 2.4	7.9 ± 2.2	0.69
Fasting insulin (μU/mL)	6.7 ± 5.5	7.8 ± 5.4	0.73
HOMA-R	2.5 ± 2.4	2.6 ± 1.8	0.27
SBP (mmHg)	131 ± 16	134 ± 16	0.86
DBP (mmHg)	74 ± 11	74 ± 11	0.65
Total cholesterol (mmol/L)	5.15 ± 0.92	5.24 ± 0.87	0.44
Triglycerides (mmol/L)	1.18 (0.88–1.64)	1.35 (1.10–2.28)	0.05[a]
HDL (mmol/L)	1.36 ± 0.40	1.28 ± 0.38	0.82
LDL (mmol/L)	3.10 ± 0.82	3.18 ± 0.75	0.35
Creatinine (μmol/L)	71 (62–80)	80 (71–102)	<0.001[a]
Adiponectin (μg/mL)	7.8 (4.9–12.8)	8.7 (5.5–14.6)	0.32[a]
Resistin (ng/mL)	10.8 (6.9–17.6)	14.4 (8.1–22.2)	0.02[a]
CRP (mg/dL)	0.052 (0.018–0.139)	0.076 (0.035–0.180)	0.046[a]
Smoking history (%)	48.6	57.1	0.33[b]
Medications			
Insulin (%)	22.3	43.4	0.02[b]
Sulfonylurea (%)	34.2	36.1	0.77[b]
Glitazone (%)	10.7	6.7	0.09[b]
Statin (%)	26.4	37.1	0.38[b]
Aspirin (%)	5.4	28.9	<0.001[b]

Data are presented as means ± SD or median (interquartile range).
CRP, C-reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure.
[a]*P*-value by Mann–Whitney *U*-test.
[b]*P*-value by χ^2-test.
Non-labeled *P*-value by Student's *t*-test.

by use of Spearman's method. The association of serum resistin with stroke was assessed in multiple logistic regression models. A *P*-value <0.05 was considered statistically significant.

RESULTS

The baseline clinical characteristics of the study subjects are presented according to the presence or absence of CVD (Table 1). Cases had significantly higher TG, creatinine, resistin levels and CRP than controls. Other anthropometric data did not show any significant differences between the two groups. Serum resistin levels were significantly higher in patients with CVD than in those without CVD ($P = 0.024$). However, the levels of serum resistin were highest in patients with stroke among the CVD (stroke 16.5 [8.1–28.3] *vs* control, $P = 0.007$) (Figure 1a). The serum resistin levels had significantly univariate correlations with the levels of creatinine and CRP, but not with other anthropometric variables (Table 2).

As we reported previously, the serum resistin levels were significantly high ($P < 0.001$) according to the presence of the G allele (-420C/G). Next, we estimated serum resistin levels in multiple logistic regression analyses. The serum resistin levels were independently associated with stroke after adjustment for age, sex, BMI and genotype of *RETN* SNP -420 (Table 3; Model 1). After additional adjustment for HbA_{1c}, systolic BP, diastolic BP, LDL, HDL, triglyceride, and history of coronary disease (Table 3; Model 2), and even after further adjustment for creatinine, CRP, insulin treatment, sulfonylurea treatment and aspirin treatment (Table 3; Model 3), the significance still remained. Interestingly the genotype of *RETN* SNP -420 was not a significant factor in Model 1, but it was significant in Models 2 and 3 (CC *vs* GG).

Furthermore, we calculated the serum resistin levels in each genotype and found that serum resistin levels were significantly higher in cases of the CC and CG genotype groups than in controls (cases and controls; 14.2 ± 11.4 ng/dL *vs* 9.6 ± 6.1 [$P = 0.04$] in CC, 22.1 ± 13.1 *vs* 13.5 ± 6.9 [$P < 0.01$] in CG, 19.5 ± 12.2 *vs* 19.0 ± 11.0 [$P = 0.91$] in GG). In multiple regression analysis using serum resistin levels as the covariate in each genotype group, we found that high blood levels of resistin were a significant independent risk factor for stroke in the CG genotype group (odds ratio [OR] for stroke for 5-ng/mL increase in serum resistin levels, 1.66 [95% CI 1.03–2.68]) and showed a tendency for increased risk in the CC genotype group (OR 1.220, 95% CI 0.614–2.43). This means that, at least for diabetic patients with the CG genotype, measuring the serum resistin levels is more useful for detecting high-risk patients for susceptibility for stroke than just checking the genotype.

Based on these data, we divided the enrolled patients by their median serum resistin concentrations (High or Low) and their genotypes (CC, CG, GG) into six groups, just for an example. Odds ratios for stroke against the CC + Low group were calculated in each group by multivariate logistic-regression analysis (Figure 1b). The odds ratios increased according to the G allele mutation and high serum resistin concentration. Patients with the GG genotype and high serum resistin levels showed the highest odds ratio, 5.69 (95% CI 1.24–26.1), compared with the CC + Low group. However, we failed to show significance between High and Low within each genotype. Systolic blood pressure was also detected as a significant factor in this calculation.

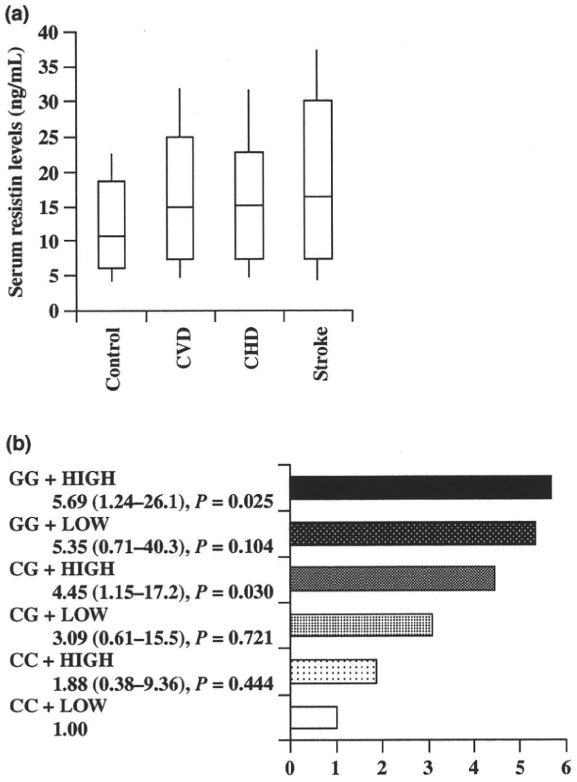

Figure 1 | (a) The resistin concentration (ng/mL) in control, total cardiovascular diseases (CVD) (coronary heart disease [CHD] + stroke) and each CVD. Box plots show median, interquartile range and non-outlier range. Extreme values are excluded from the box plots. (b) Odds ratio for stroke according to the combination of *RETN* genotype (-420C/G) and resistin levels (high or low) in multivariate logistic-regression analysis. The enrolled patients were divided by their serum resistin concentrations at median (high or low) and their genotypes (CC, CG, GG) into six groups. After adjustment for age, sex, body mass index, systolic blood pressure, serum levels of triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, C-reactive protein and creatinine, the multivariate logistic-regression analysis were made and each odds ratio against the CC + Low group was calculated. Right column shows odds ratio (confidence intervals).

DISCUSSION

In the present study, both the serum resistin levels and its genotype at -420 (C>G) were associated with the prevalence of stroke in Japanese type 2 diabetic patients, even after adjustment for known atherosclerotic risk factors in the multiple logistic regression analysis. As serum resistin levels shows a significant odds ratio independently from its SNP-420, its measurement could

Table 2 | Spearman's correlation coefficients of serum resistin levels to anthropometric and biochemical variables in Japanese type 2 diabetic patients

	r	P
Age (years)	0.08	0.18
Duration of diabetes (years)	0.03	0.65
Body mass index (kg/m^2)	0.08	0.20
HbA_{1c} (%)	−0.03	0.60
Fasting blood glucose (mmol/L)	−0.15	0.08
Fasting insulin (μU/mL)	−0.06	0.57
HOMA-R	−0.13	0.21
Systolic blood pressure (mmHg)	0.05	0.41
Diastolic blood pressure (mmHg)	−0.07	0.25
Triglycerides (mmol/L)	−0.06	0.51
HDL-cholesterol (mmol/L)	−0.11	0.07
LDL-cholesterol (mmol/L)	−0.03	0.63
Creatinine (umol/L)	0.27	<0.001
Adiponectin	0.09	0.15
CRP	0.13	0.03

Spearman's *r* correlation across all cases and controls. *r* value with resistin. CRP, C-reactive protein; HDL, high density lipoprotein cholesterol; HOMA-R, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein cholesterol.

also be helpful for the risk prediction of stroke in Japanese type 2 diabetic patients (Table 3).

Recent studies have shown that the resistin levels are significantly correlated with coronary artery calcification and are predictive of coronary atherosclerosis in humans[15,16]. Ukkola *et al.* and Norata *et al.*[17,18] described the association among this -420 (C>G) polymorphism, the resistin levels and cardiovascular risk factors. However, the association between the serum resistin levels and CHD seemed to be negative[10–13], and might be controversial for this polymorphism and CVD[17,19]. Differences in the cohorts might explain the different results, depending on which ethnic group was tested[8,20,21], or which diabetic cohort was explored. Indeed, methodological limitations in the commercially available ELISA assays might also result in variations among serum levels, which might cause difficulties when comparing results from different publications.

Although few studies have been carried out for stroke, our data showed that stroke was most strongly associated with the levels of resistin and its polymorphism (Figure 1).

After all, it is noteworthy that in a recent report by Efstathiou *et al.*[22], high resistin levels might have been strongly associated with an increased risk of 5-year mortality or disability after atherothrombotic ischemic stroke. However, because they did not measure the prestroke resistin levels, it is still unclear whether or not resistin is a key player in the pathogenesis of stroke or just a marker or indicator of the inflammatory status. To answer this, more studies will be required.

There are some limitations in the interpretation of the present study. First, we examined type 2 diabetic patients in Japan who were relatively lean compared with those in other developed countries. It would be hard to extrapolate the results of the present study to non-diabetic patients, obese diabetic patients or other

Table 3 | Multiple logistic regression analyses of serum resistin levels with history of stroke

Adjusted for	Model 1		Model 2		Model 3	
	Odds ratio (CI)	P	Odds ratio (CI)	P	Odds ratio (CI)	P
Resistin	1.32 (1.09–1.59)	0.004	1.34 (1.06–1.69)	0.013	1.33 (1.02–1.73)	0.039
Genotype of *RETN* SNP-420						
CC *vs* CG	1.55 (0.63–3.84)	0.34	1.34 (0.44–4.09)	0.61	1.43 (0.46–4.50)	0.54
CC *vs* GG	1.75 (0.56–5.42)	0.34	3.67 (1.02–13.2)	0.046	3.81 (1.03–14.1)	0.046
Age	1.03 (0.99–1.08)	0.13	1.02 (0.97–1.08)	0.38	1.03 (0.97–1.09)	0.35
Sex	1.18 (0.51–2.72)	0.69	1.03 (0.35–3.02)	0.96	1.02 (0.35–3.04)	0.97
BMI	1.06 (0.95–1.18)	0.32	1.01 (0.88–1.14)	0.93	1.02 (0.89–1.16)	0.81
HbA_{1c}			0.79 (0.51–1.22)	0.28	0.74 (0.46–1.20)	0.22
SBP			1.04 (1.01–1.07)	0.02	1.04 (1.00–1.07)	0.045
DBP			0.98 (0.93–1.04)	0.51	0.99 (0.94–1.04)	0.63
LDL			1.01 (0.99–1.02)	0.53	1.01 (0.99–1.02)	0.51
HDL			0.97 (0.94–1.01)	0.14	0.97 (0.94–1.01)	0.15
Triglycerides			1.00 (1.00–1.01)	0.33	1.00 (1.00–1.01)	0.31
History of CHD			1.95 (0.71–5.33)	0.20	1.68 (0.56–5.06)	0.36
Creatinine					0.95 (0.63–1.41)	0.78
CRP					1.01 (0.85–1.21)	0.89
Insulin therapy					1.95 (0.47–8.14)	0.36
Sulfonylurea therapy					1.80 (0.54–6.01)	0.34
Aspirin therapy					1.15 (0.34–1.41)	0.82

Odds ratio and 95% confidence interval (CI) for the existence of stroke for 5-ng/mL increase in serum resistin levels.
BMI, body mass index; CHD, coronary heart diseases; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; SNP, single nucleotide polymorphism.

ethnic groups. Second, this was a kind of cross-sectional study at the point of estimating serum resistin levels; we cannot determine any cause–effect relationship based on this study design. Third, the results were influenced by survivor effects, and the true prevalence of atherosclerotic diseases might be underestimated.

Some previous reports showed that the blood levels of resistin were positively related to the systemic inflammatory status. Although we cannot change our genotype to lower our susceptibility for stroke, there is the possibility of lowering the risk of stroke in diabetic patients, even those with the CG genotype, by multifactorial intervention aimed at reducing the systemic inflammation status, that is, by treatment with glitazone. Our results suggest that using the genotype and serum levels of resistin to discriminate between diabetic responders and non-responders will contribute to the development of effective strategies and improve the prognosis in this population. In conclusion, the present results suggest that serum resistin levels might be also a good marker of susceptibility to stroke as well as *RETN* polymorphism, and the measurement of both *RETN* gene polymorphism and serum resistin levels might be useful to detect the susceptibility to stroke and might provide an incremental value in the risk prediction for stroke, beyond the current approaches, among Japanese type 2 diabetic patients. Our findings need to be confirmed by further studies.

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REFERENCES

1. Patel L, Buckels AC, Kinghorn IJ, *et al.* Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 2003; 300: 472–476.
2. Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, *et al.* Serum resistin (FIZZ3) protein is increased in obese humans. *J Clin Endocrinol Metab* 2003; 88: 5452–5455.
3. Vozarova de Courten B, Degawa-Yamauchi M, Considine RV, *et al.* High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. *Diabetes* 2004; 53: 1279–1284.
4. Kawanami D, Maemura K, Takeda N, *et al.* Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. *Biochem Biophys Res Commun* 2004; 314: 415–419.
5. Burnett MS, Lee CW, Kinnaird TD, *et al.* The potential role of resistin in atherogenesis. *Atherosclerosis* 2005; 182: 241–248.
6. Osawa H, Yamada K, Onuma H, *et al.* The G/G genotype of a resistin single-nucleotide polymorphism at -420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. *Am J Hum Genet* 2004; 75: 678–686.
7. Cho YM, Youn BS, Chung SS, *et al.* Common genetic polymorphisms in the promoter of resistin gene are major determinants of plasma resistin concentrations in humans. *Diabetologia* 2004; 47: 559–565.
8. Osawa H, Onuma H, Ochi M, *et al.* Resistin SNP-420 determines its monocyte mRNA and serum levels inducing type 2 diabetes. *Biochem Biophys Res Commun* 2005; 335: 596–602.
9. Tsukahara T, Nakashima E, Watarai A, *et al.* Polymorphism in resistin promoter region at -420 determines the serum resistin levels and may be a risk marker of stroke in Japanese type 2 diabetic patients. *Diabetes Res Clin Pract* 2009; 84: 179–186.
10. Burnett MS, Devaney JM, Adenika RJ, *et al.* Cross-sectional associations of resistin, coronary heart disease, and insulin resistance. *J Clin Endocrinol Metab* 2006; 91: 64–68.
11. Lim S, Koo BK, Cho SW, *et al.* Association of adiponectin and resistin with cardiovascular events in Korean patients with type 2 diabetes: The Korean atherosclerosis study (KAS) A 42-month prospective study. *Atherosclerosis* 2008; 196: 389–404.
12. Pilz S, Weihrauch G, Seelhorst U, *et al.* Implications of resistin plasma levels in subjects undergoing coronary angiography. *Clin Endocrinol (Oxf)* 2007; 66: 380–386.
13. Weikert C, Westphal S, Berger K, *et al.* Plasma resistin levels and risk of myocardial infarction and ischemic stroke. *J Clin Endocrinol Metab* 2008; 93: 2647–2653.
14. Lehrke M, Reilly MP, Millington SC, *et al.* An inflammatory cascade leading to hyperresistinemia in humans. *PLoS Med* 2004; 1: e45.
15. Reilly MP, Lehrke M, Wolfe ML, *et al.* Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 2005; 111: 932–939.
16. Mohty D, Pibarot P, Despres JP, *et al.* Age-related differences in the pathogenesis of calcific aortic stenosis: The potential role of resistin. *Int J Cardiol* 2009; in press.
17. Norata GD, Ongari M, Garlaschelli K, *et al.* Effect of the -420C/G variant of the resistin gene promoter on metabolic syndrome, obesity, myocardial infarction and kidney dysfunction. *J Intern Med* 2007; 262: 104–112.
18. Ukkola O, Kunnari A, Kesaniemi YA. Genetic variants at the resistin locus are associated with the plasma resistin concentration and cardiovascular risk factors. *Regul Pept* 2008; 3: 56–59.
19. Kunnari A, Ukkola O, Kesaniemi YA. Resistin polymorphisms are associated with cerebrovascular disease in Finnish Type 2 diabetic patients. *Diabet Med* 2005; 22: 583–589.
20. Menzaghi C, Coco A, Salvemini L, *et al.* Heritability of serum resistin and its genetic correlation with insulin resistance-related features in nondiabetic Caucasians. *J Clin Endocrinol Metab* 2006; 91: 2792–2795.
21. Hivert MF, Manning AK, McAteer JB, *et al.* Association of variants in RETN with plasma resistin levels and diabetes-related traits in the Framingham Offspring Study. *Diabetes* 2009; 58: 750–756.
22. Efstathiou SP, Tsiakou AG, Tsioulos DI, *et al.* Prognostic significance of plasma resistin levels in patients with atherothrombotic ischemic stroke. *Clin Chim Acta* 2007; 2: 78–85.

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糖尿病診療のためのガイドライン

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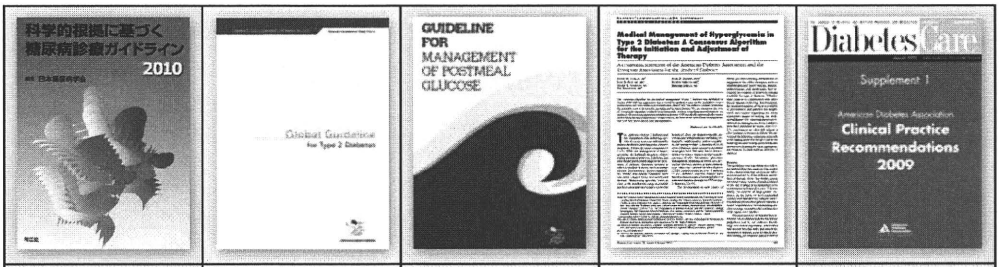
はじめに

糖尿病の増加は世界規模の脅威であり，世界各国では国を挙げて糖尿病対策に取り組んでいる．糖尿病対策として最も効果的なのは糖尿病の早期発見と早期からの適切な治療であるが，その際，適切な糖尿病診療の実践のためのガイドラインの存在は必須である．日常の臨床の現場で個別的な対応が求められるのは当然のことだが，基本的なガイドラインがあってこそ，患者一人ひとりにとって最も適切な選択肢を見極めることができる．ガイドラインなしに糖尿病診療に当たることは，羅針盤のない船を操縦するようなものである．

そこで，国際糖尿病連合(International Diabetes Federation；IDF)をはじめ，多くの国内外の糖尿病関連団体が，糖尿病診療のためのガイドラインを策定している[1-5](図1)．日本糖尿病学会でも，日常臨床のさまざまな場において活用できるように，数種類のガ



	科学的根拠に基づく糖尿病診療ガイドライン 2010[1]	Global Guideline for Type 2 Diabetes 2005(IDF)[2]	GUIDELINE FOR MANAGEMENT OF POSTMEAL GLUCOSE 2007(IDF)[3]	A consensus statement of ADA/EASD 2009(ADA)[4]	Clinical practice recommendation 2009(ADA)[5]
HbA1c	5.8～6.5%*	<6.5%	<6.5%	<7.0%	<7.0%
空腹時血糖値 (mg/dL)	110～130*	<110	<100	—	70～130
食後血糖値 (mg/dL)	140～180*	<145	<140	—	<180

図1　糖尿病診療ガイドライン(抜粋)の血糖コントロール指標とその目標値

＊：血糖コントロール「良」の評価．

イドブックを発行してきたが，本稿では，「科学的根拠に基づく糖尿病診療ガイドライン2010」を中心に，糖尿病診療のためのガイドラインについて概説する．

「科学的根拠に基づく糖尿病診療ガイドライン2010」の概要

1.「糖尿病治療ガイド」[6]と「科学的根拠に基づく糖尿病診療ガイドライン」

日本糖尿病学会は，糖尿病臨床の第一線にある実地医家，研修医，医学生そしてコメディカルスタッフのための糖尿病治療関連の小冊子である「糖尿病治療ガイド」を1999年に発行した．その後，本書は1～2年ごとに刊行され，現在では2010年度版が発行されている．2007年度版については英語版も刊行された．本書の核心部分は，「糖尿病治療のエッセンス」としてまとめられ，実地医家の先生方の外来で活躍している．その他，日本糖尿病学会は，「小児・思春期糖尿病管理の手びき」，「糖尿病専門医研修ガイドブック」を刊行し，さまざまな需要に対応してきた．

一方，「科学的根拠に基づく糖尿病診療ガイドライン」の発行は，evidence-based medicine(EBM)の実践が求められる時代を迎え，厚労省研究班による新しい視点でのガイドラインの策定が検討されたことに端を発している．この報告書は大きな反響を呼び，2年後の2004年に書籍として初版が刊行された．本書の特徴は，あくまでも糖尿病診療に関する国内外のエビデンスを基盤とし，ここから導かれる項目をステートメントとして掲げる，という姿勢を貫いていることである．改訂第2版(2007年)[1]を経て，2010年9月に改訂第3版が刊行された．

2. ガイドラインの内容

本書の構成は，初版から同じである．糖尿病の全領域が項目別に分類され，それぞれの項で，診療上の指針となる重要なステートメント(推奨)が簡潔に記載されている．推奨の強さはグレードで評価し，グレードAは「行うよう強く勧める」，グレードBは「行うよう勧める」，グレードCは「行うように勧めるだけの根拠が明確でない」，グレードDは「行わないよう勧める」とされた．大多数はグレードAあるいはBであるが，妊婦に対する極端な食事制限などがC，Dとなっている．ステートメントに次いで解説が記されているため，ステートメントやグレードの背景が理解しやすい(図2)．また，これらの根拠であり，かつ解説のなかで引用されている臨床研究などの文献は，エビデンスとしての水

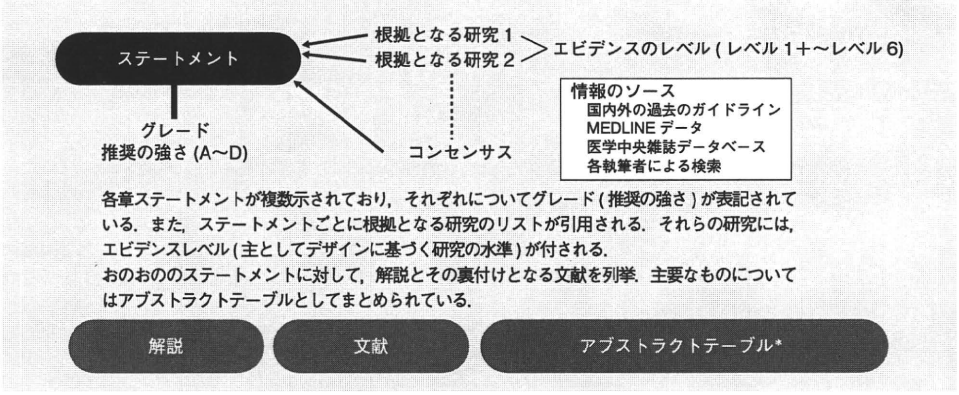


図2 ガイドラインの構成

*：文献の内容を要約したもの．（日本糖尿病学会編「科学的根拠に基づく糖尿病診療ガイドライン2010」より引用改変）

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準が付されたうえで列挙され(表1)，最後にアブストラクトテーブルとしてコンパクトにまとめられている．

2010年度版の基本的な方針は，①糖尿病診療における実際的な治療ガイドよりは，糖尿病領域におけるエビデンス集とする，②積極的に日本発の新しいエビデンスを収載するが，臨床治験は原則として含めない，③文献検索の際の簡便な道しるべとなる「アブストラクトテーブル」を継続して掲載する，である(本書の序文より)．また「糖尿病と歯周病」および「糖尿病と感染症，シックデイ」が新章として加えられ，全25項目となった．その他の事項として，①ステートメントでは薬剤名は「分類名」による記載で，「商品名」は一切記載されていない，②全体の頁数が増大していない，③文献の執筆者の記載を「3名＋et al(ほか)」とするなど，細部にわたって配慮されている．

この版の策定委員会は糖尿病を専門とする医師26名，臨床疫学者1名で構成され，執筆協力者8名とともに23項目について分担執筆した．原稿のすべては複数の査読委員(50名)による査読を受け，再び執筆者に戻され意見交換をし，さらに最終段階では編集委員長と査読委員長が全体の統一を図ったという．このように多数の糖尿病や疫学を専門とする方々に支えられて本書が完成した．

3. 2010年度版のトピックス

まず，2010年7月に新しい糖尿病診断基準がスタートしたが[7]，これが新しい内容として掲載された．これまでHbA1cに求められていた役割は，①血糖コントロールの指標(DCCT, Kumamoto Study, UKPDSなど)，②疫学調査における糖尿病診断の指標(国民健康栄養調査：厚労省1997年～)，③糖尿病の臨床診断における補助的指標(糖尿病の診断基準：日本糖尿病学1999年～)，④糖尿病のリスク判定の指標(特定健診・特定保健指導：厚労省2008年～)であったが，新しい糖尿病の診断基準ではHbA1cを補助的診断からより積極的に取り入れたのである(図3)．

HbA1c値については，「HbA1c(JDS値)」，「HbA1c(国際標準値)」そして「HbA1c(NGSP値)」の3種類が記

表1　ガイドラインで用いたエビデンスのレベル(各研究へ付された水準)

水準(レベル)	それに該当する臨床研究デザインの種類
1＋	水準1の規模を含むランダム化比較試験のシステマティックレビューまたはメタアナリシス
1	十分な症例数(全体で400例以上)のランダム化比較試験
2＋	水準2の規模を含むランダム化比較試験のシステマティックレビューまたはメタアナリシス
2	小規模(全体で400例未満)のランダム化比較試験
2－	さらに小規模(全体で50例未満)のランダム化比較試験，クロスオーバー試験(ランダム化を伴う)，オープンラベル試験(ランダム化を伴う)
3	非ランダム化比較試験，コントロールを伴うコホート研究
4	前後比較試験，コントロールを伴わないコホート研究，症例対照研究
5	コントロールを伴わない症例集積(10～50例程度)
6	10例未満の症例報告

注)文献情報に基づかず，対応する文献のない場合："コンセンサス"と記載．
注)括弧内の症例は目安である．

(科学的根拠に基づく糖尿病診療ガイドライン2010より引用)

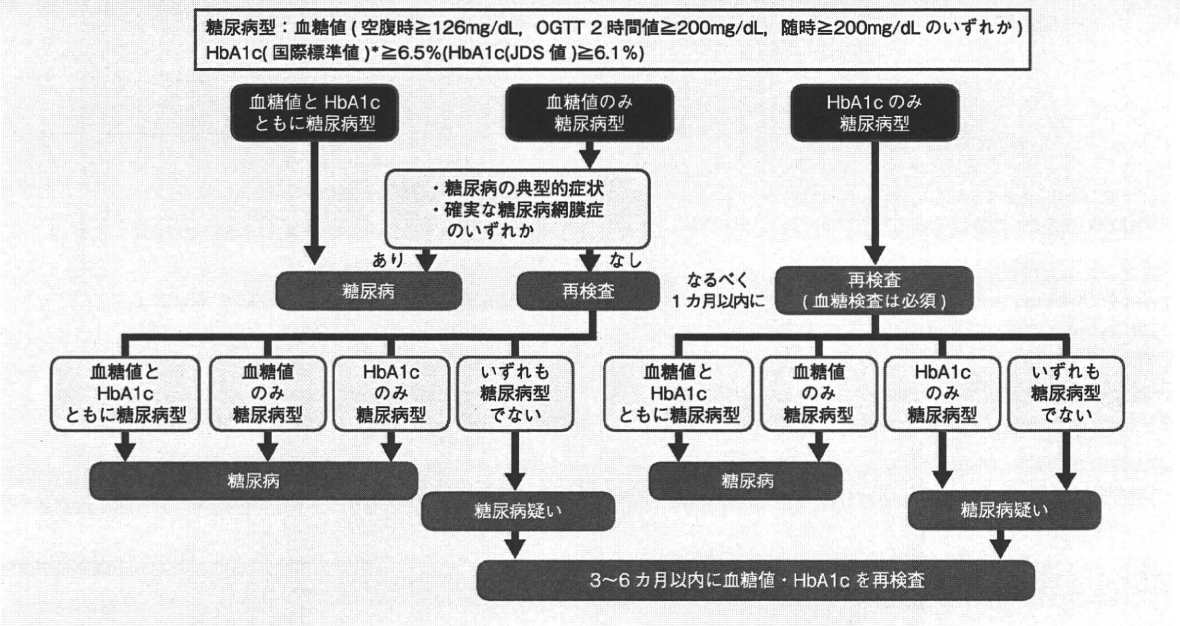

図3　糖尿病の新しい臨床診断（2010年7月1日施行）

＊：HbA1c(国際標準値)(％)は現行のJDS値で表記されたHbA1c(JDS値)(％)に0.4％を加えた値で表記する．

載されている．「HbA1c(JDS値)」とは従来どおりの値で，「HbA1c(国際標準値)」は日本以外の諸外国で現在用いられているHbA1c(JDS値)より0.4％高いNGSP値に相当する値である．新しいHbA1c(国際標準値)の臨床での運用時期については決定していないが，国際会議や論文発表などの際には，国際的に標準化された新しいHbA1c(国際標準値)を直ちに用いることが推奨されている(表2)．

表2　HbA1c の表記に関して

本書では HbA1c 値に関し，米国などにおける基準に基づく HbA1c(NGSP 値）との整合性を図るため，従来からの JDS(Japan Diabetes Society；日本糖尿病学会）標準検体に依拠した HbA1c 値に 0.4% を加えた値を HbA1c（国際標準値）として記述している．また，従来の HbA1c 値について記載する場合には，HbA1c(JDS 値）と記している．

近い将来，日常臨床，検診，健康診断等における表記は，すべて新しい HbA1c（国際標準値）を用いることになるが，その運用の開始は日本糖尿病学会が別途告示する日からとなる．

なお，英文論文や英文著書，国際学会の発表における HbA1c の記載は，平成 22 年 7 月 1 日より国際標準値による新しい表記法に移行している．

(科学的根拠に基づく糖尿病診療ガイドライン2010より引用)

IDF によるガイドライン

糖尿病に関連した国内外の代表的なガイドラインのうち，IDFによる2型糖尿病の診療ガイドライン(2005年)[2]は，リソースが限られている地域や国においても運用しうるという視点から策定されたもので，エビデンスに基づいていること，筋がとおっていること，実行可能であること，そして患者や主治医にとって到達可能であること，などを満たすことが念頭に置かれている．2010年度版の策定にあたり，血糖管理の到達目標および2型糖尿病治療のアルゴリズムに関する作業部会が開催され筆者も参加する機会を得た．会議では2日間にわたる白熱した討論が続いたが，血糖管理目標の指標とその目標値については，HbA1c，

連載
ガイドラインを考える
第4回

表3　食後血糖値の管理に関するガイドライン

糖尿病の管理における血糖コントロールの目標
HbA1c ＜ 6.5%
空腹時血糖＜ 100mg/dL
食後２時間血糖＜ 140mg/dL

- ●血糖値を最適にコントロールするためには，空腹時血糖値と食後血糖値のどちらをも目標とした治療法が必要である．
- ●血糖を最適にコントロールするためには，食後血糖値の適切な管理が不可欠である．
- ●したがって，空腹時及び食後高血糖の治療は，HbA1c 値にかかわらず同時に開始すべきである．
- ●適切な治療法を決定する上で費用は重要な要因であるが，血糖をコントロールすることは糖尿病の合併症治療よりも，はるかに安価である．

EBM：Evidence-based Medicine

根拠（エビデンス）を重視するが，患者さんの価値観も大切にし，最終的には主治医が専門的な技能や臨床経験を駆使して医療を実践する．医療経済に配慮する．

病気のみを診るのではなく，科学的な根拠に基づいて全人的に患者さんを診る．

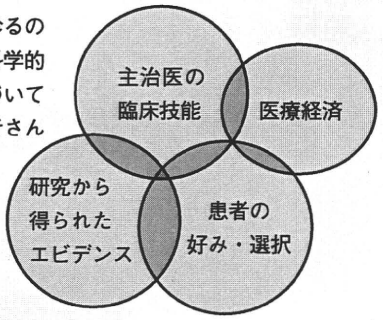

図4　「エビデンス」と「EBM」は同意語ではない

空腹時血糖値および食後2時間値とし，それぞれの到達目標をそれぞれ，7.0％未満，100mg/dL未満および140mg/dL未満とする，という案がまとまった．2007年にIDFが報告した「食後高血糖管理のためのガイドライン」[3](表3)に記されたHbA1c＜6.5％よりやや高い値が推奨された理由はいくつかあるが，安全に到達することが可能か，という点もそのうちの1つである．

治療のアルゴリズムは「生活習慣の改善のみ」が最初のステップであり，その後すべてのステップでも重要であることが強調された．日本，中国，インド以外の国では，HbA1cの到達目標に達したか否かで治療法をステップアップするtreatment-basedのアルゴリズムが使われている[4,5]．日本では病態に合わせたindividual-basedの治療が進められているが，年齢，糖尿病の罹病歴，病態，合併症，患者の受け入れなど個別化しうる要因のうち，何が重要かは明記されていない．また，IDFガイドラインでは薬剤のコストが重要な位置を占めており，エビデンスがあっても高価であれば選択肢として下位になる．IDFガイドラインが推奨するガイドラインが目指すところを理解し，日本の事情にあわせて共有しうるものは積極的に取り入れることも大切と思われた．

おわりに

2型糖尿病が世界中で爆発的に増えているのにもかかわらず，多くの国や地域ではまだ，糖尿病診療ガイドラインがない．あったとしても浸透していないので，糖尿病が診断されないまま放置されていたり，適切な治療を受けていない糖尿病患者が多数存在する．日本は糖尿病診療のためのリソースが豊富で，かつ，糖尿病をもつ人は皆が等しく適切な治療を受けることができるなど，恵まれた環境にある．にもかかわらず，到達目標であるHbA1c＜7.0％ (国際標準値)に到達しているのは全糖尿病患者のうち40％程度といわれている．このギャップを埋めるために「科学的根拠に基づ

く糖尿病診療ガイドライン」は何ができるのだろうか．本書が提供しているのは，EBMの実践に必要な3つの要素[8]のうち，研究から得られたエビデンスのみである．主治医の臨床技能や患者の好み・選択，ましてや第4の大切な要因と認識されるようになった医療経済には触れられていない(図4)．

糖尿病診療に関するガイドラインが真にユーザーフレンドリーであるためには，コストの問題は避けて通れない．また，エビデンスを過信しすぎず，患者の価値観も配慮し，主治医の裁量権で最良の糖尿病診療を行うことの大切さも認識していかねばならない．

● References

1) 日本糖尿病学会 編：科学的根拠に基づく糖尿病診療ガイドライン 2010. 南江堂，東京，2010
2) Global Guideline for Type 2 Diabetes 2005(http://www.idf.org/webdata/docs/IDF% 20GGT2D.pdf)
3) GUIDELINE FOR MANAGEMENT OF POSTMEAL GLUCOSE 2007 (http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf)
4) American Diabetes Association：Standards of medical care in diabetes--2009.*Diabetes Care* **32**：S13-S61，2009
5) Nathan DM, Buse JB, Davidson MB et al：Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **32**：193-203，2009
6) 日本糖尿病学会 編：糖尿病治療ガイド 2008-2009. 文光堂，東京，2008
7) 糖尿病診断基準に関する調査検討委員会：糖尿病の分類と診断基準に関する委員会報告．糖尿病 **53**：450-467，2010
8) Haynes RB, Sackett DL, Gray JM et al：Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions. *ACP J Club* **125**：A14-A16，1996

Long-term mortality and causes of death among patients with type 1 diabetes in Japan

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INTRODUCTION

The Diabetes Epidemiology Research International (DERI) mortality study, beginning in 1986, is an international collaborative study that brought together diabetes researchers and clinicians from 4 countries (Finland, USA, Israel and Japan). In 1991 the study issued its first report demonstrating that Japanese patients with type 1 diabetes had a much worse prognosis than patients in Finland, USA and Israel, with the most frequent cause of death being diabetic nephropathy (1,2). The DERI study is still ongoing in Finland, USA, and Japan. In this presentation, we report on the prognosis of Japanese patients with type 1 diabetes by evaluating the latest data available as of January 1, 2005.

AIMS

To investigate long-term prognosis including causes of death among patients with type 1 diabetes in Japan.

METHODS

A total of 1,387 patients (556 males and 831 females) were enrolled in the study after being identified from two nationwide type 1 diabetes surveys in Japan. Subjects were diagnosed as having type 1 diabetes that developed prior to 18 years of age, during the period 1965-1979. Type 1 diabetes was defined as requiring initiation of insulin therapy, as a rule, within 1 month of diagnosis. All patients were tracked for survival status until January 1, 2005, with this status determined based on the questionnaires sent to their attending physicians or the residents' records. The cause of death was determined by the DERI mortality classification committee (MCC) (2) from the information of attending physicians or death certificates. The MCC consisted of three members from the USA, Finland, and Japan. The causes of death were divided into 9 groups.

1. diabetic renal disease
2. acute diabetic complications
3. accident/suicide
4. cardiovascular disease
5. infections
6. malignant neoplasms
7. other non-diabetic causes
8. other diabetic causes
9. unknown

Survival status as of January 1, 2005 was expressed in terms of standardized mortality ratio (SMR), crude mortality rate (CMR), and cumulative survival rates. Mortality was compared between male and female patients using the log rank test, and the Cox proportional-hazards model after adjustment for duration of disease prior to the start of follow-up.
Statistical analyses were performed using SAS 9.1. A P value of < 0.05 was considered as statistically significant (two-tailed).

RESULTS

Table 1. Characteristics of the subjects, crude death rate, and standardized mortality ratio (SMR) of patients with type 1 diabetes in Japan.

	Gender		Overall
	Male	Female	
No. of subjects (males/females)	556	831	1,387 (556/831)
Age at diagnosis (years)	8.7 ± 4.2	8.9 ± 4.0	8.8 ± 4.1
Attained age (years)	36.2 ± 7.2	37.0 ± 7.1	36.7 ± 7.1
Duration of diabetes (years)	27.6 ± 6.5	28.1 ± 6.4	27.9 ± 6.4
Follow-up (years)	24.3 ± 6.5	24.5 ± 6.3	24.4 ± 6.4
Follow-up (person-years)	13,491	20,377	33,868
No. of deaths	105	118	223
Crude death rate at 35-year follow-up (per 100,000 person-years) (95% CI)	778 (628-936)	579 (479-686)	658 (573-745)
SMR at 35-year follow-up (95% CI)	9.6 (7.7-11.5)	14.3 (11.8-16.9)	10.6 (9.3-12.0)

All data are expressed as mean ± SD. 95% confidence intervals (CI) calculated by using the Poisson distribution are given in parentheses.

One thousand one hundred and three patients were confirmed as alive as of January 1, 2005, and 223 deaths (16.1%) were observed (confirmation rate: 95.6%). The SMR was 10.6 (males, 9.6; females 14.3).

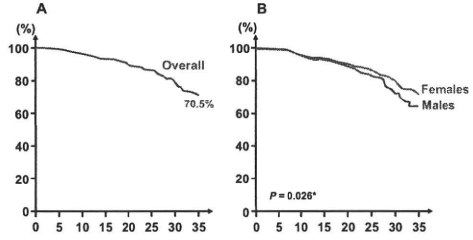

Figure 1. Cumulative survival rate of patients with type 1 diabetes in Japan. (A) All subjects; (B) Subjects by gender.

The cumulative survival rate at 35 years follow up was 70.5% (A). Males' cumulative survival rate was significantly lower than females' cumulative survival rate (P=0.026). Male patients were shown to be at 1.37-fold higher mortality risk compared to female patients by the Cox proportional-hazards model (95% CI, 1.02–1.85).

The time from the initiation of dialysis to death was 5.5 ± 4.8 years in 89 patients who died following initiation of dialysis.

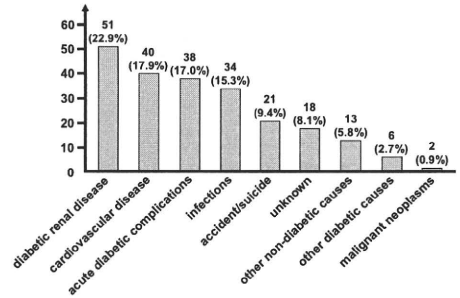

Figure 2. Number of deaths in Japanese patients with type 1 diabetes according to cause of death.

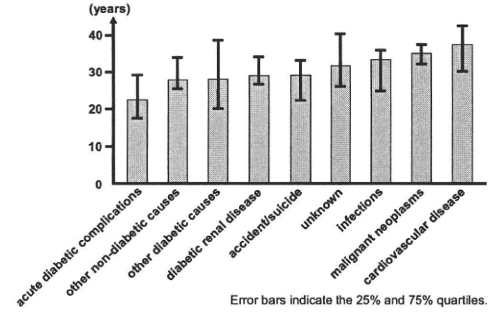

Figure 3. The median age of death in Japanese patients with type 1 diabetes according to cause of death.

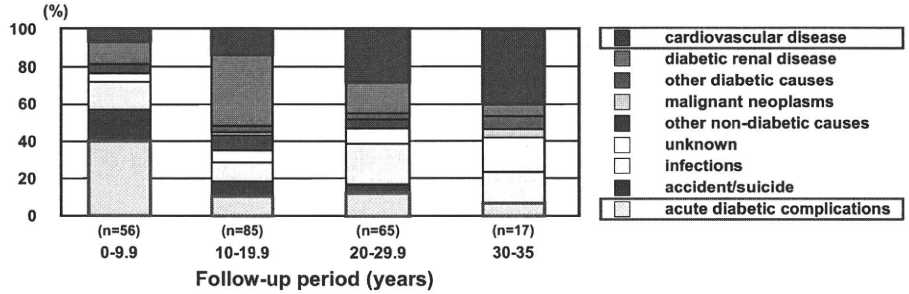

Figure 4. The causes of death according to follow-up period in patients with type 1 diabetes in Japan.

The leading causes of death were diabetic renal disease, cardiovascular disease, and acute diabetic complications (Fig.2). The longer the duration of follow-up, the lower the mortality from acute diabetic complications, and the greater the mortality from cardiovascular disease (Fig. 4). Therefore, the age of death was younger in decedents with acute diabetic complications and older in those with cardiovascular disease (Fig. 3).

Conclusion

The mortality risk of Japanese patients diagnosed as having type 1 diabetes between 1965 and 1979 was 10.6-fold higher than that of the general population. Males had a 1.37-fold higher mortality risk than females. Diabetic renal disease, cardiovascular disease and acute diabetic complications were the leading causes of death. However, as the duration of follow-up increased, acute diabetic complications contributed less and cardiovascular disease contributed more to mortality.

References

1. DERI Mortality Study Group. Diabetes Care 14:49-54, 1991
2. DERI Mortality Study Group. Diabetes Care 14:55-60, 1991

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Long-term mortality and causes of death among patients with type 1 diabetes in Japan

Aims: To investigate long-term prognosis including causes of death among patients with type 1 diabetes in Japan.

Methods: A total of 1,387 patients (556 males and 831 females) were registered from two nationwide type 1 diabetes surveys in Japan. They were diagnosed as type 1 diabetes at less than 18 years of age between 1965 and 1979. All patients were tracked for survival status until January 1, 2005, with this status determined based on the questionnaires sent to their attending physicians or the residents' records. Causes of death were identified through questionnaires or death certificates. Their survival status as of January 1, 2005 was expressed in terms of standardized mortality ratio (SMR) and crude mortality rate (CMR). Mortality was compared between the male and female patients by using the Cox proportional-hazards model. The causes of death for deceased cases were divided into 9 groups (1. diabetic renal disease; 2. acute diabetic complications; 3. accident/suicide; 4. cardiovascular disease; 5. infections; 6. malignant neoplasms; 7. other non-diabetic causes; 8. other diabetic causes; 9. unknown) and were also compared by duration of diabetes. Statistical analyses were performed by using SAS 9.1. This study was approved by the Institutional Review Board of Jikei University School of Medicine, Tokyo, Japan.

Results: The mean age at diagnosis was 8.8 ± 4.1 (SD) years, with a duration of diabetes of 27.9 ± 6.4 years. One thousand one hundred and three patients were confirmed as alive as of January 1, 2005, and 223 deaths (16.1%) were observed (confirmation rate: 95.6%). The SMR was 10.6 (males, 9.6; females 14.3), and the CMR was 658/100,000 person-years (males, 778; females, 579). The male patients were shown to be at 1.37-fold higher mortality risk compared to the female patients (95% CI, 1.02–1.85). The causes of death identified included diabetic renal disease (51 patients; 22.9%), cardiovascular disease (40; 17.9%), acute diabetic complications (38; 17.0%), infections (34; 15.3%), accidents and suicides (21; 9.4%), unknown cause (18; 8.1%), other non-diabetic causes (13; 5.8%), other diabetic causes (6; 2.7%), and malignant neoplasms (2; 0.9%). Leading causes of death included acute diabetic complications among those with less than 10 years' duration of disease, diabetic renal disease among those with 10 to 20 years' duration, infections among those with 20 to 30 years' duration, and cardiovascular disease among those with 30 to 40 years' duration. Thus, the longer the duration of disease, the less the mortality from acute diabetic complications, and the greater the mortality from cardiovascular disease. The time from the initiation of dialysis to death was shown to be 5.5 ± 4.8 years in 89 patients who were confirmed to have been dead after initiation of dialysis.

Conclusion: The mortality risk of patients diagnosed as type 1 diabetes between 1965 and 1979 in Japan was shown to be 10.6-fold higher than that of the general population. The males were found to be at 1.37-fold higher mortality risk than the females. Diabetic renal disease, cardiovascular disease and acute diabetic complications were found to be the leading causes of death. However, as the duration of disease became longer, acute diabetic complications contributed less and cardiovascular disease contributed more to mortality.

Blindness and laser photocoagulation in patients with childhood-onset type 1 diabetes in Japan

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ABSTRACT

Aim: The aim of the study was to investigate trends in the incidence of blindness and the association with laser photocoagulation in patients with type 1 diabetes in Japan.

Methods: Patients diagnosed between 1965 and 1979 aged under 18 years old were studied. The status of blindness and laser photocoagulation was identified as of 1 January 1995. To examine the time trend, we divided the cohort into two groups: 285 patients diagnosed between 1965 and 1969 (65–69 cohort) and 769 patients diagnosed between 1975 and 1979 (75–79 cohort). Survival analysis was performed using the Kaplan–Meier method. Cox proportional hazard models were used to assess the demographic characteristics.

Results: Blindness developed in 60 subjects in the 65–69 cohort and 15 subjects in the 75–79 cohort. The incidence of blindness in the 75–79 cohort was significantly lower than that in the 65–69 cohort ($p<0.0001$). In spite of no change in the use of laser photocoagulation in the 75–79 cohort compared with the 65–69 cohort, the hazard ratio for the blindness in those who received laser photocoagulation in the 75–79 cohort decreased significantly to 0.55 ($p<0.01$) compared with those in the 65–69 cohort when adjusted for the age of onset, sex, and time of diagnosis.

Conclusion: The incidence of blindness decreased significantly for the subjects diagnosed more recently. The change in quality and the earlier introduction of laser photocoagulation might have contributed to the decreased incidence of blindness observed over time.

Blindness is associated with a substantial reduction in quality of life among type 1 as well as type 2 diabetic patients.[1] An early study in Japan by Hibi *et al* in 1982 demonstrated that the prevalence of blindness was approximately 13.3% in 90 patients who were aged >25 years.[2]

The clinical application of laser photocoagulation for the treatment of advanced diabetic retinopathy was initiated in 1959.[3] Early treatment with scattered photocoagulation in the late 1980s did prove effective in type 2 diabetes, but was not effective in preventing advanced retinopathy in type 1 diabetes.[4] In the late 1990s and early 2000s a few reports started to provide evidence of improvements in visual outcome with photocoagulation therapy in type 1 diabetes.[5 6] However, there are no reports that have focused on the relationship between laser photocoagulation and the incidence of blindness.

The aim of the present study was to estimate the incidence of the use of laser photocoagulation and of blindness, and to examine whether or not laser photocoagulation contributed to the decreased incidence of blindness, if there was such a decrease.

PATIENTS AND METHODS

Subjects

The study subjects were selected from 1408 patients with childhood-onset type 1 diabetes in the Japanese cohort of the Diabetes Epidemiology Research International Study Group[7 8]. The subjects satisfied all of the following three criteria: (1) developed the disease before 18 years of age; (2) started insulin therapy within 1 month of diagnosis; and (3) diagnosed between 1965 and 1969 and alive at the end of 1969, or diagnosed between 1970 and 1979 and alive at the end of 1979. The Diabetes Epidemiology Research International Mortality Study was a population-based follow-up study initiated in 1986 to examine the mortality status of childhood-onset type 1 diabetes internationally.[7 8] The degree of the case ascertainment of the cohort was estimated to be 75% according to the reported incidence of type 1 diabetes during that period.[7–9] All attending physicians obtained informed consent from the patients at the time of questionnaire survey. The study was approved by the Institutional Review Board of Jikei University School of Medicine.

Methods

A questionnaire[10] was sent to the attending physicians on the clinical status of the patients: whether the patients "received or did not receive" laser photocoagulation and were "positive or negative" for blindness at the time point of January 1995. If the patient had "received" laser photocoagulation, we retraced and recorded the year and month of the first laser treatment. If the patient had been "positive" for blindness, we retraced and recorded the year and month of the diagnosis of blindness.

Statistical analysis

Out of the total cohorts we chose two groups according to the calendar year of diagnosis, namely those diagnosed between 1965 and 1969 (the 65–69 cohort) and those diagnosed between 1975 and 1979 (the 75–79 cohort). The group diagnosed between 1970 and 1974 was excluded from the analysis (n = 354), since we designed this study to analyse the follow-up period of the two cohorts on the basis that the relationship between the length of the recruitment period and the start time of the follow-up was the same. The follow-up time was calculated from 1970 for the 65–69 cohort and