Orthostatic Hypertension in Patients With Type 2 Diabetes

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OBJECTIVE — The prevalence and clinical importance of orthostatic hypertension (OHT) in diabetic patients has not been elucidated, in contrast to orthostatic hypotension, which is occasionally found in diabetic patients with autonomic neuropathy.

RESEARCH DESIGN AND METHODS — The prevalence and severity of orthostatic hypertension was investigated in 277 Japanese male patients with type 2 diabetes, including 90 hypertensive patients and 128 nondiabetic age-matched male subjects. Patients treated with antihypertensive drugs were excluded from the study. OHT was defined as an increase in diastolic blood pressure (DBP) from <90 to ≥90 mmHg and/or an increase in systolic blood pressure (SBP) from <140 to ≥140 mmHg after standing from supine position. Clinical profiles and several serum biochemical parameters were determined in addition to chest X-rays and electrocardiograms.

RESULTS — The prevalence of OHT in normotensive and hypertensive diabetic patients was significantly higher than in control subjects (12.8 vs. 1.8%, $P < 0.01$, for normotensive patients; 12.6 vs. 11.1%, not significant, for hypertensive patients). Orthostasis induced a mean increase of 6.8 ± 11.4 mmHg in SBP and 9.1 ± 5.2 mmHg in DBP in diabetic patients with OHT compared with those without OHT (−1.0 ± 9.0 and 3.8 ± 6.6 mmHg, respectively). Vibration sensation in the lower limb was reduced in diabetic patients with OHT, but the percent coefficient of variation of RR interval, cardio-to-thoracic ratio on chest X-ray, and serum triglyceride levels were higher in these patients compared with normotensive diabetic patients without OHT.

CONCLUSIONS — Orthostatic hypertension is a novel complication in normotensive diabetic patients and may associate with early stage neuropathy and development of sustained hypertension.

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Orthostatic hypertension (OHT) is a cause of labile hypertension and is occasionally found in patients with mild or borderline hypertension. The clinical importance of OHT has not been reported in patients with diabetes, in contrast to orthostatic hypotension, which is a well-known ominous complication caused by autonomic denervation in patients with long-term poor control of blood glucose levels.

Orthostasis causes gravitational shift in circulating blood from the intrathoracic space to lower extremities and reduces venous return to the heart. Thus, a fall in stroke volume reduces the pulse pressure, whereas the mean blood pressure is usually maintained by autonomic regulation (1). On the other hand, diabetic patients show occasional disturbance of parasympathetic autonomic regulation preceding overt autonomic neuropathy. Thus, a relative enhancement of sympathetic tone may elicit a hypersensitive response to the orthostasis-induced elevation of blood pressure. Thus, OHT may develop into sustained hypertension and result in the development of vascular complications. In the present study, we examined the prevalence and background clinical profile of OHT in Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We studied 405 Japanese male subjects, including 277 patients with type 2 diabetes who were consecutively recruited from workers who visited the clinic of a public transportation company to undergo an annual health check for type 2 diabetes. Patients taking antihypertensive drugs were excluded from the study. The diagnosis of type 2 diabetes was based on World Health Organization criteria (2). Subjects were treated with or without oral hypoglycemic drugs. We also recruited a group of 128 age-matched nondiabetic normotensive men who were free of chronic renal failure, central nervous system disease, and malignancies.

Blood pressure was measured on the right arm in sitting, supine, and then standing position. Supine blood pressure was measured 3–5 min after lying on the bed, and then remeasured 1 min after standing. Blood pressure was measured twice in each position, and the average value was used for analysis. Hypertension was defined as sitting SBP ≥140 mmHg and/or sitting DBP ≥90 mmHg, and it was classified into three stages according to the fourth Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC IV) criteria (3), as follows: stage 1, SBP 140–159 mmHg and/or DBP 90–99 mmHg; stage 2, SBP 160–179 mmHg and/or DBP 100–109 mmHg; and stage 3, SBP ≥180 mmHg and/or DBP ≥110 mmHg. Normotension was classified into

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Abbreviations: CTR, cardio-to-thoracic ratio; CVRR, coefficient of variation of RR interval; DBP, diastolic blood pressure; ECG, electrocardiogram; IMT, intima media thickness; JNC IV, fourth Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure; OHT, orthostatic hypertension; QTc, corrected QT interval; SBP, systolic blood pressure.

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

Table 1—*Comparison of OHT and orthostatic hypotension in normotensive and hypertensive subjects with and without type 2 diabetes*

	OHT	Orthostatic hypotension	Orthostatic normotension	Number of total cases
Nondiabetic subjects (n = 128)				
Normotensive	2 (1.8)	3 (2.7)	105 (95.5)	110 (100)
Hypertensive	2 (11.1)	2 (11.1)	14 (77.8)	18 (100)
Diabetic patients (n = 277)				
Normotensive	24 (12.8)*	13 (7.0)	150 (80.2)	187 (100)
Hypertensive	11 (12.2)	4 (4.4)	75 (83.3)	90 (100)

Data are n (%). *P = 0.001 vs. nondiabetic normotensive subjects with OHT.

the following: optimum, SBP <120 mmHg and DBP <80 mmHg; normal, SBP <130 mmHg and DBP <85 mmHg; and high normal, SBP 130–139 mmHg and DBP 85–89 mmHg. OHT was defined as an increase of DBP from <90 to ≥90 mmHg (1) and/or an increase of SBP from <140 to ≥140 mmHg 1 min after standing from supine position.

Venous blood samples were taken in the morning after an overnight fast. The samples were analyzed for blood glucose, HbA_{1c}, total and HDL cholesterol, triglycerides, and creatinine. HbA_{1c} levels were measured by high performance liquid chromatography (normal, 4.0–5.7%). An electrocardiogram (ECG) was recorded for 200 beats in the supine position. The QT interval was corrected by heart rate (QTc). $SV_1 + RV_5$ (summated amplitude of R wave at the precordial lead V_5 and S wave at the lead V_1) was determined as a voltage parameter, and the coefficient of variation of RR interval (CVRR) was computed (4). Vibration sense was measured with a C64 tuning fork on bilateral toes, and the mean of perceptible time was used.

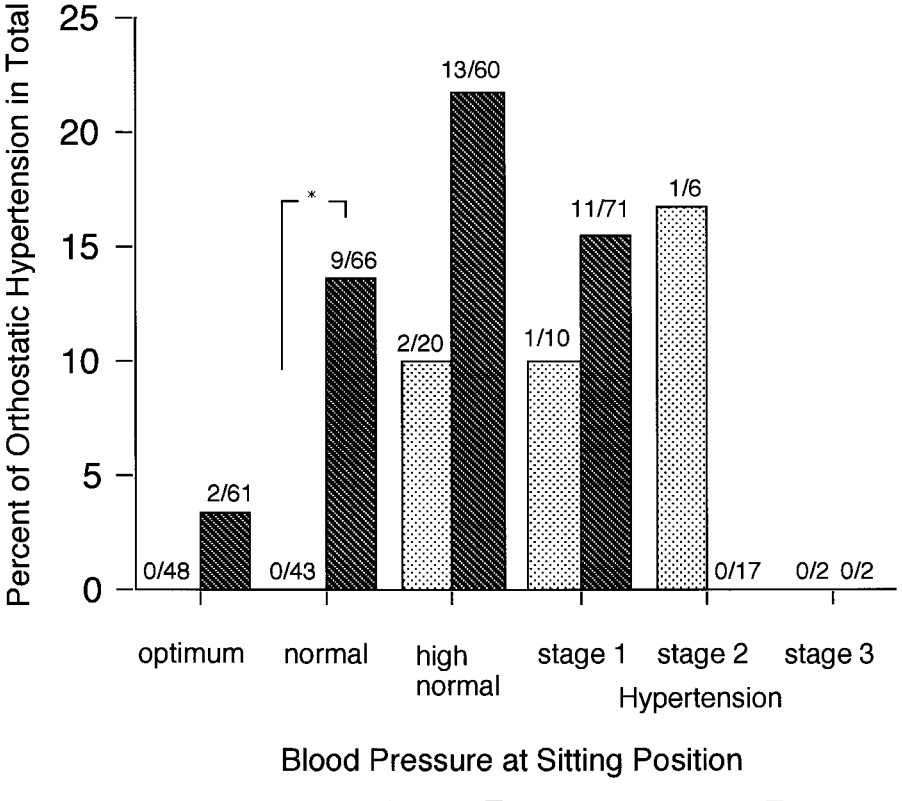

Figure 1—*The percentage distribution of diabetic (▨) and nondiabetic subjects (▤), with OHT classified according to sitting blood pressure based on the hypertension criteria of JNC IV. *P < 0.05. Numbers above bars indicate the subjects with OHT (n/N).*

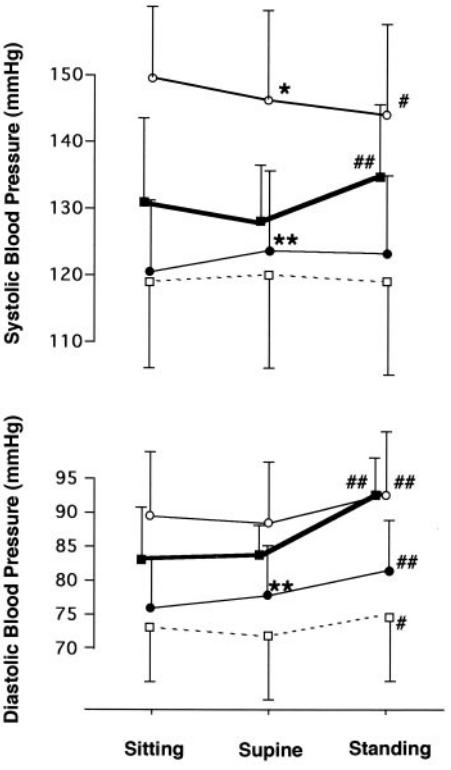

Figure 2—*Orthostatic changes in systolic (upper panel) and diastolic (lower panel) blood pressure in diabetic patients with OHT (■), normotensive diabetic patients without OHT (●), hypertensive diabetic patients without OHT (○), and normotensive nondiabetic subjects without OHT (□). Data represent the means ± 1 SD. *P < 0.05 and **P < 0.001 vs. blood pressure in the sitting position; #P < 0.05 and ##P < 0.001 vs. blood pressure in the supine position.*

Statistical analysis

All data are expressed as the means ± SD. Differences between groups were examined for statistical significance using unpaired and paired Student's t test and χ^2 test. $P < 0.05$ denoted the presence of a statistically significant difference.

RESULTS

Prevalence of OHT

Of the 277 diabetic patients, 90 (32.4%) were hypertensive (Table 1). The prevalence of OHT in normotensive and hypertensive diabetic patients was equally high compared with hypertensive nondiabetic subjects (12.8 and 12.2 vs. 10%, respectively), although the preva-

Table 2—*Clinical profiles of diabetic patients with OHT, normotensive and hypertensive diabetic patients, and nondiabetic normotensive subjects without OHT*

	Diabetic OHT	Diabetic normotensive patients without OHT	Diabetic hypertensive patients without OHT	Nondiabetic normotensive subjects without OHT
n	35	150	75	105
Age (years)	50.9 ± 9.0	52.3 ± 7.3	52.3 ± 7.9	47.1 ± 13.6
Family with hypertension (%)	30.3	22.7	34.7	—
Duration of diabetes (years)	4.1 ± 4.9	5.1 ± 5.3	5.0 ± 5.5	—
Alcohol intake (g/day)	29.3 ± 32.7	30.7 ± 32.2	28.3 ± 29.7	30.1 ± 37.8
Smoker (%)	52.4	52.5	50.6	55.1
BMI (kg/m^2)	25.2 ± 3.7	24.0 ± 3.2	24.6 ± 3.8	22.2 ± 3.0
Fasting blood glucose (mmol/l)	9.01 ± 1.85	8.51 ± 2.44	8.78 ± 2.50	4.88 ± 0.60
HbA_{1c} (%)	7.4 ± 1.1	7.2 ± 1.4	7.2 ± 1.2	5.1 ± 0.6
Total cholesterol (mmol/l)	5.46 ± 0.88	5.35 ± 0.95	5.71 ± 1.16	4.58 ± 1.1
Triglycerides (mmol/l)	2.56 ± 1.67*	1.88 ± 1.45	2.96 ± 4.78†	1.48 ± 0.90
HDL cholesterol (mmol/l)	1.18 ± 0.28	1.24 ± 0.32	1.25 ± 0.31	1.37 ± 0.46
Creatinine (mg/dl)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.2
SBP (mmHg)	130.7 ± 12.5‡	120.4 ± 10.6	149.6 ± 10.7‡	118.0 ± 9.5
DBP (mmHg)	82.9 ± 7.8‡	75.8 ± 7.2	89.3 ± 9.0‡	73.3 ± 7.7
Pulse rate (/min)	71.4 ± 9.8	70.4 ± 8.3	71.9 ± 9.4*	71.5 ± 10.4
Retinopathy (%)	50.0	40.3	43.2	0
Proteinuria (%)	14.7	14.1	20.3	6.2
Diminished Achille's tendon reflex (%)	14.7	9.4	9.4	10.8
Vibration sense (s)	11.1 ± 2.5§	12.5 ± 3.1	12.5 ± 3.1	12.4 ± 3.1
IMT (mm)	0.68 ± 0.09	0.66 ± 0.15	0.72 ± 0.17†	NA
CTR (%)	46.0 ± 4.7*	44.3 ± 4.5	45.5 ± 4.3*	43.7 ± 5.0
SVI + RV5 (mV)	2.61 ± 0.70	2.45 ± 0.71	2.66 ± 0.74	NA
QTc (s)	0.407 ± 0.021	0.404 ± 0.020	0.413 ± 0.030*	NA
CVRR (%)	3.0 ± 1.5*	2.5 ± 1.3	2.5 ± 1.1	(3.3 ± 1.0)‖

Data are means ± SD. *$P < 0.05$ vs. normotensive diabetic subjects; †$P < 0.01$ vs. normotensive diabetic subjects; ‡$P < 0.001$ vs. normotensive diabetic subjects; §$P < 0.05$ vs. normotensive and hypertensive diabetic subjects; ‖refer to reference no. 13.

lence in normotensive nondiabetic subjects was significantly lower (1.8%). Thus, the prevalence of OHT was significantly higher in normotensive diabetic patients compared with normotensive nondiabetic subjects ($P = 0.001$). When sitting blood pressure was classified based on JNC IV criteria (3), no differences were present in the prevalence of OHT between diabetic and nondiabetic subjects with high normal blood pressure and hypertension (Fig. 1). On the other hand, among normotensive subjects, 9 (13.6%) of 66 diabetic subjects developed OHT in contrast to no OHT in nondiabetic subjects ($P < 0.05$). Orthostatic hypotension was found in diabetic and nondiabetic subjects independent of hypertension, and it was excluded from further analysis (Table 1).

Orthostatic changes in blood pressure

In diabetic patients with OHT, orthostasis induced a mean increase of 6.8 ± 11.4 and 9.1 ± 5.2 mmHg in SBP and DBP, respectively. In contrast, SBP in hypertensive diabetic patients showed a significant decrease by −2.1 ± 8.2 mmHg, whereas SBP on standing did not change significantly in normotensive nondiabetic subjects and diabetic patients (Fig. 2). DBP in normotensive nondiabetic subjects and normotensive and hypertensive diabetic patients without OHT increased significantly after standing from supine position (2.9 ± 7.3, 3.6 ± 6.2, and 4.2 ± 7.2 mmHg, respectively).

Differences in clinical profile

There were no differences in age, treatment, duration of diabetes, alcohol intake, smoking habit, BMI, pulse rate, proteinuria, fasting blood glucose, HbA_{1c}, total cholesterol, or HDL cholesterol among diabetic patients with OHT, normotensive diabetic subjects without OHT, and hypertensive diabetic subjects without OHT (Table 2). In diabetic patients with OHT, the percentage of patients who had family members with hypertension was lower than in hypertensive diabetic patients without OHT and higher than that seen in normotensive diabetic patients without OHT, although there was no statistical significance. Serum triglyceride levels and cardio-to-thoracic ratios (CTRs) on the chest X-rays in diabetic patients with OHT and in those with hypertension were significantly higher than in normotensive diabetic patients without OHT. The vibration sense in diabetic patients with OHT was decreased compared with normotensive and hypertensive patients without OHT. There was no difference in Achilles tendon reflex between diabetic patients with OHT and those without OHT. The intima media thickness (IMT) and prevalence of left ventricular hypertrophy and ischemic heart disease on ECG in hypertensive diabetic patients were higher than in normotensive diabetic subjects without OHT. There was no statistical difference in IMT and ECG ab-

normalities between diabetic patients with OHT and normotensive diabetic patients without OHT. The percent CVRR was significantly higher in diabetic patients with OHT compared with normotensive patients without OHT.

CONCLUSIONS — The major finding of the present study was the high prevalence of OHT in diabetic patients (fivefold) compared with in nondiabetic subjects. In particular, the prevalence of OHT in normotensive diabetic patients was higher than in normotensive nondiabetic subjects. The prevalence of OHT in normotensive nondiabetic subjects was as low as 2% and was similar to the previously reported rate of 4.2% among 2,000 aviators (1).

Kario et al. (5) reported that among 110 asymptomatic elderly hypertensive patients without treatment, 7.2% had OHT, defined as a rise in SBP ≥20 mmHg during a 70° head-up tilt. In another study involving 1,800 hypertensive patients, 10% of the subjects were found to have OHT (6). Therefore, OHT could be considered to be a relatively common phenomenon in hypertensive patients. In our study, the prevalence of OHT in hypertensive cases was high not only in diabetic patients but also in nondiabetic subjects. In contrast, in normotensive cases, the prevalence of OHT was high in diabetic patients with normal sitting blood pressure.

Only a few studies have investigated the pathogenesis of OHT (6–8). The likely mechanisms of OHT include *1*) excessive venous pooling, with an initial drop in cardiac output followed by overcompensation with an excessive release of catecholamines (6); *2*) nephroptosis, with orthostatic activation of the renin-angiotensin system (7); and *3*) vascular adrenergic hypersensitivity (8). None of the diabetic patients with OHT had microhematuria suggestive of nephroptosis. These patients had a reduced mean time of vibration perception compared with those without OHT, suggesting the presence of neuropathy. On the other hand, CVRR remained higher in diabetic patients with OHT than in those without OHT. Because CVRR is known to decrease in parallel with parasympathetic autonomic nerve dysfunction, which proceeds to sympathetic nerve dysfunction in diabetic patients (3,9,10), the rather high CVRR suggests the preserved parasympathetic nervous system activity and may reflect the hypersensitivity of cardiopulmonary baroreflex. The patients with OHT also showed high levels of serum triglycerides that were similar to those in hypertensive patients without OHT. Hypertriglyceridemia is a hallmark of the insulin resistance syndrome (11), which is associated with overstimulation of sympathetic nervous system activity (12). In this regard, treatment of autonomic neuropathy in diabetic patients with tolrestat, an aldose reductase inhibitor, is reported to reduce orthostatic elevation of blood pressure (13). Therefore, the hypersensitivity of the cardiopulmonary baroreflex and sympathetic nervous system may contribute to the pathogenesis of OHT in the diabetic state.

The high prevalence of OHT supports the importance of high normal blood pressure as a risk for coronary heart disease in diabetic patients, as is stated in JNC IV (3). Payen et al. (14) reported that an orthostatic increase in blood pressure might be a determining factor for development of sustained hypertension. Although the prognosis of OHT is not well defined, the increased mean CTR in patients with OHT to a level similar to that in hypertensive patients implies that OHT may accelerate vascular injury.

In conclusion, our results indicate that OHT is a novel complication in normotensive diabetic patients with early stage neuropathy, and they suggest that OHT may associate with the development of hypertension and vascular complications.

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References

1. Schneider EC, Truesdell D: A statistical study of the pulse rate and the arterial blood pressures in recumbency, standing and after a standard exercise. *Am J Physiol* 61:429–474, 1922
2. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. I. Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
3. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 157:2413–2446, 1997
4. Pfeifer MA, Cook D, Brodsky J, Tice D, Reenan A, Swedine S, Halter JB, Porte D Jr: Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* 31:339–345, 1982
5. Kario K, Eguchi K, Nakagawa Y, Motai K, Shimada K: Relationship between extreme dippers and orthostatic hypertension in elderly hypertensive patients. *Hypertension* 31:77–82, 1998
6. Streeten DH, Auchincloss JH Jr, Anderson GH Jr, Richardson RL, Thomas FD, Miller JW: Orthostatic hypertension: pathogenetic studies. *Hypertension* 7:196–203, 1985
7. Takada Y, Shimizu H, Kazatani Y, Azechi H, Hiwada K, Kokubu T: Orthostatic hypertension with nephroptosis and aortic disease. *Arch Intern Med* 144:152–154, 1984
8. Benowitz NL, Zevin S, Carlsen S, Wright J, Schambelan M, Cheitlin M: Orthostatic hypertension due to vascular adrenergic hypersensitivity. *Hypertension* 28:42–46, 1996
9. Pagani S, Malfatto G, Pierini S, Casati R, Masu Am, Poli M, Guzzetti S, Lombardi F, Cerutti S, Malliani A: Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst* 23:143–153, 1988
10. Gottsater A, Ahmed M, Fernlund P, Sundkvist G: Autonomic neuropathy in type 2 diabetic patients is associated with hyperinsulinaemia and hypertriglyceridaemia. *Diabet Med* 16:49–54, 1999
11. Howard BV: Insulin resistance and lipid metabolism (Review). *Am J Cardiol* 84: 28J–32J, 1999
12. Peles E, Goldstein DS, Akselrod S, Nitzan H, Azaria M, Almog S, Dolphin D, Halkin H, Modan M: Interrelationships among measures of autonomic activity and cardiovascular risk factors during orthostasis and the oral glucose tolerance test. *Clin Auton Res* 5:271–278, 1995
13. Giugliano D, Acampora R, Marfella R, Maro GD, Rosa ND, Misso L, Ceriello A, Quatraro A, D'Onofrio F: Tolrestat in the primary prevention of diabetic neuropathy. *Diabetes Care* 18:536–541, 1995
14. Payen DM, Safar ME, Levenson JA, Totomokouo JA, Weiss YA: Prospective study of predictive factors determining borderline hypertensive individuals who develop sustained hypertension: prognostic value of increased diastolic orthostatic blood pressure. *Am Heart J* 103:379–384, 1982
15. Kageyama S: Autonomic function test using R-R interval variation in ECG. *No to Shinkei* 36:433–439, 1984