Turkish Journal of Endocrinology and Metabolism, (2003) 1 : 23-29 **ORGINAL ARTICLE**

Microalbuminuria, Nondipping and Diastolic Dysfunction in Normotensive Type 2 Diabetic Patients

Mehtap Cakir* Nilgün Baskal Sevim Güllü** Murat Erdogan** Elhan Atilla*** Çetin Erol**** Gürbüz Erdogan****

Ankara University, School of Medicine, Ankara, Turkey
** Department of Internal Medicine*
*** Department of Endocrinology and Metabolism*
**** Department of Biostatistics*
***** Department of Cardiology*

Microalbuminuria is an independent marker for cardiovascular morbidity and mortality however its relation with diastolic dysfunction in normotensive, well-controlled type 2 diabetic patients is not clearly documented. In twenty normoalbuminuric and 16 microalbuminuric type 2 diabetic patients, twenty-four hour ambulatory blood pressure monitoring, left ventricular echocardiographic evaluation, 12-hour daytime and nighttime urinary albumin excretion rate measurements were performed. A ³ 10% drop in systolic blood pressure at night was accepted as the criteria for normal dipping ("dippers"). Mean day/night systolic blood pressure values of normoalbuminuric group were significantly higher than the microalbuminuric group (1.09±0.09 vs. 1.02±0.06, p=0.013). Twenty-four hour systolic blood pressures (110.3±6.3 mmHg vs. 103.5±8.8 mmHg, p=0.013, respectively) and diastolic blood pressures (79±5.1 mmHg vs. 75.1±5.1 mmHg, p=0.044, respectively) were significantly higher in nondippers compared to dippers. Diastolic dysfunction rates didn't differ significantly between normo- and microalbuminuric groups (40% (8/20) vs. 43.8% (7/16), respectively, p>0.05). Microalbuminuria wasn't related with a more atherogenic lipid profile, increased rate of retinopathy and higher left ventricular mass index. These results indicate that, even in normotensive and well-controlled type 2 diabetic patients, microalbuminuria is related to nondipping. However, similar diastolic dysfunction rates between normo- and microalbuminuric subjects suggest that, good metabolic control in the presence of normotension may alleviate the increased likelihood of diastolic dysfunction and higher left ventricular mass index attributed to microalbuminuria and nondipping in the previous studies.

Key words: Microalbuminuria, 24-hour ambulatory blood pressure monitoring, diastolic dysfunction, nondipping, normotensive.

Introduction

Microalbuminuria (MA) is accepted as an early marker of diabetic nephropathy. It is also an independent risk factor for increased cardiovascular morbidity and mortality in type 2 diabetic patients (1). To elucidate the pathogenesis of this enhanced risk, many studies have focused on differences between cardiovascular risk parameters in normo- and microalbuminuric type 2 diabetic subjects. Higher blood pressure (BP) values based on 24-hour (24-h) ambulatory BP recordings and controversial results about a more atherogenic lipid profile have been reported in microalbuminuric subjects with type 2 diabetes. Lack of a normal nocturnal BP fall (nondipping), which was found to be related to MA, was proposed as the missing pathogenetic link between MA and cardiovascular

Correspondence address:

Mehtap Cakýr
Ankara University, School of Medicine, Ankara, Turkey
Department of Internal Medicine

disease. This hypothesis emerged from studies which showed increased cardiovascular target organ damage in "nondipper" hypertensive subjects with or without diabetes.

Diabetic patients have an increased rate of congestive heart failure. The increased rate has been attributed to diabetic cardiomyopathy, which occurs despite normal coronary arteries, with a major contribution of myocardial microvascular damage. Left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy. Previous studies have found asymptomatic diastolic dysfunction in both hypertensive (2) and normotensive type 2 diabetic subjects (2-4).

The primary objective of this study was to assess the association of MA and diastolic dysfunction in normotensive and well-regulated type 2 diabetic patients. Secondary objectives were to compare nondipping, retinopathy status, left ventricular mass index (LVMI) and lipid profile between normo- and microalbuminuric type 2 diabetic patients.

Subjects and Methods

Thirty six type 2 diabetic outpatients were enrolled to the study. All patients were between 35-60 years, had casual BP less than 140/90 mmHg, normal resting ECGs, HbA1c levels <7.5% (4-6%) and serum creatinine levels <1.2 mg/dL. Diagnosis of type 2 DM was made according to WHO criteria (5). Patients with other systemic disease, hypertension, any cardiac symptoms and/or pathological echocardiographical findings, dipstick positive proteinuria and hematuria were excluded from the study. None of the patients were using medications which may influence diastolic function for any reason (e.g. digoxin, beta-blockers, calcium channel blockers). Informed consent was given by all participants after a detailed description of the procedures. The protocol was approved by the local Ethics Committee.

Body mass index was calculated as (weight in kg) / (height in metres)^2. Three auscultatory BP measurements in different visits were taken in outpatient clinic, after 10 minutes of rest, from the patients right arm in the sitting position by a physician with a sphygmomanometer using Korotkoff phase V as the diastolic value. The mean of such three measurements were named casual BP (cas-BP). Twenty-four hour ambulatory BP was measured by a portable automatic BP monitor (Profilomat ERKA, Disetronic Medical Systems, Burgdorf, Switzerland) using oscillometry (6). Only those oscillometric recordings in which more than 90% of the programmed readings were successful were included in the analysis. The device was programmed to measure BP every 30 min. daytime between 6:00 A.M. and 22:00 P.M. and every 1 hour nighttime between 22:00 P.M. and 6 A.M according to the recommendations of European Consensus Conference on non-invasive ambulatory blood pressure monitoring (ABPM) (7). Subjects with a nocturnal reduction in SBP less than 10% were classified as nondippers (8). Mean BP was calculated by using the formula [SBP + (2 x DBP)] / 3. Fundoscopic examination was performed with ophtalmoscopy by an experienced ophtalmologist and defined as nil, background retinopathy and proliferative retinopathy according to ETDRS criteria (9).

Blood samples were drawn after an overnight fasting. HbA1c measurements were performed with high performance liquid chromatographic method (Bio-Rad Diagnostics, California, USA). Fasting plasma glucose (FPG), creatinine, BUN, LDL-, HDL-, VLDL-, total cholesterol and triglyceride levels were determined by routine laboratory methods. From two separate urine samples, daytime and nighttime, urinary albumin excretion rates were assessed by using radioimmunoassay (Double Antibody albumin RIA, DPC, California, USA). A urinary albumin excretion (UAE) rate of 20-200 µg/min. was defined as MA.

Echocardiographic examination was performed by an experienced physician using the Hewlett-Packard Sonos 5500 ultrasound system. Each patient was examined supine in left lateral position. M-mode meaurements of interventricular septum (IVS) and left ventricular posterior wall (LVPW) thickness, left atrial diameter (LAD), left ventricular end-systolic (LVESD) and end-diastolic (LVEDD) diameters were taken according to the American Society of Echocardiography guidelines (10). Fractional shortening (FS) was calculated according to the formula: FS(%)=[(LVEDD - LVESD) / LVEDD] x 100. Left ventricular mass was calculated by using the formula of Devereux

and Reichek described elsewhere (11) and indexed to body surface area to give LVMI. Left ventricular hypertrophy was assessed using the cut-off levels >134 g / m^2 for men and > 110 g / m^2 for women. Doppler pulsed wave analysis of left ventricular diastolic filling was performed with apical four-chamber views and with sample volume at the tips of the mitral leaflets in the position providing the best color-flow projection. In all subjects, wave forms were recorded over three consecutive cycles, and the following measurements were made; VE: peak velocity of early left ventricular filling (E wave) and VA: peak velocity of late (atrial) ventricular filling (A wave), deceleration time (DT), isovolumic relaxation time (IRT). The ratio between early and late flow velocity peaks (E /A) was calculated from these measurements. Relaxation abnormality was defined as E / A <1 (12).

The data are presented as mean ± standard deviation (SD). In statistical analysis, when the same variable is measured on several occasions for each subject, repeated measures ANOVA was used to test different hypotheses for between-subject effects, within-subject effects, and interaction between them. Continuous variables were evaluated by using Student's t and Mann-Whitney U test, where applicable. Differences between groups for discrete variables were evaluated by Chi-square and Fisher's Exact test, where applicable. Correlations between continuous variables were calculated by Pearson's correlation coefficient. When there was a failure of the parametric assumptions, non-parametric tests were used.

Results

Albuminuria and blood pressure measurements

Twenty patients were normoalbuminuric (NA-group) and 16 patients had MA (MA-group). The two groups were matched according to basal characteristics (Table 1). When casual BPs were compared with 24-h and daytime BPs, a positive but weak correlation was found between both 24-h SBP and daytime SBP and cas-SBP (r=0.34, p=0.04 and r=0.37, p=0.025, respectively). No correlation was noted between UAE rate and any other BP parameters obtained from ABPM except mean day/night SBP ratio which was significantly higher in NA-group than MA-group (1.1±0.1 vs. 1.0±0.1, p=0.013) (Table 2).

Differences between dippers and nondippers

To analyse the relationship between nondipping and ambulatory BP, metabolic indices and clinical

Table 1. Clinical profiles of normoalbuminuric and microalbuminuric groups ($\overline{X} \pm SD$).

Patient characteristics	Normoalbuminuric group (n=20)	Microalbuminuric group (n=16)	p
Sex (Female / Male)	11/9	7 / 9	NS[a]
Age (years)	48 ± 7	48 ± 7	NS
Duration of DM (years)	4 ± 3	4 ± 4	NS
Therapy(d/o/i)[b]	5/14/1	7/8/1	NS
BMI(kg/ m^2)	27.9 ± 4.8	28.3 ±5.4	NS
Cas-SBP(mmHg)	115.6 ± 12.6	110.6 ± 11.8	NS
Cas-DBP(mmHg)	74.9 ± 7.4	73.1 ± 5.5	NS
Fundus (n/b/p)[c]	19/1/0	13/2/1	NS
FPG (mg/dl)	124.6 ± 31.1	122.1 ± 31.5	NS
HbA1c (%)	6.5 ± 1.0	6.7 ± 0.7	NS
BUN (mg/dl)	12.9 ± 3.7	14.4 ± 3.9	NS
Creatinine(mg/dl)	0.8 ± 0.2	0.7 ± 0.1	NS
Total cholesterol (mg/dl)	203.8 ± 41.5	195.1 ± 54.4	NS
LDL-cholesterol(mg/dl)	121.3 ± 24.9	116.1 ± 44.3	NS
HDL-cholesterol (mg/dl)	41.5 ± 11.1	39.8 ± 7.5	NS
VLDL-cholesterol(mg/dl)	33.0 ± 14.0	36.8 ± 21.9	NS
Triglycerides(mg/dl)	188.6 ± 82.0	183.6 ± 109.3	NS
Daytime MA (µg/min.)[d]	4.75 (0.02-18.7)	30.2 (20.2-189.4)	<0,05
Nighttime MA (µg/min.)[d]	2.6 (0.01-15.5)	22.6 (2.2-59.1)	<0,05

[a] NS:nonsignificant, p>0.05, [b] d, diet; o, oral hypoglycemic agents; i,insulin
[c] n, normal; b, background retinopathy; p, proliferative retinopathy. [d] Data are given as median.

Table 2. Casual and 24-hour blood pressure profile comparisons of normo- and microalbuminuric groups ($\overline{X} \pm SD$).

Ambulatory blood pressure recordings	Normoalbuminuric group (n=20)	Microalbuminuric group (n=16)	p
Cas-SBP (mmHg) [a]	115.6 ± 12.6	110.6 ± 11.8	NS [b]
Cas-DBP	74.9 ± 7.4	73.1 ± 5.5	NS
24-hourHR (beat/min.)	75.4 ± 8.2	77.0 ± 5.3	NS
24-hour SBP	108.8 ± 8.8	108.0 ± 6.1	NS
24-hour DBP	78.2 ± 5.4	77.5 ± 5.5	NS
Daytime SBP	110.5 ± 8.1	108.5 ± 6.1	NS
Daytime DBP	79.6 ± 5.4	78.0 ± 6.1	NS
Nighttime SBP	102.1 ± 13.1	106.3± 8.1	NS
Nighttime DBP	72.2 ± 7.1	73.6 ± 7.2	NS
Mean daytime BP	89.9 ± 6.2	88.7 ± 5.7	NS
Mean nighttime BP	82.5 ± 8.7	84.5 ± 6.7	NS
Day/night SBP	1.1 ± 0.1	1.0 ± 0.1	0.01
Non-dipper (n / %)	12 /60	14 / 87.5	NS

[a] All BP measurements in mmHg.
[b] NS: nonsignificant, $p > 0.05$.

Table 3. Left ventricular echocardiographic measurements in normo- and microalbuminuric groups ($\overline{X} \pm SD$).

Echocardiographic measurements	Normoalbuminuric group (n=20)	Microalbuminuric group (n=16)	p
LAD (cm)	3.3 ± 0.5	3.4 ± 0.4	NS
IVS (cm)	1.0 ± 0.1	1.0 ± 0.2	NS
LVPW (cm)	0.9 ± 0.1	0.9 ± 0.2	NS
LVESD (cm)	2.9 ± 0.5	2.8 ± 0.4	NS
LVEDD(cm)	4.7 ± 0.6	4.9 ± 0.4	NS
FS (%)	38.8 ± 5.3	41.7 ± 4.7	NS
EF (%)	67.8 ± 5.5	70.7 ± 5.2	NS
VE (s)	0.6 ± 0.1	0.7 ± 0.2	NS
VA(s)	0.6 ± 0.1	0.7 ± 0.2	NS
E / A <1 (n / %)	(8 / 40)	(7 / 43.8)	NS
E/A (mean)	1.0 ± 0.2	1.0 ± 0.4	NS
DT > 220 ms(n /%)	(4 / 20)	(2 / 12.5)	NS
IRT >100 ms	(7 / 35)	(5 / 31.3)	NS
High LVMI (n / %)	(4 / 20)	(4 / 25)	NS

parameters, two groups were formed as dippers (10/36) and nondippers (26/36) regardless of MA (data not shown). There was no difference between dippers and nondippers in terms of age, sex, diabetes duration, type of therapy, fasting plasma glucose, HbA1c, lipid profiles, BMI, cas-SBP, cas-DBP, LVMI and retinopathy. Twenty-four hour SBPs (110.3±6.3 mmHg vs. 103.5±8.8 mmHg, p=0.013, respectively) and DBPs (79±5.1 mmHg vs. 75.1±5.1 mmHg, p=0.044, respectively) were significantly higher in nondippers compared to dippers. Furthermore, nighttime MA was higher in nondippers compared to dippers (16.8±16.2 µg / min.vs. 4.7±5.43 µg / min., p=0.03, respectively).

Left ventricular functions and left ventricular mass index

Left ventricular thickness, chamber dimensions, mass indexes, systolic and diastolic functions were similar in NA- and MA-groups (Table 3). Diastolic dysfunction (relaxation abnormality) was found in 40% (8/20) of NA-group and in 43.8% (7/16) of MA-group (p>0.05). Left ventricular mass index wasn't found to be related to casual and other BP parameters measured with ABPM. Although insignificant, patients with high LVMI (n=8) in the whole study group (n=36), displayed a higher rate of nondippers (80% vs. 53.8%, p>0.05) and reti-

opathy (25% vs. 7.1%, p>0.05), compared to patients with normal LVMI (n=28).

Discussion

There are two major findings of this study. First of all, in the absence of poor glycemic control and intervening diseases such as hypertension, MA is still associated with nondipping. Secondly, diastolic dysfunction rates may be similar in normo- and microalbuminuric type 2 diabetic subjects, if they are normotensive and good metabolic control is achieved.

The relation between MA and nondipping estalished in our study, has been shown in some (13,14), but not all (15), of the previous studies based on 24-h AMBP recordings. However, the patient population in these studies were very heterogenous. Except a few studies (15,16) which included only normotensive type 2 diabetic patients, many studies have recruited hypertensive subjects even some continuing antihypertensive medication during the study. However, MA and nondipping already may occur as a result of hypertension in the absence of DM. In other words, in order to verify a relation between MA and nondipping, it may be crucial to exclude hypertensive subjects. As our patient population was normotensive, the relation between MA and nondipping is more clear and significant.

In type 1 DM, patients without renal disease are generally normotensive and hypertension develops after MA. However, this is not the case in type 2 diabetes, BP generally rises along with degree of MA in these patients. The pathophysiology of BP rise along with MA is not clear but it seems that autonomic neuropathy (AN) plays a critical role. The BP decrease occuring at night is partly due to reduced sympathetic tone and increased vagal tone during sleep. Any abnormalities of the autonomic nervous system may alter such behaviour. Nondipping is accepted as an early sign of autonomic dysfunction in type 2 diabetes (17,18). In a very interesting study by Spallone et al., in normotensive non-proteinuric type 2 diabetic subjects, AN was the unique determinant of not only day-night SBP difference but also of 24-h SBP (19). This exciting finding is in accordance with our finding that, 24-h SBP and DBPs were significantly higher in nondippers compared to dippers. Although, there is only limited data available about AN in microalbuminuric patients; in the Hoorn study, an independent association between impaired cardiovascular autonomic function and MA has been found and autonomic dysfunction has been accepted as a possible contributor to the presence of MA (20). Taken together, the above studies suggest that, in the absence of hypertension, AN, by causing nondipping and increasing the intraglomerular BP burden, may increase MA in a type 2 diabetic kidney (19,21). These hemodynamic changes, in turn, contribute to a vicious cycle of gradually increasing systolic BP and MA (22). Assuming AN as the missing link, between MA, nondipping and systemic hypertension in type 2 diabetic patients, also explains the increased cardiovascular mortality in microalbuminuric subjects, as AN may induce fatal arrythmias.

As mentioned above, the primary objective of the present study was assessment of a link between MA and diastolic dysfunction. There are a few reports showing diastolic dysfunction in patients with normotensive type 2 diabetic patients (2, 3,4,23). Diastolic dysfunction was noted in nearly 40% of our patients which is a similar rate found in (47%) a recent prevalence study of Zaalgoitia et al. performed in well-controlled, normotensive type 2 diabetic subjects (3). The real question is, however, whether MA or nondipping is related to diastolic dysfunction. In "The Strong Heart study", the patient group with diastolic dysfunction had a significantly higher albumin/creatinine ratio, which could point out a relationship, but that patient group also had significantly higher fasting glucose (172 mg/dL vs. 206 mg/dL, p=0.002) and HbA1c (%7.8 vs. %8.5, p=0.01) levels, which are known contributors to diastolic dysfunction (2). On the contrary, in the study by Poirier et al, there was no difference between patients with diastolic dysfunction and normal function with regard to MA, as suggested in our study (4).

With respect to nondipping, to the authors' knowledge, there are two studies evaluating the putative role of nondipping in diastolic dysfunction and LVMI in type 2 diabetic patients (24,25). Both of these studies have suggested a relation between nondipping, MA and LVMI, while one of them found no association with diastolic dysfunction (25). Although these two studies, had the same objective with the present one, the common point

which essentially separates them from our study, is their design which included hypertensive subjects. Because hypertension itself causes MA, nondipping and left ventricular hypertrophy in the absence of diabetes, exclusion of hypertensive subjects may be more informative to reveal such an association in type 2 diabetes mellitus. Nevertheless, although valuable for clear demonstration of disease pathogenesis, strict inclusion criteria brings a disadvantage together. That is difficulty of forming a highly selected patient group reaching large numbers, which was also a limitation for our study.

Although microalbuminuric group included a significantly higher rate of nondippers compared to normoalbuminuric group, similar LVMI and diastolic dysfunction rates were found in our study. A possible explanation for this similarity, may be the patients' well-regulated and normotensive character, which probably preserved them from many complications of type 2 diabetes.

A second explanation for this finding may be the low BP values of our patient population (24-h SBP, 108.8 ± 8.8 mmHg vs. 108.0 ± 6.1 mmHg and 24-DBP, 78.2 ± 5.4 mmHg vs. 77.5 ± 5.5 mmHg, normo- and microalbuminuric groups, respectively). The BP levels of both normo- and microalbuminuric patients were lower than the optimal BP values recommended for diabetic patients.

As a conclusion, in the absence of poor glycemic control and hypertension, MA is probably associated with nondipping, but may not be associated with diastolic dysfunction. Prospective studies evaluating autonomic dysfunction in normotensive and well-controlled type 2 diabetic patients, will further illuminate the complicated relationship between MA and nondipping and the degree of their contribution to cardiovascular complications.

References

1. Mogensen CE: Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* **310**: 356-360, 1994.
2. Liu JE, Palmieri V, Roman MJ, Bella JN, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB: The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: The Strong Heart Study. *J Am Coll Cardiol* **37**: 1943-1949, 2001.
3. Zaalgoitia M, Ismaeil MF, Anderson L, Maklady FA: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. *Am J Cardiol* **87**: 320-323, 2001.
4. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes. *Diabetes Care* **24**: 5-10, 2001.
5. WHO Expert Committee on Diabetes Mellitus: Second Report, World Health Organisation, Technical Report Series, Geneva, No. 646, 1980.
6. Ertürk S, Ertug AE, Ates K, Duman N, Aslan SM, Nergisoglu G: Relationship of ambulatory blood pressure monitoring data to echocardiographic findings in haemodialysis patients. *Nephrol Dial Transplant* **11**: 2050-2054, 1996.
7. The Scientific Commitee: Consensus document on non-invasive blood pressure monitoring. *J Hypertens* **8**: 135-140, 1990.
8. Roman MJ, Pickering TG, Schwartz JE, Cavallini MC, Pini R, Devereux RB: Is the absence of a normal nocturnal fall in blood pressure (nondipping) associated with cardiovascular target organ damage? *J Hypertens* **15**: 969-978, 1997.
9. Early treatment diabetic retinopathy study research group: Fundus photographic risk factors for progression of diabetic retinopathy, Early treatment diabetic retinopathy study report number 12, *Ophtalmology* **98**: 823-833, 1991.
10. Sahn DJ, De Maria A, Kisslo J, Weyman A, Committee on M-mode standardization of the American Society of Echocardiography: Recommendations regarding quantification in M-mode echocardiography, Results of a survey of echocardiographic measurements. *Circulation* **58**: 1072-1083, 1978.
11. Devereux RB, Reichek N: Echocardiographic determination of left ventricular mass in man, Anatomic validation of the method. *Circulation* **55**: 613-618, 1977.
12. Lenihan DJ, Gerson MC, Hoit BD, Walsh RA: Mechanisms, diagnosis and treatment of diastolic heart failure. *Am Heart J* **130**: 153-166, 1995.
13 Equiluz-Bruck S, Schnack C, Kopp HP, Schernthaner G: Nondipping of nocturnal blood pressure is related to urinary albumin excretion rate in patients with type 2 diabetes mellitus. *Am J Hypertens* **9**: 1139-1143, 1996.
14. Inaba M, Negishi K, Takahashi M, Serizawa N, Maruno Y, Takahashi K, Katayama S: Increased night: day blood pressure ratio in microalbuminuric normotensive NIDDM subjects. *Diab Res Clin Pract* **40**: 161-166, 1998.
15. Nielsen S, Schimtz A, Poulsen PL, Hansen KW, Mogensen CE: Albuminuria and 24-h ambulatory blood pressure in normoalbuminuric and microalbuminuric NIDDM patients. *Diabetes Care* **18**: 1434-1441, 1995.
16. Jermendy G, Ferenczi J, Hernandez E, Farkas K, Nadas J: Day-night blood pressure variation in normotensive and hypertensive NIDDM patients with asypmtomatic neuropathy. *Diab Res Clin Pract* **34**: 107-114, 1996.
17. McKinlay S, Foster C, Clark A, Clark S, Kemp F, Denver E, Coats AJS: Increased blood pressure variability during 24h blood pressure monitoring as an early sign of auto-

nomic dysfunction in non-insulin-dependent diabetics. *J Hum Hypertens* **8**: 887-890, 1994.

18. Fogari R, Zoppi A, Malamani G, Lazzari P, Destro M, Corradi L: Ambulatory blood pressure monitoring in normotensive and hypertensive type 2 diabetics. *Am J Hypertens* **6**: 1-7, 1998.
19. Spallone V, Maiello MR, Cicconetti E, Pannone A, Barini A, Gambardella S, Menzinger G: factors determining the 24-h blood pressure profile in normotensive patients with type 1 and type 2 diabetes. *J Hum Hypertens* **15**: 239-246, 2001.
20. Smulders YM, Jager A, Gerritsen J, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Stehouwer CDA: Cardiovascular autonomic function is associated with (micro-)albuminuria in elderly Caucasian subjects with impaired glucose tolerance or type 2 diabetes. *Diabetes Care* **23**:1369-1374, 2000.
21. Ueda Y, Wataru A, Yamachika S, Nagataki S: Loss of nocturnal decline in blood pressure in diabetic patients with autonomic neuropathy. *Jpn Heart J* **33**: 801-815, 1992.
22. Schmitz A, Vaeth M, Mogensen CE: Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. *Diabetologia* **37**: 1251-1258, 1994.
23. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A: Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. *J Am Soc Echocardiogr* **14**: 885-891, 2001.
24. Rutter MK, McComb JM, Forster J, Brady S, Marshall SM: Increased left ventricular mass index and nocturnal systolic blood pressure in patients with type 2 diabetes mellitus and microalbuminuria. *Diabetic Med* **17**: 321-325, 2000.
25. Nielsen FS, Ali S, Rossing P, Bang LE, Svendsen TL, Gall MA, Smidt UM, Kastrup J, Parving HH: Left ven-tricular hypertrophy in non-insulin dependent diabetic patients with and without nephropathy. *Diabetic Med* **14**: 538-546, 1997.