Masked Hypertension, Urinary Albumin Excretion Rate, and Echocardiographic Parameters in Putatively Normotensive Type 2 Diabetic Patients

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OBJECTIVE — To evaluate the impact of masked hypertension in normotensive type 2 diabetic patients on microvascular complications and echocardiographic parameters.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted in 135 normotensive patients with type 2 diabetes. Patients underwent urinary albumin excretion rate (UAER) measurement, echocardiography, and 24-h ambulatory blood pressure monitoring (ABPM). Patients with increased daytime blood pressure levels (≥135/85 mmHg) were classified as having masked hypertension.

RESULTS — The prevalence of masked hypertension was 30% ($n = 41$). Normotensive and masked hypertensive subjects, based on ambulatory blood pressure, were not different in terms of age, diabetes duration, smoking status, BMI, waist circumference, serum creatinine, glycemic, or lipid profiles. The office systolic blood pressure was higher in those with masked hypertension (127.8 ± 7.5 vs. 122.9 ± 10.2 mmHg, $P = 0.003$) than in the normotensive group. UAER also was increased in the group with masked hypertension (21.3 μg/min [range 2.5–1,223.5] vs. 8.1 μg/min [1.0–1,143.0], $P = 0.001$), as was the interventricular septum (1.01 ± 0.15 vs. 0.94 ± 0.13 cm, $P = 0.015$) and posterior wall (0.96 ± 0.12 vs. 0.90 ± 0.10 cm, $P = 0.006$) thickness. After adjustments for diabetes duration, sex, smoking, LDL cholesterol, and A1C values, all associations were sustained for daytime systolic blood pressure but not for office systolic blood pressure.

CONCLUSIONS — Type 2 diabetic patients with masked hypertension have higher UAER as well as enlargement of ventricular walls compared with the normotensive patients, according to ABPM. Therefore, ABPM is important to identify this high-risk group so as to be able to take interventionist measures.

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Hypertension is a major risk factor for the development and progression of chronic complications in type 2 diabetes (1,2). Blood pressure evaluation over a 24-h ambulatory blood pressure monitoring (ABPM) period correlates better with outcomes than ordinary office blood pressure measurements in both hypertensive subjects (3) and the general population (4). In addition, systolic ambulatory blood pressure is associated with the urinary albumin excretion rate (UAER), even in normoalbuminuric type 2 diabetic patients (5). The ABPM also allows the analysis of other blood pressure parameters, otherwise not documented by the office blood pressure evaluation, such as nocturnal dipping patterns, presence of white-coat hypertension, blood pressure loads, and a novel subgroup of patients with masked hypertension (6).

Masked hypertension is defined by elevated mean daytime blood pressure levels at 24-h ABPM (blood pressure ≥135/85 mmHg) in office normotensive individuals (blood pressure <140/90 mmHg). In a population-based study, it was detected in 9% of the individuals tested (7). Before the ABPM became available, these patients were not detected and were believed to have the same risk for cardiovascular events as the normotensive population. However, emerging evidence shows that masked hypertension is associated with higher left ventricle wall thickness (7) and increased cardiovascular mortality (8) in comparison with normotensive individuals. This issue has yet to be examined in patients with diabetes. The aim of this study is to analyze the impact of masked hypertension in type 2 diabetic patients with regard to microvascular complications and echocardiographic parameters.

RESEARCH DESIGN AND METHODS

— A cross-sectional study was performed in 135 patients with type 2 diabetes selected from a cohort of 270 patients followed since 1994 at the outpatient clinic of the Hospital de Clínicas de Porto Alegre. The inclusion criteria were a diagnosis of type 2 diabetes (aged >30 years at onset of diabetes, no previous episode of ketoacidosis or documented ketonuria, and treatment with insulin only after 5 years of diagnosis) and blood pressure levels at office evaluation <140/90 mmHg on at least two occasions during a 6-month period and on the day of the office examination and ABPM. Patients with creatinine >1.5 mg/dl, other renal diseases, cardiac arrhythmia, or postural hypotension were excluded. The ethics committee of the hospital approved this

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Abbreviations: ABPM, ambulatory blood pressure monitoring; UAER, urinary albumin excretion rate.

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

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study, and informed consent was obtained from all patients.

Patient evaluation

Patients underwent an interview and clinical examination to record demographic and anthropometrical data, as previously described (9). Indirect ophthalmoscopy was performed through dilated pupils by an ophthalmologist, and, for the purpose of this study, patients were classified only according to the presence or absence of any degree of diabetic retinopathy.

Blood pressure evaluations were performed 1 week after withdrawal from all medications with antihypertensive effect. The mean of two office blood pressure examinations (measured with a mercury sphygmomanometer using the left arm and with the patient in a sitting position, after a 5-min rest, on the same day as the ABPM) was considered for the analyses. ABPM was performed by oscillometry (Spacelabs 90207, ser. nos. 207/024751 and 207/038016, with calibration certification), with a 15-min interval in the daytime and 20-min interval in the nighttime periods. Patients were advised to maintain their usual daily activities. Sleep time was recorded as the period between the time when the patient went to bed and the time when the patient woke up the next morning. All ABPM evaluations were performed on a normal workday. The means of 24-h daytime and nighttime systolic and diastolic blood pressure were recorded, as were blood pressure loads (percentage of 24-h and daytime blood pressure measurements ≥140/90 mmHg and nighttime ≥120/80 mmHg). The patients' blood pressure status was classified, according to ABPM, into normotension (daytime ambulatory blood pressure mean <135/85 mmHg) and masked hypertension (daytime ambulatory blood pressure mean ≥135/85 mmHg) (10,11).

Echocardiograms ($n = 101$) were obtained according to the recommendations of the American Society of Echocardiography (12), using standard parasternal and apical views with subjects in the partial left decubitus position using a commercially available instrument (Hewellet Packard Sonus 1000). Left ventricular mass was calculated based on wall thickness and was adjusted to the body surface area. The cardiologist who performed the echocardiograms was unaware of the subjects' clinical or laboratorial characteristics. The glomerular filtration rate was estimated using the formula of the Modification of Diet in Renal Disease Study (13): $186 \times [\text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742, \text{if female}) \times (1.210, \text{if of African descendant})]$.

Patients were classified, according to UAER, into four groups: low normoalbuminuric (UAER <10 μg/min, $n = 69$), high normoalbuminuric (UAER 10–19 μg/min, $n = 22$), microalbuminuric (UAER 10–199 μg/min, $n = 36$), and macroalbuminuric (UAER ≥200 μg/min, $n = 8$), based on 24-h sterile and timed urine collections, two of three samples, 6 months apart. Those patients using ACE inhibitors or angiotensin receptor blockers had these medications stopped 1 week before urine collection.

Laboratory methods

UAER was measured by immunoturbidimetry (Microalb; Ames-Bayer, Tarrytown, NY) (intra- and interassay coefficients variation of 4.5 and 11.0%, respectively). A1C was measured by a high-performance liquid chromatography system (normal range 4–6%; Merck-Hitachi 9100). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method (Biodiagnóstica). Creatinine was measured by the Jaffé method and the lipid profile by a colorimetric method.

Statistical analysis

Student's t test or χ^2 tests were used to compare clinical and laboratorial data. Quantitative variables without a normal distribution were submitted to logarithmic transformation. Data are expressed as the means ± SD except for UAER, triglycerides, serum creatinine, and blood pressure loads (median [range]). Sequential models of multiple linear regressions were performed with the following dependent variables: log UAER, interventricular septum, posterior wall thickness, and left ventricular mass. P values <0.05 (two tailed) in the univariate analysis were considered to be significant.

RESULTS — Masked hypertension was found in 41 (30%) normotensive type 2 diabetic patients. Both groups (normotension and masked hypertension, based on ABPM) were not different regarding age, diabetes duration, smoking status, BMI, and waist circumference (Table 1). There was an excess of male prevalence in the masked hypertension group (71 vs. 45%, $P = 0.005$). With regard to laboratorial characteristics, there was no difference between the groups for glycemic and lipid profiles, as well as for serum creatinine and estimated glomerular filtration rate. The office systolic blood pressure was higher in patients with masked hypertension (127.8 ± 7.5 vs. 122.9 ± 10.2 mmHg, $P = 0.003$) (Table 2). The office diastolic blood pressure was comparable in the two groups. The daytime blood pressure measurements were higher in the masked hypertension group, as expected, because it was part of the definition of the group. The same was true for most of 24-h and nighttime blood pressure measurements.

UAER was increased in the masked hypertension (21.3 μg/min [2.5–1,223.5] vs. 8.1 μg/min [1.0–1,143.0], $P = 0.001$) in comparison with the normotension group (Fig. 1). Likewise, the prevalence of masked hypertension increased with the progression of UAER, starting from the high normoalbuminuric group (low normoalbuminuric: 17%, high normoalbuminuric: 32%, microalbuminuric: 50%, and macroalbuminuric: 50%; P for trend = 0.003), reflecting increased kidney damage in these patients.

Patients with masked hypertension also had higher interventricular septum (1.01 ± 0.15 vs. 0.94 ± 0.13 cm, $P = 0.015$) and posterior wall (0.96 ± 0.12 vs. 0.90 ± 0.10 cm, $P = 0.006$) thickness than the normotension group. The left ventricular mass tends to be enlarged in patients with masked hypertension (150.2 ± 32.90 vs. 140.5 ± 26.5 g/1.73 cm^2) but did not reach conventional statistic significance ($P = 0.111$).

Subanalyses were performed on patients who were not on ACE inhibitors/angiotensin receptor blockers (88% of the sample, $n = 119$) or not on medications with antihypertensive effects (77% of the sample, $n = 104$) and similar results were found (data not shown). The prevalence of any degree of diabetic retinopathy was similar in both groups (masked hypertension 30% vs. normotension 34%, $P = 0.678$).

Because patients with masked hypertension had higher office systolic blood pressure levels (+4.9 mmHg), the present findings could be attributed to this difference. To elucidate the real association of masked hypertension with UAER and the echocardiographic parameters and to evaluate the possible confounding effect of a higher office systolic blood pressure, two approaches were applied and are presented subsequently.

The first approach was to perform multiple linear regression analysis with the potential outcomes of increased blood

Table 1—*Clinical and laboratorial characteristics according to blood pressure classification*

	Normotension	Masked hypertension	*P*
n	94	41	
Age (years)	56.2 ± 10.5	56.1 ± 9.7	0.941
Diabetes duration (years)	9.5 ± 7.6	9.1 ± 6.2	0.762
Male subjects	42 (45)	29 (71)	0.005
Whites	70 (75)	33 (81)	0.605
Smokers	23 (25)	14 (35)	0.118
Waist circumference (cm)			
Male subjects	98.9 ± 11.1	99.9 ± 10.2	0.717
Female subjects	95.5 ± 9.4	94.2 ± 11.0	0.697
BMI (kg/m^2)	28.4 ± 4.4	28.0 ± 4.2	0.621
Diabetic retinopathy	26 (34)	9 (30)	0.678
UAER (μg/min)	8.1 (1.0–1,143.4)	21.3 (2.5–1,223.5)	0.001
Fasting plasma glucose (mg/dl)	153.9 ± 68.3	154.6 ± 55.2	0.955
A1C (%)	7.8 ± 2.0	7.8 ± 2.2	0.993
Total cholesterol (mg/dl)	191.9 ± 40.5	203.3 ± 39.3	0.134
HDL cholesterol (mg/dl)	47.4 ± 12.7	45.3 ± 13.2	0.372
Triglycerides (mg/dl)	123.0 (46.0–974.0)	144.5 (43.0–475.0)	0.278
Creatinine (mg/dl)	0.8 (0.5–1.4)	0.9 (0.3–1.5)	0.911
Estimated glomerular filtration rate (ml/min per 1.73 m^2)*	98.6 ± 27.3	102.7 ± 46.4	0.606
Antihypertensive effect drugs	21 (22)	10 (24)	0.715

Data are means ± SD, median (range), or *n* (%). Data available for diabetic retinopathy: *n* = 106; 76 with normotension and 30 with masked hypertension. *Measured by Modification of Diet in Renal Disease (MDRD) Study equation.

pressure (UAER and echocardiographic parameters: interventricular septum and posterior wall thickness and left ventricular mass) as the dependent variables. Therefore, four models were constructed with diabetes duration, sex, smoking status, LDL cholesterol, A1C, and one of the blood pressure measurements (office systolic or daytime systolic blood pressure) as independent variables. The daytime systolic blood pressure remains significantly associated with the outcomes in the four models (UAER: $R = 0.402$, $R_a^2 = 0.118$, $P = 0.029$; interventricular septum thickness: $R = 0.380$, $R_a^2 = 0.086$,

Table 2—*Blood pressure characteristics according to blood pressure classification*

	Normotension	Masked hypertension	*P*
n	94	41	
Office			
Systolic blood pressure (mmHg)	122.9 ± 10.2	127.8 ± 7.5	0.003
Diastolic blood pressure (mmHg)	76.0 ± 7.2	77.4 ± 7.4	0.309
Pulse pressure (mmHg)	46.9 ± 9.2	50.4 ± 8.1	0.041
24 h			
Systolic blood pressure (mmHg)	119.7 ± 7.3	134.8 ± 9.5	<0.001
Diastolic blood pressure (mmHg)	71.8 ± 6.1	81.9 ± 6.3	<0.001
Pulse pressure (mmHg)	47.9 ± 6.9	53.0 ± 10.0	0.003
Systolic blood pressure load (%)	10.7 (0–47.4)	48.8 (1.2–98.6)	<0.001
Diastolic blood pressure load (%)	3.2 (0–30.6)	23.9 (1.2–95.2)	<0.001
Daytime			
Systolic blood pressure (mmHg)	122.3 ± 7.1	138.1 ± 7.8	—
Diastolic blood pressure (mmHg)	74.3 ± 6.1	85.4 ± 6.3	—
Pulse pressure (mmHg)	47.9 ± 6.6	58.8 ± 10.1	—
Systolic blood pressure load (%)	4.7 (0–32)	47.2 (1.5–98.3)	—
Diastolic blood pressure load (%)	2.2 (0–50.3)	22.9 (1.5–95.8)	—
Nighttime			
Systolic blood pressure (mmHg)	114.2 ± 10.3	127.3 ± 14.3	<0.001
Diastolic blood pressure (mmHg)	65.5 ± 74.9	74.9 ± 9.5	<0.001
Pulse pressure (mmHg)	48.7 ± 7.7	52.4 ± 11.1	0.060
Systolic blood pressure load (%)	24.4 (0–100.0)	68.8 (0–100.0)	0.003
Diastolic blood pressure load (%)	0 (0–86)	26.3 (0–98.0)	<0.001

Data are means ± SD or median (range).

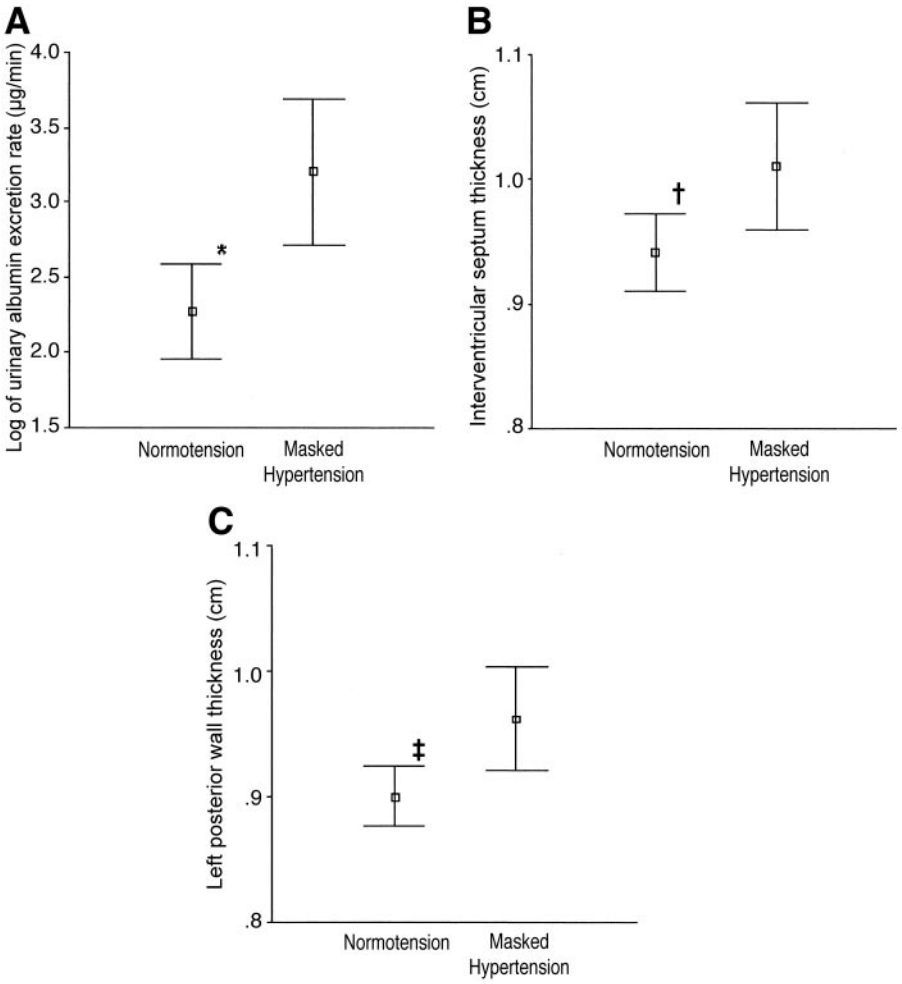

Figure 1—*UAER* (A)*, interventricular septum thickness* (B)*, and left posterior wall thickness* (C) *in the normotension and masked hypertension groups.* *P = *0.001;* † P = *0.015;* ‡ P = *0.006.*

$P = 0.022$; posterior wall thickness: $R = 0.404$, $R_a^2 = 0.107$, $P = 0.045$; and left ventricular mass: $R = 0.322$, $R_a^2 = 0.043$, $P = 0.049$). When the systolic office pressure was the blood pressure included in the model, it did not continue to be significantly associated with the outcomes ($P > 0.05$). When both office systolic and daytime systolic blood pressure were included simultaneously in each one of the models, only the daytime systolic blood pressure remained significantly associated to the renal and cardiac outcomes.

The second approach was to stratify the patients according to office systolic blood pressure in normal-high (130–140 mmHg) and normal-low (<130 mmHg) blood pressure groups. These values were adopted because they are current goals of blood pressure treatment in diabetic patients and, at the same time, capture the higher values of blood pressure (i.e., the group that could confound the results). The presence of high-normal office systolic blood pressure was not associated with UAER (11.2 μg/min [1–1,223.5] vs. 8.4 μg/min [1.7–169.6], $P = 0.074$), interventricular septum thickness (0.96 ± 0.16 vs. 0.97 ± 0.12 cm, $P = 0.830$), left posterior wall thickness (0.92 ± 0.11 vs. 0.91 ± 0.11 cm, $P = 0.660$), or left ventricular mass (142.4 ± 32.3 vs. 145.2 ± 25.2 g/1.73 m^2, $P = 0.635$). Likewise, the presence of high-normal office blood pressure did not discriminate the patients with diabetic nephropathy (micro- or macroalbuminuria) (odds ratio 1.83 [95% CI 0.87–3.85], $P = 0.108$). In contrast, patients with masked hypertension had a significant increase in the risk for this complication (3.74 [1.72–8.14], $P = 0.001$). These analyses suggest that the effect observed for masked hypertension cannot be attributed only to the small increase observed in office blood pressure.

CONCLUSIONS — In this sample of normotensive type 2 diabetic patients, approximately one-third of the individuals had masked hypertension, and it was associated with target-organ damage, represented by higher UAER, as well as greater interventricular septum and posterior wall thickness. These associations remain after adjustments for possible confounding factors and cannot be attributed only to elevations of the office blood pressure levels.

The linkage of blood pressure levels and micro- and macrovascular diabetes complications is well known (1). The development of portable ambulatory blood pressure equipment has allowed the accumulation of evidence showing that 24-h blood pressure values present better correlation to outcomes than office blood pressure (3,4). In addition, ABPM allows the separation of the population into four groups: true normotensive (normotension in both office and 24-h ABPM), true hypertensive (hypertension in both the office and 24-h ABPM), white-coat hypertensive (hypertension in office and normotension in 24-h ABPM), and, more recently, masked hypertensive (normotension in office and hypertension in 24-h ABPM) subjects. Patients in this peculiar group otherwise have not been identifiable because their routine office blood pressure exam is normal and physicians would not be aware they belong to a high-risk group.

Masked hypertension is reported to affect 2–26% of the population (8,14–18). This large variation might be due to differences in the definition of normal ambulatory blood pressure levels as well as to variations in patient demographic characteristics, such as age and BMI (16,19). The data from the Pressione Arteriose Monitorate e Loro Associazioni Study (8), a large cohort of individuals ($n = 2,051$) evaluated by ABPM, showed a prevalence of 9% in the general population and 14.5% among normotensive subjects. The frequency of masked hypertension in the diabetic population had not been evaluated previously, and the present data suggest a high prevalence (30%) among type 2 diabetic patients. Therefore, association of masked hypertension and chronic complications in type 2 diabetic patients also had not been analyzed. As far as we know, this is the first report of an increased UAER and ventricular wall thickness in type 2 diabetic patients with masked hypertension.

In previous reports in nondiabetic patients, masked hypertension has been associated with diminished sensitivity of

arterial baroreflex (14), aortic stiffness (verified by carotid-femoral pulse wave velocity) (20), increased left ventricle mass index (7,16), and cardiovascular mortality (8). Patients with masked hypertension have shown an adverse clinical and metabolic profile in some contexts (8,14,16). In children and adolescents, the diagnosis of masked hypertension was associated with increased BMI and a parental history of hypertension (16). In nondiabetic adults, there is a progressive increase in male sex prevalence, age, BMI, total cholesterol, and blood glucose throughout the spectrum of blood pressure abnormalities, from the truly normotensive group across the white-coat hypertensive, masked hypertensive, and truly hypertensive groups (8). Moreover, most previous reports (8,14,16) identified higher levels of office blood pressure in masked hypertension patients. Based on this, it could be hypothesized that the worst outcomes found in the masked hypertension group are explained solely by higher office blood pressure levels because it is well known that there is not a threshold for blood pressure and target-organ lesion, as the two variables have a continuous correlation (21). However, our results, as well as those from the Pressione Arteriose Monitorate e Loro Associazioni Study, remain significant after further adjustment for the difference in office blood pressure as well as for other relevant clinical and laboratorial confounders (7,8,22).

The reason why some individuals have normal office blood pressure and high values during the ABPM is, at present, unknown (23). One possibility is that some patients react to stressful daily activities with an elevation in blood pressure. An increase in blood pressure levels during exercise, as has been verified in offspring of type 2 diabetic patients with insulin resistance (24), could be one of the situations related to blood pressure elevation during the day in masked hypertensive patients. On the other hand, the increase in blood pressure during the day could be due to arterial stiffness, because the patients with masked hypertension, in this sample, had a higher pulse pressure, reflecting the isolated elevation of systolic blood pressure.

There are two practical implications of the present results. First, the simple office blood pressure evaluation cannot identify patients with masked hypertension and thus cannot provide them with the potential benefits of antihypertensive treatment. Therefore, ABPM should be part of the initial evaluation of normotensive type 2 diabetic patients to identify those patients with masked hypertension. Second, type 2 diabetic patients with masked hypertension probably would benefit from antihypertensive interventions, in the same way as has been demonstrated in prehypertension nondiabetic subjects (25) and normotensive type 2 diabetic patients in the Micro-Heart Outcomes Prevention Evaluation Study (26). The American Diabetes Association position statement on diabetes treatment affirms that all patients aged >55 years should be prescribed an ACE inhibitor (ramipril) regardless of the obtained blood pressure values (27), and this might particularly be useful in patients with masked hypertension.

No association was found between masked hypertension and diabetic retinopathy, in contrast to the results of classical hypertension trials (1). This could be attributed to the fact that "any degree of diabetic retinopathy" was used as the outcome, which included mild retinal damage as opposed to more advanced retinal disease found in the UK Prospective Diabetes Study (1). Furthermore, this sample is constituted by office normotensive patients and the results cannot be compared with those from hypertension trials.

One possible limitation of this report mainly is the cross-sectional design, which holds off conclusions about the cause-and-effect relationship between masked hypertension and the renal and ecocardiographic outcomes. However, this limitation does not obscure the main results of this study.

In conclusion, type 2 diabetic patients with masked hypertension have elevated UAER values, a higher prevalence of high-normal albuminuria, micro- and macroalbuminuria, and enlargement of ventricular walls in comparison with normotensive patients. The evaluation of normotensive type 2 diabetic patients with 24-h ABPM, especially those with UAER ≥10 μg/min, seems to be important in order to identify this high-risk group. However, replication of these findings in different settings and clinical trials evaluating masked hypertension treatment also are needed to determine potential renal and cardiovascular protection.

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