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Microalbuminuria in White and Black Hypertensive Nondiabetic Brazilian Patients

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Abstract

Microalbuminuria (MAU) is a predictor of cardiovascular mortality in patients with diabetes mellitus (DM) and hypertension (HTN) and also in an unselected population. The American Diabetes Association (ADA) and the National Kidney Foundation (NKF) define MAU as an albumin/creatinine ratio (ACR) between 30 and 300 μg/mg in both men and women. Aim: To evaluate the possible relationship among MAU, HTN and gender and ethnicity in Brazilian nondiabetic primary hypertensive patients. Design: Population-based study. Participants: Ninety-eight men and women, seventy-two black and twenty-six white nondiabetic primary hypertensive patients aged 20 years or older were selected. Forty healthy individuals, paired according to age, gender, and ethnics were used as controls. Methods: Early-morning midstream urine was used. Urinary albumin was spectrophotometrically measured with Coomassie Brillant Blue G-250. Creatinine was determined by a method based on Jaffe's reaction. ACR (μg albumin/mg creatinine) was calculated. Data are expressed as medians. Results: ACR level was significantly higher in 98 hypertensive patients (38.00) than in 40 control individuals (23.00) ($P < 0.001$). ACR level was significantly higher in 48 hypertensive male (46.00) than in 50 hypertensive female (34.00) ($P = 0.008$). No significant effect of ethnicity on ACR levels between 26 hypertensive Whites (35.50) and 72 hypertensive Blacks (38.00) was observed ($P = 0.978$). Conclusions: The ACR level, significantly higher in hypertensive patients than in control individuals, supports data from the literature. To our knowledge, this is the first study demonstrating that the ACR level is significantly higher in men than in women. The lack of an ethnicity effect supports what was already asserted, namely, that in Brazil, at an individual level, color, as determined by physical evaluation, is a poor predictor of genomic African

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ancestry, as estimated by molecular markers.

Keywords

Albumin Creatinine Rate, Microalbuminuria, Primary Hypertension, Ethnic Groups, Brazilian

1. Introduction

Primary (essential) hypertension (HTN) is a multifactorial disease influenced by a combination of genetic and environmental factors [1]. Once HTN develops, it tends to become self-perpetuating by amplifying mechanisms mediated by secondary structural changes in blood vessels, heart, and kidney. The long-term sequelae from HTN are atherosclerotic vascular disease complications, cardiac hypertrophy and failure, stroke, and renal failure [2]. The primary cause of human essential HTN is not yet known, despite intensive research on the various mechanisms that may be involved in its development [3].

Urinary albumin excretion (UAE) is a predictor of cardiovascular mortality in patients with diabetes mellitus (DM) and HTN and also in an unselected population [4]. The American Diabetes Association (ADA) and the National Kidney Foundation (NKF) define microalbuminuria (MAU) as an albumin/creatinine ratio (ACR) between 30 and 300 μg/mg in both men and women [5] [6]. The gold standard for measuring urine albumin excretion is a 24-hour urine collection [6]. A more convenient method to detect MAU, however, is the ACR measured in a random urine specimen [7]. The prevalence of MAU in the general population is 6% to 8%, whereas in patients with HTN and DM this percentage increases from 10% to 15% and from 15% to 20%, respectively [4]. MAU is extremely common in hypertensive outpatients worldwide and especially in patients with known cardiovascular risk factors [8]. In 2010, Haller *et al*. carried out a survey to assess the level of the awareness among physicians in five European countries of the clinical value of MAU as a predictor of cardiovascular-disease risk. They evaluated the level of understanding of those physicians surveyed regarding MAU and its use as a diagnostic marker as well as their approach to diagnosis, prevention, and treatment. Only 42.5% of those diabetologists and 35.5% of the cardiologists had examined MAU in their type 2 DM and hypertensive patients, which suggests that MAU is under valuated as a risk factor for cardiovascular damage. Actions to raise awareness and further teaching towards the appropriate use of MAU as a diagnostic tool are certainly needed [9].

The aim of the present study is to evaluate whether MAU is influenced by sex and ethnicity among Brazilian primary hypertensive nondiabetic patients by considering healthy subjects as controls.

2. Methods

This study was approved by the Ethical Committee of the Federal University of Minas Gerais (UFMG). All patients and control subjects gave written informed consent. Patients of any gender and race were eligible for inclusion in the study as long as they were older than 20 years of age, and had primary HTN. All subjects were studied as outpatients. Patients and control subjects were consecutively screened by the same physician (ELGM) for a two-year period, and underwent a thorough clinical interview as well as physical examination. All of their symptoms and signs indicative of either primary HTN or any other cardiovascular disease were analyzed, as well as the patients' personal antecedents and the types of (cardiovascular or non-cardiovascular) medication they were making use of.

2.1. Patient Criteria

Patients included in the study were those who had primary HTN, whether systolic blood pressure (SBP) of ≥140 mm Hg or diastolic blood pressure (DBP) of ≥90 mm Hg, on three separate determinations. The criteria for patient exclusion were among others: non-agreement in participating in the study, secondary HTN, heart failure, renal failure (serum creatinine level ≥1.5 mg/dL or 133 μmol/L in man and ≥1.4 mg/dL or 124 μmol/L in woman), hepatic alterations and DM. Premenopausal women were not studied during the menstruation phase of their menstrual cycle. The population studied was divided into two subgroups and compared according to the following variables: SBP, DBP and ACR.

2.2. Protein Determination

A random urine sample, the early-morning midstream specimen, was used. In the laboratory, urine sample was visually and chemically examined with dipstick test (Urofita 10U bioBRÁSDiagnósticos, Biobrás S.A., Belo Horizonte, MG, Brazil). All urine samples were negative for blood and for all chemical compounds evaluated. Many methods have been developed to measure the total protein content of biological fluids. Dye-binding methods are based on the ability of proteins to bind dyes, such as Coomassie Brilliant Blue (CBB). The dye-binding method of greatest contemporary interest uses CBB G-250 for assay of total protein in cerebrospinal fluid or urine [10]. Only a small amount of protein is normally excreted in urine, and most of it is albumin. The remaining excretion almost entirely consists of the Tamm-Horsfall glycoprotein (THGP), also known as uromucoid, which is probably secreted by the distal tubules. In the present study, THGP was separated from albumin by adjusting the urine pH to 8.0 [11]. The mixture was filtered on filter paper, and the clear filtrate was used for albumin determination. Urinary albumin was spectrophotometrically measured with CBB G-250 (Sigma Chemical Company, St. Louis, MO, USA) according to Bradford [12] modified by Peterson [13]. Bovine serum albumin (Sigma Chemical Company) was used as standard. The result is expressed in µg/mL urine filtrate.

2.3. Creatinine Determination

Creatinine was determined in one urine sample separated, before adjusting the urine pH to 8.0, by using a kit of reagents which was based on the Jaffe's reaction (Katal Biotecnológica Indústriaae Comércio Ltda, Belo Horizonte, MG, Brazil), and is expressed in mg/mL.

2.4. Statistical Analysis

Descriptive statistics are reported as medians from the irregular distribution of the variables studied. Differences between the groups were evaluated by the nonparametric Kruskall-Wallis test, since the population studied had a non-Gaussian distribution with nonhomogeneous variance. A P value of <0.05 was considered statistically significant.

3. Results

Patients and Control Subjects Characteristics

Ninety-eight patients (26 White, and 72 Black) fulfilled the study inclusion criteria without fulfilling the exclusion criteria. Patients went on with their usual diets of intake of fluid, electrolytes, calories, or other macronutrient/micronutrient composition. Serum sodium, chloride, potassium, blood urea and serum creatinine values were normal in all patients. Twenty-eight (28.6%) patients were using a diuretic, 24 (24.5%) an ACE inhibitor, 10 (10.2%) a calcium channel blocker, 9 (9.2%) a β-blocker, 7 (7.1%) a selective α_2-agonist, whereas 20 patients (20.4%) were using no medication. Patients in this study were otherwise healthy, but for their HTN. Forty healthy normotensives (SBP <140 mm Hg or DBP consistently <90 mm Hg on three separate determinations) individuals (17 White and 23 Black), paired according to ethnicity, gender and age (±5), were used as normal controls, thereby constituting the control subgroup.

The baseline characteristics of hypertensive patients and controls individuals are shown in **Table 1**. ACR was significantly higher in hypertensive patients than in controls subjects (**Table 1** and **Figure 1**).

ACR level was significantly higher in 48 hypertensive males (46.00 µg albumin/mg creatinine) than in 50 hypertensive females (34.00 µg albumin/mg creatinine) ($P = 0.008$) (**Figure 2**).

There was no significant effect of ethnicity on ACR levels between 26 hypertensive Whites and 72 hypertensive Blacks, respectively (**Table 2** and **Figure 3**).

4. Discussion

In our study, from 98 hypertensive patients evaluated, 74 (75.5%) had MAU, despite ACE inhibitor use, and 24 (24.5%) had normal albuminuria. On the other hand, from our 40 healthy controls, all had normal albuminuria (**Table 1** and **Figure 1**). Since it is known that treatment with an ECA inhibitor reduces MAU, the prevalence and degree of albuminuria would have been even higher if the patients were not using these drugs.

The first report on MAU in nondiabetic essential hypertensive patients dates back to 1974. It was carried out

Table 1. Baseline characteristics of the study population.

Parameter	Patients	Controls	*P* value
Number	98	40	-
Demographic			
Age (years)[a]	51.50 (39.00 - 61.50)	47.00 (35.00 - 56.25)	0.186
Gender (M/F)	48/50	20/20	0.913
Race (W/B)	26/72	17/23	0.072
Physiologic			
SBP (mm Hg)[a]	160.00 (150.00 - 170.00)	125.00 (120.00 - 130.00)	<0.001
DBP (mm Hg)[a]	90.00 (90.00 - 100.00)	80.00 (80.00 - 80.00)	<0.001
Biochemical			
ACR (µg alb/mg creat)[a]	38.00 (30.00 - 63.00)	23.00 (21.50 - 28.00)	<0.001

M: male; F: female; W: White; B: Black; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACR: albumin/creatinine ratio; alb: albumin; creat:creatinine; [a]Median value; numbers in parenthesis are the interquartile ranges 25% to 75%.

Table 2. ACR values for White and Black hypertensive patients.

Parameter	White	Black	*P* value
Number	26	72	-
ACR (µg alb/mg creat)[a]	35.50 (30.00 - 74.00)	38.00 (29.50 - 57.00)	0.978

ACR: albumin/creatinine ratio; alb: albumin; creat: creatinine; [a]Median value; numbers in parenthesis are the interquartile ranges 25% to 75%.

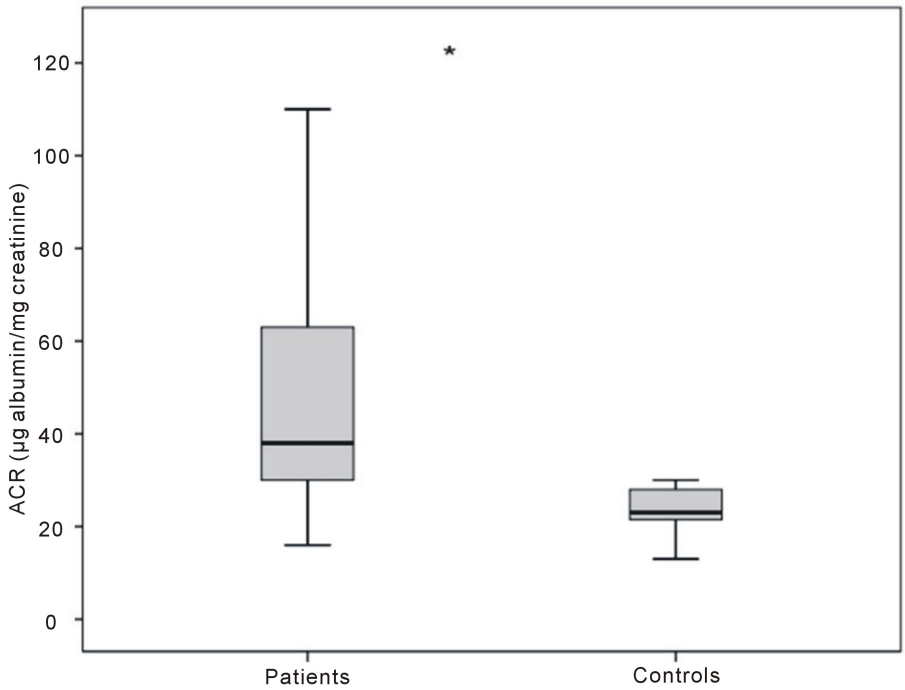

Figure 1. Comparison of ACR values between hypertensive patients and healthy subjects as controls. The symbol (*) indicates statistically significant difference.

by Parving *et al*., who evaluated the urinary albumin excretion (UAE) rate in 32 patients with benign essential HTN (14 effectively treated and 18 untreated or insufficiently treated), compared with 8 normal subjects as control. A 24-hours collected urine was used for albumin determination by radioimmunoassay. The UAE rate was significantly increased in both the insufficiently treated groups, compared to the effectively treated and normal groups [14].

In 1994, Olinic *et al*. reported the results of a study designed to evaluate the UAE in 62 patients with essential

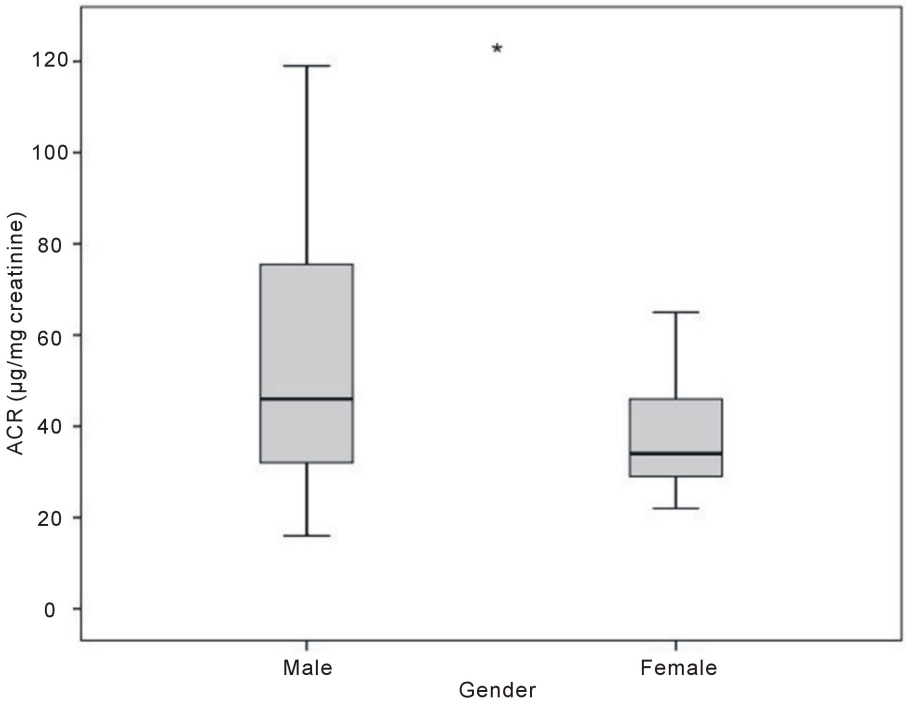

Figure 2. Comparison of ACR values between male and female hypertensive nondiabetic Brazilian patients. The symbol (*) indicates statistically significant difference.

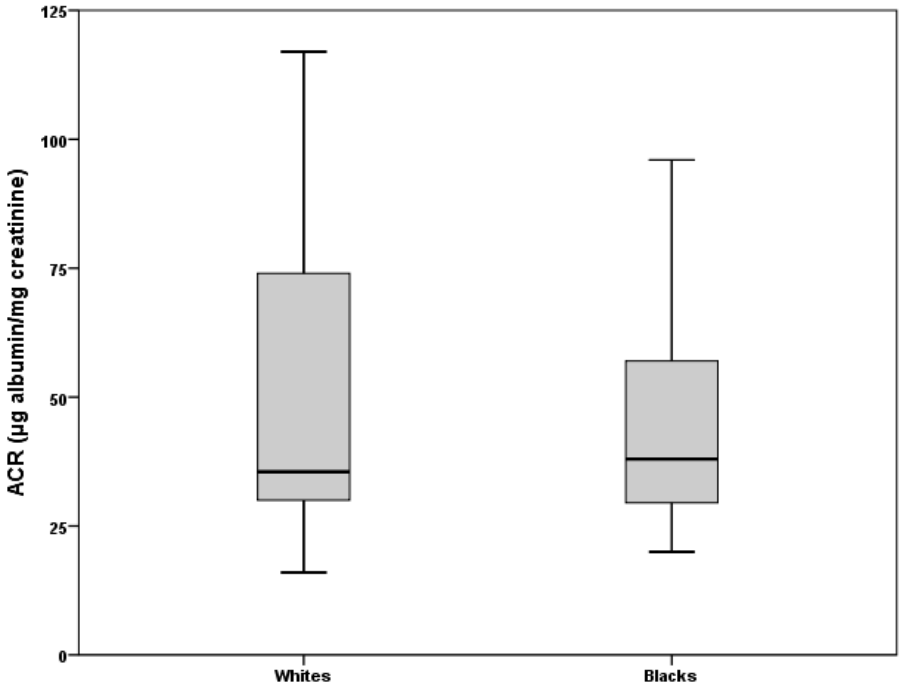

Figure 3. Comparison of ACR values between White and Black hypertensive nondiabetic Brazilian patients.

HTN, none of whom had prior proteinuria or any history of nephropathy or uropathy. Albuminuria was measured by radial immunodiffusion. The UAE was significantly higher ($P < 0.001$) in the group of hypertensive patients, compared to a group of 20 control subjects. A positive correlation between MAU and the duration of

HTN was found (r = 0.64; $P < 0.001$). According to the authors, MAU might represent a marker of severity of vascular involvement in hypertensive patients [15].

In 1997, Pontremoli *et al*. evaluated the prevalence of MAU and its relationship with several cardiovascular risk factors and target organ damage in a cohort of 787 untreated patients with essential HTN. Albuminuria was measured as the ACR in three nonconsecutive, first-morning urine samples. The prevalence of MAU was 6.7%. Albuminuric patients were more likely to be men and to be characterized by higher blood pressure, body mass index, uric acid levels, and lower HDL cholesterol and HDL cholesterol-to-LDL cholesterol ratio. K-means cluster analysis as carried out on the entire cohort of patients confirmed that MAU was associated with worse cardiovascular risk profile. They concluded that the prevalence of MAU in essential HTN was lower than previously reported (between 10% and 40%). Increased UAE was associated with worse cardiovascular risk profile and was a concomitant indicator of early target organ damage (e.g. electrocardiographic [ECG] abnormalities and retinal vascular changes) [16].

In 2000, de la Sierra *et al*. reported the results of a study carried out to evaluate the clinical and biochemical profile associated with the presence of MAU in a group of 188 nondiabetic, untreated essential hypertensive patients (100 men, 88 women) aged 55.8 ± 11.7 years. UAE was determined in two 24-h urine collections. Clinical and biochemical evaluations and 24-h ambulatory blood pressure monitoring were performed at baseline. Patients with MAU showed significantly higher creatinine, serum uric acid and triglycerides, as well as lower HDL-cholesterol. They concluded that, in essential hypertensive patients, the presence of MAU was associated with elevated blood pressure. Likewise, MAU was associated with the degree of renal impairment, and with increased uric acid and triglycerides and decreased HDL-cholesterol [17]. In the same year, Jensen *et al*. reported the results of a study carried out to assess the predictive impact of MAU on the subsequent development of ischemic heart disease among young and middle-aged individuals with arterial HTN or borderline HTN. Between 1983 and 1984, the authors obtained blood pressure, urinary ACR, plasma total and HDL cholesterol levels, body mass index, and smoking status in a population-based sample of 2085 subjects, aged 30 to 60 years, who were free from ischemic heart disease, DM, and renal or urinary tract disease. Untreated arterial HTN or borderline HTN was present in 204 subjects, who were followed until 1993 by the National Hospital and Death Certificate Registers with respect to development of ischemic heart disease. During 1978 person-years, 18 (9%) of the hypertensive subjects developed ischemic heart disease. MAU, defined as urinary ACR above the upper decile (1.07 mg/mmol), was the strongest predictor of ischemic heart disease. According to the authors, MAU was the strongest independent determinant of ischemic heart disease among hypertensive or borderline hypertensive subjects. The authors recommended that UAE should be measured regularly in a hypertension clinic, and a rigorous control of blood pressure and of other atherosclerotic risk factors was recommended in hypertensive patients with MAU [18].

In 2005, Reboldi *et al*. authored an article reviewing available evidence on the clinical value of MAU in subjects with essential HTN. They reported that, in those subjects, the prevalence of MAU ranged from roughly 4% to 46% across different studies, and those differences might be explained by the huge intra-individual variability in UAE, age and ethnicity, discrepancies in the technique of measurement and different definitions of MAU. The authors recommended the determination of MAU in the initial work-up of subjects with essential HTN, as suggested in the guidelines [19].

4.1. Gender Effect

In our study we observed that ACR level was significantly higher in 48 hypertensive men than in 50 hypertensive women. To the best of our knowledge, this is the first study concerning the evaluation of the effect of gender on ACR in primary hypertensive nondiabetic patients.

4.2. Ethnicity Effect

In 1995, Summerson *et al*. reported the results of a study carried out to examine the prevalence of MAU in 71 white and 38 black patients with essential HTN (SBP > 160 mmHg and/or DBP > 95 mmHg on two or more clinic visits or currently receiving medication to treat HTN)and without either DM or clinical proteinuria. The subjects were representative of the total hypertensive population at the Family Practice Ambulatory Care Unit for age, sex, and race. Timed, overnight urine samples were collected for determination of UAE rates. MAU was defined as a UAE rate >30 µg/min. The prevalence of MAU in their sample was 20%. The Black hypertensive

patients were found to be younger and to have a higher body mass index compared with their White counterparts. The Black patients also had a grater mean UAE rate and were more likely to have MAU than the White patients. According to the authors, their data were the first to show that the prevalence of MAU was greater in Black compared with White hypertensive patients. These results were consistent with the higher prevalence and more severe consequences of HTN among African-Americans. According to the authors, their data suggested that MAU was more prevalent during the course of HTN in Black patients and thus might be an early marker for end-organ damage susceptibility [20].

In 2007, Arar *et al*. reported the results of a study carried out in order to estimate heritability of MAU and to perform a genome-wide linkage analysis to identify chromosomal regions influencing urine ACR in 486 Mexican Americans from 26 multiplex families. Significant heritability was demonstrated for urine ACR (h = 24%, $P < 0.003$) after accounting for age, sex, body mass, triglycerides, and HTN. Genome scan revealed significant evidence of linkage of urine ACR to a region on chromosome 20q12 (LOD score of 3.5, $P < 0.001$) near marker D20S481. This region also exhibited a LOD score of 2.8 with diabetes status as a covariate and 3.0 with HTN status as a covariate suggesting that the effect of this locus on urine ACR was largely independent of DM and HTN. They concluded that their findings indicated that there is a gene or genes located on human chromosome 20q12 that might have functional relevance to albumin excretion in Mexican Americans. Identifying and understanding the role of the genes that determine albumin excretion would lead to the development of novel therapeutic strategies targeted at high-risk individuals in whom intensive preventive measures might be most beneficial [21].

The lack of ethnicity effect on MAU observed in the present study is in disagreement with the results of Summerson *et al*. [20], who found that UAE rates were significantly higher in Black hypertensive patients than in White ones. On the other hand, the lack of ethnicity effect on MAU supports the data reported by Parra *et al*. [22], who carried out a study to ascertain to what degree the physical appearance of a Brazilian individual would be predictive of genomic African ancestry. Their data suggested that in Brazil, at an individual level, color, as determined by physical evaluation, is a poor predictor of genomic African ancestry, as estimated by molecular markers [22].

5. Conclusions

The evidences presented in our study show that in a selected population of nondiabetic Brazilian subjects: 1) ACR was significantly higher in those (n = 98) with primary HTN, than in those (n = 40) healthy controls; 2) in those patients with primary HTN, ACR level was significantly higher in male (n = 48) than in female (n = 50); 3) in those patients with primary HTN (n = 98), the ACR was not influenced by skin color.

The results of i-SEARCH, given its importance as a strong, early and independent marker of increased cardiovascular risk in HTN, thus require in clinical practice a more rigorous MAU screening of hypertensive patients [8]. We propose moreover that, in clinical practice, ACR should be measured in all hypertensive patients.

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