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Original Article

Microalbuminuria in untreated prehypertension and hypertension without diabetes

Erhan Tenekecioglu[1], Mustafa Yilmaz[1], Osman Can Yontar[1], Kemal Karaagac[1], Fahriye Vatansever Agca[1], Ahmet Tutuncu[1], Mustafa Kuzeytemiz[1], Adem Bekler[2], Muhammed Senturk[1], Ufuk Aydin[3], Şerafettin Demir[4]

[1]Bursa Yuksek Ihtisas Education and Research Hospital, Cardiology, Bursa, Turkey; [2]Çanakkale Onsekiz Mart University, Cardiology, Çanakkale, Turkey; [3]Bursa Yuksek Ihtisas Education and Resarch Hospital, Cardiovascular Surgery, Bursa, Turkey; [4]Adana State Hospital, Cardiology, Adana, Turkey

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Abstract: Objective: Hypertension (HT) and prehypertension (preHT) were independent predictors of cardiovascular diseases. Urinary albumin leakage is a manifestation of generalized vascular damage. B-type natriuretic peptide (BNP) is a vasoactive peptide secreted by left ventricle in response to myocytic stretch. We aimed to investigate relationship between microalbuminuria (MA) and BNP in untreated elevated blood pressures. Methods: Of 105 untreated prehypertensive subjects (53 men, 52 women), 100 hypertensive subjects (51 men, 49 women) and 57 normotensive subjects (32 men, 25 women) none had history of diabetes. Urine albumin excretion was measured by immunoradiometric assay in morning urine sample. Results: The prevalence of MA was higher in hypertensive group than in prehypertensive group and in normotensive group (Hypertensive group; 33.9%, prehypertensive; 25.9%, normotensive; 10%). Subjects with HT had higher prevalence of microalbminuria; larger body mass index, higher levels of triglycerides, blood glucose and creatinin were more common in subjects with HT than in those with preHT. In hypertensive group; patients with microalbuminuria had higher systolic blood pressure (SBP), BNP, LVMI and lower eGFR as compared to those without MA. MA was significantly correlated with LVMI, BNP and SBP. In multivariate regression analysis, SBP (β: 0.361; $P < 0.001$), LVMII (β: 0.267; $P = 0.011$) and BNP (β: 0.284; P = 0.005) were independent variables associated with MA in hypertensives. In prehypertensive group; patients with microalbuminuria had higher SBP, BNP, LVMI and lower eGFR as compared to those without MA. MA was significantly correlated with LVMI, BNP and SBP. In multivariate regression analysis, SBP (β: 0.264; P = 0.002), LVMI (β: 0.293; $P = 0.001$) and BNP (β: 0.168; $P = 0.045$) were associated with MA in prehypertensives. Conclusions: In preHT and HT, SBP, BNP and LVMI are associated with MA. In the evaluation of increased blood pressures, in case of increased BNP and LVMI, MA should be investigated even in prehypertensive stages. The subjects with increased blood pressures should get medical treatment to prevent the effects on vascular structure and myocardium even in prehypertensive phase.

Keywords: Microalbuminuria, prehypertension, hypertension, brain natriuretic peptide, left ventricular mass

Introduction

Hypertension (HT) is one of the major risk factor for cardiovascular disease and a leading cause of mortality and morbidity worldwide. Even in high-normal levels [1], described as prehypertension (preHT) [2-4], increased blood pressure (BP) was associated with various cardiovascular events [5-7].

Urinary albumin leakage is a manifestation of generalized vascular damage [8]. Microalbuminuria (MA) (urinary albumin excretion (UAE) of 30-300 mg/24 h has been determined as an important prognostic indicator, in various clinical conditions, and has been reported to be associated with increased cardiovascular risk and progressive renal damage. In patients with HT, MA has been pointed as a marker of cardiovascular complications and a reliable predictor of ischaemic heart diseases [9, 10]. Left ventricular hypertrophy and increased carotid artery intima-media thickness, both subclinical cardiovascular diseases, are associated with MA in individuals at increased risk of cardiovascular disease in whom blood pressures are over the normal ranges [11-13].

B-type natriuretic peptide (BNP) is a vasoactive peptide which is secreted by the left ventricle (LV) in response to myocytic stretch and is involved in regulating volume homeostasis and cardiac remodeling [14, 15]. BNP is utilized in the clinical setting as a diagnostic tool to identify heart failure (HF) and LV dysfunction in addition to providing prognostic information in patients with HF, HT, and coronary artery disease(CAD) [16-19]. Several studies have shown a definite relationship between BNP and myocardial stiffness particularly in HT [20, 21].

Through these data we hypothesized that as in HT, preHT may have detrimental effects on left ventricle and systemic vasculature. In this study we aimed to investigate the relationship between untreated preHT, MA and BNP level.

Methods

The study population consisted of two main groups; normotensive control group, and patients with increased blood pressures. The group with increased BP was comprised of 205 newly diagnosed patients (104 male, 101 female). The subjects for the study were chosen from the patients applied to our polyclinic for increased BP. No subjects received antihypertensive treatment before and at the time of the study. The secondary causes of increased BP were ruled out by laboratory, radiological, and other clinical examinations. All subjects with increased BP were classified according to the Joint National Committee VII report 7 (JNC VII) criteria: preHT (n = 105), HT (n = 100). None of the patients had angina pectoris, and no regional wall motion abnormalities were present on two dimensional echocardiograms. The normotensive control group included 57 adult patients (32 male, 25 female) with structurally normal hearts. Subjects with any systemic disease such as hemolytic, hepatic, and renal diseases or any disease that could cause myocardial impairment were excluded. None of the subjects had cerebrovascular disease before.

Weight and height were measured to calculate body surface area (square meters) and body mass index (kilograms per square meter). The study protocol was approved by the Science and Ethics Committee of our institution. Informed consent was obtained from each patient.

Echocardiographic studies

In this study, a Vingmed Vivid Seven Doppler echocardiographic (GE Vingmed Ultrasound, Horten, Norway) unit with a 2.5 MHz flat phasedarray (FPA) probe was used. During echocardiography, a one-lead ECG was recorded continuously. During transthoracic echocardiography (TTE), the left ventricular end-diastolic diameter (LVDD), wall thickness, and LA diameter were measured from parasternal M-mode recordings according to the standard criteria [22]. During TTE, ejection fraction was calculated with the modified Simpson's method by measuring the left ventricular end-diastolic and end-systolic volumes with apical four-chamber view [23]. The left ventricular mass was calculated from M-mode records taken on parasternal long-axis images according to the following formula (corrected American Society of Echocardiography cube method): LVM = 0.8 × (1.04 [(IVSd + PWd + LVDD) 3- (LVDD)3]) + 0.6 g where LVM is left ventricular mass, PWd is the posterior wall thickness at diastole, IVSd is the interventricular septum thickness at diastole, and LVDD is the left ventricular diastolic diameter [24, 25]. To take into account differences in body size that may influence heart size, the left ventricular mass was divided by height to create a left ventricular mass index.

A voided morning urine sample, at the baseline examination, was used to measure urinary albumin concentration as determined by radioimmunoassay (ICN, gamma counter micromedic 27027 USA). The urine albumin creatinine ratio (UACR) was used as the index of the urine albumin excretion. To define microalbuminuria in morning urine specimens, we used the UACR cutoff value of 30-300 g/mg for both men and women. Subjects with UACR < 30 g/mg were defined as having normoalbuminuria, and those with UACR > 300 g/mg were defined as having macroalbuminuria.

For BNP measurements, blood samples were placed on ice and processed within 60 min. An established sequential sandwich immunoassay (Biosite, Inc., San Diego, California) was used for the quantification of BNP [10, 11]. The minimal detectable concentration is 5 pg/ml. The coefficient of variation is 5.0% at 52.5 pg/ml. Serum lipid levels (total cholesterol [TC], high density lipoprotein cholesterol [HDL-C], and triglyceride [TG]) were measured using automated enzymatic methods at each facility

Table 1. Characteristics of the study groups

	Normotensive group (n = 57)	Prehypertensive group (n = 105)	Hypertensive group (n = 100)
Age (years)	51.28 ± 3.11	50.07 ± 6.64	52.17 ± 4.83
Gender (Male)	32 (56%)	53 (51%)	51 (51%)
Heart rate (beats/min)	78.24 ± 10.18	79.43 ± 11.73	76.95 ± 9.68
BMI (kg/m^2)	24.84 ± 3.72	25.33 ± 3.48	25.09 ± 2.95
SBP (mmHg)	110.78 ± 8.49	131.46 ± 5.13$^{\#}$	154.3 ± 11.52$^{\#}$
DBP (mmHg)	71.66 ± 6.83	81.84 ± 6.26$^{\#}$	91.1 ± 9.60$^{\#}$
Smoking (n. %)	29 (50%)	48 (46%)	51 (51%)
Glucose (mg/dl)	117.6 ± 29.0	115.9 ± 23.7	118.6 ± 25.2
Total Cholesterol (mg/dl)	206.6 ± 22.3	209.1 ± 25.2	211.0 ± 20.9
LDL-C (mg/dl)	114.2 ± 18.3	112.9 ± 15.0	116.4 ± 13.0
HDL-C (mg/dl)	47.8 ± 15.2	45.9 ± 13.8	46.2 ± 14.0
Triglyserid (mg/dl)	155.5 ± 77.2	153.9 ± 82.0	156.8 ± 74.1
BNP (ng/l)	43.56 ± 19.81	140.63 ± 72.38$^{\#}$	173.65 ± 81.04$^{\#,\beta}$
Creatinine (mg/dl)	0.73 ± 0.18	0.81 ± 0.14¶	0.87 ± 0.17$^{\#,\beta}$
eGFR (ml/min/1.73 m^2)	74.03 ± 5.20	68.94 ± 5.73$^{\#}$	68.43 ± 6.78$^{\#}$
Urinary albumin (mg/g Cr)	20.12 ± 12.92	31.84 ± 19.39$^{\#}$	41.99 ± 34.73$^{\#,\blacktriangledown}$
CRP (mg/L)	3.48 ± 1.81	6.99 ± 3.74$^{\#}$	10.31 ± 8.65$^{\#,\beta}$
Echocardiograhic parameters			
LVEF (%)	73.22 ± 6.55	74.01 ± 7.51	74.01 ± 5.12
Mitral-E (m/s)	0.86 ± 0.16	0.73 ± 0.13$^{\#}$	0.69 ± 0.13$^{\#}$
Mitral-A (m/s)	0.68 ± 0.06	1.02 ± 0.23$^{\#}$	0.92 ± 0.12$^{\#}$
Mitral E/A	1.26 ± 0.23	0.75 ± 0.20$^{\#}$	0.76 ± 0.15$^{\#}$
LVMI (g/m^2)	57.96 ± 14.02	63.79 ± 10.26$^{\square}$	67.65 ± 15.95$^{\#,¥}$

$^{\#}p < 0.001$ versus normotensive group; $^{\P}p < 0.005$ versus normotensive group; $^{\square}p < 0.005$ versus normotensive group: $^{\beta}p < 0.005$ versus prehypertensive group; $^{\blacktriangledown}p < 0.05$ versus prehypertensive group; $^{¥}p < 0.001$ versus prehypertensive group.

[26]. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation [27, 28]. To exclude patients with diabetes mellitus, the hemoglobin A1c (HbA1c) level was measured using well established methods and high-performance liquid chromatography with an appropriate gel column and an automated analyzer [29, 30].

Statistical analysis

Statistical Package of the Social Sciences (SPSS 13.0) software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Data were presented as mean ± SD. The chi-square test was used for categorical variables. The Mann-Whitney test was used to compare variables between groups. Relationships between variables were examined with Pearson correlation coefficients. In prehypertensive and hypertensive groups, multivariate regression analyses were performed to examine the predictors of abnormal albuminuria in study groups with preHT and HT. A *P*-value < 0.05 was considered to be statistically significant.

Results

The clinical variables of the healthy, prehypertensive, and hypertensive groups are listed in **Table 1**. Among the three groups, age, gender, heart rates, body mass index, fasting glucose levels, and lipid profiles were similar. The echocardiographic parameters of the normotensive, prehypertensive, and hypertensive subgroups are shown in **Table 1**.

In hypertensive group IVS was significantly increased when compared to the prehypertensive group (*P* = 0.022). LVMI was significantly increased in hypertensive group as compared to the prehypertensive group (p = 0.004). BNP was significantly increased in hypertensive group when compared to the prehypertensive group (p < 0.001). While Mitral-A was signifi-

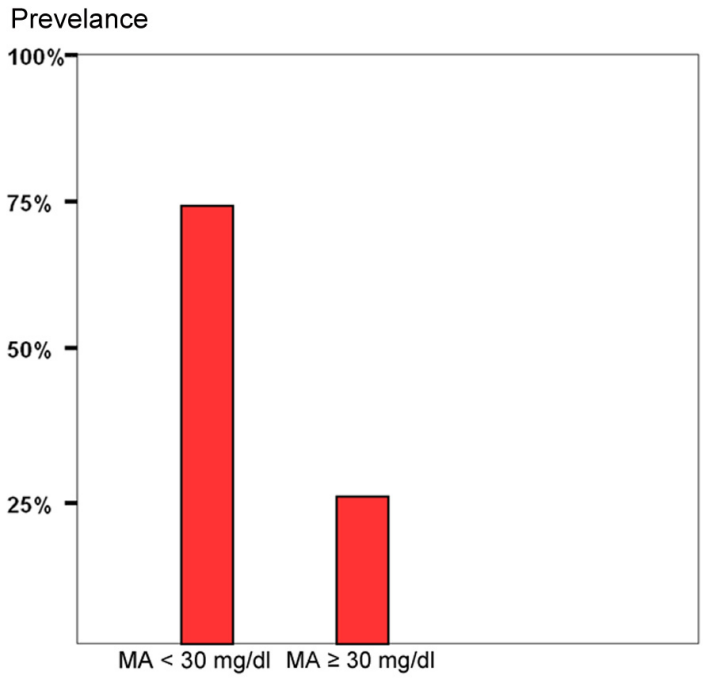

Figure 1. Prevelance of MA in patients with preHT.

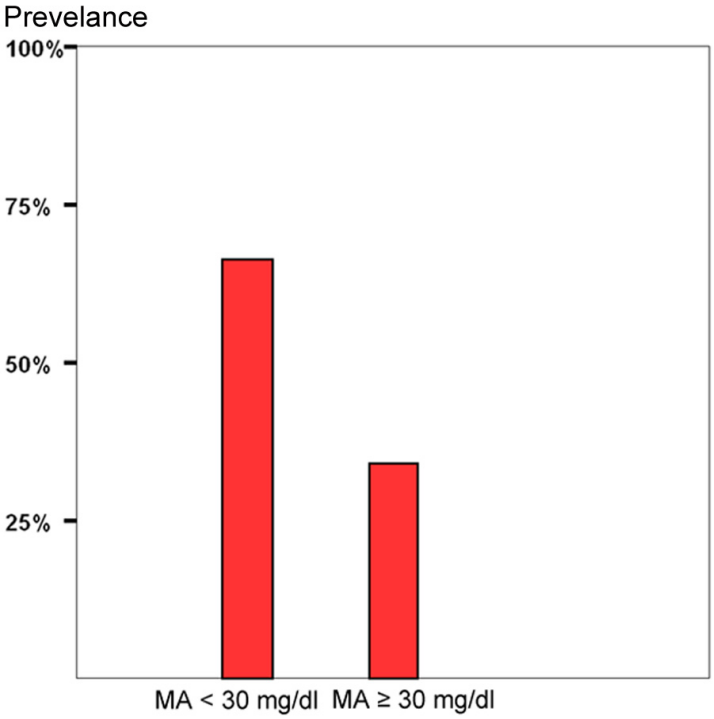

Figure 2. Prevelance of MA in patients with HT.

cantly decreased in hypertensive group, Mitral E/A ratio was found similar between hypertensive and prehypertensive groups.

Figures 1 and **2** show the distribution of the MA (UACR; mg/g creatinine [mg/g Cr]) in patients with preHT and HT, respectively. MA was detected 25.9% of prehypertensive subjects and 33.9% of hypertensive subjects.

In preHT group; patients with MA had higher SBP, BNP, LVMI and lower eGFR as compared to those without MA (**Table 2**). MA was significantly correlated with LVMI ($r = 0.25$, $p < 0.05$), BNP ($r = 0.72$, $p < 0.001$) and SBP ($r = 0.51$, $p < 0.001$). LVMI was significantly correlated with BNP ($r = 0.28$, $p < 0.05$) and SBP ($r=0.32$, $p < 0.05$). **Table 3** shows the results of multivariate regression analysis demonstrating relationships between UAE and other variables in prehypertensive patients. SBP, BNP, eGFR and LVMI independently associated with microalbuminuria in a multivariate regression analysis (**Table 3**).

In hypertensive group; patients with MA had higher SBP, BNP, LVMI and lower eGFR as compared to those without MA (**Table 4**). MA was significantly correlated with LVMI ($r = 0.59$, $p < 0.001$), BNP ($r = 0.55$, $p < 0.001$) and SBP ($r = 0.40$, $p < 0.005$). LVMI was significantly correlated with BNP ($r = 0.52$, $p < 0.001$) and SBP ($r = 0.69$, $p < 0.001$). In multivariate regression analysis, SBP, LVMI and BNP were the independent variables associated with MA in hypertensive subjects (**Table 5**).

Discussion

In our study, the average value of UAE and prevalence of MA were higher in hypertensives than in patients with preHT and these values were higher in prehypertensives than in subjects with normal BPs. The principal finding of our study was that both in untreated prehypertensive and in untreated hypertensive subjects, SBP, BNP and LVMI were significantly associated with MA.

Table 2. Characteristics of the prehpertensive patients according to the albuminuria status

	Microalbuminuria (-) (n = 71)	Microalbuminuria (+) (n = 34)	*P* value
Age (years)	50.52 ± 3.68	49.91 ± 2.88	0.18
Gender (Male)	33 (46%)	20 (58%)	0.29
BMI (kg/m^2)	24.96 ± 3.64	25.03 ± 3.58	0.45
SBP (mmHg)	129.66 ± 4.75	135.23 ± 3.70	< 0.001
DBP (mmHg)	82.23 ± 7.13	81.02 ± 3.84	0.35
Smoking (n. %)	34 (47%)	14 (41%)	0.53
Glucose (mg/dl)	113.9 ± 23.6	115.3 ± 21.2	0.56
Total cholesterol (mg/dl)	209.2 ± 16.4	206.5 ± 18.1	0.62
LDL-C (mg/dl)	112.6 ± 17.1	110.8 ± 15.0	0.67
HDL-C (mg/dl)	46.3 ± 13.6	44.6 ± 15.1	0.78
Triglyserid (mg/dl)	154.5 ± 72.4	156.2 ± 69.9	0.73
UACr (mg/g)	21.40 ± 5.71	53.62 ± 19.81	< 0.001
BNP (ng/l)	117.90 ± 57.12	188.09 ± 78.46	< 0.001
Creatinine (mg/dl)	0.81 ± 0.13	0.80 ± 0.16	0.72
eGFR (ml/min/1.73 m^2)	70.98 ± 5.62	64.52 ± 2.74	< 0.001
Transthoracic echocardiograhic parameters			
LVEF (%)	74.33 ± 7.37	73.36 ± 7.88	0.55
Mitral-E (m/s)	0.75 ± 0.14	0.68 ± 0.09	0.006
Mitral-A (m/s)	1.04 ± 0.24	0.98 ± 0.23	0.21
Mitral E/A	0.76 ± 0.22	0.72 ± 0.13	0.32
LVMI	62.67 ± 9.67	66.14 ± 11.18	< 0.001

Table 3. Multivariate regression analysis demonstrates the relationship of microalbuminuria to other variables in prehypertensive patients

	R2 = 0.492, F = 19.148, P < 0.001	
	Standardized coefficient	*P* value
eGFR	-0.210	0.020
BNP	0.168	0.045
LVMI	0.293	0.001
SBP	0.264	0.002
Mitral-E	-0.018	0.819

PreHT is reported in approximately 30% of the general adult population and has been the subject of many studies [31]. After Framingham Heart Study, prehypertensive patients were reported for having increased risk of developing HT in their subsequent life as compared to the subjects with normal blood [32, 33]. Beside the sustained HT, preHT was also determined as an independent predictor of cardiovascular diseases [5]. PreHT is associated with both microvascular and macrovascular pathology [34, 35]. Prehypertensive subjects have increased common carotid artery intima-media thickness and increased calcium deposition in the coronary arteries and also accelerated development of left ventricular hypertrophy and diastolic dysfunction [36, 37].

MA is a marker of cardiovascular complications and a crucial predictor of ischaemic cardiovascular diseases in patients with essential HT [38]. The main significance of MA is that it has been demonstrated as a sign for generalized vascular dysfunction [39]. Various studies emphasized that abnormal albuminuria could be a phenotype of systemic arterial endothelial damage caused by increased BP or, with dysfunction of the endothelium of the glomerular capillary resulting in altered glomerular filtration function [40-42]. BNP is secreted from ventricular myocytes in response to increased ventricular filling pressure or volume; consequently, an increase in BP stimulates the BNP secretion [43, 44].

In the analysis of the groups with preHT and HT, we found that SBP, BNP and LVMI were independent predictors of microalbuminuria in each increased BP group. Although this was a cross-sectional study and causal relationship between MA and these factors cannot be eluci-

Table 4. Characteristics of the hypertensive patients according to the albuminuria status

	Microalbuminuria (-) (n = 45)	Microalbuminuria (+) (n = 55)	*P* value
Age (years)	56.22 ± 10.30	57.67 ± 9.04	0.08
Gender (Male)	33 (46%)	20 (58%)	0.45
BMI (kg/m^2)	25.48 ± 3.04	24.93 ± 3.28	0.14
SBP (mmHg)	146.11 ± 7.60	161.00 ± 9.73	< 0.001
DBP (mmHg)	92.66 ± 10.03	89.81 ± 9.12	0.15
Smoking (n. %)	23 (51%)	28 (50%)	0.98
Glucose (mg/dl)	116.2 ± 20.8	118.1 ± 24.2	0.44
Total cholesterol (mg/dl)	212.7 ± 15.8	209.9 ± 16.1	0.52
LDL-C (mg/dl)	116.2 ± 14.8	114.9 ± 14.2	0.47
HDL-C (mg/dl)	45.1 ± 12.6	43.8 ± 14.1	0.64
Triglyserid (mg/dl)	152.8 ± 74.1	153.9 ± 72.9	0.71
UACr (mg/g)	21.04 ± 4.85	59.12 ± 39.09	< 0.001
BNP (ng/l)	115.21 ± 36.69	221.47 ± 75.95	< 0.001
Creatinine (mg/dl)	0.84 ± 0.16	0.90 ± 0.17	0.13
eGFR (ml/min/1.73 m^2)	72.20 ± 5.57	65.34 ± 6.11	< 0.001
Transthoracic echocardiograhic parameters			
LVEF (%)	73.59 ± 5.74	74.35 ± 4.57	0.47
Mitral-E (m/s)	0.70 ± 0.13	0.69 ± 0.10	0.70
Mitral-A (m/s)	0.95 ± 0.12	0.90 ± 0.11	0.07
Mitral E/A	0.74 ± 0.16	0.76 ± 0.14	0.51
LVMI	66.36 ± 9.53	84.06 ± 18.78	< 0.001

Table 5. Multivariate regression analysis demonstrates the relationship of microalbuminuria to other variables in hypertensive patients

	R2 = 0.562. F = 30.482. P < 0.001	
	Standardized coefficient	*P* value
eGFR	-0.197	0.077
BNP	0.284	0.005
LVMI	0.267	0.011
SBP	0.361	< 0.001

dated, the results suggest several possibilities. Elevated blood pressure is considered to cause renal dysfunction. In our study, MA was more prevalent in hypertensive and prehypertensive subjects than in subjects with normal blood pressures. The significant difference in the prevalance of MA between hypertensive patients (55%), prehypertensive subjects (32%) and normotensive subjects (10%) supports the close and independent correlation between urinary albumin extraction rate and increased blood pressure levels [45, 46]. Despite the previous studies, in our study, SBP, not with DBP, was associated with MA in prehypertensive and hypertensive groups [47]. Left ventricular load is determined not only by cardiac output and peripheral vascular resistance, but also by the stiffness of conduit arteries. With this explanation, we can say that, beside the increased left ventricular pressure, BNP levels also reflect the stiffness of the conduit arteries. An increase in vascular structural stiffness, that might be parallel to the progression of nephrosclerosis, could result in pressure-related microvascular damage in the kidney [48] and ultimately increase the abnormal albuminuria. Previously, some studies have reported the association of increased BNP levels and abnormal albuminuria in hypertensive subjects [49]. Consistent with previous studies, we have found that, BNP was significantly associated with abnormal albuminuria in untreated hypertensive and prehypertensive subjects. To our knowledge, our study is the first to show the association of increased BNP levels and abnormal albuminuria in prehypertensive subjects, independent from other risk factors of UAE. This relation between BNP and MA should alert the clinician in case of increased BNP in patients with preHT.

In HyperGEN study, a positive association between MA, LV mass and wall thickness in normotensive and hypertensive adults has

been reported [50]. Furthermore, Arnlov et al. found that, MA is associated with early structural changes in myocardium that have not affected left ventricular functions [51]. In our study, there was a close correlation between abnormal albuminuria and LVMI in prehypertensive and hypertensive study groups. An increase in albuminuria may reflect left ventricular mass increase and a significant correlation between albuminuria and LVMI may indicate similar progressive damage to hypertensive organs, in the heart (increased left ventricular mass) and kidney (albuminuria) in both study groups with increased blood pressure.

In our study, subjects with preHT and HT had abnormal albuminuria despite having no diabetes. Contrary to previous studies [8] in subjects with preHT, high-normal blood pressure comprimised the renal functions and induced MA even without diabetes. Not only for inspection of renal functions but also for the follow-up of blood pressure progression, MA was found usefull. In a prospective study of Wang et al. [33] 1.499 non-diabetic, non-hypertensive individuals has demonstrated that those in the highest quartile of the UAE had an adjusted OR of 1.93 for developing hypertension and 1.45 for BP progression. These data suggested that subclinical abnormalities in the kidney and vascular endothelium might precede the progression to higher BP levels. It was shown that the progression of BP from preHT to HT can be delayed by angiotensin receptor blocker therapy [52], and screening for MA may identify a subgroup of patients who are at high risk for developing CVD and could benefit from early therapy and closer follow-up. At that point, MA should be considered in the treatment strategy of patients with increased blood pressure even in prehypertensive stage.

In conclusion, the present study demonstrated that the prevalence of abnormal albuminuria was 55% and 32% in untreated hypertensive and prehypertensive subjects, respectively. MA was positively correlated with SBP, BNP and LVMI in untreated hypertensive and prehypertensive patients. In case of increased SBP, BNP and LVMI, the patients should be investigated for MA. High prevalance of MA in prehypertensive subjects emphasized that these subjects should be followed closely for renal functions even without having any clinical finding. PreHT has subclinical detrimental effects on vascular tree even without diabetes. The improvement in vascular endothelium and renal functions with anti-hypertensive treatment in preHT is the subject of furher prospective randomized trials.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Erhan Tenekecioglu, Kardiyoloji Kliniği, Bursa Yuksek Ihtisas Eğitim ve Arastirma Hastanesi, Yildirim, Bursa, Turkey. Tel: +90 5057807280; Fax: +90 224 3605055; E-mail: erhantenekecioglu@yahoo.com

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