Usefulness of Home Blood Pressure Measurement in the Morning in Type 2 Diabetic Patients

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OBJECTIVE — Recently, repeated home blood pressure (HBP) measurements in the morning for a long period have been shown to have a stronger predictive power for mortality in patients with hypertension than occasional casual/clinic blood pressure (CBP) measurements. We studied whether HBP in the morning in type 2 diabetic patients is useful for prediction of diabetic complications.

RESEARCH DESIGN AND METHODS — The occurrence of diabetic complications (nephropathy, retinopathy, coronary heart disease [CHD], and cerebrovascular disease [CVD]) were examined in relation to morning HBP as well as to CBP in 170 type 2 diabetic patients treated with antidiabetic and antihypertensive drugs. Blood pressure was measured at the clinic during the day and at home after awakening in the morning. Clinic hypertension (CH) and morning hypertension (MH) were defined as systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg. The relation of CH and MH to the prevalence of these events was examined.

RESULTS — There were no significant differences in the prevalence of nephropathy, retinopathy, CHD, and CVD between the two groups with (n = 131) and without CH (n = 39), whereas the prevalences of these events in the patients with MH (n = 97) were significantly higher ($P <$ 0.05) than in those without MH (n = 73). The prevalence of nephropathy was highly associated with systolic MH.

CONCLUSIONS — Elevations of HBP in the morning in diabetic patients are strongly related to microvascular and macrovascular complications, especially nephropathy. It is concluded that the control of MH may prevent vascular complications in type 2 diabetic patients.

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The goal of long-term care for diabetic patients is to prevent the development of micro- and macrovascular complications (1). To achieve this purpose, adequate control of blood pressure and good glycemic control are crucial (1). The American Diabetes Association recommended that the blood pressure goal should be lowered to <130/80 mmHg in the clinic setting (1).

Recently, a discrepancy between screening blood pressure and ambulatory blood pressure has been noted (2). It has also been shown that home blood pressure (HBP) measurement in the morning has a stronger predictive power for mortality than casual/clinic blood pressure (CBP) measurements (3–5).

To evaluate the usefulness of HBP measurement in the morning in diabetic patients, we examined whether blood pressure elevations in the morning detected by HBP were more predictive than CBP for microvascular and macrovascular complications in type 2 diabetic patients, as observed in patients with essential hypertension (3–5).

RESEARCH DESIGN AND METHODS

Subjects

We studied 170 type 2 diabetic patients who visited our clinic regularly. The diagnosis of type 2 diabetes was based on the World Health Organization (WHO) criteria (6). Of 170 patients, 153 (90%) were treated with oral hypoglycemic drugs and/or insulin regimens for diabetes, whereas 80 (47%) were treated with antihypertensive drugs at the beginning of the study.

Study design

CBP was measured once during each clinic visit. HBP was measured once each morning, in the sitting position within 10 min after awakening, for 1 month. For CBP measurements, when patients with diabetes had systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg, we classified these patients as having clinic hypertension (CH) by the criteria of the World Health Organization (WHO) and International Society of Hypertension guidelines (7). When the mean HBP levels in the morning were ≥130 mmHg SBP and/or ≥85 mmHg DBP, we classified these patients as having morning hypertension (MH). When these values were <130 mmHg SBP and <85 mmHg DBP, we classified these patients as having clinic normotension (CN) or morning normotension (MN), respectively.

The microvascular complications detected in this study were nephropathy and retinopathy. Occurrence of nephropathy

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Abbreviations: CBP, clinic blood pressure; CH, clinic hypertension; CHD, coronary heart disease; CN, clinic normotension; CVD, cerebrovascular disease; DBP, diastolic blood pressure; HBP, home blood pressure; MH, morning hypertension; MN, morning normotension; ROC, receiver operating characteristic; 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—*Patient characteristics*

	CH group			CN group			
	MH group	MN group	Total	MH group	MN group	Total	All subjects
Number	74	57	131	23	16	39	170
Age (years)	67 ± 8	64 ± 8	66 ± 9	71 ± 9†	63 ± 9	68 ± 10	66 ± 9
Sex (female/male)	47/27	24/33	74/57	7/16	9/7	16/23	90/80
BMI (kg/m^2)	24 ± 3†	23 ± 2	23 ± 3*	23 ± 3†	22 ± 3	22 ± 3	23 ± 3
Blood pressure (mmHg)							
SBP							
Clinic	167 ± 18†	158 ± 14	163 ± 17*	124 ± 12†	117 ± 9	121 ± 11	153 ± 26
Morning	163 ± 19†	127 ± 7†	147 ± 24‡	166 ± 17†‡	116 ± 10	146 ± 29‡	147 ± 25‡
DBP							
Clinic	97 ± 14†	93 ± 9	95 ± 12*	75 ± 8	73 ± 9	74 ± 9	90 ± 14
Morning	88 ± 11†‡	75 ± 8‡	83 ± 12‡	88 ± 15†‡	69 ± 10	80 ± 16‡	82 ± 13‡
Laboratory variables							
HbA_{1c} (%)	6.5 ± 0.9	6.5 ± 0.9	6.5 ± 0.9	6.7 ± 1.0	6.4 ± 0.7	6.6 ± 0.9	6.5 ± 0.9
Triglycerides (mg/dl)	153 ± 77	140 ± 92	148 ± 83	138 ± 74	109 ± 46	126 ± 65	143 ± 80
Total cholesterol (mg/dl)	198 ± 32	196 ± 31	197 ± 32	182 ± 44	204 ± 24	191 ± 38	196 ± 33
LDL cholesterol (mg/dl)	109 ± 32	101 ± 31	106 ± 31	92 ± 34	122 ± 21	105 ± 33	106 ± 32
HDL cholesterol (mg/dl)	61 ± 16	66 ± 18	63 ± 17	57 ± 24	59 ± 10	58 ± 20	62 ± 18
Serum creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2*	1.1 ± 0.4†	0.7 ± 0.2	1.0 ± 0.4	0.9 ± 0.3
Urinary albumin excretion (μg/mg creatinine)	212 ± 524†	11 ± 8	125 ± 405*	1,113 ± 2,449†	7.5 ± 5.0	660 ± 1,943	248 ± 1,013

Data are means ± SD. The SBP and DBP levels in all patients were measured at the clinic and at home. *$P < 0.01$ versus patients with CN; †$P < 0.01$ versus patients with MN; and ‡$P < 0.01$ versus patients measured at the clinic.

was evaluated at the beginning of the study, whereas occurrence of retinopathy was evaluated at least once within 6 months before the study. The macrovascular complications defined were coronary heart disease (CHD) and cerebrovascular diseases (CVDs). Prevalence of these events was confirmed by medical history at the beginning of the study.

Glycemic control was evaluated by HbA_{1c} values. Other variables, including serum concentrations of lipid and creatinine, were also measured.

All subjects were divided into two groups: with CH or MH and without CH or MH.

Finally, we examined whether CBP and HBP is more predictive of these events.

Analytical methods

CBP was measured by nurses at the clinic in the daytime in the left arm after a 5-min rest in a sitting position using an automatic device based on the cuff-oscillometric method (FT-200; Parama-Tech, Fukuoka, Japan). HBP was measured at home in the morning within 10 min after awakening, by the patient or a family member, in the left arm in a sitting position. Semiautomatic devices based on the cuff-oscillometric principle that generate a digital display of both SBP and DBP were used. All devices met the criteria set by the Association for the Advancement of Medical Instrumentation. A standard arm cuff was used to measure both CBP and HBP.

Venous samples were collected during each clinic visit and were analyzed for HbA_{1c} levels and concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and creatinine. HbA_{1c} levels were measured by high-performance liquid chromatography (normal range 4.5–5.7%).

Albumin concentration in random spot urine was measured by the latex agglutination photometric immunoassay method. Microalbuminuria and clinical albuminuria were defined as urinary albumin excretion ≥30 and ≥300 μg/mg creatinine, respectively (8).

Statistical analysis

All values are presented as means ± SD. Mean values were compared using unpaired Student's *t* test. To compare the prevalence of microvascular and macrovascular complications in the two groups with and without hypertension, Yates' continuity corrected χ^2 test with two-tailed *P* value was performed and odds ratios were calculated; if prevalence of the events was 0, 0.5 was added to all values before calculating the odds ratio and 95% CIs were provided. Multiple logistic analysis was used to determine the contribution of the variables to the events. Correlation between HBP and CBP levels was calculated. In addition, receiver operating characteristic (ROC) curves for HBP and CBP with various end points were used to examine whether HBP and CBP measurements behave differently in allowing ascertainment of the true risk or whether the 130/85 mmHg cutpoints are better for HBP than for CBP. This analysis was performed using the GraphPad Prism software (version 3.02; GraphPad Software, San Diego, CA) and the Statistical Package for the Biosciences (SPBS; Winesteem Institute of Community Medicine, Tokyo, Japan). $P < 0.05$ was considered statistically significant.

RESULTS

— The characteristics of all subjects are shown in Table 1. The prevalences of nephropathy, retinopathy, CVD, and CHD in all subjects were 43, 26, 18, and 11%, respectively (Table 2).

Comparing the characteristics of patients with and without CH, the following

Table 2—*Prevalence of microvascular and macrovascular events*

	CH group (n = 131)			CN group (n = 39)				
	MH group (n = 74)	MN group (n = 57)	Total (n = 131)	MH group (n = 23)	MN group (n = 16)	Total (n = 39)	All subjects (n = 170)	Odds ratio (95% CI)
Medical events								
Nephropathy	69†	0	39	91†	0	54	43	0.6 (0.3–1.1)
Microalbuminuria	67†	0	32	52†	0	31	32	1.0 (0.5–2.3)
Clinical albuminuria	12†	0	7	39†	0	24	10	0.2 (0.1–0.7)*
Retinopathy	32†	18	28	33†	6	24	26	1.3 (0.5–2.9)
Nonproliferative	18	9	15	4	0	3	12	6.4 (0.8–50)
Preproliferative	9†	2	6	13	0	8	7	0.8 (0.2–3.1)
Proliferative	5	8	7	17†	6	13	8	0.5 (0.2–1.6)
CHD	8	11	9	35†	0	20	11	0.5 (0.2–1.3)
CVD	23†	11	18	35†	0	21	18	0.8 (0.3–1.9)
Medical treatment								
Therapy for hypertension								
Oral drugs	61†	35	48	70†	6	44	47	1.2 (0.6–2.5)
Therapy for diabetes								
Oral drugs or insulin	91	86	89	100	88	95	90	0.2 (0.0–1.5)

Data are %. The prevalence is a percent ratio of patients with MH, MN, CH, CN, or all patients. Odds ratio for CH and CN groups was calculated. *$P < 0.01$ versus patients with CN; †$P < 0.01$ versus patients with MN.

trends were noted. The prevalence of CH was four times higher than CN. BMI in CH patients was slightly higher than in CN patients. In contrast, serum creatinine concentration and urinary excretion of albumin in CH patients were significantly lower ($P < 0.01$) than in CN patients. No significant differences in other variables were noted between the two groups. A total of 48% of CH patients were being treated with antihypertensive drugs, compared with 44% of CN patients (Table 2).

When we compared the prevalence of diabetic complications in the two groups, there were no significant differences in the prevalence of nephropathy, retinopathy, CHD, and CVD between the two groups. However, the prevalence of clinical albuminuria in CH patients was lower than in CN patients (Table 2).

The CH patients were further divided into two groups: with and without MH (Table 1). BMI in MH patients was slightly higher than in MN patients. SBP, DBP, and urinary excretion of albumin in MH patients were significantly higher ($P < 0.001$) than in MN patients. There were no significant differences in other variables between the two groups. Nephropathy was observed in 69% of MH patients, whereas there was no nephropathy in MN patients. The prevalences of retinopathy and CVD in MH patients were also significantly higher than in MN patients (Table 2). The prevalence of treatment with antihypertensive drugs was higher in MH than in MN (Table 2).

The CN patients were also divided into two groups: with and without MH (Table 1). The means of age, BMI, SBP, and DBP in MH patients were significantly higher ($P < 0.01$) than in MN patients. Serum creatinine concentration and urinary excretion of albumin were also higher in MH than in MN (Table 2). No significant differences in other variables were shown between the two groups. However, the prevalence of nephropathy in MH patients was high (91%), whereas no nephropathy was observed in MN patients. The prevalences of retinopathy, CHD, and CVD in MH patients were also higher than in MN patients. More MH patients than MN patients were being treated with antihypertensive drugs (Table 2).

Comparing the characteristics of the

Table 3—*Characteristics of patients with and without MH*

	MH group	MN group
Number (%)	97 (57)‡	73 (43)‡
Age (years)	68 ± 9	64 ± 9
Sex (female/male)	54/43	33/40
BMI (kg/m^2)	24 ± 3*	23 ± 2
Blood pressure (mmHg)		
SBP	164 ± 19*	124 ± 9
DBP	88 ± 12*	73 ± 9
Laboratory variables		
HbA_{1c} (%)	6.5 ± 0.9	6.5 ± 0.9
Triglycerides (mg/dl)	149 ± 77	133 ± 85
Total cholesterol (mg/dl)	195 ± 36	197 ± 30
LDL cholesterol (mg/dl)	105 ± 33	106 ± 30
HDL cholesterol (mg/dl)	60 ± 19	64 ± 17
Serum creatinine (mg/dl)	0.9 ± 0.4†	0.8 ± 0.2
Urinary albumin excretion (μg/mg creatinine)	430 ± 1,322*	11 ± 7

Data are means ± SD. The blood pressure in both groups was measured at the home. *$P < 0.01$ and †$P < 0.05$ versus patients with MN, ‡number in parenthesis is a percent ratio of patients in each group for all subjects.

Table 4—*Prevalence of microvascular and macrovascular events in patients with and without MH*

	MH group (n = 97)	MN group (n = 73)	Odds ratio (95% CI)
Medical events			
Nephropathy	43	0	417.9 (25.0–7,000)*
Microalbuminuria	32	0	184.2 (11.0–3,060)*
Clinical albuminuria	10	0	34.2 (2.0–578)*
Retinopathy	18	9	2.0 (1.0–4.3)*
Nonproliferative	13	5	1.9 (0.7–5.2)
Preproliferative	14	0	19.5 (1.1–338)*
Proliferative	13	8	1.7 (0.6–4.8)
CHD	42	10	2.0 (0.8–5.0)*
CVD	60	10	4.1 (1.6–10.6)*
Medical treatment			
Therapy for hypertension			
Oral drugs	35	12	4.3 (2.2–8.3)*
Therapy for diabetes			
Oral drugs/or insulin	53	37	2.0 (0.7–5.7)

Data are %. The numbers are percent ratios of the events occurred in patients of each group obtained from all subjects and of patients treated with drugs for hypertension or diabetes obtained from all subjects. *P < 0.01 versus patients with MH.

two patient groups with and without MH, the following trends were noted (Table 3). The means of age, sex, HbA_{1c} levels, and lipid concentrations were not different between the two groups. However, SBP and DBP, based on HBP in the morning, in MH patients were significantly higher ($P < 0.001$) than in MN patients. Serum creatinine concentration and urinary albumin excretion were also higher in MH patients (Table 3). The prevalences of treatment with antihypertensive and antidiabetic drugs were 3 and 1.5 times higher, respectively, in MH patients compared with MN patients (Table 4).

The prevalence of nephropathy in MH patients was 75%, whereas no nephropathy was noted in MN patients. The prevalence of retinopathy in MH patients was twice that found in MN patients, although there was no difference in the prevalences of nonproliferative and proliferative retinopathies between the two groups (Table 4). The prevalences of CHD and CVD in MH patients were four and six times higher, respectively, than in MN patients.

Specifically, the prevalence of nephropathy in all subjects was highly associated ($P < 0.001$) with systolic MH, but not with age, sex, HbA_{1c}, serum lipid concentrations without LDL cholesterol, and use of antidiabetic drugs by multiple logistic analysis. However, prevalence of nephropathy was associated with BMI, LDL cholesterol concentration, serum creatinine concentration, and use of antihypertensive drugs and was negatively associated with clinic DBP (Table 5).

The relationships between SBP and DBP in morning and clinic measurements were described by regression equations of morning SBP = 0.23 clinic SBP + 111 and morning DBP = 0.26 clinic DBP + 58, respectively. The correlations were poor (morning versus clinic SBP, r = 0.05, P = 0.004; morning versus clinic DBP, r = 0.09, P = 0.0001). In comparison of ROC curves for HBP and CBP with the events, the areas under ROC curves of morning SBP (0.86 ± 0.39) and morning DBP (0.70 ± 0.52) were significantly higher ($P < 0.001$ and $P = 0.035$, respectively) than those of clinic SBP (0.52 ± 0.60) and clinic DBP (0.57 ± 0.59) in nephropathy, indicating that HBP has a higher predictive value than CBP. In contrast, there were no statistical differences between them in other events. In nephropathy (Fig. 1), sensitivities of the 130-mmHg threshold in morning and clinic SBP were 1.00 (1.00–1.00 95% CI) and 0.18 (0.10–0.29), respectively, whereas those of the 85-mmHg threshold in morning and clinic DBP were 0.49 (0.37–0.61) and 0.43 (0.31–0.55), respectively. Specificities of the 130-mmHg threshold in morning and clinic SBP were 0.68 (0.58–0.77) and 0.85 (0.76–0.91), respectively, whereas those of the 85-mmHg threshold in morning and clinic DBP were 0.75 (0.65–0.83) and 0.73 (0.64–0.82), respectively.

CONCLUSIONS — In type 2 diabetic patients who were regularly treated with diet and exercise or medications for hyperglycemia and hypertension, we found that one half of CH patients had MN, whereas two thirds of CN patients

Table 5—*Multivariate-adjusted odds ratios and 95% CIs of risk factors for nephropathy*

	Multivariate-adjusted odds ratio	95% CI
Age (years)	1.03	0.97–1.10
Sex (female/male)	0.85	0.29–2.45
BMI (kg/m^2)	1.29†	1.08–1.55
HbA_{1c} (%)	0.84	0.49–1.45
Clinic blood pressure		
SBP (mmHg)	1.00	0.97–1.04
DBP (mmHg)	0.93†	0.89–0.98
Morning blood pressure		
SBP (mmHg)	1.07‡	1.04–1.10
DBP (mmHg)	1.02	0.97–1.07
Triglycerides (mg/dl)	1.00	0.99–1.01
Total cholesterol (mg/dl)	0.98	0.96–1.01
LDL cholesterol (mg/dl)	1.03*	1.00–1.06
HDL cholesterol (mg/dl)	1.02	0.99–1.06
Serum creatinine (mg/dl)	43.2*	1.53–1,225
Antihypertensive drugs	5.90*	1.27–9.49
Antidiabetic drugs	4.89	0.86–27.7

Odds ratio for continuous variables represent a difference of 1 SD. *P < 0.05; †P < 0.01; ‡P < 0.001.

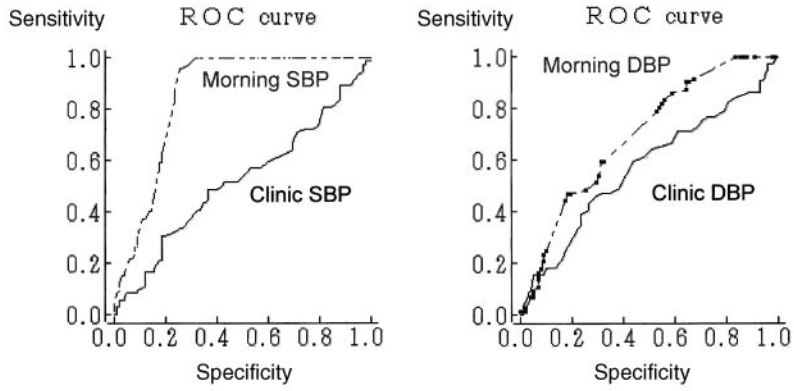

Figure 1—*ROC analysis in nephropathy.*

had MH. The prevalences of nephropathy, retinopathy, CHD, and CVD in patients with MH were significantly higher than in patients without MH, even though they had CN. In contrast, the prevalence of these vascular disturbances was significantly lower in patients without MH than in patients with MH, even though they had CH. Specifically, nephropathy, including clinical albuminuria, was observed in patients with systolic MH but not in any patients without MH. The difference is not related to age, sex, BMI, HbA_{1c}, serum lipid concentrations, or use of antidiabetic and antihypertensive drugs. The finding in the present cross-sectional study indicates that micro- and macrovascular complications of type 2 diabetic patients may be strongly related to HBP in the morning rather than CBP.

The reason for the underlying relation of high HBP in the morning rather than high CBP to the vascular complications is not clearly determined by this study. However, several possibilities are postulated. First, type 2 diabetic patients have high prevalence of increased CBP but normal HBP in the morning (white coat hypertension) (9,10). White coat hypertension seems to be a low risk for vascular complications (11,12). Second, O'Brien et al. (13) and Imai et al. (14) reported that nocturnal decline in blood pressure in patients with essential hypertension is often diminished (nondipper hypertension) and sometimes inverts to become a nocturnal elevation (inverted dipper hypertension). Nondipper hypertension, particularly inverted dipper hypertension, accelerates vascular disturbances (15,16), including microalbuminuria (17). Many studies have reported that type 2 diabetic patients have nondipper hypertension (18–23). Therefore, it seems that blunted nocturnal and/or inverted dipper hypertension may cause micro- and macrovascular complications in type 2 diabetic patients. Third, a morning surge in blood pressure may be related to these events. A number of reports indicate that the early morning surge in blood pressure acts as a trigger for vascular events (22,23). Most diabetic patients have the morning surge (23). These phenomena in diabetic patients are considered to be caused by many neuroendocrine and hematological factors, including autonomic neuropathy (18–23), which may result in glomerular hyperfiltration, hypercoagulability, and hypofibrinolysis, promoting micro- and macrovascular disturbances (17–23). In fact, a high prevalence of these phenomena was observed in MH but not in MN. In addition, the severity of MH in CN patients tended to be greater than in CH patients. Moreover, the relation of MBP and CBP levels was a greater range, indicating true and white coat hypertension, and MBP level in some patients was higher than the corresponding CBP level, indicating that reverse dipping hypertension might occur, although we did not measure 24-h ambulatory blood pressure. It is hypothesized that treatment with antihypertensive drugs reduced daytime blood pressure but did not restore blunted nocturnal hypertension, did not decrease nocturnal hypertension, and could not attenuate the morning surge in blood pressure (21,24). The greater range in relation of MBP and CBP, and the negative association between events of nephropathy and clinic DBP may be partially explained by the effect of treatment with antihypertensive drugs, as hypothesized above.

Analysis by ROC curves also indicates that HBP has a stronger predictive power than CBP, especially in nephropathy. The cutpoints of 130/85 mmHg have higher sensitivity in morning measurement than in clinic measurement, although specificity in the cutpoint of 130 mmHg SBP in the morning measurement was lower than in the clinic measurement. Accordingly, measurement of HBP in the morning is a useful method of determining these phenomena, as indicated by the Ohasama study (2–5,14,16,24), and high HBP levels in the morning in type 2 diabetic patients may be related to micro- and macrovascular complications of diabetes.

All findings indicate that high BP levels in the morning, obtained by means of self-measurement in type 2 diabetic patients, should be treated as hypertension.

In summary, in patients with type 2 diabetes, hypertension based on self-measurement of BP in the morning after awakening is strongly related to micro- and macrovascular complications, especially nephropathy. It is concluded that control of MH may prevent vascular complications in type 2 diabetic patients.

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References

1. American Diabetes Association: Summary of revisions for the 2002 Clinical Practice Recommendations. *Diabetes Care* 25 (Suppl. 1):S3, 2002
2. Aihara A, Imai Y, Sekino M, Kato J, Ito S, Ohkubo T, Tsuji I, Satoh H, Hisamichi S, Nagai K: Discrepancy between screening blood pressure and ambulatory blood pressure: a community-based study in Ohasama. *Hypertens Res* 21:127–136, 1998
3. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S: Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 16:971–975, 1998
4. Imai Y, Ohkubo T, Tsuji I, Hozawa A, Nagai K, Kikuya M, Aihara A, Sekino M, Michimata M, Matsubara M, Ito S, Satoh

H, Hisamichi S: Relationships among blood pressures obtained using different measurement methods in the general population of Ohasama, Japan. *Hypertens Res* 22:261–272, 1999
5. Imai Y, Nishiyama A, Sekino M, Aihara A, Kikuya M, Ohkubo T, Matsubara M, Hozawa A, Tsuji I, Ito S, Satoh H, Nagai K, Hisamichi S: Characteristics of blood pressure measured at home in the morning and in the evening: the Ohasama study. *J Hypertens* 17:889–898, 1999
6. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
7. Guidelines Subcommittee: 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 17:151–183, 1999
8. American Diabetes Association: Clinic practice recommendations 2002: diabetic nephropathy. *Diabetes Care* 25 (Suppl. 1): S85–S89, 2002
9. Burgess E, Mather K, Ross S, Josefsberg Z: Office hypertension in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 34:684–685, 1991
10. Puig JG, Ruilope LM, Ortega R: Antihypertensive treatment efficacy in type II diabetes mellitus: dissociation between causal and 24-hour ambulatory blood pressure. *Hypertension* 26:1093–1099, 1995
11. Pickering TG: White coat hypertension. *Curr Opin Nephrol Hypertens* 5:192–198, 1996
12. Nielson FS, Gaede P, Vedel P, Pederson O, Parving HH: White coat hypertension in NIDDM patients with and without incipient and overt diabetic nephropathy. *Diabetes Care* 20:859–863, 1997
13. O'Brien E, Sheridan J, O'Mallely K: Dipper and non-dippers (Letter). *Lancet* 2:397, 1988
14. Imai Y, Abe K, Munakata M, Sakuma H, Hashimoto J, Imai K, Sekino H, Yoshinaga K: Circadian blood pressure variation under different pathophysiological conditions. *J Hypertens* 8 (Suppl. 6):125–132, 1990
15. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T: Silent cerebrovascular disease in the elderly: correlation with ambulatory pressure. *Hypertension* 16:692–699, 1990
16. Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Sato H, Hisamichi S: Relationship between nocturnal decline in blood pressure and mortality: the Ohasama Study. *Am J Hypertens* 10:1201–1207, 1997
17. Opsahl JA, Abraham PA, Halstension CE, Keane WF: Correlation of office and ambulatory blood pressure measurements with urinary albumin and N-acetyl-beta-D-glucosaminidase excretion in essential hypertension. *Am J Hypertens* 1:1175–1205, 1988
18. Fogari R, Zoppi A, Malamani GD, Lazzari P, Albonico B, Corradi L: Urinary albumin excretion and nocturnal blood pressure in hypertensive patients with type II diabetes mellitus. *Am J Hypertens* 7:808–813, 1994
19. Spallone V, Bernardi L, Ricordi L, Solda P, Maiello MR, Calciati A, Gambardella S, Fratino P, Menzinger G: Relationship between the circadian rhythms of blood pressure and sympathovagal balance in diabetic autonomic neuropathy. *Diabetes* 42:1745–1752, 1993
20. Farmer CK, Goldsmith DJ, Quin JD, Dallyn P, Cox J, Kingswood JC, Sharpstone PF: Progression of diabetic nephropathy-is diurnal blood pressure rhythm as important as absolute blood pressure level? *Nephrol Dial Transplant* 13:635–639, 1998
21. Sturrock ND, George E, Pound N, Stevenson J, Peck GM, Sowter H: Non-dipping circadian blood pressure and renal impairment are associated with increased mortality in diabetes mellitus. *Diabet Med* 17:360–364, 2000
22. White WB: Cardiovascular risk and therapeutic intervention for the early morning surge in blood pressure and heart rate. *Blood Press Monit* 6:63–72, 2001
23. Aronson D: Impaired modulation of circadian rhythms in patients with diabetes mellitus: a risk factor for cardiac thrombotic events? *Chronobiol Int* 18:109–121, 2001
24. Imai Y, Ohkubo T, Tsuji I, Satoshi H, Hisamichi S: Clinical significance of nocturnal blood pressure monitoring. *Clin Exp Hypertens* 21:717–727, 1999