Risk Factor Analyses for Macrovascular Complication in Nonobese NIDDM Patients

Multiclinical Study for Diabetic Macroangiopathy (MSDM)

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To examine the characteristic features of risk factors for macroangiopathy (MA) in nonobese Japanese NIDDM patients, 899 NIDDM patients with and without MA were registered from 40 facilities. Of these, 386 subjects were identified as having any form of MA (total MA); these included 211 with ischemic heart disease (IHD), 163 with cerebrovascular disease (CVD), and 77 with peripheral vascular disease (PVD). Univariate analyses revealed the following common risk factors for total MA, IHD, CVD, and PVD: age, hypertension, systolic blood pressure (sBP) or diastolic blood pressure (dBP), duration of diabetes, diabetic microangiopathy (retinopathy, nephropathy, and neuropathy), low HDL cholesterol level, and higher LDL cholesterol/HDL cholesterol ratio. Additional significant risk factors for specific conditions were also identified, respectively, as male sex for total MA, IHD, and PVD, smoking for IHD and PVD, and high fasting plasma glucose level for total MA and CVD. With stepwise multivariate logistic regression analysis, older age, duration of diabetes, smoking, and low LDL cholesterol/HDL cholesterol ratio were identified as significant and independent risk factors for total MA, IHD, CVD, and PVD. Other risk factors identified were high dBP for IHD, CVD, and PVD, high sBP for total MA, and low BMI for PVD. These results clearly demonstrated that duration of diabetes, smoking, hypertension, and dyslipidemia are major risk factors for MA in NIDDM patients. Since the mean BMI was similar for both groups (~23 kg/m^2) and there were no significant differences in immunoreactive insulin levels before and after 75-g oral glucose challenge testing, obesity and hyperinsulinism at the time of the analyses were not considered to play an important role for the pathogenesis of MA in Japanese NIDDM patients. By using the χ^2 test, cutoff points were determined for six of the most commonly measured risk factors. The cutoff point was the level beyond which a significantly higher prevalence of MA occurred. The cutoff points (rounded slightly upward in some cases) for fasting plasma glucose, sBP, dBP, serum total cholesterol level, serum triglyceride level, and BMI were 140 mg/dl, 140 mmHg, 80 mmHg, 180 mg/dl, 120 mg/dl, and 23 kg/m^2, respectively. When these cutoff points were used as control criteria, the prevalence of MA was significantly lower in subjects whose risk factor measurements remained under the proposed control criteria for four or more of the six variables. In conclusion, in nonobese NIDDM patients, age, hypertension, and dyslipidemia were found to be risk factors for MA. Duration of diabetes was also demonstrated as an independent risk factor, indicating the close association of deranged glucose metabolism with the pathogenesis of MA in NIDDM patients. It seems to be crucial to control these risk factors for the prevention of MA in NIDDM patients. *Diabetes* 45 (Suppl. 3):S19–S23, 1996

Macrovascular complications are the leading cause of morbidity and mortality in subjects with diabetes in modern industrialized populations, including Japan (1–5). However, it is also well known that there are substantial differences among these populations in the incidence of macroangiopathy (MA). For instance, the incidence of deaths from coronary artery disease in Japanese NIDDM patients (4,5) is far lower than that observed in European and North American NIDDM patients (1–3). Although the main reason for these differences has been thought to be a different lifestyle, the precise reasons are still unclear at present. Possible reasons for differences in the incidence of MA between Japanese and white NIDDM patients are the differential distribution of risk factors and susceptibility to these risk factors. Japanese NIDDM patients are mostly nonobese and normo- or hypoinsulinemic at the time when diabetes is noted. Therefore, we examined risk factors for MA in Japanese nonobese NIDDM patients to compare them with white NIDDM patients.

RESEARCH DESIGN AND METHODS

Subjects. A total of 899 patients with NIDDM were registered from 40 facilities in various districts of Japan during 1990 to 1992. Of the 899

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CVD, cerebrovascular disease; dBP, diastolic blood pressure; FPG, fasting plasma glucose; IHD, ischemic heart disease; MA, macroangiopathy; OGTT, oral glucose tolerance test; PVD, peripheral vascular disease; sBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

TABLE 1
Clinical features of NIDDM patients with and without MA

		MA			
	Without MA	Total	IHD	CVD	PVD
Total number	513	386	211	163	77
Age (years)	59 ± 10	63 ± 8*	62 ± 8*	65 ± 8*	62 ± 9*
Sex (M/F)	252/215	233/136*	139/78†	101/62	53/24†
Smoking (+/−)	135/176	143/138	94/80†	58/53	38/27†
Hypertension (+/−)	55/283	70/159*	32/101†	36/65*	20/32*
sBP (mmHg)	133 ± 20	142 ± 21*	140 ± 20*	145 ± 22*	144 ± 22*
dBP (mmHg)	76 ± 12	79 ± 11*	79 ± 12†	80 ± 12*	80 ± 12†
BMI (kg/m^2)	23 ± 4	23 ± 4	23 ± 4	23 ± 3	22 ± 3
Duration of diabetes (years)	11 ± 8	14 ± 9*	15 ± 9*	15 ± 9*	15 ± 9*
FPG (mg/dl)	151 ± 50	159 ± 61†	154 ± 58	166 ± 64*	162 ± 69
HbA_{1c} (%)	8.1 ± 2.0	8.0 ± 2.0	7.9 ± 1.9	8.1 ± 2.0	7.8 ± 1.9
Retinopathy (+/−)	184/226	177/142*	93/88	91/59*	38/22*
Nephropathy (+/−)	116/312	135/213*	73/133†	67/87*	39/35†
Neuropathy (+/−)	173/253	187/159*	107/98*	91/61*	47/23*
TC (mg/dl)	203 ± 43	208 ± 41	207 ± 39	210 ± 44	200 ± 38
HDL cholesterol (mg/dl)	50 ± 15	45 ± 16*	44 ± 15*	46 ± 17†	41 ± 14*
LDL cholesterol (mg/dl)	127 ± 38	133 ± 36	134 ± 35	136 ± 37†	129 ± 36
LDL/HDL cholesterol	2.8 ± 1.4	3.3 ± 1.4*	3.4 ± 1.5*	3.3 ± 1.4*	3.5 ± 1.5*
TG (mg/dl)	138 ± 111	148 ± 96	147 ± 97	147 ± 85	144 ± 81

Data are means ± SD. *$P < 0.01$ vs. patients without MA. †$P < 0.05$ vs. patients without MA.

NIDDM patients, 386 were identified as having MA. Ischemic heart disease (IHD) was diagnosed based on *1*) clinical symptoms and signs of angina (repeated episodes of chest pain and compatible electrocardiographic findings) and *2*) documentation of myocardial infarction (abnormal and persistent Q or QS waves on electrocardiogram and other supportive findings such as asynergic wall motion on echocardiography). Silent ischemia (a positive stress test without anginal pain) was also included in IHD in this study.

Cerebrovascular disease (CVD), including both cerebral infarction and transient ischemic attacks, was diagnosed using clinical symptoms and findings on computed tomography. Subjects with subarachnoidal hemorrhage, subdural hemorrhage, cerebral bleeding, and cerebral embolism originating from cardiac thrombi were excluded from the study. Peripheral vascular disease (PVD) was diagnosed by angiography, low ankle pressure index (≤0.8), and ulcer, gangrene, or a history of amputation. PVD was also diagnosed when there was intermittent claudication with a unilateral decrease of arterial pulse on the popliteal, posterior tibial, or dorsal pedal artery, or when two or more of the following signs were found: *1*) unilaterally decreased arterial pulse on the popliteal, posterior tibial, or dorsal pedal artery; *2*) previous gangrene and/or ulcer; *3*) moderate or severe calcification of the popliteal, posterior tibial, or dorsal pedal artery; or *4*) unilateral positive findings using plethysmography.

Methods. At registration, a medical history was taken for each subject, including current smoking habits and morbidity, and each patient received a standard physical examination, which included measurements of body height, body weight, and systolic blood pressure (sBP) and diastolic blood pressure (dBP) with the patient in the sitting position. BMI was calculated according to the formula: BMI = weight (kilograms)/height (meters squared). Blood was drawn after an overnight fast for the determination of fasting plasma glucose (FPG), HbA_{1c}, serum total cholesterol (TC), serum HDL cholesterol, and serum triglyceride (TG) levels. LDL cholesterol levels were calculated according to the formula: LDL cholesterol = TC − (HDL cholesterol) − (0.2 × TG) (6).

Data for a 75-g oral glucose tolerance test (OGTT) were also collected in patients in whom this test was performed.

Statistical analysis. The relationship between these clinical features and macroangiopathy were examined using the following statistical analyses. Results for continuous variables of interval scale are given as means ± SD. Subjects with and without MA were compared using Student's *t* test and a χ^2 test when appropriate. Multivariate logistic regression analysis was conducted using the Statistical Analysis System/Matrix Program Package to analyze the association between independent variables and MA. $P < 0.05$ was taken as a significant level.

RESULTS

Distribution of MA in NIDDM patients. Among 386 NIDDM patients with MA, 211 (55%) subjects were suffering from IHD, including 43 with effort angina pectoris, 17 with unstable angina pectoris, 90 with myocardial infarction, and 61 with silent myocardial ischemia. Furthermore, 163 (42%) were suffering from CVD (including 152 with cerebral infarction and 9 with transient ischemic attack), and 77 (20%) had PVD.

Relation of clinical characteristics to MA in NIDDM patients. To understand the relationship between clinical parameters and MA in NIDDM patients, the clinical parameters of subjects with any kind of MA (total MA), IHD, CVD, and PVD were compared with those in subjects without MA (Table 1). Age, sBP, dBP, duration of diabetes, FPG, and LDL cholesterol/HDL cholesterol ratio were significantly higher in total MA subjects than in those without MA. On the other hand, HDL cholesterol was significantly lower in total MA subjects than in subjects without MA. The prevalences of male and of having hypertension, diabetic retinopathy, nephropathy, and neuropathy were significantly higher in total MA subjects than in those without MA.

Similar tendencies were also observed in subjects with IHD, CVD, or PVD. Age was older in the subjects with IHD, CVD, and PVD than in subjects in the population without MA. The prevalences of male sex and being a current smoker were higher in subjects with IHD and PVD than in those without MA. The prevalence of hypertension was higher in subjects with IHD, CVD, and PVD than in those without MA. sBP, dBP, and LDL cholesterol/HDL cholesterol ratio were significantly higher and duration of diabetes was longer in subjects with IHD, CVD, and PVD than in those without MA. The prevalences of diabetic retinopathy, nephropathy, and neuropathy were significantly higher in subjects with IHD, CVD, and PVD except for retinopathy in subjects with IHD. HDL cholesterol was significantly lower in subjects with IHD, CVD, and PVD than in those without MA. In addition,

TABLE 2
Significant risk factors for MA in NIDDM examined by stepwise multivariate logistic regression analysis

	MA			
	Total	IHD	CVD	PVD
Age	$P < 0.001$ (−0.2997)	$P < 0.01$ (−0.2980)	$P < 0.001$ (−0.6859)	$P < 0.01$ (−0.3924)
Sex (male)	—	—	—	—
Duration of diabetes	$P < 0.01$ (−0.2297)	$P < 0.01$ (−0.2482)	$P < 0.05$ (−0.2534)	$P < 0.05$ (−0.2556)
Smoking	$P < 0.05$ (−0.1907)	$P < 0.01$ (−0.2256)	$P < 0.05$ (−0.2044)	$P < 0.01$ (−0.2872)
BMI	—	—	—	$P < 0.05$ (0.3010)
sBP	$P < 0.01$ (−0.2431)	—	—	—
dBP	—	$P < 0.05$ (−0.1917)	$P < 0.001$ (−0.4201)	$P < 0.01$ (−0.3491)
FPG	—	—	—	—
TC	—	—	—	—
HDL cholesterol	—	—	—	—
LDL/HDL cholesterol	$P < 0.01$ (−0.2412)	$P < 0.01$ (−0.2542)	$P < 0.01$ (−0.3464)	$P < 0.001$ (−0.3936)
TG	—	—	—	—

Standardized estimates are shown in parentheses.

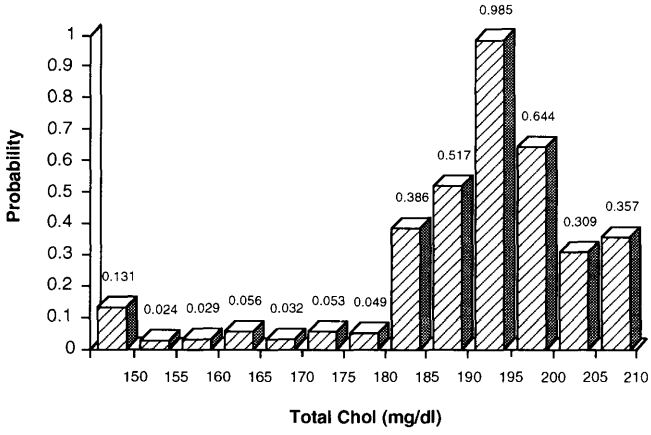

FIG. 1. The effects of serum TC levels on the distribution of NIDDM patients with and without MA. Subjects were divided into four groups according to the presence or absence of MA and serum TC levels indicated in the figure. The probability of a higher prevalence of MA in subjects whose TC levels were beyond the indicated values was calculated using a χ^2 test.

FPG and LDL cholesterol were significantly higher in subjects with CVD than in those without MA.

Multivariate logistic regression analysis was used to assess the independent effect of each variable while controlling for the effects of multiple other risk factors. The results of this analysis are presented in Table 2 as the significant probability associated with each variable. After adjustment for the variables indicated in Table 2, age, duration of diabetes, current smoking, and LDL cholesterol/HDL cholesterol ratio continued to be independent risk factors for total MA, IHD, CVD, and PVD. In addition, sBP for total MA, dBP for IHD, CVD, and PVD, and low BMI for PVD were indicated as significant and independent risk factors. Table 3 summarizes the results of a 75-g OGTT performed before the initiation of treatment for diabetes. There were no significant differences in plasma glucose levels and concentrations of immunoreactive insulin between subjects without MA and total MA, IHD, CVD, or PVD at any time point before and after glucose loading.

Subsequently, we determined a cutoff point for each variable at which changes in the prevalence of total MA reached statistically significant levels using a χ^2 test. Figure 1 shows the results in determining a cutoff point for TC. The prevalence of total MA in subjects with higher TC was significantly or almost significantly higher than in subjects with lower TC at all TC levels of <180 mg/dl. Similarly, cutoff points were determined for the five other most commonly measured clinical parameters: FPG, sBP, dBP, TG, and BMI. The cutoff points were 140 mg/dl for FPG, 135 mmHg for sBP, 76 mmHg for dBP, 120 mg/dl for TG, and 23 kg/m^2 for BMI (Table 4).

Furthermore, we examined the relationship between prevalence of total MA and the number of variables lower than the cutoff point for each variable. In this analysis, we used as control criteria the values of each cutoff point (rounded upward in some cases), i.e., 140 mg/dl for FPG, 140 mmHg for sBP, 80 mmHg for dBP, 180 mg/dl for TC, 120 mg/dl for TG, and 23 kg/m^2 for BMI. To avoid the influence of age, the age of those without MA was adjusted to that of subjects with MA. Table 5 shows the result of this analysis. The prevalence of the total MA gradually increased as the num-

TABLE 3
Plasma glucose and serum immunoreactive insulin levels before and after oral 75-g glucose challenge in NIDDM patients with and without MA

	Without MA	MA			
		Total	IHD	CVD	PVD
n	85	77	55	26	22
Plasma glucose (mg/dl)					
Before 75 g glucose	140 ± 43	140 ± 50	139 ± 52	147 ± 43	135 ± 31
30 min after	229 ± 60	226 ± 57	220 ± 60	239 ± 59	214 ± 31
60 min after	290 ± 74	284 ± 69	278 ± 69	289 ± 77	276 ± 52
120 min after	285 ± 109	305 ± 99	308 ± 104	301 ± 89	307 ± 78
Immunoreactive insulin (μIU/ml)					
Before 75 g glucose	9 ± 10	9 ± 7	9 ± 7	10 ± 8	7 ± 3
30 min after	20 ± 16	21 ± 16	22 ± 18	19 ± 9	14 ± 13
60 min after	32 ± 24	34 ± 40	35 ± 46	28 ± 16	20 ± 19
120 min after	35 ± 24	44 ± 33	46 ± 33	39 ± 30	30 ± 25

Data are means ± SD.

TABLE 4
Cutoff points of FPG levels, sBP, dBP, serum TC levels, serum TG, and BMI in NIDDM

Variable and category	Rate of MA (%)	*P* value
FPG		
<140 mg/dl	38 (142/376)	0.009
≥140 mg/dl	47 (190/404)	
sBP		
<135 mmHg	32 (124/383)	<0.001
≥135 mmHg	53 (201/377)	
dBP		
<76 mmHg	36 (125/348)	0.001
≥76 mmHg	48 (198/409)	
TC		
<180 mg/dl	37 (87/238)	0.048
≥180 mg/dl	44 (259/588)	
TG		
<120 mg/dl	36 (153/422)	<0.001
≥120 mg/dl	49 (182/373)	
BMI		
<23 kg/m^2	41 (186/455)	0.099
≥23 kg/m^2	47 (158/338)	

ber of variables that exceeded control criteria increased. The prevalence of MA was significantly higher in subjects having three or more variables exceeding control criteria.

DISCUSSION

Dyslipidemia, hypertension, hyperinsulinemia, and obesity have been considered major risk factors for MA in the white NIDDM population (1–3). The major purpose of this study was to learn whether these variables are risk factors for MA in Japanese NIDDM patients, who are characterized as being nonobese and lacking hyperinsulinemia.

In univariate analysis (Table 1), age, hypertension, sBP, dBP, duration of diabetes, HDL cholesterol, and LDL cholesterol/HDL cholesterol ratio in subjects with any form of MA, IHD, CVD, and PVD were significantly different from those without MA, and similar risk factors were noted for individual types of MA in NIDDM patients. In addition, male sex and smoking were risk factors for IHD and CVD, and FPG was a risk factor for CVD. Therefore, it is possible to conclude that hypertension, dyslipidemia, and smoking are significant risk factors for MA in Japanese nonobese NIDDM patients, as well as in white NIDDM patients.

TABLE 5
Relationship between prevalence of MA and the number of variables exceeding control criteria for NIDDM

Number of variables exceeding control criteria	Prevalence of MA (%)	*P* value
0*	36 (4/11)	0.356
1–6	50 (199/395)	
0–1	38 (21/55)	0.059
2–6	52 (182/351)	
0–2	42 (60/141)	0.029
3–6	54 (143/265)	
0–3	44 (105/239)	0.003
4–6	59 (98/167)	
0–4	47 (152/323)	0.019
5–6	62 (51/83)	
0–5	48 (187/386)	0.006
6	80 (16/20)	

Variable: 1, FPG <140 mg/dl; 2, sBP <140 mmHg; 3, dBP <80 mmHg; 4, cholesterol <180 mg/dl; 5, TG <120 mg/dl; 6, BMI <23 kg/m^2.

In a large body of literature we failed to find an association between the degree of hyperglycemia and MA in NIDDM patients (2). However, recent reports from the Honolulu Heart Study (6) and the Framingham Study (7) have demonstrated that postchallenge plasma glucose concentrations and HbA_{1c} levels, respectively, are significant and independent risk factors for CVD. Our finding that FPG was one of the risk factors for CVD (Table 1) is in accordance with these results.

Although the duration of diabetes and microangiopathy (retinopathy, nephropathy, and neuropathy) were significantly correlated with MA in univariate analyses (Table 1), the correlation between these two variables (data not shown) was very high ($P < 0.01$). Similarly, the correlations between hypertension and sBP or dBP were very high. Also, for the 75-g OGTT, measurements of immunoreactive insulin could be obtained for only about half of subjects. For these reasons, microangiopathy, hypertension, and the status of insulin secretion were not used as independent variables in multivariate analysis. In multivariate analysis, age, duration of diabetes, current smoking behavior, and LDL cholesterol/HDL cholesterol ratio were demonstrated to be significant and independent risk factors for MA in NIDDM patients (Table 2). These risk factors were common risk factors for subjects with total MA, IHD, CVD, and PVD. Furthermore, sBP positively correlated with total MA, and dBP also positively correlated with IHD, CVD, and PVD. In addition, BMI negatively correlated with PVD. In multivariate analysis, both age and duration of diabetes were independently correlated with MA. However, since a high correlation between age and duration of diabetes was noted, we performed analysis after age adjustment. Even in this analysis (data not shown), the duration of diabetes remained as a significant risk factor.

High circulating levels of TC (8) and low circulating levels of HDL cholesterol (9) have been reported as risk factors for MA in NIDDM as in nondiabetic subjects. Although significant correlations of TC (Fig. 1) and HDL cholesterol (Table 1) to MA were observed in univariate analyses, both TC and HDL cholesterol were not significantly correlated with MA in multivariate analysis (Table 2). The reason for these results may be explained by the significant correlation of TC and HDL cholesterol to the LDL cholesterol/HDL cholesterol ratio.

Recently, hyperinsulinism has been reported as an independent risk factor for MA in NIDDM (10–12). However, no significant differences in serum immunoreactive insulin levels before and after oral 75-g glucose loading were observed between subjects with and without MA (Table 2). Since hyperinsulinism usually accompanies obesity, these results agree with the results that there were no significant differences in BMI between those without and with MA. Thus, hyperinsulinism and insulin resistance, which have been postulated as major risk factors for MA in white NIDDM patients, seem not to play an important role in the pathogenesis of MA in Japanese nonobese NIDDM patients. However, most of our NIDDM subjects have been reported to have been overweight or gone through a stage of obesity with probable hyperinsulinemia before the onset of diabetes. Therefore, hyperinsulinemia may play some role in the initial or early atherosclerotic lesion during the prediabetic stage.

To determine a putative treatment goal for the six most commonly measured risk factors, a cutoff point for each risk factor was defined (Table 4). Proposed control criteria for each variable were obtained from the cutoff points for each variable as follows: FPG <40 mg/dl; sBP <140 mmHg; dBP <80 mmHg; TC <180 mg/dl; TGs <120 mg/dl; and BMI <23 kg/m^2. The result is that the prevalence of MA increases in subjects having three or more variables exceeding the control criteria (Table 5), which indicates that the number of variables exceeding each cutoff point should be two or less to decrease the occurrence of MA. However, further prospective intervention study is necessary to determine the final definite treatment goals for the prevention of MA in NIDDM patients.

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