The prevalence of microalbuminuria and relevant cardiovascular risk factors in Turkish hypertensive patients

Türk hipertansiyon hastalarında mikroalbuminüri sıklığı ve ilişkili kardiyovasküler risk faktörleri

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ABSTRACT

Objectives: A growing body of data illustrates the importance of microalbuminuria (MAU) as a strong predictor of cardiovascular risk in the hypertensive population. The present study was designed to define the prevalence of MAU and associated cardiovascular risk factors among Turkish hypertensive outpatients.

Study design: Representing the Turkish arm of the multinational i-SEARCH study involving 1,750 sites in 26 countries around the world, a total of 1,926 hypertensive patients from different centers were included in this observational and cross-sectional survey study. Patients with reasons for a false-positive MAU test were excluded. The prevalence of MAU was assessed using a dipstick test, and patients were inquired about comorbidities, comedication, and known cardiovascular risk factors.

Results: The overall prevalence of MAU was 64.7% and there was no difference between genders. Most of the patients (82.5%) had uncontrolled hypertension, 35.6% had dyslipidemia, and 35.5% had diabetes, predominantly type 2. Almost one-third of the patients (26.4%) had at least one cardiovascular-related comorbidity, with 20.3% having documented coronary artery disease (CAD). Almost all patients (96.8%) had one or more risk factors for cardiovascular disease in addition to hypertension, including family history of myocardial infarction or CAD, diabetes, dyslipidemia, lack of physical exercise, and smoking. A trend towards higher MAU values in the presence of CAD was determined.

Conclusion: Microalbuminuria tests should be routinely used as a screening and monitoring tool for the assessment of subsequent cardiovascular morbidity and mortality among hypertensive patients.

ÖZET

Amaç: Mikroalbuminürinin (MAU) hipertansiyon hastalarında kardiyovasküler riskin önemli bir öngördürücüsü olduğu yolunda gittikçe artan veri bulunmaktadır. Bu çalışma, ayaktan takip edilen hipertansif hastalarda MAU sıklığının ve ilgili kardiyovasküler risk faktörlerinin tanımlanması amacıyla tasarlandı.

Çalışma planı: Dünya çapında 26 ülkeden 1750 merkezin katılımı ile yürütülen çokuluslu i-SEARCH çalışmasının Türkiye kolunu temsil eden gözlemsel, kesitsel ve çokmerkezli bu çalışmaya Türkiye'den toplam 1926 hipertansiyon hastası alındı. Yalancı pozitif MAU testine yol açacak nedenlere sahip hastalar çalışmaya alınmadı. Mikroalbuminüri sıklığı "dipstick" testi ile belirlendi; ayrıca, çalışma grubunda eşlik eden hastalıklar, kullanılan ilaçlar ve kardiyovasküler risk faktörleri soruşturuldu.

Bulgular: Mikroalbuminüri sıklığı %64.7 bulunurken, cinsiyete göre farklılık gözlenmedi. Hastaların büyük çoğunluğunda (%82.5) kontrolsüz hipertansiyon, %35.6'sında dislipidemi, %35.5'inde tip 2 ağırlıklı olmak üzere diyabet saptandı. Hastaların yaklaşık üçte birinde (%26.4) kardiyovasküler risk ile ilişkili komorbidite, %20.3'ünde koroner arter hastalığı (KAH) vardı. Hastaların tamamına yakınında (%96.8), hipertansiyona ek olarak bir veya daha çok sayıda kardiyovasküler risk faktörü (miyokart enfarktüsü veya KAH için aile öyküsü, diyabet, dislipidemi, fiziksel egzersiz eksikliği ve sigara içme) bulunmaktaydı. Koroner arter hastalığı varlığında daha yüksek MAU değerlerine doğru bir eğilim gözlendi.

Sonuç: Mikroalbuminüri testleri, hipertansiyon hastalarında gelişebilecek olan kardiyovasküler morbidite ve mortaliteyi değerlendirmede rutin olarak kullanılabilecek tarama ve izleme aracıdır.

Received: December 24, 2010 *Accepted:* August 23, 2011

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Microalbuminuria, subclinical increase in urinary albumin excretion rate of 30-300 mg/day in a random urine spot check,[1] has been considered to be an independent risk factor for morbidity and mortality related to cardiovascular disease and nephropathy not only in diabetic populations[2] but also in nondiabetic hypertensives,[3] as well as among nondiabetic and nonhypertensive general population.[4,5]

Microalbuminuria is considered to be a measure of generalized vascular leakiness for albumin[6] secondary to endothelial dysfunction.[7] It is known to be an integrated marker of structural and functional abnormalities in hypertension, such as hypertensive cardiovascular abnormalities, renal and endothelial dysfunction,[8] suggesting a common pathophysiology[9] for coronary vasomotor abnormalities and MAU. Therefore, MAU has been considered to be the major independent determinant of ischemic heart disease among hypertensive patients.[10]

In this context, reduction in the MAU rate has been reported to correspond to a reduction in cardiovascular events and mortality in hypertensive patients, particularly when renin-angiotensin system-blocking drugs are used in their treatment.[8,11]

Hence, a retrospective analysis of data from the LIFE study showed that a reduction in MAU was associated with a significantly reduced risk for nonfatal myocardial infarction, stroke, and cardiovascular death.[8] Accordingly, the magnitude of decreases in albuminuria achieved with renin-angiotensin system intervention was reported to be related not only to the degree of renal protection, but also to the degree of reduction in cardiovascular risk among type 2 diabetic patients with diabetic nephropathy,[12] and also among those with nondiabetic renal disease.[13]

Despite numerous trials demonstrating the benefits of lowering high blood pressure among hypertensive patients,[14] available data suggest that the rates of treatment and control remain suboptimal,[14,15] which increases the likelihood of cardiovascular complications. Since the level of albuminuria has been closely related to the risk level during antihypertensive treatment, alterations in albuminuria seem to reflect the risk factor status if routinely screened in hypertensive patients.[8] While such a screening for MAU is recommended in international treatment guidelines for hypertensive patients,[16] it is often skipped and underappreciated by physicians due to insufficient awareness of its value as a marker of cardiovascular risk.[9] There is considerable uncertainty concerning the prevalence of MAU among hypertensive patients, the reported rates varying from as low as 4%[17] to as high as 40%[18] and even to 70%.[9]

Abbreviations:

ACE *Angiotensin-converting enzyme*
CAD *Coronary artery disease*
MAU *Microalbuminuria*

Considering the potential role of baseline albuminuria in predicting subsequent risk levels for cardiovascular complications in patients with essential hypertension,[5] the present study was designed to evaluate the prevalence of MAU and associated cardiovascular risk factors among hypertensive patients.

PATIENTS AND METHODS

Study population

The multinational observational study called i-SEARCH was conducted in 26 countries around the world including 21,050 patients.[9] Of these, 1,926 hypertensive patients from different centers of Turkey composed the Turkish arm and were surveyed in an observational and cross-sectional design aiming to determine the prevalence of MAU and the risk factors associated with MAU. Over a 6-month study period, the study population initially consisted of 2,066 patients presenting to medical centers. Of these, 2032 patients gave written informed consent to participate in the study. After exclusion of 106 patients who failed to meet inclusion criteria or had missing entries in their Case Report Form with respect to cardiovascular history or albumin and creatinine levels, the remaining 1,926 patients constituted the final population. Ethics committee approvals for the study were obtained from all participating centers. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki and with the standards of the International Conference on Harmonization/Good Clinical Practice.

The sample was composed of male and female outpatients, aged 18 years or older, currently under treatment of or with newly diagnosed essential arterial hypertension, defined as a seated systolic/diastolic blood pressure of >140/90 mmHg measured at rest during a single clinical visit. Exclusion criteria were the presence of the following: acute fever (>38 °C), renal disease (serum creatinine >20 mg/l), concomitant urinary tract infection, cimetidine therapy, pregnancy, menstrual bleeding and, in order to prevent false-positive results, strenuous physical activity in the preceding 24 hours.

Study design and procedures

The study protocol included assessment of data derived from the Case Report Form of each patient, including demographic features, body mass index (kg/m^2), waist circumference (cm), waist/hip ratio, vital signs (blood pressure, pulse pressure, heart rate), urinary albumin excretion, cardiovascular history, cardiovascular risk factors, comorbidities, symptoms and signs of cardiovascular disease, and current chronic drug therapy. Urinary albumin excretion was determined with a standardized sample collection and urinary dipstick screening test for MAU using the reagent strips provided by the sponsor (Microalbustix, Bayer Leverkusen, Germany), which have a sensitivity of 82.6%.[19] Possible urine albumin levels were 10, 30, 80 or 150 mg/l. Levels of cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C-reactive protein, and serum creatinine were recorded, if they had been assessed within the past 12 months. The Sokolow index, used to assess the presence of left ventricular hypertrophy, calculated from the last available electrocardiogram, and left ventricular function (ejection fraction) were also included in each patient's Case Report Form.

Statistical analysis

Data on population characteristics for demographic features, past history of hypertension, comorbidities, and current treatment were summarized into counts of nonmissing data and shown as mean±standard deviation or percent where appropriate. Subgroup comparisons were done by the chi-square test and Student's t-test according to the characteristics of data.

RESULTS

Characteristics of the study population are summarized in Table 1. The mean age was 56.9±11.4 years, and 41.1% of the subjects were aged 60 years or beyond. Females accounted for 56.9%. The mean body mass index was 29.6±5.1 kg/m^2 and 40.7% of the patients had clinical obesity with a body mass index of 30 kg/m^2 or greater. Almost two-thirds of the patients (67.5%) had an abnormally high waist circumference exceeding 88 cm in women and 102 cm in men; and the mean waist/hip ratio was 0.9±0.1. The majority of the patients (82.5%) were found to have uncontrolled hypertension. The mean duration of hypertension was 7±6.3 years and almost one-third of the population was hypertensive for ≥10 years. Systolic and diastolic blood pressures were 153.1±21.9 mmHg and 91.8±11.9, respectively, with a

Table 1. Demographic features, vital signs, and past history of hypertension in the study population

	n	%	Mean±SD
Age (years)			56.9±11.4
Gender	1913		
Male	825	43.1	
Female	1088	56.9	
Body mass index (kg/m^2)	1899		29.6±5.1
<18 kg/m^2	3	0.2	
18 to <25 kg/m^2	289	15.2	
25 to <28 kg/m^2	497	26.2	
28 to <30 kg/m^2	337	17.8	
30 to <35 kg/m^2	518	27.3	
≥35 kg/m^2	255	13.4	
Waist circumference*	1874		100.5±13.9
Normal	610	32.6	
Abnormal	1264	67.5	
Waist / hip ratio			0.9±0.1
Hypertension			
Duration (years)	1736		7.0±6.3
<5 years	729	42.0	
5 to <10 years	458	26.4	
≥10 years	549	31.6	
Hypertension control**	1926		
Yes	337	17.5	
No	1589	82.5	
Vital signs			
Systolic blood pressure (mmHg)	1922		153.1±21.9
<120 mmHg	55	2.9	
120 to <130 mmHg	125	6.5	
130 to <140 mmHg	209	10.9	
140 to <160 mmHg	721	37.5	
160 to <180 mmHg	527	27.4	
≥180 mmHg	285	14.8	
Diastolic blood pressure (mmHg)	1922		91.8±11.9
<80 mmHg	154	8.0	
80 to <85 mmHg	333	17.3	
85 to <90 mmHg	88	4.6	
90 to <100 mmHg	650	33.8	
100 to <110 mmHg	511	26.6	
≥110 mmHg	186	9.7	
Pulse pressure (mmHg)			61.2±16.1
Heart rate (bpm)			78.2±11.2
Sinus rhythm	1866	96.9	

*Waist circumference was considered normal for <102 cm (men) and <88 cm (women); abnormal for ≥102 cm (men) and ≥88 cm (women). **Blood pressure was considered to be uncontrolled if systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg.

mean pulse pressure of 61.2±16.1 mmHg. The mean heart rate was 78.2±11.2 bpm (Table 1).

Concerning cardiovascular risk factors, 35.6% had dyslipidemia and 35.5% had diabetes, predominantly type 2 (Table 2). Nearly one-third of the patients (26.4%) had evidence for cardiovascular-related comorbidities, with 20.3% having documented coronary artery disease. Almost all patients (96.8%) had one or more risk factors for cardiovascular disease in addition to hypertension, which included history of myocardial infarction or CAD, diabetes, dyslipidemia, lack of physical exercise, or history of smoking (Table 2).

The majority of the patients (86.3%) were prescribed cardiovascular medications, while 55% were also on a special diet for cardiovascular disease risk reduction. Most commonly prescribed drugs were antiplatelet/anticoagulant agents (53.8%), angiotensin-converting enzyme inhibitors (40.9%) and beta-blockers (36.1%) as antihypertensives, and lipid-lowering agents (34.8%) (Table 3). Statins were the most widely prescribed lipid-lowering drugs, with 32.6% of the patients. Among the subgroup of patients with hypertension and concomitant diabetes, 42.2% of patients were receiving oral hypoglycemic drugs and/or insulin.

Prevalence of microalbuminuria

Among the study population, relatively few patients had impaired renal function. Only 1.9% had previously known albuminuria; however, urinalysis with a one-time dipstick test revealed that 64.7% of the study population had evidence for MAU, with similar prevalence rates in women (64.4%) and men (65%) (Table 2). Gender did not have any influence on the prevalence of MAU and waist circumference did not differ significantly between patients with and without MAU (Table 2). There was also no difference with respect to beta-blocker, ACE inhibitor, and angiotensin-receptor blocker use between patients with and without MAU. Beta-blockers, angiotensin-receptor blockers and ACE inhibitors were prescribed in 235 (34.6%), 198 (29.1%) and 270 (39.7%) patients without MAU compared to 461 (37.0%), 350 (28.1%), and 517 (41.5%) patients with MAU, respectively. The prevalences of MAU with respect to varying levels urinary albumin excretion and the presence of CAD are shown in Figure 1.

DISCUSSION

Microalbuminuria has been associated with an increased risk for renal and cardiovascular morbidity

Table 2. The prevalences of microalbuminuria, cardiovascular risk factors, and comorbidities

	n	%	Mean±SD
Microalbuminuria	1926		
Present	1246	64.7	
Absent	680	35.3	
Male (n=825)			
Present	536	65.0	
Absent	289	35.0	
Female (n=1088)			
Present	701	64.4	
Absent	387	35.6	
Waist circumference (cm)			
Present (n=1214)			100.8±13.4
Absent (n=673)			100.1±14.8
Risk factors for cardiovascular disease			
At least one risk factor			
Present	1864	96.8	
Absent	62	3.2	
Family history of MI / CAD	591	30.7	
Lack of regular physical exercise	1550	80.5	
Smoking			
Current	389	20.2	
Former	264	13.7	
Additional risk factors			
Total cholesterol (mmol/l)			5.3±1.3
HDL cholesterol (mmol/l)			1.3±0.5
LDL cholesterol (mmol/l)			3.2±1.0
Triglycerides (mmol/l)			1.8±1.1
C-reactive protein (mg/dl)			0.9±1.0
Duration of diabetes (years)			7.6±8.3
Current diabetics	670	35.5	
Type 1 diabetes	20	5.6	
Type 2 diabetes	338	94.4	
Creatinine clearance (ml/min)	1431		99.7±36.9
<30 ml/min	5	0.4	
30 to <60 ml/min	152	10.6	
60 to <80 ml/min	282	19.7	
80 to <120 ml/min	648	45.3	
≥120 ml/min	344	24.0	
Comorbidities (n=1926)			
At least one comorbidity	508	26.4	
Coronary artery disease	390	20.3	
Congestive heart failure	86	4.5	
Atrial fibrillation	75	3.9	
History of ischemic stroke	54	2.8	
History of transient ischemic attack	38	2.0	
Peripheral artery disease	23	1.2	
Overall	15	0.8	
Endarterectomy	6	42.9	

MI: Myocardial infarction; CAD: Coronary artery disease; *At least one additional cardiovascular risk represents one of the following: family history of MI or documented CAD, lack of regular physical exercise, current or former smoking, known hyperlipidemia, or diabetes mellitus.

Table 3. Past and present history of medical treatment for cardiovascular disease

Drugs	n	%
Thiazide diuretics	461	23.9
Aldosterone antagonists	37	1.9
Loop diuretics	52	2.7
Calcium-channel blockers	445	23.1
Beta-blockers	696	36.1
Alpha-blockers	52	2.7
Angiotensin-receptor blockers	548	28.5
Angiotensin-converting enzyme inhibitors	787	40.9
Lipid-lowering agents	671	34.8
Statins	627	32.6
Fibrates	63	3.3
Antiplatelet / anticoagulant agent	1037	53.8
Aspirin	1017	52.8
Warfarin	37	1.9

and all-cause mortality in diabetic and/or hypertensive patients and in elderly subjects.[5]

Microalbuminuria was found in 64.7% of the screened population in our study, which was in accordance with the upper limits of prevalence rates defined in published studies.[9,17,18] In fact, the high prevalence of MAU determined in some countries, as well as in Turkey, within the entire i-SEARCH survey has been related to involvement of patients with diabetes, CAD, and albuminuria unlike their exclusion in past studies.[9] Moreover, inclusion of all three grades of hypertension according to the European Society of Hypertension-European Society of Cardiology (ESC/ESH) 2003 guidelines[16] in the i-SEARCH survey was also stated to be responsible for the observation of high MAU prevalence.[9] Nonetheless, the finding of such a high MAU prevalence among hypertensive patients seems to be significant owing to well-known long-term detrimental effects of MAU on the cardiovascular system.

Besides our findings on lack of regular physical activity, dyslipidemia, prominent risk factors, and concomitant diseases such as diabetes, congestive heart failure, and CAD, atrial fibrillation was a remarkable accompaniment for MAU. Of 75 patients with atrial fibrillation, 59 (78.7%) had MAU.

This was compatible with the results of the LIFE study,[8] in which a 4- to 5-fold increase in risk for cardiovascular events was observed in the presence of high albumin excretion rates, suggesting an association with cardiac organ damage.

On the other hand, unlike the overall results of the i-SEARCH survey showing a higher risk for MAU among males with higher waist circumference values,[9] there was no gender influence on the risk for MAU in our population, nor any association with waist circumference.

Our results were in accordance with the well-known interaction between the MAU level and accompanying CAD, which was also supported by observations from the HOPE study,[11] reporting a close relationship between MAU and the cardio-renal risk. The prevalence of MAU (50%) detected among diabetic hypertensive patients in the present study was similar to that obtained in the DEMAND study,[20] in which albuminuria was not an exclusion criteria and not all the diabetics were hypertensive. In fact, blood pressure-lowering in type 2 diabetes was shown to have a remarkable cardiovascular protective effect regardless of the drug(s) used, leading to an assumption that cardiovascular benefit in diabetes may mainly originate from lowering blood pressure per se.[21,22]

Concerning the role of drug treatment, prescription of cardiovascular and antidiabetic drugs includ-

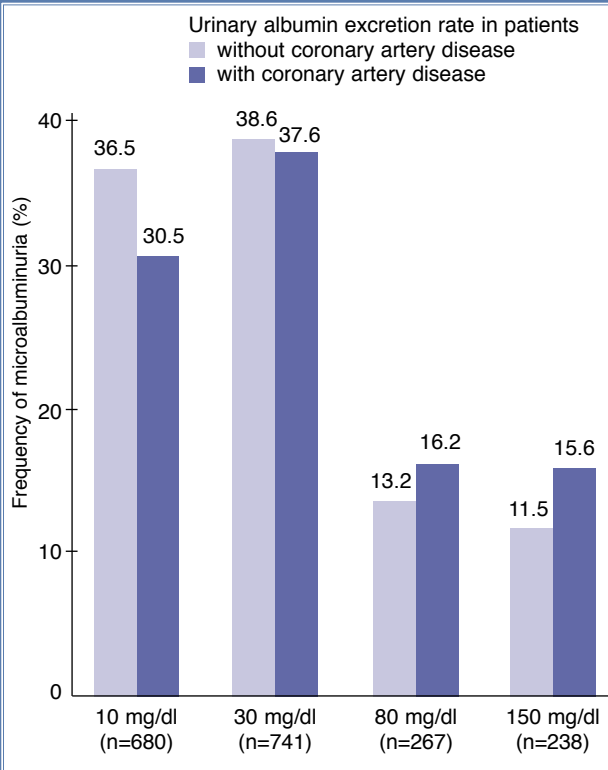

Figure 1. Prevalence of microalbuminuria in the study population with respect to different levels urinary albumin excretion and the presence of coronary artery disease.

ing calcium-channel blockers, thiazides, aldosterone antagonists, loop diuretics, alpha-blockers, digitalis, oral nitrates, antiarythmic drugs, biguanides, sulfonylureas, insulin, and anticoagulants including warfarin/Coumadin was shown to be associated with increased risk for MAU.[9] However, there was no significant association between MAU risk and the use of ACE inhibitors, angiotensin receptor antagonists, and beta-blockers in the present study, indicating the importance of normalization of MAU as a therapeutic goal in reducing cardiovascular risk besides achieving tight blood pressure control.[9]

In fact, evidence from the IRMA-2,[23] IDNT,[24] and LIFE[8] studies suggested that beta-blockers, ACE inhibitors, and calcium-channel blockers were all associated with increased risk for MAU. The limited efficacy of drugs in preventing diabetic nephropathy accompanying cardiovascular disease has been reported to mandate use of renin-angiotensin system-blocking agents.[9] Therefore, failure of such drugs to effectively reduce MAU was accused for the related increase in MAU risk. Therefore, our results contradictory to the past studies in terms of MAU risk reduction obtained via beta-blockers and ACE inhibitors may indicate the successful management of the underlying conditions targeted with these drugs as far as our study population is concerned.

Supporting the lack of MAU risk related with the use of ACE inhibitors, they were recommended as primary preventive intervention against nephropathy[25] based on recent evidence concerning prevention of MAU with ACE inhibition.[26] Angiotensin receptor antagonists such as irbesartan have been considered to be the first-line therapy in all major guidelines and are especially recommended in patients with diabetic nephropathy.[27]

Even though hypertension-associated diseases are still the leading cause of death, poor blood pressure control is evident in more than 70% of hypertensive patients worldwide.[28] In this respect, while the vast majority of the patients in the present study were receiving treatment for hypertension, the detection of poor blood pressure control over three-quarters of the study population seems notable in terms of high rates of MAU, in line to data obtained from the i-SEARCH study. In this context, since benefits of treating hypertension are not fully attained until a patient has been treated for 4 to 5 years,[29] aggressive blood pressure lowering has been considered to be essential in reducing cardiovascular morbidity and mortality in the hypertension in relation to leading to appropriate reductions in MAU and associated cardiovascular risk.[8,9,30]

In conclusion, we propose that MAU has a high prevalence rate among hypertensive outpatients with cardiovascular risk factors and/or concomitant CAD or diabetes. Being an early and independent modifiable risk marker responsive to antihypertensive medication, MAU should be routinely used as a screening and monitoring tool in the assessment of subsequent cardiovascular morbidity and mortality in hypertensive patients.

Limitations

Although the use of a standardized procedure for determining MAU in all participating centers increases the possibility of a reliable interpretation of our results, the measurement of MAU on a single occasion comprises the main limitation to the present study and contradicts the international guidelines recommending triple testing.[9] However, data obtained in the NHANES III survey[31] indicate that at least 65% of patients with a positive test will also test positive on a subsequent occasion.

Acknowledgments

This study was funded by a research grant from Sanofi-Aventis. There are no conflict of interest issues for any of the authors, nor for the results.

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Key words: Albuminuria/complications/epidemiology; cardiovascular diseases; coronary artery disease; hypertension/complications; prevalence; risk factors; Turkey/epidemiology.

Anahtar sözcükler: Albuminüri/komplikasyon/epidemiyoloji; kardiyovasküler hastalık; koroner arter hastalığı; hipertansiyon/komplikasyon; prevalans; risk faktörü; Türkiye/epidemiyoloji.

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