High Blood Pressure as Risk Factor in Diabetic Retinopathy Development in NIDDM Patients

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The correlation between diabetic retinopathy and blood pressure was analyzed in 742 type II diabetic patients. Systolic and pulse blood pressures were significantly higher in the patients with retinopathy than in those without (mean systolic pressure 142 vs. 139 mmHg, $P < .01$; mean pulse pressure 60.5 vs. 56.4 mmHg, $P < .001$). There was no difference in the diastolic blood pressure between these two groups. The correlation between blood pressure and the components of retinopathy (including microaneurysms, hemorrhages, and exudates) was also analyzed. Even when the patients with microaneurysms or dot hemorrhages, blot hemorrhages, or hard or soft exudates were separately evaluated, systolic and pulse blood pressures were higher in those with one of these diabetic changes than in patients without them.

To avoid the influence of nephropathy, the patients were divided into nonproteinuric or proteinuric groups. In the nonproteinuric group, pulse blood pressure was higher in patients with retinopathy than in those without. In the proteinuric group, systolic blood pressure was also higher in patients with retinopathy than in those without. However, these observed differences in blood pressure were slight after the division of the patients. With respect to the components of retinopathy, systolic and pulse blood pressures were significantly higher in the patients with blot hemorrhages than in those without in both nonproteinuric and proteinuric groups (nonproteinuric: systolic pressure 142 vs. 137 mmHg, $P < .005$, and pulse pressure 60.4 vs. 55.5 mmHg, $P < .001$; proteinuric: systolic pressure 155 vs. 146 mmHg, $P < 0.01$, and pulse pressure 69.0 vs. 63.5 mmHg, $P < .05$). In regard to other components (microaneurysms, dot hemorrhages, or hard or soft exudates), no significant difference was found in blood pressure when analyzed in both nonproteinuric and proteinuric patients.

Systolic, diastolic, and pulse blood pressures did not correlate with blood glucose level in any of our patients. These data revealed that systolic hypertension is a risk for diabetic retinopathy, especially for blot hemorrhage. *Diabetes Care* 10:20–25, 1987

Although an elevated blood pressure has been postulated as one of the risk factors for the development and acceleration of diabetic retinopathy, demonstration of an unequivocal association between high blood pressure and retinopathy is lacking, possibly because the association is not strong and is masked by other risk factors (1). Nevertheless, recent epidemiological studies indicated the close relationship between elevated blood pressure and diabetic retinopathy (2–4), especially in patients with severe retinopathy (5,6) or retinal exudates (7).

In our previous study, we systematically evaluated diabetic complications and their risk factors in Japanese diabetic patients and found that an elevated blood pressure was closely correlated with retinal derangement, coronary insufficiency, and cerebrovascular diseases (8). The purpose of this study is to delineate further the relationship between high blood pressure and diabetic retinopathy in the same patients.

PATIENTS AND METHODS

All non-insulin-dependent diabetic patients seen at the outpatient clinic of Asama General Hospital, Saku, Japan, from

TABLE 1
Associations between diabetic retinopathy and other variables

Variable	Without retinopathy	With retinopathy	P
Age (yr)	61.6 ± 12.0 (469)*	63.4 ± 10.5 (273)	<.05
Age at onset of diabetes (yr)	53.4 ± 11.8 (469)	51.6 ± 10.8 (273)	<.05
Duration of diabetes (yr)	9.19 ± 5.55 (469)	12.8 ± 5.63 (273)	<.001
Fasting blood glucose (mg/dl)	155 ± 36.0 (469)	174 ± 38.3 (273)	<.001
Postprandial blood glucose (mg/dl)	210 ± 58.4 (469)	246 ± 56.5 (273)	<.001
Systolic blood pressure (mmHg)	139 ± 17.3 (469)	142 ± 18.2 (273)	<.01
Diastolic blood pressure (mmHg)	82.2 ± 9.84 (469)	81.9 ± 9.93 (273)	NS
Pulse blood pressure (mmHg)	56.4 ± 12.8 (469)	60.5 ± 14.1 (273)	<.001
Blood urea nitrogen (mg/dl)	16.5 ± 4.76 (463)	17.9 ± 7.67 (272)	<.01
Serum creatinine (mg/dl)	0.931 ± 0.208 (461)	1.00 ± 0.455 (272)	<.05
Serum triglyceride (mg/dl)	133 ± 76.2 (437)	138 ± 81.1 (266)	NS
Serum cholesterol (mg/dl)	214 ± 43.6 (461)	218 ± 45.7 (272)	NS
Body weight (% ideal body wt)	105 ± 15.0 (469)	104 ± 12.9 (273)	NS
Sex (F/M)	262/207	172/101	NS
Insulin treated	99/469†	129/273	<.001
Proteinuria (>30 mg/dl)	46/469	66/273	<.001
Sclerosis of the retinal vessels	289/467	222/272	<.001
Patellar tendon reflex (diminished)	162/466	138/271	<.001
Ischemic changes in ECG (present)	146/468	95/273	NS
Cerebrovascular attacks (present)	33/469‡	15/273	NS
Cataract (present)	60/469	61/273	<.001

Statistical analyses were performed by Student's t test and χ^2-test.
*Means ± SD, with number of patients in parentheses.
†Number of patients with attribute/total number of patients.
‡Includes old attacks after diagnosis of diabetes.

January to May 1982 were recorded. Out of 848 patients, 742 in whom retinas and the presence of proteinuria had been examined, were evaluated retrospectively in our study. The retinas of 57 patients were not examined, and the presence or absence of proteinuria could not be determined in 87 patients.

The fundoscopic examinations of retina were performed from January to December 1982 by an ophthalmologist (K.O.) with direct ophthalmoscopy and ophthalmographs after dilation of the pupils. In patients with diabetic retinopathy, presence or absence of microaneurysms or dot hemorrhages (which are small red lesions and not distinguishable from each other), blot hemorrhages (hemorrhagic lesions that are larger than microaneurysms or dot hemorrhages), and hard and soft exudates (cotton-wool spots) were individually recorded. When the ophthalmologic findings on the right and left eyes were different, the data on the more advanced side in each patient were used for the analysis.

All patients were seen at the outpatient clinic every 2 or 4 wk, and the capillary blood glucose was measured at each visit by the Hagedorn-Jensen method (9). Systolic (phase I) and diastolic (phase V) blood pressures were measured with a mercury sphygmomanometer at each visit after at least 5 min of rest in the supine position. The presence of proteinuria was checked semiquantitatively with Combistix (Miles, Sankyo, Tokyo, Japan). The measurement was made more than 3 times from January to December 1982. When all measurements were >30 mg/dl, proteinuria was regarded as present. The patients with chronic urinary tract infection (14 patients), tumor (1 patient), collagen vascular diseases (10 patients), uncontrolled heart failure (1 patient), and whose proteinuria could not be examined more than 3 times (61 patients) were excluded from the analysis.

For fasting and 2-h postprandial blood glucose levels and systolic and diastolic blood pressures, the mean values throughout the follow-up period in each patient from initial visit to May 1982 were used for analysis. The average number of measurements per patient was 62 (range 6–156) for fasting and 54 (range 6–138) for postprandial blood glucose. For blood pressure, average number of measurements was 96 (range 6–264). The difference between mean systolic and diastolic blood pressures was defined as the pulse pressure. The mean systolic blood pressure was >160 mmHg in 88 patients and >170 mmHg in 31 patients. The mean diastolic blood pressure was >95 mmHg in 77 patients and >100 mmHg in 30 patients. Hypertensive patients were treated with salt restriction and/or antihypertensive drugs with the treatment goal of <160 mmHg for systolic and <95 mmHg for diastolic blood pressures. For 262 patients, antihypertensive drugs were used (89 received diuretics), and mean systolic and diastolic blood pressures were 153 and 87.2 mmHg, respectively; these values were 133 and 79.3 mmHg, respectively, in patients receiving no antihypertensive drug. For other clinical variables, the latest data from January to December 1982 were

TABLE 2
Associations between blood pressure and components of diabetic retinopathy

	Microaneurysm or dot hemorrhage			Blot hemorrhage			Hard exudate			Soft exudate		
	With	Without	P	With	Without	P	With	Without	P	With	Without	P
SBP (mmHg)	142 ± 18.3 (234)*	139 ± 17.4 (508)	<.05	146 ± 17.8 (175)	138 ± 17.3 (567)	<.001	147 ± 17.0 (74)	139 ± 17.7 (668)	<.001	146 ± 17.7 (57)	139 ± 17.7 (685)	<.005
DBP (mmHg)	82.1 ± 10.1	82.1 ± 9.77	NS	83.0 ± 9.92	81.8 ± 9.85	NS	83.7 ± 9.49	81.9 ± 9.90	NS	83.7 ± 8.62	82.0 ± 9.96	NS
PBP (mmHg)	59.9 ± 14.0	56.9 ± 13.1	<.005	63.0 ± 14.0	56.3 ± 12.9	<.001	63.0 ± 13.0	57.3 ± 13.4	<.001	62.6 ± 14.1	57.7 ± 13.3	<.01

SBP, systolic blood pressure; DBP, diastolic blood pressure; PBP, pulse blood pressure; NS, not significant.
Statistical analysis was performed by Student's *t* test.
*Means ± SD are given, with number of patients in parentheses.

used for the analyses. Not all the clinical variables were measured in some patients. In each analysis, patients with missing data were excluded.

Univariate statistical analysis was performed by the χ^2-method and Student's *t* test. Multivariate analysis was performed by discriminant analysis (10).

RESULTS

Diabetic retinopathy and associated risk factors. The correlation between retinopathy and 23 variables is summarized in Table 1. Systolic and pulse blood pressures but not diastolic blood pressure, were higher in patients with than in those without diabetic retinopathy. The patients with retinopathy were also significantly different from patients without it in that *1*) patients were older, *2*) onset of diabetes was earlier, *3*) duration of diabetes was longer, *4*) blood glucose level was higher for both fasting and postprandial, and *5*) prevalence of insulin usage was higher. The prevalence of other diabetic complications (proteinuria, increased blood urea nitrogen and creatinine levels in the blood, cataracts, and diminished deep tendon reflex) was also higher in the patients with retinopathy. The prevalence of macroangiopathy (ischemic changes in ECG and cerebrovascular diseases) was the same in patients with and without diabetic retinopathy.

Relationship between blood pressure and components of diabetic retinopathy. In patients with diabetic retinopathy, an association between a component of diabetic retinopathy, (e.g., microaneurysm or dot hemorrhage, blot hemorrhage and hard or soft exudate) and blood pressure was analyzed (Table 2). With respect to all components of retinopathy, systolic and pulse blood pressures were higher in the patients with diabetic change than in the patients without it. Diastolic blood pressure was similar regardless of whether patients had any of the components of diabetic retinopathy.

Association between diabetic retinopathy and blood pressure in patients with or without proteinuria. To assess the influence of renal damage (as indexed by proteinuria) on the association of high blood pressure and diabetic retinopathy, patients were divided into proteinuric and nonproteinuric groups, and the correlation between elevated blood pressure and the presence of retinopathy was analyzed in each group (Table 3). In proteinuric patients, systolic and pulse blood pressures were higher than in nonproteinuric patients regardless of presence or absence of retinopathy. When the nonproteinuric group was evaluated, pulse blood pressure was slightly but significantly higher in the patients with retinopathy. However, systolic and diastolic blood pressure were comparable in the patients with or without retinopathy. In the proteinuric group, only systolic blood pressure was significantly higher in patients with retinopathy.

The association between blood pressure and individual components of diabetic retinopathy was further analyzed separately in the nonproteinuric and proteinuric patients (Table 4). Systolic and pulse blood pressures were significantly higher in the patients with blot hemorrhages than in those without in both nonproteinuric and proteinuric groups. In nonpro-

TABLE 3
Associations between blood pressure and diabetic retinopathy in nonproteinuric and proteinuric patients

Blood pressure	Nonproteinuric patients			Proteinuric patients		
	Without retinopathy	With retinopathy	*P*	Without retinopathy	With retinopathy	*P*
Systolic (mmHg)	138 ± 17.2 (423)*	139 ± 17.0 (207)	NS	145 ± 17.9 (46)†	153 ± 17.4 (66)‡	<.05
Diastolic (mmHg)	82.3 ± 9.85	80.8 ± 9.21	NS	81.5 ± 9.81	85.5 ± 11.3‡	NS
Pulse (mmHg)	55.6 ± 12.3	58.1 ± 13.3	<.05	63.4 ± 15.2‡	68.0 ± 14.0‡	NS

NS, not significant.
Statistical analysis was performed by Student's *t* test.
*Means ± SD, with number of patients in parentheses.
†$P < .01$ and ‡$P < .001$ vs. comparable group in nonproteinuric patients.

teinuric patients, only pulse pressure was higher in the patients with hard exudates than those without. However, in both the nonproteinuric and proteinuric groups, there was no difference in the blood pressure, regardless of whether the patients had microaneurysms, dot hemorrhages, or soft exudates.

Correlation coefficients between blood pressure and other variables. Age correlated most strongly with systolic and pulse blood pressures but not with diastolic blood pressure (Table 5). Also, duration of diabetes correlated positively with systolic and pulse blood pressures but negatively with diastolic blood pressure. However, blood glucose level (either fasting

TABLE 4
Associations between blood pressure and components of diabetic retinopathy in nonproteinuric and proteinuric patients

	Systolic (mmHg)	Diastolic (mmHg)	Pulse (mmHg)
Nonproteinuric patients			
Without microaneurysm or dot hemorrhage	138 ± 17.3 (455)*	82.2 ± 9.80	56.0 ± 12.5
With microaneurysm and dot hemorrhage	138 ± 16.7 (175)	80.7 ± 9.25	57.5 ± 13.1
P value	NS	NS	NS
Without blot hemorrhage	137 ± 17.1 (507)	81.8 ± 9.82	55.5 ± 12.4
With blot hemorrhage	142 ± 16.7 (123)	81.8 ± 9.04	60.4 ± 13.0
P value	<.005	NS	<.001
Without hard exudate	138 ± 17.2 (586)	81.8 ± 9.72	56.1 ± 12.7
With hard exudate	142 ± 15.3 (44)	81.6 ± 9.00	60.8 ± 11.9
P value	NS	NS	<.05
Without soft exudate	138 ± 17.2 (594)	81.8 ± 9.81	56.3 ± 12.7
With soft exudate	141 ± 14.7 (36)	81.6 ± 7.08	59.2 ± 12.2
P value	NS	NS	NS
Proteinuric patients			
Without microaneurysm or dot hemorrhage	146 ± 17.4 (53)†	81.2 ± 9.59	65.0 ± 15.0‡
With microaneurysm and dot hemorrhage	153 ± 18.1 (59)‡	86.2 ± 11.4‡	67.0 ± 14.3‡
P value	NS	NS	NS
Without blot hemorrhage	146 ± 17.7 (60)‡	82.1 ± 10.2	63.5 ± 14.5‡
With blot hemorrhage	155 ± 17.3 (52)‡	85.8 ± 11.3§	69.0 ± 14.4‡
P value	<.01	NS	<.05
Without hard exudate	149 ± 18.2 (82)‡	82.7 ± 11.2	66.0 ± 15.0‡
With hard exudate	153 ± 17.5 (30)†	86.8 ± 9.47§	66.4 ± 13.9
P value	NS	NS	NS
Without soft exudate	149 ± 17.7 (91)‡	83.0 ± 10.9	65.5 ± 14.5§
With soft exudate	156 ± 18.8 (21)‡	87.3 ± 9.93§	68.5 ± 15.4§
P value	NS	NS	NS

NS, not significant.
Statistical analysis was performed by Student's *t* test.
*Means ± SD are given, with number of patients in parentheses.
†$P < .005$, ‡$P < .001$, and §$P < .05$ vs. comparable group in nonproteinuric patients.

TABLE 5
Correlation coefficients between blood pressure and other variables

Variable	Systolic	P	Diastolic	P	Pulse	P
Diastolic blood pressure	0.661 (742)	<.001				
Pulse blood pressure	0.835 (742)	<.001	0.138 (742)	<.001		
Age	0.405 (742)	<.001	0.009 (742)	NS	0.528 (742)	<.001
Age at onset of diabetes	0.359 (742)	<.001	0.059 (742)	NS	0.431 (742)	<.001
Duration of diabetes	0.091 (742)	<.05	−0.099 (742)	<.01	0.192 (742)	<.001
Fasting blood glucose	−0.025 (742)	NS	0.027 (742)	NS	−0.035 (742)	NS
Postprandial blood glucose	−0.038 (742)	NS	−0.061 (742)	NS	−0.006 (742)	NS
Blood urea nitrogen	0.188 (735)	<.001	0.039 (735)	NS	0.219 (735)	<.001
Serum creatinine	0.170 (733)	<.001	0.077 (733)	<.05	0.168 (733)	<.001
Serum triglyceride	0.150 (703)	<.001	0.135 (703)	<.001	0.099 (703)	<.01
Serum cholesterol	0.217 (733)	<.001	0.125 (733)	<.001	0.195 (733)	<.001
Body weight	0.251 (742)	<.001	0.277 (742)	<.001	0.128 (742)	<.001

NS, not significant.
*Number of patients in parentheses.

or postprandial) did not correlate with any blood pressure. Blood urea nitrogen, serum creatinine and lipid levels, and body weight correlated significantly with blood pressure.

Effect of blood pressure and blood glucose on retinopathy and proteinuria. To compare the strength of correlation between these two factors and diabetic retinopathy and proteinuria, discriminant analysis was used (Table 6). With retinopathy, postprandial blood glucose was more strongly related than systolic blood pressure. In contrast, the correlation between proteinuria and systolic blood pressure was stronger than that between proteinuria and postprandial blood glucose.

DISCUSSION

We analyzed the association between diabetic retinopathy and 23 other clinical parameters, including blood pressure, and found that patients with retinopathy had significantly higher systolic and pulse blood pressures than those without retinopathy (Table 1). A correlation between high blood pressure and diabetic retinopathy was also found in patients with either component of retinopathy (Table 2).

TABLE 6
Results of discriminant analyses relating diabetic retinopathy and proteinuria to postprandial blood glucose and systolic blood pressure

	Retinopathy			Proteinuria		
Variable	Coefficient	F	P	Coefficient	F	P
Postprandial blood glucose	0.662	68.4	<.001	0.575	28.5	<.001
Systolic blood pressure	0.259	10.5	<.005	0.747	47.1	<.001
Constant	−0.059			−0.272		
Estimated error rate (%)	35.6			32.3		

F values are used to test the null hypothesis that the coefficient of each variable in the discriminant function is 0.
Variables are used after standardization.

It may be questioned whether hypertension is a reflection of diabetic nephropathy in the patients studied and the correlation between retinopathy and blood pressure is merely a coexistence rather than a cause-effect relationship. In diabetic patients it has been reported that, even when diabetic nephropathy is not associated, prevalence of hypertension is high in elderly and obese patients (11–14). In our patients, blood pressure, including systolic, diastolic, and pulse blood pressures, did not correlate with blood glucose level (Table 5). On the other hand, there was a high correlation between systolic blood pressure and proteinuria, which indicates a possibility that the origin of hypertension in the patients was diabetes (Table 6). Although our data on nephropathy (indexed by proteinuria) were not based on histologic examination and therefore remain tentative, the patients were divided into proteinuric and nonproteinuric groups to avoid the influence of renal damage. In both groups the differences observed in blood pressure between the patients with and those without retinopathy were slight (Table 3) when compared with the differences obtained in all the patients (Table 1). This suggests that hypertension did not correlate with retinopathy independently. However, when the patients were analyzed with regard to the components of diabetic retinopathy, this assumption proved inadequate. Even after the division of the patients into proteinuric and nonproteinuric groups, systolic and pulse blood pressures were significantly higher in patients with blot hemorrhage than those without in both groups (Table 4). In regard to other components of retinopathy (microaneurysms, dot hemorrhages, or hard or soft exudates), there was no association between blood pressure and the components of retinopathy. These data suggest that systolic hypertension is closely correlated with a particular lesion of diabetic retinopathy, i.e., blot hemorrhage. We thought that when retinal vessels were affected by diabetic changes and hypertension was also present, increased intravascular pressure or increased intravascular pulse pres-

sure resulted in small leakages of blood in that lesion. For this reason, systolic hypertension was thought to be a risk for diabetic retinopathy, and it did not cause specific changes of retinopathy but modified or varied the diabetic changes in retinas.

The correlation coefficient between age and systolic and pulse blood pressures was high (Table 5), and older patients were more susceptible to diabetic retinopathy (Table 1). These results suggest that the correlation between blood pressure and diabetic retinopathy may reflect the correlation between age and retinopathy. However, the association of retinopathy with age was much less significant than that with blood pressure ($P < .05$ vs. $P < .01$ for systolic or vs. $P < .001$ for pulse pressure), and current age significantly correlated with duration of diabetes, which is a strong risk factor on retinopathy between age and diabetes duration, $r = .257$, $P < .001$). Thus, we think that age itself has only limited influence, if any, on the development of diabetic retinopathy.

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