In the subgroup without DM, 25 and 14 CVEs occurred in patients receiving the low and standard doses, respectively.

The S:L CVE risk ratio for the prevalence of fatal or nonfatal CVEs was 0.94 (95% CI, 0.46–1.92) in the subgroup with DM and 0.54 (95% CI, 0.28–1.05) in the subgroup without DM. The S:L risk ratio for the overall population was 0.70 (95% CI, 0.43–1.12) (**Figure 2**). For the combined prevalence of MI, AP, and death from any cause, the S:L risk ratios were 0.54 (95% CI, 0.18–1.63) and 0.79 (95% CI, 0.24–2.55) in the subgroups with and without DM, respectively. None of the differences were statistically significant. In patients with DM and a history of CVD, the S:L hazard ratio was 0.35 (95% CI, 0.06–1.93), whereas in patients with DM and without a history of CVD, the S:L hazard ratio was 1.23 (95% CI, 0.05–2.85).

The relative risk (RR) for CVEs in the DM subgroup, adjusted for dose group, age, sex, and CVD risk factors, was 1.87-fold (95% CI, 1.09–3.20; $P = 0.02$) higher in patients with HbA_{1c} <8.0% and 3.79-fold (95% CI, 1.92–7.48; $P < 0.01$) higher in patients with HbA_{1c} ≥8.0% than that observed in the subgroup without DM (**Figure 3**). When the risk for CVEs in patients with neither DM nor a history of CVD was assigned a reference value of 1, the RR in patients with DM but without a history of CVD (calculated in the same manner) was 3.34 (95% CI, 1.77–6.31; $P < 0.01$). In patients without DM but with a history of CVD, the RR was 3.57 (95% CI, 1.88–6.78; $P < 0.01$). In patients with DM and a history of CVD, the RR was 3.73 (95% CI, 1.57–8.86; $P < 0.01$).

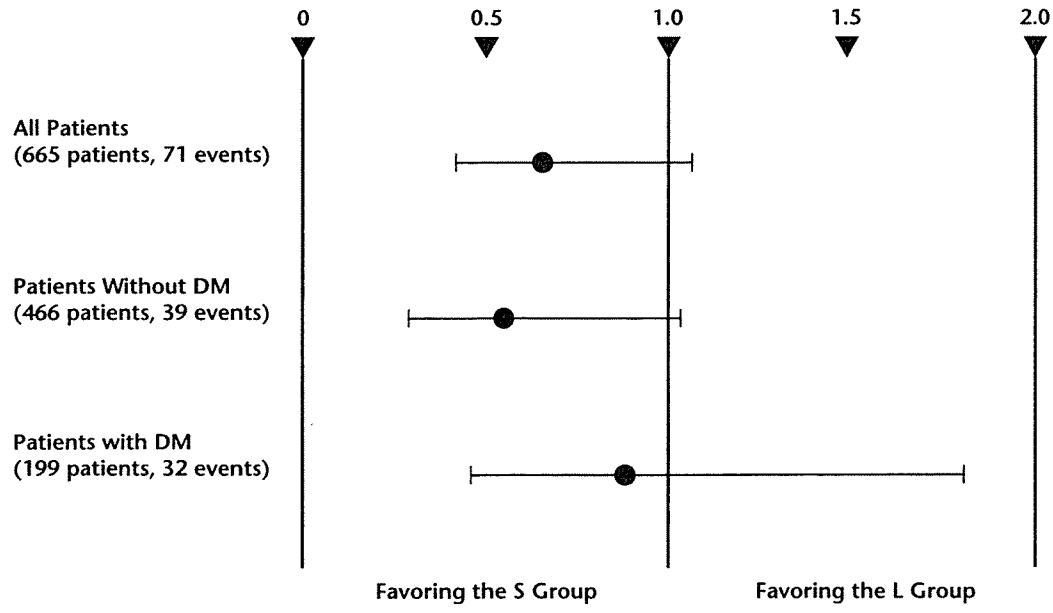

Figure 2. Risk ratios (95% CI) for the prevalence of fatal and nonfatal cardiovascular events (primary end point) in the Pravastatin Anti-atherosclerosis Trial in the Elderly.[1] Risk ratios were calculated using Cox regression analysis adjusted for age, sex, diabetes mellitus (DM), smoking history, hypertension, and history of cardiovascular disease. S = standard-dose pravastatin; L = low-dose pravastatin. No significant between-group differences were found.

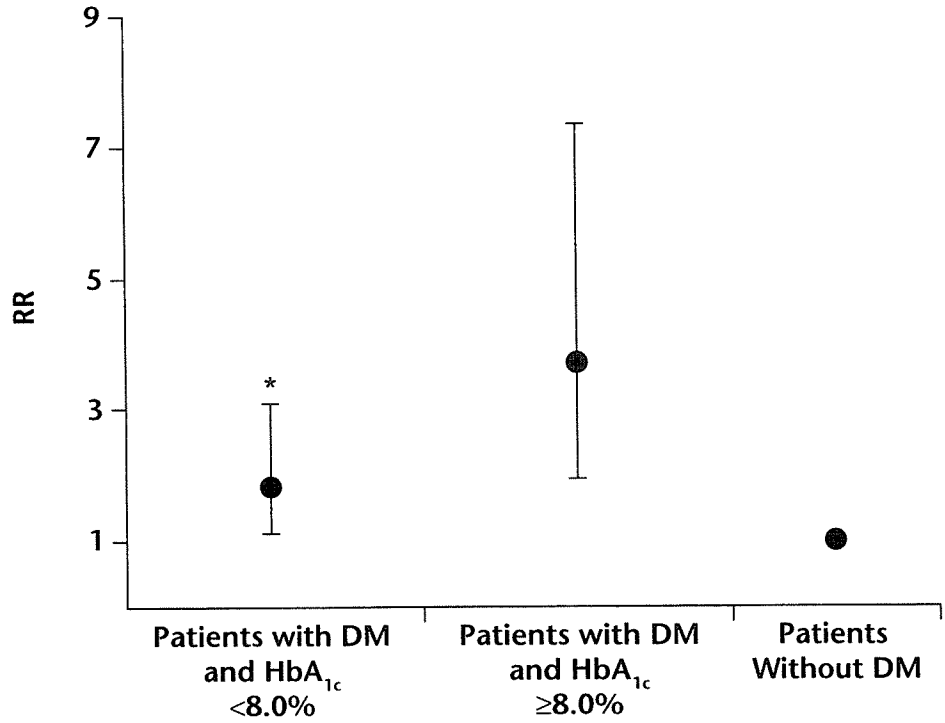

Figure 3. Risk ratios (RRs) (95% CI) for cardiovascular events.[1] Glycosylated hemoglobin (HbA_{1c}) concentrations were measured on enrollment. RRs were calculated from Cox regression analysis adjusted for group, age, sex, smoking history, hypertension, and history of cardiovascular disease. *P = 0.02 versus patients without diabetes mellitus (DM); †P < 0.01 versus patients without DM.

Table III shows the baseline characteristics of 2 subsets of patients with DM (ie, HbA_{1c} <8.0% vs HbA_{1c} ≥8.0%) compared with patients without DM. Because their baseline HbA_{1c} concentrations were not measured, 7 patients with DM were excluded from the analysis of the effect of the extent of glycemic control on CVE prevalence. No significant within-group differences in age or serum lipid levels were observed.

Tolerability

In PATE,[1] the prevalence of adverse events other than CVEs and malignant disease was similarly low in the L group (19 events in 5.4% [18/334] of patients) and the S group (26 events in 6.0% [20/331] of patients). The most common adverse drug reactions observed in the study were a slight elevation in creatine kinase activity (6 cases in the L group; 12 in the S group) and gastrointestinal symptoms (5 cases in the L group; 6 in the S group). Forty-two of 45 adverse events were mild, but 3 events were moderate (L group, decreased peripheral leukocyte count [from 3900 to 2400 cells/μL in 1 patient]; S group, increased blood urea nitrogen [from 20 to 27 mg/dL in 1 patient; from 21 to 29 mg/dL in 1 patient). All 3 of the moderate adverse events resolved on continuation of drug therapy. No serious adverse events were reported in PATE. The prevalence of adverse drug reactions was statistically similar between the groups with and without DM.

Table III. Baseline demographic and clinical characteristics of patients in the Pravastatin Anti-atherosclerosis Trial in the Elderly.

Characteristic	Patients with DM*		Patients Without DM (n = 466)
	HbA_{1c} <8.0% (n = 152)	HbA_{1c} ≥8.0% (n = 40)	
Pravastatin dose, no. (%)			
Low	78 (51.3)	24 (60.0)	230 (49.4)
Standard	74 (48.7)	16 (40.0)	236 (50.6)
Demographic			
Age, mean (SD), y	72.5 (5.4)	72.9 (5.4)	72.9 (5.8)
Sex, no. (%)			
Female	116 (76.3)	30 (75.0)	378 (81.1)
Male	36 (23.7)	10 (25.0)	88 (18.9)
Clinical			
Lipid levels, mean (SD), mg/dL			
TC	254 (15)	251 (15)	253 (15)
HDL-C	57 (15)	57 (16)	55 (15)
LDL-C	162 (24)	160 (25)	167 (24)†
TG	152 (80)	160 (74)	152 (88)
HbA_{1c}, %	6.5 (0.8)	8.7 (0.7)	–
Risk factors, no. (%)			
HTN‡	74 (48.7)	17 (42.5)	242 (51.9)
History of CVD	28 (18.4)	11 (27.5)	132 (28.3)
Smokers	14 (9.2)	4 (10.0)	39/460§ (8.5)

DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HTN = hypertension; CVD = cardiovascular disease.

*Seven patients with DM were excluded from this analysis because their baseline HbA_{1c} levels were not measured.

†$P = 0.03$ versus patients with DM.

‡*Hypertension* was defined as systolic/diastolic blood pressure ≥160/≥90 mm Hg[25] and/or the use of antihypertensive drugs.

§Data were unavailable in 6 patients.

DISCUSSION

DM is a significant risk factor for CVEs in elderly patients with hypercholesterolemia.[5] The results of the present analysis suggest that patients with DM have a similar risk for CVEs as those with a history of CVD. The risk was higher when glycemia was poorly controlled. Although the duration of DM in patients in PATE was not recorded, it has been shown to be proportional to the risk for CVEs.[5] Thus, glycemic control is important in reducing the risk for CVD in elderly patients.

The CARE trial,[19] the 4S,[20,21] and the Heart Protection Study[22] have shown that cholesterol-lowering therapy provides effective prevention of CVEs in patients with and without DM. However, in PATE,[1] CVE risk reduction with pravastatin in patients with DM was less than that in patients without DM. TC and LDL-C levels were decreased in both subgroups, although the difference between the L and S groups was statistically significant ($P < 0.01$).

The discontinuation rate among all patients in PATE was 23.9%, which is similar to the 4-year discontinuation rate of 24.7% observed in the similarly designed West of Scotland Coronary Prevention Study (WOSCOPS),[26] but lower than the 31.3% rate observed in the Helsinki Heart Study.[27]

The daily doses of pravastatin used in the 2 treatment groups in PATE were 5 and 10 mg, a difference of 5 mg. This difference was smaller than that in the CARE trial[19] (40 mg). In the present analysis, the decrease in LDL-C level in patients with DM was not small. Moreover, statins are known to have pleiotropic effects. The decreased risk for CVEs may have been significant in both the L and S groups if a placebo group had been available for comparison. Also, had the LDL-C level been decreased more, a significant risk reduction may have been found. However, the risk reduction was not significant in either of the 2 treatment groups, perhaps because of the small (6%) difference in LDL-C reduction observed between the 2 groups. Furthermore, no linear relationship was found between the degree of TC and LDL-C reduction and the risk for CVEs in CARE[19] or WOSCOPS,[26] in which pravastatin was used.

The small difference between the doses given to the 2 groups in PATE may have obscured the expected CVE risk reduction in elderly patients with DM. The disease picture in elderly patients with DM and hypercholesterolemia is likely so complicated that cholesterol lowering alone may not reduce the risk for CVEs. As for the subgroup with DM, the number of patients with a history of CVD was statistically similar between the L and S groups. In patients with a history of CVD, the S:L hazard ratio was 0.35 (95% CI, 0.06–1.93), whereas in patients with no history of CVD, the S:L hazard ratio was 1.23 (95% CI, 0.53–2.85). The number of patients with DM was too small to analyze the impact of the difference in CVE risk in patients or to allow for further adequate analysis of CVE risk.

The Pravastatin in Elderly Individuals at Risk of Cardiovascular Disease (PROSPER) study,[28] a large, randomized, placebo-controlled trial in which patients in the active-treatment arm received pravastatin 40 mg/d, showed that cholesterol-lowering therapy in elderly patients reduced the risk for CVD. Eleven percent of elderly patients in the PROSPER study had a history of DM. Compared with placebo, pravastatin carried a hazard ratio of 0.79 ($P < 0.01$) in the group of patients without a history of DM and 1.27 (P = NS) in the group in whom DM was reported. However, as in the present study, the number of patients with DM in the PROSPER study was too small to allow an accurate analysis of the effects of therapy.

Freeman et al[29] reported that patients receiving pravastatin had a significantly reduced risk for DM compared with placebo. It is unclear whether this effect

came about in PATE, because changes in glycemia were not recorded. Although patients with DM in the S group had a lower prevalence of CVEs than those in the L group, no clear conclusion could be reached regarding which dose is better for elderly patients with DM. In these patients, there are cardiovascular risk factors in addition to DM (eg, exaggerated platelet adhesiveness, impaired renal function), and these risk factors affect one another. Due to the small sample size and small differences in LDL-C levels, differences in CVE prevalence between the L and S groups in patients with DM were not significant.

Study Limitations and Future Direction

The results of this analysis suggest that pravastatin is effective in reducing the risk for CVEs. However, due to nonsignificant differences in LDL-C reduction between the 2 treatment groups and the small sample size of the study, this study did not show the efficacy of pravastatin in improving hypercholesterolemia. Further study will be necessary to confirm this finding. In addition, the influence of diet was not investigated in this analysis. In future studies, monitoring diet and exercise habits in studies of low- versus standard-dose pravastatin may reveal an expected similarity in the changes in TC and LDL-C levels between treatment groups.

It is clear that elderly patients with DM have an increased risk for CVD. It is hoped that the significance of cholesterol-lowering therapy in such patients can be established.

CONCLUSIONS

In this post hoc analysis of the effect of long-term cholesterol-lowering therapy (low- and standard-dose pravastatin) on cardiovascular outcomes in elderly patients with DM, dose had no effect on the risk for CVEs in these patients as it did in those without DM. In addition, poorer glycemic control in patients with DM was related to a higher risk for CVEs. The lack of pravastatin efficacy found in the subgroup with DM may have been attributable to the small differences in LDL-C levels found between the 2 treatment groups and/or the small sample size of the study.

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Appendix II. Blood glucose levels (mg/dL) used to determine the presence of diabetes mellitus (DM) according to the Japan Diabetes Society.[23]

Diabetic Status	Venous Plasma	Capillary Whole Blood	Venous Whole Blood
Healthy/normal	FPG <110 and 1hPG <160 and 2hPG <120	FPG <100 and 1hPG <160 and 2hPG <120	FPG <100 and 1hPG <140 and 2hPG <110
Borderline	Neither normal nor diabetic	Neither normal nor diabetic	Neither normal nor diabetic
DM	FPG ≥140 and/or 2hPG ≥200	FPG ≥120 and/or 2hPG ≥200	FPG ≤120 and/or 2hPG ≤180

FPG = fasting plasma glucose; 1hPG = 1-hour plasma glucose level on oral glucose (75 mg) tolerance test (OGTT); 2hPG = 2-hour plasma glucose level on OGTT.

The New Worldwide Definition of Metabolic Syndrome Is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions

Additional analysis from the Japan Diabetes Complications Study

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS — The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS — At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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*Members of the JDCS Study Group have been listed previously (1).

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation (b, c, and d include specific treatment for each abnormality)*

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS— Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? 2) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? *3*) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

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Energy intake and obesity in Japanese patients with type 2 diabetes

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Energy intake and obesity in Japanese patients with type 2 diabetes

Sir—Obesity is known to be one of the most important risk factors for the development and deterioration of type 2 diabetes. Nevertheless, we have previously revealed a discrepancy in body-mass indices (BMI) between white and Japanese patients with type 2 diabetes (about 29 kg/m^2 in white patients from the UK Prospective Diabetes Study [UKPDS] *vs* 23 kg/m^2 in Japanese patients from the Japan Diabetes Complications Study [JDCS]) whose other characteristics were very similar.[1] Moreover, by contrast with white patients with type 2 diabetes who have a higher BMI than does the white population as a whole (about 24 kg/m^2), the BMI of Japanese patients is similar to that of the general Japanese population, indicating that Japanese patients with type 2 diabetes are not obese, at least on average.[1]

We recently completed the baseline nutrition analysis of our JDCS patients. Comparing our results with those of the UKPDS,[2] we were surprised to find that the mean daily energy intake of both cohorts was almost the same despite the large differences in BMI and bodyweight (table). In other words, the UKPDS patients developed obesity with a relatively lower energy intake than the JDCS patients, considering the mean height difference between the groups. Accordingly, the daily energy intake per unit of bodyweight was 22% lower in the UKPDS patients than in the JDCS patients. Moreover, 19% of male (27% of female) patients in our cohort overate, taking more than 35 kcal per ideal bodyweight daily. Of those patients, 20% of men (29% of women) had a BMI greater than 25 kg/m^2, which is regarded as being overweight. Accordingly, only 3·8% of male and 7·8% of female patients in the JDCS study population had obesity associated with actual overeating.

This finding runs contrary to the conventional wisdom that the major pathophysiological background to type 2 diabetes is insulin resistance and obesity associated, at least to some extent, with excessive energy intake.

Obesity is known to have preceded and triggered the explosive increase in diabetes among Pacific Islanders and Pima Indians.[3] In Japan, however, despite the lack of a major increase in mean BMI and a decrease in mean total dietary intake since the 1970s, the prevalence of type 2 diabetes is now very high: a sixth of the adult population in Japan had known or strongly suspected diabetes in the most recent national survey. This proportion is much higher than in the European population,[3] and the prevalence is still increasing. The results of recent large-scale epidemiological surveys also suggested that a disturbance of insulin secretion rather than insulin resistance was strongly associated with the development of the disease in Japanese and Chinese patients, unlike in the European population.[4]

Risk factors other than obesity and insulin resistance seem to affect the development of type 2 diabetes in Japanese people. Additionally, even relatively mild obesity could have a major effect on the pathogenesis of diabetes in the Japanese population.[5]

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	JDCS	UKPDS
Patients (men/women)	1076 (576/500)	108 (61/47)
Age (years)	59·4 (7·4)	55·1 (7·7)
Bodyweight (kg)	58·6 (10·1)	78·2 (12·2)
Body-mass index (kg/m^2)	23·1 (3·0)	27·9 (4·3)
Glycohaemoglobin A1C (%)	7·7 (1·4)	7·1 (1·5)
Total energy intake (kcal/day)	1580 (398)	1650 (424)
Men	1778 (428)	1797 (63)*
Women	1598 (390)	1439 (44)*
Total energy intake per kg weight (kcal/kg daily, mean)	27·0	21·1

Values are mean (SD) unless otherwise indicated. *SE.

Total energy intake and other characteristics of patients with type 2 diabetes from Japan Diabetes Complications Study (JDCS) and UK Prospective Diabetes Study (UKPDS)

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≪日本人の糖尿病治療の前向き研究≫ Japan Diabetes Complications Study (JDCS)

曽根博仁　山田信博*　JDCSグループ

要旨

- アジア人糖尿病の大規模臨床試験や前向き疫学研究に基づくエビデンスは，これまで不十分であった．
- JDCSは，日本全国の2型糖尿病患者2,200人余を前向きに追跡している臨床研究である．
- JDCSのデータにより，日本人と欧米人の糖尿病患者を比較すると，肥満や合併症の頻度，合併症のリスクファクターなど，さまざまな違いがみられることが明らかになった．
- 日本人糖尿病患者に最適化された治療のためには，多数の日本人糖尿病患者から得られた臨床エビデンスがさらに充実することが望まれる．

糖尿病の人種差と日本のエビデンスの必要性

2000年の糖尿病患者数は世界人口の2.8%（1億7,100万人）に達し[1]，糖尿病は全世界で290万人の過剰死亡（全死亡の5.2%）を引き起こしたと推測されている[2]．その中でも患者数で世界5位のわが国は，文字通りの「糖尿病大国」といえる[1]．とくに2型糖尿病は，世界的に蔓延する疫病にもたとえられるが，その病態には，かなりの人種・民族間のバリエーション（ethnic differences）があることが知られるようになってきた[3,4]．

これまでの糖尿病の疫学・大規模臨床研究の多くは欧米白人患者を対象としており，一部研究はアフリカ系やヒスパニック系の患者を含むものの，多くの東アジア人を含んだ研究はまれであった．したがって，われわれが日本人糖尿病患者を診療する際にも，これらの欧米の研究から得られたエビデンスを用いざるをえなかった．しかしアジア人と欧米人の糖尿病患者との病態の相違を考慮すると，欧米の大規模臨床研究のエビデンスを，そのまま日本人患者の治療に適用しうるのかは疑問である．

日本人糖尿病患者の大規模臨床試験 JDCS

1996年以来継続されているJapan Diabetes Complications Study（JDCS）[5]の主目的は，①現代日本の2型糖尿病患者の各種病態や治療状況などについて前向き調査を行い，日本人に適した糖尿病治療エビデンスの確立に寄与する，②欧米以外でははじめての糖尿病患者対象の大規模介入研究として，生活習慣介入を中心とした強化治療の有効性を検討する，の2つである．登録者は全国の糖尿病専門施設59ヵ所に通院するHbA_{1c} 6.5%以上の2型糖尿病患者2,205名（臨床的特徴はTable 1に示す）で，血糖・血圧・血清脂質・肥満度・合併症などさまざまな項目について，年1回の調査が続けられている．とくに合併症については，あらかじめ定められた診断基準に基づき専門

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委員により発症の判定が行われている.

糖尿病患者は肥満で食べ過ぎか

欧米では，糖尿病患者の大部分は食べ過ぎと運動不足のため肥満しているとされる[6]．しかし日本人糖尿病患者は一般の人々と比較して，平均的にそれほど肥満しているようにはみえない．そこで，JDCS の登録時データを，英国(United Kingdom Prospective Diabetes Study：UKPDS)や米国(National Health and Nutrition Examination Survey：NHANES)の糖尿病患者のデータと比較したところ[7,8]，糖尿病罹患期間，年齢，血糖コントロールなど多くの指標が各集団でかなり類似していたにもかかわらず，英国や米国人糖尿病患者の body mass index(BMI)は，日本人患者と比較して著明に高値であることが明らかになった(Table 1)．

Table 1. JDCS(登録時)と英国，米国の糖尿病患者の臨床的特徴の比較

	JDCS (日本)	UKPDS (英国)	NHANES (米国)
症例数(人)	2,205	2,015	441
年齢(歳)	59	62	59
糖尿病罹患期間(年)	11	9	13
血圧(mmHg)	132/77	140/80	135/72
空腹時血糖(mg/dl)	158	147	データなし
HbA_{1c}(%)	7.7	7.9	7.8
総コレステロール (mg/dl)	201	205	209
トリグリセリド (mg/dl)	125	137	データなし
body mass index (BMI)(kg/m^2)	23.1	29.4	32.3
一般人口の平均 BMI (kg/m^2)	22.7	24.1	28.5

[文献 6, 7)より引用，改変]

また英・米国人糖尿病患者は，一般人と比較して平均肥満度が高かったのに対して，日本人 2 型糖尿病患者は一般人と肥満度がほとんど変わらず，前述の欧米の認識と日本の実態とのズレが実際に存在することが確認された．逆に日本人では肥満していなくても血糖コントロールがよくない患者が多いという見方もできる．JDCS と UKPDS 症例の食事調査結果を比較してみると，意外にも両コホートの平均摂取エネルギー量がそれほど違わなかったことから[9]，摂食量と太りやすさの関係が，両人種間でかなり異なる可能性が考えられる．

細小血管(毛細血管)合併症の現状

JDCS における網膜症(担当：山形大学眼科，山下英俊教授ほか)発症率を，開始時 HbA_{1c}別に Fig. 1 に示したが，HbA_{1c} 9% 以上の群では，その後 4 年間に 3 割以上が網膜症を発症していた．一方，HbA_{1c} 7% 未満であっても発症は完全に抑制されておらず，網膜症発症予防のためには非常に厳格な血糖コントロールを要することを示している．また開始後 6 年間の糖尿病腎症(担当：埼玉医科大学内科，片山茂裕教授ほか)の発症リスクも，HbA_{1c} 7% 未満の群と比較すると 9% 以上の群のリスクは 4.5 倍に達した．

最近のヨーロッパの 1 型糖尿病患者を対象にした研究[10]では，HbA_{1c}と罹病年数で統計的に調整すると，糖尿病神経障害と心血管合併症のリスクファクターの多くが共通であると報告された．しかし JDCS 登録患者については，ウエスト/ヒップ比以外の心血管リスクファクターで有意な神経障害のリスクファクターになっているものはみられず[11]，糖尿病合併症のリスクファクターも病型や人種による差があることが示唆された．

心血管合併症の特徴

JDCS 8 年間の途中解析結果では，患者 1,000 人あたりの 1 年間の冠動脈疾患発症数は 8.8(男性 10.6，女性 6.8)，脳血管障害は 7.9(男性 8.5，女性 7.0)であった．これは，一般住民を対象にした久山町研究の最近の冠動脈疾患発症率(男性 3.48，女性 1.81)[12]と比べてもかなり高いことがわかる．また英国の 2 型糖尿病患者の大規模臨床研究 UKPDS[13]と比較すると，JDCS では虚血性心疾

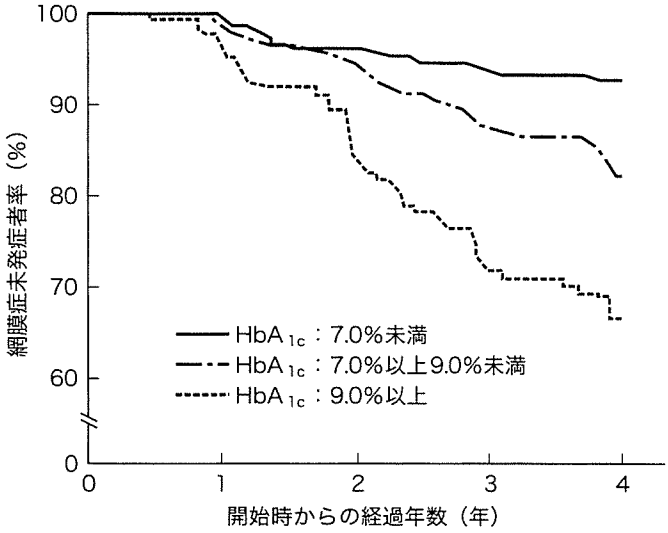

Fig. 1. JDCSにおける糖尿病網膜症発症リスク
JDCS開始時のHbA_{1c}値により層別化した網膜症未発症率の推移.

患は約半数，脳血管障害はJDCSがやや多い程度であった.

糖尿病患者における血圧と血清脂質コントロールの重要性○

糖尿病患者の心血管合併症抑制のためには，血糖と並んで血圧と血清脂質コントロールもきわめて重要である．JDCSにおいても，LDLコレステロール100 mg/dl未満の患者に対する160 mg/dl以上の患者の冠動脈疾患リスクは3.1倍(95%信頼区間：1.6～6.3)になり，収縮期血圧130 mmHg未満の患者に対する150 mmHg以上の患者の脳卒中リスクは2.2倍(95%信頼区間：1.2～3.9)に上昇していた.

それにもかかわらず，糖尿病患者の血圧・血清脂質のコントロールは十分とはいえない[14]．たとえば米国の国民健康栄養調査(NHANES 1999～2000)[8]では，糖尿病患者のうち，収縮期血圧130 mmHg未満かつ拡張期血圧80 mmHgを満たす「コントロール良好者」は36%にすぎず，逆に収縮期血圧140 mmHg以上または拡張期血圧90 mmHg以上の「コントロール不良者」は40%に達していた．また総コレステロール200 mg/dl以上の「コントロール不良者」も52%みられたことが報告されている．この米国患者[8]とJDCS登録患者[15](Table 2)の血圧や血清脂質コントロール不良者率はほとんど変わらず，日本でも米国同様，多くの患者が治療目標に達していないことがわかる．一方，薬物治療では，JDCS登録患者と米国の糖尿病患者では，前述のように血圧や脂質の平均値が極端には違わないにもかかわらず，降圧薬・高脂血症薬の使用頻度が2～3倍も違うことが示唆されており(Table 3)[16]，日本人と欧米人とで，これらの薬物に対する感受性が異なる可能性も考えられる.

日本人糖尿病患者におけるメタボリックシンドローム○

メタボリックシンドロームとは，インスリン抵抗性を基盤とした心血管リスクファクター(耐糖能障害，(腹部)肥満，高血圧，血清脂質異常など)の重積が，心血管疾患を相乗的に増加させる病態である．2型糖尿病患者における，メタボリックシンドローム合併の冠動脈疾患発症に及ぼす影響を検討するために，JDCS患者を対象に，メタボリックシンドロームとその構成因子の有無によって冠動脈疾患発症リスクがどのくらい変わるかを検討した(Table 2)[15].

その結果，女性糖尿病患者では，WHOによるメタボリックシンドローム診断基準を構成する個別因子にあてはまっても，冠動脈疾患ハザード比は有意には上昇しなかったのに対し，WHO基準(Table 4)のメタボリックシンドロームと診断された場合(すでに存在する糖尿病に加え，ほかの項目2個以上を併せ持った場合)は，2.8倍(95%信頼区間：1.0～7.9)の有意な冠動脈疾患リスクの上昇がみられた．すなわちWHO基準は，日本人女性糖尿病患者の冠動脈疾患予測には有用であった．しかし，米国のNational Cholesterol Education Program/Adult Treatment PanelⅢ(NCEP-ATPⅢ)基準(Table 4)によりメタボリックシンドロームと診断された女性糖尿病患者では，そうでない女

Table 2. WHO, NCEP-ATPIIIのメタボリックシンドローム診断基準と，その各項目を満たす患者の比率，および満たした際の心血管疾患ハザード比(95%信頼区間)

個別項目	患者比率(%)		冠動脈疾患ハザード比		脳卒中ハザード比	
	男	女	男	女	男	女
1a. BMI>30 or ウエスト/ヒップ比>0.90(男性)，>0.85(女性)	39.4	37.5	1.3(0.7～2.5)	1.2(0.5～3.0)	1.3(0.7～2.6)	1.1(0.5～2.3)
1b. 腹囲≧85 cm(男性)，90 cm(女性)	36.7	9.6	1.7(0.9～3.0)	1.0(0.2～4.4)	0.90(0.4～1.9)	1.1(0.3～3.7)
2a. 収縮期血圧≧140 または拡張期血圧≧90 mmHg	38.9	38.9	0.8(0.4～1.6)	1.0(0.4～2.6)	2.1(1.1～4.3)*	2.4(1.1～5.5)*
2b. 収縮期血圧≧130 または拡張期血圧≧85 mmHg	60.7	62.2	0.9(0.5～1.6)	0.9(0.4～2.2)	1.4(0.7～2.9)	1.8(0.7～4.5)
3. トリグリセリド(TG)≧150 mg/dl	24.8	21.0	2.9(1.6～5.3)*	1.7(0.6～4.4)	1.1(0.5～2.4)	0.7(0.2～1.9)
4. HDL コレステロール(HDL-C)≦40 mg/dl	19.3	36.3	1.8(0.9～3.5)	1.5(0.6～3.6)	1.0(0.4～2.5)	1.3(0.6～2.9)
5. TG≧50 mg/dl or HDL-C<35 mg/dl	28.5	27.0	2.8(1.6～5.2)*	1.8(0.7～4.5)	0.9(0.4～1.9)	1.6(0.7～3.5)
6. 尿中アルブミン排泄率>30 μg/g CRE	51.2	57.7	1.2(0.6～2.3)	2.9(0.9～8.7)	1.8(0.9～3.8)	1.1(0.5～2.4)
WHO 基準によるメタボリックシンドローム	51.2	52.5	1.3(0.7～2.4)	2.8(1.0～7.9)*	2.0(0.9～4.1)	3.7(1.4～9.9)*
NCEP-ATPIII基準によるメタボリックシンドローム	45.0	38.0	1.9(1.0～3.6)*	1.7(0.7～4.0)	1.4(0.7～2.8)	1.3(0.6～2.8)

NCEP-ATPIII：National Cholesterol Education Program/Adult Treatment PanelIII(米国)　[文献15)より引用，改変]

* $p<0.05$

Table 3. 日本と米国における糖尿病患者の降圧薬・高脂血症薬の使用状況と血圧および血清脂質の状況(平均±標準偏差)

	JDCS (登録時)	MGH Revere Health Care Center
患者数[男性の比率%]	2,205[55]	128[39]
年齢(歳)	59±7	66±12
HbA_{1c}(%)	7.7±1.4	7.7±1.5
収縮期血圧(mmHg)	132±16	136±18
拡張期血圧(mmHg)	77±10	73±10
総コレステロール(mg/dl)	201±35	180±37
降圧薬服用率(%)	28	80
高脂血症薬服用率(%)	26	57

[文献16)より引用]

性患者と比較して冠動脈疾患リスクの有意な上昇はみられなかった[15]．

一方，男性糖尿病患者では，冠動脈疾患発症リスクは，WHO 基準によるメタボリックシンドロームの存在によっては有意に上昇せず，NCEP-ATPIII基準によるメタボリックシンドロームの存在によっては 1.9 倍(95% 信頼区間：1.0～3.6)と一応有意には上昇したものの，その上昇度は，「トリグリセリド上昇(150 mg/dl 以上)」の 1 項目を満たした場合のリスク上昇度(2.9(同：1.6～5.3)倍)より小さかった[15]．このことは，日本人男性糖尿病患者において，現行基準に基づくメタボリックシンドロームの診断は，心血管疾患の発症予測にそれほど有用ではなかったことを示すとともに，中国人のデータ[17]と合わせて，東アジア人糖尿病患者におけるトリグリセリドの重要性を示唆している．

さらに，最近発表された International Diabetes Federation (IDF) のメタボリックシンドロームの診断基準(Table 4)は，腹囲に人種差を取り入れる

Table 4. 現在までの主なメタボリックシンドロームの診断基準または定義

診断基準の種類	WHO 修正基準	NCEP-ATPⅢ基準	IDF 新基準	日本の新基準
判定	2型糖尿病，耐糖能障害，空腹時高血糖，インスリン抵抗性のうちいずれかと，下記のうち2つ以上を満たすもの	下記のうち3つ以上を満たすもの	腹囲とほかの2つ（腹囲閾値は人種により異なる）	腹囲とほかの2つ
（腹部）肥満	BMI＞30 kg/m²または ウエスト/ヒップ比 ＞0.90（男性） ＞0.85（女性）	腹囲 ＞102 cm（男性） ＞89 cm（女性）	腹囲（日本人の場合） ≧85 cm（男性） ≧90 cm（女性）	腹囲 ≧85 cm（男性） ≧90 cm（女性）
トリグリセリド（mg/dl）	≧150 または	≧150（＝1.70 mmol/l）	≧150*	≧150* または
HDL-コレステロール（mg/dl）	＜35（男性） ＜39（女性）	＜40（男性） ＜50（女性）	＜40（男性） ＜50（女性）*	＜40*
血圧（mmHg）	≧140/90	≧130/85	≧130/85*	≧130/85*
空腹時血糖（mg/dl）		≧110（＝6.1 mmol/l）	≧100*	≧110*
尿中微量アルブミン	＞20μg/min または ＞30μg/g Cr			

* それぞれの異常に対する薬物治療を実施している場合も含む．

など世界共通で使用されることを前提にしているが，JDCSの患者においては，上記の2つの従来基準よりも心血管疾患予測能力が低かった[18]．欧米の研究においては，糖尿病患者であっても，メタボリックシンドロームの合併は，心血管疾患の有意な上昇に結び付くことが報告されているが[14]，日本人糖尿病患者では定義や性別により違いがみられることが明らかになった．

おわりに

多くの患者・糖尿病専門医・関係者の努力の賜物であるJDCSは，日本人2型糖尿病の代表的なコホートとして，その病態に関する貴重なデータを含む．欧米人とは基礎的病態が大きく異なる可能性がある日本人糖尿病患者の診療や保健施策においては，日本人患者のデータから得たエビデンスが求められており，その意味でもJDCSの今後の展開が期待される．

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