

PAPER DETAILS

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Does Microalbuminuria has Positive Predictive Value in Patients With Essential Hypertension for Renovascular Hypertension?

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Abstract

Background: Renovascular disease is an important correctable cause of secondary hypertension. We aimed to research whether microalbuminuria might be an indicator for renovascular hypertension among the essential hypertensive patients.

Method: 330 essential hypertensive patients were enrolled to the study. Patients were divided into 2 groups: group 1 (microalbuminuria) and group 2 (normoalbuminuria). Urine albumin concentrations were measured by nephelometry after 24-hour urine collection. All subjects were examined by renal duplex doppler ultrasonography and who had renal artery stenosis then MR angiography was performed.

Results: Microalbuminuria was detected in 107 of 330 essential hypertensive patients (32.42%). Mean CrCl levels ($108,14 \pm 19,83$ vs $116,36 \pm 18,62$, $p=0,002$) were significantly lower in the group of patients with microalbuminuria. 3/107 (2.80%) of the patients had renal artery stenosis in the group of patients with microalbuminuria and 8/223 (3.58%) of the patients had renal artery stenosis in the group of patients with normoalbuminuria. This study showed a sensitivity of 2.8%, specificity 96.41%, positive predictive value 27.27%, negative predictive value 67.40%.

Conclusion: We suggest that microalbuminuria isn't an indicator for renovascular hypertension in patients with essential hypertension.

Keywords: Renovascular hypertension, essential hypertension, microalbuminuria, renal doppler ultrasonography.

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Introduction

Hypertension is a major public health problem affecting more than one billion individuals worldwide.¹ Renovascular disease is an important correctable cause of secondary hypertension. Although the frequency of renovascular hypertension is variable, it accounts for less than 1 percent of cases of mild to moderate elevations in blood pressure.² However, the incidence of this disease markedly increasing in patients with acute (even if superimposed upon a preexisting elevation in blood pressure), severe, or refractory hypertension.^{3,4} Atherosclerosis and fibromuscular dysplasia (FMD) is the major causes, accounting for ~90% of renovascular hypertension cases.²

The gold standard for diagnosing renal artery stenosis is renal arteriography. On the other hand, less invasive tests have been evaluated for screening purposes.^{2,5} The following noninvasive tests can be used for screening for renal artery stenosis⁶, magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and duplex doppler ultrasonography (DDU).

Microalbuminuria (MA) is defined as persistent elevation of albumin in the urine, of 30–300 mg/day (20–200 microg/min). Microalbuminuria occurs from progressive, subclinical, structural and functional changes within the kidney and represents a sensitive marker of early renal disease.^{7,8} Microalbuminuria was first associated with essential hypertension in non-diabetic individuals by Parving et al.⁹ and it is also confirmed in subsequent studies.^{10,11} Microalbuminuria is a common indicator for cardiovascular risk factors and is associated with an increased incidence of all-cause and, in particular, cardiovascular (CV) mortality.^{12,13}

Based on these information, in the present study we aimed to research the whether microalbuminuria might be an indicator for renovascular hypertension in patients with essential hypertension.

Materials and Methods

330 essential hypertensive patients who had routine follow-up and therapy in nephrology outpatient clinic were enrolled to the study. The study was conducted in the department of nephrology, Dicle University, Faculty of Medicine, from January 2009 – to January 2010. The study protocol was approved by the Local Human Research Ethics Committee and informed consent was obtained from all patients at the time of study enrollment. The inclusion criteria were as follows; subjects aged between 18–65 years, those with essential hypertension. The exclusion criteria were as follows; subjects with diabetes mellitus, secondary hypertension, any malignant disease, congestive heart failure, macroalbuminuria, cerebrovascular disease, chronic kidney disease, hyperlipidemia, smoking history, obesity (body mass index (BMI) ≥ 30 kg/m²) and who doesn't want to participate in the study. Patient's demographic characteristics were taken from patient's files and themselves. Anthropometric measurement including waist circumference was measured at the minimum circumference between the iliac crest and the rib cage.

All patients of systolic and diastolic blood pressures were measured from the right arm after at least 5 minutes resting. Hypertension was diagnosed according to the guidelines presented in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁴ Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg on at least three measurements performed in a medical office and/or use of antihypertensive drugs.

24-hour urine samples were collected from all patients, and creatinine and protein were studied in the urine. Creatinine clearance (CrCl) was calculated by the standard formula (urine creatinine x urine volume / serum creatinine x 1440). Urine albumin concentrations were measured by nephelometry (Dade Behring Diagnostic, Marburg Germany) according to turbidimetric method at 404 nm after 24-hour urine collection. Microalbuminuria is defined as persistent elevation of albumin in the urine, of 30–300 mg/day (20–200 microg/min).

Blood samples were taken after 12 hour fasting for analysis of serum biochemical (Urea, Creatinine, Na, K, Ca, Albumin, LDL cholesterol), hematological (Hgb) and serological (CRP) parameters.

All subjects were examined by renal DDU with a 3,5 MHz curvilinear-array transducer. The examinations were started with the patient in the supine position to visualize the origin and proximal course of the renal arteries. A significant renal artery stenosis was defined by peak systolic velocity above/equal 180 cm/sec. Patients who had renal artery stenosis findings in renal DDU, and then MR angiography was performed for confirmation.

Statistical analysis

The data were analyzed using SPSS software version 16.0. Data were expressed as mean \pm standard deviation (SD). The dependent and independent variables were analyzed by Student t test and Chi-square test. Pearson's correlation test was used for the analysis of the relationship between the parameters. *P* values <0.05 were considered statistically significant.

Result

These hypertensive patients were divided into 2 groups: group 1 (microalbuminuria) and group 2 (normoalbuminuria). Microalbuminuria was detected in 107 of 330 essential hypertensive patients (32.42%). Male/Female (M/F) was 42/65 in group 1 and 95/128 in group 2, there was no significantly difference between the two groups ($p>0.05$). Microalbuminuria in female hypertensive patients and male hypertensive patients were 33.67% and 30.65%, respectively. Distribution of study population according to microalbuminuria and normoalbuminuria in male and female is shown in table 1.

Table 1. Distribution of study population according to microalbuminuria and normoalbuminuria in male and female.

	<i>Male</i>	<i>Female</i>	<i>Total</i>
Micralbuminuria	42 (30,65%)	65 (33,67 %)	107 (32,42 %)
Normoalbuminuria	95 (69,35%)	128 (66,33 %)	223 (67,58 %)

The mean age was $39,63 \pm 14,25$ years and the mean duration of diagnosed hypertension was $28,70 \pm 32,16$ months in group 1 and those were $38,78 \pm 13,32$ years and $30,36 \pm 21,82$ months respectively in group 2. According to the age and the mean duration of diagnosed hypertension, there was no significantly difference between the two groups ($p>0.05$).

Hypertensive patients with microalbuminuria had significantly higher waist circumference, BMI, mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) than hypertensive patients with normoalbuminuria ($p<0.05$). Table 2, shows the demographic, clinical and anthropometric characteristics of the groups.

We also compared the laboratory characteristics of the groups; Na, K, CRP and ferritin levels were significantly higher, while mean CrCl levels were significantly lower in the group of patients with microalbuminuria ($p<0.05$).

Table 2: Demographic, clinical and anthropometric characteristics of the groups.

Parameters	Microalbuminuria Group 1 (n=107)	Normoalbuminuria Group 2 (n=223)	p
Age (years)	39,63±14,25	38,78±13,32	0,652
Gender (M/F)	42/65	95/128	0,841
Waist circumference (cm)	94,93±12,40	87,67±9,00	<0,001
SBP (mm Hg)	149,81±15,70	144,40±7,41	0,001
DBP (mm Hg)	91,85±9,26	88,84±6,47	0,006
BMI (kg/m ²)	25,61±3,46	24,24±2,34	0,001
Duration of hypertension (months)	28,70±32,16	30.36±21,82	0,658

BMI, body mass index; **LDL**, low density lipoprotein; **SBP**, systolic blood pressure; **DBP**, diastolic blood pressure;

Table 3: Laboratory characteristics of the groups.

Parameters	Microalbuminuria Group 1(n=107)	Normoalbuminuria Group 2 (n=223)	P
Urea (mg/dl)	37,66±18,64	33,58±11,59	0,055
Creatinine (mg/dl)	0,90±0,27	0,87±0,21	0,398
Na (mg/dl)	138,78±3,16	135,61±4,07	<0,001
K (mg/dl)	4,04±0,53	3,91±0,40	0,040
Albumin (gr/dl)	3,99±0,48	4,07±0,40	0,206
LDL cholesterol (mg/dl)	113,77±33,67	130,33±12,74	0,169
CrCl (ml/min)	108,14±19,83	116,36±18,62	0,002
Microalbuminuria (mg/day)	106,96±70,26	11,26±7,39	<0,001
CRP (mg/lt)	5,42±2,48	1,93±1,28	<0,001
Hemoglobin (gr/dl)	13,35±1,84	13,68±1,63	0,161

CrCl, Creatinine clearance; **CRP**, C-reactive protein.

As shown in table 4, there was a significant positive correlation between micralbuminuria and CRP ($r=0,254$; $p<0.001$), and inverse correlation between micralbuminuria and Cr Cl ($r= -0.148$; $p=0.029$).

Table 4: Correlations between microalbuminuria and study parameters.

Parameters	r	p
Microalbuminuria & CRP	0.254	<0.001
Microalbuminuria & CrCl	-0.148	0.029

3/107 (2,80 %) of the patients had renal artery stenosis in the group of patients with microalbuminuria and 8/223 (3,58 %) of the patients had renal artery stenosis in the group of patients with normoalbuminuria. In 11 patients, renal artery stenoses were also confirmed by MR angiography. There was no significant differences between the groups ($p>0.05$). Renal DDU findings of the study population are shown in table 5.

This study showed a sensitivity of 2,8 %, specificity 96,41 %, positive predictive value 27,27 %, negative predictive value 67.40 %.

Table 5. Distribution of study population according to renal doppler usg findings in patients with microalbuminuria and normoalbuminuria.

<i>Renal Doppler USG</i>	<i>Microalbuminuria</i>	<i>Normoalbuminuria</i>	<i>p</i>
Normal	104	215	0,126
Renal Arter Stenoza	3	8	

Discussion

The prevalence of hypertension has increased dramatically in developing countries. The worldwide prevalence of hypertension is estimated approximately 1 billion individuals, and 7,1 million deaths per year may be attributable to hypertension.¹⁵ In a general hypertensive population, the prevalence of renovascular disease varies between 1 % and 5 %.^{16,17} The vast majority of renal arterial lesions reflect either a variant of atherosclerosis or fibromuscular dysplasia (FMD).

Prior cross-sectional studies reports that microalbuminuria may be a feature of hypertension and a marker of target-organ damage.¹⁸⁻²⁰ Recent studies suggest that microalbuminuria in essential hypertension may arise from haemodynamic changes leading to elevation in intraglomerular pressure and generalised angiopathy, perhaps related to endothelial dysfunction, characterised by renal and systemic transvascular albumin leakage.²¹

Although several studies have examined the prevalence of microalbuminuria in essential hypertension, neither of these studies examined the prevalence of microalbuminuria and its predictive value among patients with renovascular hypertension. Because microalbuminuria has been suggested as an early marker of vascular dysfunction,²² we evaluated whether microalbuminuria is an indicator for renovascular hypertension in patients with essential hypertension.

Variations in the prevalence of microalbuminuria ranging from 7 % to 58 % have been reported in the literature among patients with essential hypertension. An international, observational study, i-SEARCH, has been examined to evaluate the prevalence of microalbuminuria in a total of 21,050 hypertensive patients, from 26 countries. The overall prevalence of microalbuminuria in hypertensive patients was found 58,4 % and ranging in the different countries between 53 % and 71 %.²³

Bigazzi et al. found a high prevalence of microalbuminuria 40% in a group of 123 patients with essential hypertension.¹¹ In an another study conducted in the South India area on 1060 hypertensive patients by Shantha et al. found 35,6 % prevalence of microalbuminuria in the study population.²⁴ In the Magic study 787 untreated patients with essential hypertension in Genoa area were examined and reported very low prevalence of microalbuminuria 6,7 %.²⁵

The present study reports a 32,42 % prevalence of microalbuminuria in essential hypertensive patients. In addition, hypertensive patients with microalbuminuria had significantly higher mean SBP and DBP than hypertensive patients with normoalbuminuria ($149,81\pm15,70$ vs $144,40\pm7,41$, $p=0,001$), ($91,85\pm9,26$ vs $88,84\pm6,47$, $p=0,006$), respectively. A similar findings were observed in several previously published

reports.²³⁻²⁵ The variations in the prevalence of microalbuminuria may arise from several factors such as the severity of hypertension, differences in populations, race, coexistence of renal disease, and the methods of measurement of microalbuminuria etc.

The prevalence of microalbuminuria in male hypertensive population was higher than in female hypertensive population in both i-SEARCH and Magic study.^{23,25} In another study by Bibek et al. observed that microalbuminuric patients were more likely to be female²⁶.

In contrast to the findings of i-SEARCH and Magic study,^{23,25} but in agreement with the findings study of Bibek et al.,²⁶ our findings indicate that microalbuminuria in female hypertensive patients was higher than male hypertensive patients, 33,67 % and 30,65 %, respectively.

Valensi et al. evaluated the microalbuminuria in 270 nondiabetic obese patients with BMI = 34,7 +/- 5,7 (SD) kg/m² with or without hypertension and they reported that urinary albumin excretion was significantly higher in obese patients than in non-obese controls.²⁷ Although obese patients (BMI>30 kg/m²) were not included into the present study, BMI was significantly higher in hypertensive patients with microalbuminuria (p=0.001). Our findings is consistent with the previous studies as mentioned above.

An association of microalbuminuria and C-reactive protein has been reported previously. In a large Japanese cross-sectional study of 6453 apparently healthy individuals by Nakamura et al, CRP levels were significantly correlated with microalbuminuria in both men and women.²⁸ In an important study by Kshirsagar et al. examined the association of CRP and microalbuminuria in a large, diverse data set compiled from the National Health and Nutrition Examination Surveys (NHANES) 1999 through 2004. They found that CRP concentration was positively associated with microalbuminuria.²⁹ Compatible with the findings of Nakamura et al.²⁸ and Kshirsagar et al.,²⁹ we found that hypertensive patients with microalbuminuria had significantly higher CRP levels (5,42±2,48 vs 1,93±1,28 , p<0,001) than hypertensive patients with normoalbuminuria. Furthermore, significant positive correlation between microalbuminuria and CRP (r=0,254 ; p<0.001) was found in the present study. It is suggested that microalbuminuria seems to be associated with chronic low-grade inflammation as well as vascular dysfunction and markers of endothelial dysfunction.³⁰⁻³⁴

In the study by Bigazzi et al. no correlation was found between urinary albumin excretion and creatinine clearance.¹¹ In an another study by Cerasola et al. found a positive correlation between microalbuminuria and greater glomerular filtration rate.¹⁰

In contrast to the findings by Bigazzi et al.¹¹ and Cerasola et al.¹⁰, we found an inverse correlation between microalbuminuria and Cr Cl (r= -0,148; p=0,029). Although mean CrCl levels were within normal range in the present study, we found significantly lower mean Cr Cl levels (108,14 ± 19,83 vs 116,36 ± 18,62 , p=0,002) in the group of patients with microalbuminuria.

In the present study, 3/107 (2,80 %) of the patients had renal artery stenosis in the group of patients with microalbuminuria and 8/223 (3,58 %) of the patients had renal artery stenosis in the group of patients with normoalbuminuria. There was no significant difference in the prevalence of renal artery stenosis between the two groups (p=0,126). Moreover, this study showed a sensitivity of 2,8 %, specificity 96,41 %, positive predictive value 27,27 % , negative predictive value 67,40 %. Although this sensitivity is low, it has been argued that high specificity is the important feature of our study.

An important limitation of the study is that a relatively small number of patients with renal artery stenosis were examined. On the other hand, the number of patients in several recent studies reporting a similar prevalence of microalbuminuria among hypertensive patient.

In conclusion, we suggest that microalbuminuria isn't an indicator for renovascular hypertension in patients with essential hypertension. However, a larger number of patients with renal artery stenosis is required to confirm the results of our study.

Conflict of interest.

The authors declare no conflict of interest.

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