Diabetic Complications and Their Relationships to Risk Factors in a Japanese Population

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The relationship between diabetic complications and age, sex, duration, mode of therapy, body weight, control of blood glucose, blood pressure, and serum triglyceride and cholesterol was analyzed in a population with non-insulin-dependent diabetes in Japan. The prevalences of complications in the subjects varied from 6.5% for cerebrovascular strokes to 85.1% for sclerotic changes in retinal vessels; 35.8% of the patients had diabetic retinopathy and 19.8% had proteinuria. Univariate and multivariate analyses revealed that control of diabetes (blood glucose, mode of therapy, and duration) was closely correlated with retinopathy and proteinuria. However, blood glucose did not correlate with coronary insufficiency or cerebrovascular strokes. These macrovascular complications were related to aging and blood pressure. The data suggested that not only good glycemic control but also sufficient antihypertensive therapy was necessary for treating diabetic patients. The coefficient of determination of the risk factors was calculated for each diabetic complication. Except for sclerotic changes in retinal vessels, the coefficients were too small to fully explain the development of diabetic complications, especially for macrovascular diseases. The current data suggest that susceptibility of the individual patients to the diabetic complications is an important determinant. DIABETES CARE 1984; 7:533–38.

Diabetes mellitus is associated with an increased incidence of both microangiopathy (diabetic retinopathy and diabetic nephropathy) and macroangiopathy, including coronary insufficiency, cerebrovascular diseases, and peripheral vascular occlusions. In addition to control of blood glucose, there are many risk factors that potentially affect the development of these diabetic complications. Aging, sex, duration of diabetes, obesity, hypertension, hyperlipidemia, age at onset of diabetes, and smoking are thought to be such risk factors.[1–3] Although these factors have some influence on diabetic complications, their intensity and relationship to each complication are still unclear. Furthermore, racial factors and characteristics of the local community might confuse the understanding of the pathogenesis of diabetic complications.[4–7] For these reasons, prophylactic methods for preventing the complications of diabetes mellitus remain uncertain.

In Nagano Prefecture, Japan, the people ingest a large amount of salt and hypertension is very common in this area. We retrospectively analyzed 848 non-insulin-dependent diabetic (NIDD) patients. From these data, we report and discuss (1) prevalences of diabetic complications, (2) possible risk factors, and (3) methods of control for diabetic patients in this area.

MATERIALS AND METHODS

Eight hundred and forty-eight NIDD patients who were regularly followed in the Asama General Hospital, Saku City, Nagano Prefecture, Japan, were the subjects of the study.

Three hundred and fifty-one patients (41.4%) were men and 497 (58.6%) were women. The average age at onset of diabetes was 51.7 yr and the mean duration of the disease was 10.4 yr. About two-thirds of the patients had been followed at this hospital for more than 6 yr of their diabetic life and about one-third of the patients had been followed for more than 13 yr. Two hundred and fifty-four patients were treated with insulin and 398 were treated with oral hypoglycemic agents. The remainder were treated with diet only. Insulin therapy was used for extremely thin patients, pregnant patients, and patients with chronic infections (in-

TABLE 1
Prevalences of diabetic complications in NIDD patients

	RET	PROT	BUN	CREAT	PTR	IHD	CVA	KW	CATA
Grade	Normal	<5 mg/dl	<20 mg/dl	<1.2 mg/dl	Normal*	Normal	Normal	Normal	Normal
No. of patients	508	610	575	639	456	525	792	103	712
Prevalence	64.2%	80.2%	78.1%	87.2%	59.8%	67.4%	93.5%	14.9%	84.0%
Grade	Background†	5–30 mg/dl	>20 mg/dl	>1.2 mg/dl	Diminished	Ischemia (+)	CVA(+)‡	Group 1	Cataract† (+)
No. of patients	250	42	161	94	294	243	55	114	136
Prevalence	31.6%	5.5%	21.9%	12.8%	38.5%	31.2%	6.5%	16.5%	16.0%
Grade	Proliferative†	>30 mg/dl			Absent	Infarction‡ (+)		Group 2 or more	
No. of patients	33	109	—	—	13	11	—	472	—
Prevalence	4.2%	14.3%			1.7%	1.4%		68.5%	
Total no. of patients	791	761	736	733	763	779	847	689	848

RET = retinopathy, PROT = proteinuria, BUN = blood urea nitrogen, CREAT = serum creatinine, PTR = patella tendon reflex, IHD = ischemic changes in EKG and myocardial infarction, CVA = cerebrovascular diseases, KW = sclerotic changes in retinal vessels in Keith et al.[9] classification, and CATA = cataract. *Includes accentuated PTR; †includes patients whose lesion is unilateral; ‡includes old attacks after diagnosis of diabetes.

cluding tuberculosis) or hepatic dysfunction. The rest of the patients were initially treated with only diet for at least 3 mo. Subsequently, when the 2-h postprandial glucose level was greater than about 200 mg/dl, oral hypoglycemic agents were used. When the postprandial glucose level could not be maintained less than about 250 mg/dl by using the full dose of oral hypoglycemic agents, insulin therapy was instituted. For all insulin-treated patients, mean dose of insulin was 17.1 U/day; 53.1% of the patients had been treated with oral hypoglycemic agents or diet only before using insulin.

Fasting and 2-h postprandial blood glucose, urinalysis, chemical analyses of blood, body weight measurement, and physical examination including measurement of blood pressure with a mercury sphygmomanometer by auscultation were performed usually every 2–4 wk. In mild diabetic patients, the 50-g oral glucose tolerance test (OGTT) and recently 75-g OGTT were examined and the patients were confirmed as still having diabetes. Blood glucose was measured on capillary blood by a glucose analyzer using the Hagedorn-Jensen method.[8]

Each patient was prescribed an appropriate diet (25–35 kcal/kg) composed of 70 g of protein and 40 g of lipid, with carbohydrate making up the remaining calories.

Retinae were examined every 6–12 mo by direct ophthalmoscopy or ophthalmographs after pupillary dilatation by an ophthalmologist. Diabetic retinopathy was classified as background or proliferative. Sclerotic changes in retinal vessels were classified according to Keith et al.[9] An electrocardiogram (EKG) was recorded every 6–12 mo. When depressed ST changes and flattened or inverted T-waves in V4–V6 or

TABLE 2
P-values for correlations between diabetic complications and risk factors

Factors	RET	PROT	BUN	CREAT	PTR	IHD	CVA	KW	CATA
Age	NS	<0.01	<0.001	<0.01	NS	<0.001	<0.001	<0.001	<0.001
Sex	NS	NS	NS	<0.001	NS	NS	NS	<0.001	<0.001
DUR	<0.001	<0.01	<0.01	<0.01	<0.001	<0.05	<0.01	<0.001	<0.001
THE	<0.001	<0.01	<0.05	NS	<0.001	NS	NS	NS	<0.001
BW	<0.05	NS	NS	NS	NS	NS	NS	<0.05	NS
FBG	<0.001	<0.05	NS	NS	<0.001	NS	NS	NS	<0.01
PBG	<0.001	<0.001	NS	NS	<0.001	NS	NS	NS	<0.01
SBP	NS	<0.001	<0.001	<0.001	<0.05	<0.001	<0.05	<0.001	NS
DBP	NS	NS	NS	NS	NS	NS	NS	<0.01	NS
TG	NS	NS	NS	NS	NS	NS	NS	NS	NS
CHOL	NS	<0.05	NS	NS	NS	NS	NS	NS	NS

Complete table for all values is shown in Table 4. Abbreviations for the complications are identical to those in Table 1. DUR = duration, THE = mode of therapy (insulin, oral hypoglycemic, or diet therapy only), BW = body weight, FBG = fasting blood glucose, PBG = postprandial blood glucose, SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = serum triglyceride, and CHOL = serum cholesterol.

TABLE 3
Multi-regression analysis of risk factors on diabetic complications

	RET	PROT	BUN	CREAT	PTR	IHD	CVA	KW	CATA
Factor 1	DUR	SBP	Age	Sex	FBG	Age	Age	Age	Age
F-value	39.60‡	46.32‡	13.67‡	61.87‡	17.98‡	24.47‡	15.32‡	340.00‡	29.99‡
Factor 2	PBG	PBG	SBP	SBP	DUR	SBP	DUR	Sex	FBG
F-value	17.04‡	24.47‡	13.58‡	16.16‡	8.14†	12.43‡	6.71*	19.83‡	17.16‡
Factor 3	THE	DBP	THE	THE			DBP	SBP	Sex
F-value	13.20‡	10.49†	10.82†	14.43‡	—	—	4.27*	19.26‡	11.74‡
Factor 4	SBP	Sex	DUR	Age				PBG	BW
F-value	7.84†	7.69†	9.68†	6.24†	—	—	—	15.02‡	8.29†
Factor 5	Sex		BW	FBG					DUR
F-value	4.61*	—	4.40*	4.89*	—	—	—	—	7.00*
Factor 6			PBG						
F-value	—	—	3.91*	—	—	—	—	—	—
No. of patients	735	709	685	683	709	724	784	641	785
Coefficient of determination	17.15%	9.48%	10.46%	12.90%	4.04%	7.50%	3.59%	47.45%	9.90%

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$. Abbreviations for the complications are identical to those in Table 1. DUR = duration, SBP = systolic blood pressure, FBG = fasting blood glucose, PBG = postprandial blood glucose, THE = mode of therapy (insulin, oral hypoglycemic, or diet therapy only), DBP = diastolic blood pressure, and BW = body weight.

II, III, and aVf leads, complete right-bundle branch block or left-bundle branch block, prolonged PQ-interval, or sporadic ventricular or atrial premature beats were found in the record, ischemic changes was regarded as present.

Blood chemistry was performed by an autoanalyzer (Hitachi model 726, Tokyo, Japan).

The mean fasting and postprandial blood glucose values throughout the follow-up period in each patient were used for the analysis. The mean systolic and diastolic blood pressures throughout the same period were also used in the study. Univariate statistical analysis was performed by chi-square and correlation coefficient methods. Multivariate analysis was performed using the step-wise method of multi-regression analysis.

RESULTS

Prevalences of diabetic complications in NIDD patients. Table 1 summarizes the prevalences of diabetic complications, which include diabetic retinopathy, proteinuria, elevated blood urea nitrogen (BUN) and serum creatinine, diminished patella tendon reflex (PTR), ischemic changes in EKG, cerebrovascular attacks (CVA), sclerotic changes in retinal vessels, and senile cataract. Only 14.9% of the patients were normal with respect to sclerotic changes in the retina, but in regard to the other parameters, more than 50% of the patients had no detectable abnormalities.

Correlation between diabetic complications and risk factors. Table 2 shows univariate statistical relationships between these diabetic complications and age, sex, duration, mode of therapy (insulin, oral hypoglycemic, or diet therapy only), body weight (percent of ideal body weight), mean fasting blood glucose (throughout the follow-up period), mean postprandial blood glucose, mean systolic blood pressure, mean diastolic blood pressure, and serum triglyceride and cholesterol. The complete listing of all values in Table 2 is given in the APPENDIX (see Table 4). Retinopathy and diminished PTR strongly correlated with duration, mode of therapy, and blood glucose. Intensity of proteinuria correlated with systolic blood pressure and age in addition to duration, mode of therapy, and blood glucose. BUN and creatinine did not correlate with blood glucose.

With respect to macroangiopathies (ischemic changes in EKG, CVA, and sclerotic changes in retinal vessels), there were no relationship to diabetic control (i.e., mode of therapy, fasting blood glucose, and postprandial blood glucose). These complications were found to be correlated with aging and blood pressure. Cataract, which was the senile type, correlated to diabetes control and aging.

Hypertriglyceridemia and hypercholesterolemia were weak risk factors in the analysis.

Multi-regression analysis of diabetic complications. Relationships between risk factors and diabetic complications in the NIDD patients were also analyzed by the step-wise method of multi-regression analysis. Because the levels of serum triglyceride and cholesterol had almost no correlation to diabetic complications (Table 2), they were not used in the analysis. It was found that blood glucose, whether fasting or postprandial, was significantly related to retinopathy, proteinuria, diminished PTR, sclerotic changes in retinal vessels and cataract, and less significantly to serum BUN and creatinine concentrations (Table 3). It did not correlate to ischemic changes in EKG and CVA. On the other hand, hypertension correlated to retinopathy, proteinuria, BUN, creatinine, ischemic changes in EKG, CVA, and sclerotic changes in retinal vessels. It was not associated with cataract and diminished PTR. It is noteworthy that colineal risk factors (such as mode of therapy, fasting blood glucose, and

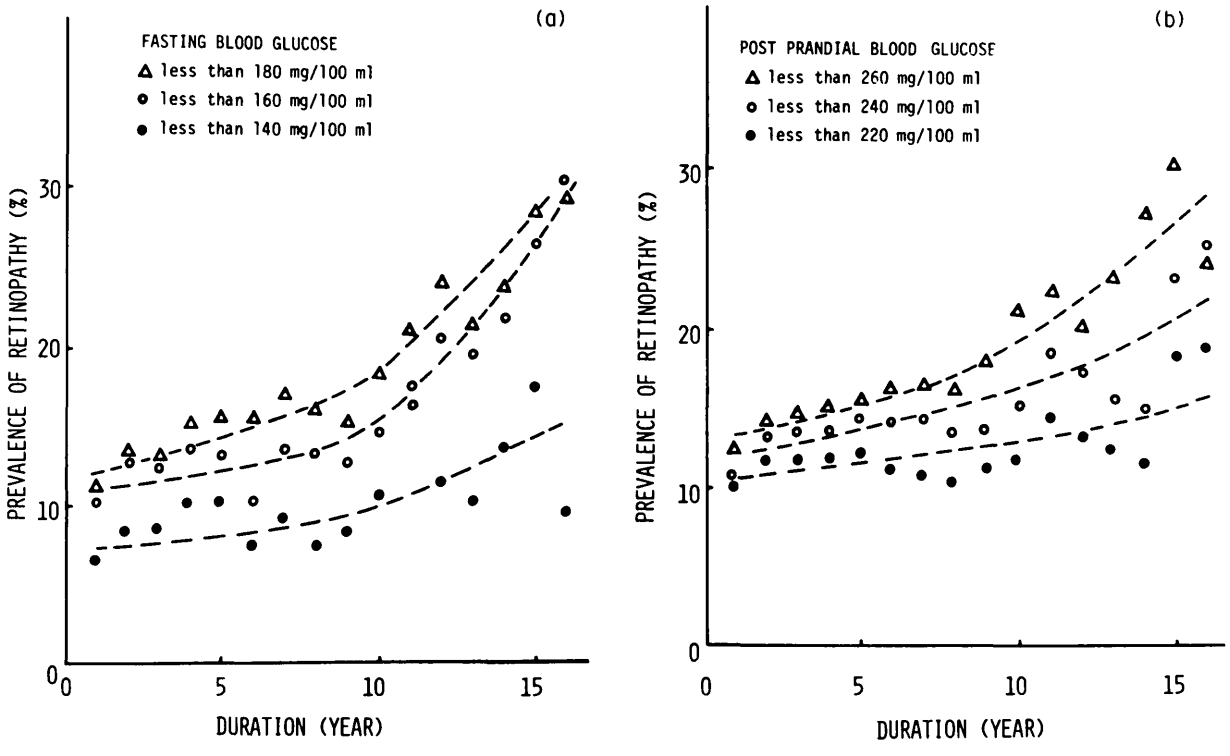

FIG. 1. Prevalence of retinopathy in relation to control of blood glucose.

postprandial blood glucose) can hardly be interpreted as significant variables at the same time in step-wise methods.

Age was related to BUN, creatinine, ischemic changes in EKG, CVA, sclerotic changes in retinal vessels, and cataract and was not related to retinopathy and diminished PTR. Mode of therapy had a similar pattern to blood glucose. Duration of diabetes was similar to blood glucose and age.

It was surprising that these risk factors explained only a part of the diabetic complications. For example, five significant risk factors (i.e., duration, postprandial blood glucose, mode of therapy, systolic blood pressure, and sex) explained only 17.2% of diabetic retinopathy; 82.8% of retinopathy was unclear as to its etiology in this analysis. In CVA, 96.4% was statistically obscure.

Prevalence of diabetic retinopathy and control of blood glucose. Since Tables 2 and 3 showed that blood glucose was one important risk factor for diabetic retinopathy, the patients were grouped according to good, fair, or poor blood glucose control, and the prevalence of retinopathy was plotted year by year after initiation of treatment. The prevalence developed very slowly when fasting blood glucose was <140 mg/dl and/or postprandial blood glucose was <220 mg/dl. (Our blood sample was capillary.) However, when blood glucose was >140 mg/dl fasting or >220 mg/dl postprandial, the prevalence of retinopathy was progressively increased, especially when the duration of treatment was longer than 10 yr.

DISCUSSION

The patients with NIDD reported here are both similar and dissimilar to those of other reports in several respects. First, NIDD is more prevalent in women than in men, the sex ratio being similar to that of developed countries.[10] Second, mean age at onset of NIDD is about 50 yr. Again, this is comparable to that of developed countries. Third, as compared with normal Japanese subjects, the patients with NIDD have relatively high incidences of hypertension, degenerative osteoarthropathies, cerebrovascular diseases, and ischemic abnormalities on the EKG. These tendencies agree well with previous reports.[11-14] However, the incidence of hypertension is greater in our study than in others, possibly due to high salt intake in our group.[15] In contrast, incidences of ischemic heart diseases are less in our study than in other reports. Fourth, marked obesity and hyperlipidemia are rare in our study because of limited intake of dietary lipid. This low intake of lipid may be responsible, at least in part, for a relatively low incidence of myocardial infarction in our group.

Univariate and multivariate analyses indicated that control of blood glucose closely correlated to the prevalences of microangiopathies such as diabetic retinopathy (Tables 2 and 3). It was also shown that long duration of diabetes was correlated to the development of diabetic retinopathy. As a practical clue, it seemed that blood glucose <140 mg/dl

TABLE 4
Correlations between diabetic complications and risk factors

Factors	Mean	SD	RET	PROT	BUN	CREAT	PTR	IHD	CVA	KW	CATA
Age (yr)	62.12	12.01	779 (4)	751 (4)	725*	722*	753 (4)	768 (4)	835 (2)	677 (4)	836 (2)
			5.95	11.62‡	0.2351§	0.1263‡	3.85	48.74§	21.04§	266.8§	30.59§
Sex	—	—	791 (2)	761 (2)	736 (2)	733 (2)	763 (2)	779 (2)	847 (1)	688 (2)	848 (1)
			2.46	2.64	1.42	101.5§	5.41	3.78	1.79	33.93§	16.36§
DUR (yr)	10.41	5.96	777 (4)	751 (4)	726*	723*	752 (4)	768 (4)	830 (2)	678 (4)	831 (2)
			70.31§	14.40‡	0.1991‡	0.09783‡	21.91§	11.60†	12.38‡	23.86§	25.07§
THE	—	—	791 (4)	761 (4)	736 (4)	733 (4)	763 (4)	779 (4)	847 (2)	688 (4)	848 (2)
			75.44§	15.05‡	11.16†	7.97	37.85§	6.49	2.00	0.99	17.06§
BW (% of IBW)	104.82	14.38	764 (4)	732 (4)	708*	706*	732 (4)	748 (4)	815 (2)	644 (4)	816 (2)
			10.71†	3.74	−0.0584	−0.0506	8.42	5.64	0.32	12.95†	4.30
FBG (mg/dl)	161.01	38.89	790 (4)	759 (4)	734*	731*	761 (4)	777 (4)	845 (2)	687 (4)	846 (2)
			69.77§	9.77†	0.00933	−0.0378	24.82§	1.74	0.28	2.74	14.06‡
PBG (mg/dl)	220.88	61.37	789 (4)	756 (4)	732*	729*	758 (4)	774 (4)	842 (2)	686 (4)	843 (2)
			78.28§	24.92§	0.02447	0.01083	23.86§	2.09	1.19	6.30	16.22‡
SBP (mm Hg)	139.84	17.98	789 (4)	756 (4)	733*	730*	759 (4)	775 (4)	842 (2)	687 (4)	843 (2)
			9.01	23.55§	0.1884§	0.1602§	13.15†	42.96§	8.67†	99.25§	0.78
DBP (mm Hg)	81.87	9.97	789 (4)	756 (4)	733*	730*	759 (4)	775 (4)	842 (2)	687 (4)	843 (2)
			0.37	4.46	0.0202	0.0713	7.35	8.89	7.48	16.75‡	2.98
TG (mg/dl)	135.72	78.07	562 (4)	578 (4)	578*	577*	581 (4)	591 (4)	593 (2)	528 (4)	594 (2)
			5.29	5.24	0.0234	0.0593	7.89	3.76	3.32	8.29	0.63
CHOL (mg/dl)	215.13	44.55	703 (4)	726 (4)	723*	721*	730 (4)	744 (4)	746 (2)	663 (4)	747 (2)
			0.73	12.38†	0.0637	−0.0181	2.78	8.60	2.18	9.34	0.33

Analyses performed by chi-square test or correlation coefficient(*). Upper figure is the number of patients and the degree of freedom is in parentheses for chi-square. Lower figure is chi-square or correlation coefficient. †$P < 0.05$; ‡$P < 0.01$; §$P < 0.001$. Abbreviations for the complications and risk factors are identical to those in Table 1 and Table 2, respectively.

fasting and <220 mg/dl postprandial was the therapeutic goal necessary for preventing diabetic retinopathy (Figure 1). In addition to blood glucose, systolic blood pressure also correlated with the development of diabetic retinopathy. With respect to renal function, our data suggested that hypertension is implicated in microangiopathy of the kidney. This finding is consonant with the finding by Mogensen that antihypertensive therapy is effective in preventing renal insufficiency of diabetic patients.[16]

With respect to macroangiopathies, blood glucose elevation did not closely correlate with the incidence of ischemic heart diseases or cerebrovascular disease. In addition, hyperlipidemia also did not correlate with the incidences of macrovascular diseases. As is generally assumed, however, a high incidence of hypertension may play a role in the development of ischemic heart and cerebrovascular diseases in the patients studied here. The aging process may also play an important role.

Although cataract formation is generally believed to be due to the aging process, our analysis indicated that high blood glucose plays an additional role in accelerating the progress of senile cataract. Since a cataract strongly disturbs the visual life of the patients, particular attention should be focused on slowing the formation of senile cataract through blood glucose control.

APPENDIX

All statistical values in Table 2 are summarized in Table 4. Analyses were performed by chi-square test or correlation coefficient. For chi-square, the patients were divided into three groups in which mean ± (standard deviation)/2 of age, duration, body weight, fasting and postprandial blood glucose, systolic blood pressure, and serum triglyceride and cholesterol were used for their division points.

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