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Microalbuminuria Prevalence in Turkish Type 2 Diabetics Without Known Albuminuria: Results of The Developing Education on Microalbuminuria For Awareness of Renal and Cardiovascular Risks in Diabetes Study-Demand-Turkey

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ABSTRACT

Aim: A multicenter study is carried out in Turkey to find out the demographic, clinical and metabolic characteristics and the prevalence of albuminuria in type 2 diabetic subjects without known albuminuria.

Material and Methods: The study population includes 1114 subjects with type 2 diabetes (F/M=649/465, mean chronological age 57.9±10.5 yrs, duration of diabetes 8.7±6.6 yrs) recruited from Diabetes Outpatient Clinics or Primary Care Settings across the Turkey by established criteria and cross-sectional selection according to Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risks in Diabetes (DEMAND) Study. The diagnosis for levels of albuminuria was done using the albumin/creatinine (A/C) ratio. It was considered as within "normal to mildly increased albuminuria" if A/C < 30mg/g; as "moderately increased albuminuria" if A/C within 30-300mg/g; as "severely increased albuminuria" if A/C > 300mg/g. A second test is needed when (A,C)=(10,10). Demographic, clinical and metabolic parameters were compared between the groups.

Results: The overall prevalence of albuminuria was 5.7% for severely increased albuminuria, 48.1% for moderately increased albuminuria, and within normal to mildly increased albuminuria in 37.3% of subjects. A second test was needed in 8.9% of subjects. The serum creatinine was normal in 76.7% of subjects, elevated in 21.0%, and suggesting chronic renal failure in 2.3%. Severely increased albuminuria was detected in 5.2% of female, 6.5% of male subjects; the same rates for moderately increased albuminuria were 48.0% and 48.2%, respectively. There is a steep increase in the prevalence of albuminuria in type 2 diabetes at HbA1c values of 10%, diabetes duration for 10 years and chronologic age 50-60 years.

Conclusion: A high prevalence of normal to mildly increased albuminuria (48.1%) associated with enhanced renal and cardiovascular risk, were detected in type 2 diabetic subjects without previously known nephropathy. Early detection, follow-up of vascular complications and more aggressive treatment for renal and vascular protection are needed. Normal to mildly increased albuminuria is undoubtedly the result of complex interactions between endocrine, metabolic, and hemodynamic factors. Population-based therapeutic modalities should be recruited and organized to lower the burden of normal to mildly increased albuminuria and diabetes mellitus in our country and others.

Key Words: *Microalbuminuria, Type 2 diabetes mellitus, Albuminuria, Diabetic nephropathy*

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Albüminürisi Bilinmeyen Türk Tip 2 Diyabetiklerde Mikroalbüminüri Prevelansı; Böbrek ve Kardiyovasküler Risklerin Bilinçlendirilmesi İçin Mikroalbüminüriye İlişkin Türkiye Demand Diyabet Araştırması Sonuçları

ÖZET

Amaç: Albüminürisi olmayan tip 2 diyabetik hastalarda demografik, klinik ve metabolik özellikler ile albüminürinin prevalansını bulmak için çok merkezli bir çalışma yapılmıştır.

Gereç ve Yöntemler: Çalışma popülasyonu, DEMAND çalışması kapsamında Türkiye çapında Diyabet Polikliniği veya Birinci Basamak Sağlık Kuruluşlarından kesitsel, alınan kriterlere göre, tip 2 diyabetli (K / E = 649/465, ortalama kronolojik yaş 57.9 ± 10.5 yıl, diyabet süresi 8.7 ± 6.6 yıl) 1114 olgu içermektedir. Albüminüri düzeyleri için tanı albümin / kreatinin (A / C) oranı kullanılarak yapıldı. A / C <30mg / g ise "normalden hafifçe artmış albüminüri"; A / C 30-300 mg / g ise "orta derecede artmış albüminüri"; A / C> 300 mg / g ise "şiddetli albüminüri" olarak kabul edildi. Demografik, klinik ve metabolik parametreler gruplar arasında karşılaştırıldı.

Bulgular: Albüminürinin genel prevalansı şiddetli albüminüri için % 5.7, orta derecede artmış albüminüri için % 48.1 ve hafifçe artmış albüminüri idi (% 37.3). Deneklerin % 8,9'unda ikinci bir test gerekti. Serum kreatinin oranı hastaların % 76,7'sinde normaldi, % 21,0'da yükseldi ve % 2,3'ünde kronik böbrek yetmezliği olduğunu düşündürdü. Ciddi derecede artmış albüminüri kadınlarda % 5,2, erkeklerde % 6,5; Orta derecede artmış albüminüri için aynı oranlar sırasıyla % 48,0 ve % 48,2 idi. Tip 2 diyabetlerde albüminüri prevalansında % 10'luk HbA1c değerlerinde, 10 yıllık diyabet süresi ve 50-60 yaş kronolojik yaşta belirgin bir artış tespit edildi.

Sonuç: Tip 2 diyabetik, önceden nefropati olmaksızın ve bilinmeyen kişilerde artmış böbrek ve kardiyovasküler risk ile ilişkili, hafif artmış albüminüri prevalansı (% 48,1) saptanmıştır. Vasküler komplikasyonların erken teşhisi, takibi ile böbrek ve vasküler korunma için daha agresif tedavi gereklidir. Normalden hafif artmış albüminüri kuşkusuz endokrin, metabolik ve hemodinamik faktörler arasındaki karmaşık etkileşimlerin sonucudur. Hafifden belirgine doğru albüminüri ve diabetes mellitus yükünü azaltmak için popülasyona yönelik terapötik yöntemler ele alınmalı ve organize edilmelidir.

Anahtar Sözcükler: *Mikroalbüminüri, Tip 2 diabetes mellitus, Albüminüri, Diyabetik nefropati*

INTRODUCTION

Type 2 diabetes mellitus is associated with a two- to threefold excess mortality (1,2), mainly from cardiovascular disease (3,4). Mogensen (5) and Jarrett (6) were first to explore the role of microalbuminuria as a marker for cardiovascular disease, and that microalbuminuria predicted independently all-cause mortality (mainly due to cardiovascular disease) among subjects with type 2 diabetes mellitus. It is also one of the components of the metabolic disturbances (insulin resistance syndrome) (7,8). A meta-analysis carried out by Dinneen and Gerstein (9) has confirmed the strong association between microalbuminuria and atherosclerotic disease.

Microalbuminuria is considered to be an early stage of diabetic nephropathy (10, 11) which is also shown to be associated with increased risk for cardiovascular disease and early mortality (12-15), morbidity (14) and with high health care costs (16). It is also the leading cause of end stage renal disease worldwide (17,18). Diabetic nephropathy affects 20–40% of diabetic subjects (10,17,18). Between 20–80% of subjects with microalbuminuria progress to severe renal disease (10,13,14,16-18). The range of albuminuria from 30 to 300 mg/g had been defined "microalbuminuria". Current guidelines recommend the use of "moderately increased albuminuria" instead of "microalbuminuria" (19).

Although moderately high prevalence of diabetes mellitus (7.2 13.7 %) and impaired glucose tolerance (6.7-7.1%) had been reported in Turkish people above the age of 20 years (20, 21), the prevalence of microalbuminuria in diabetes has not been elucidated yet in this population. The aim of this study is to find out the prevalence of albuminuria in a referred Turkish cohort of type 2 diabetic subjects without prior known albuminuria in the Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes (DEMAND) Study.

MATERIALS and METHODS

This study evaluated type 2 diabetic subjects without previously known albuminuria. We conducted a cross-sectional analysis of baseline data collected as part of the DEMAND study (22). In this study, Case Report Forms (CRFs) were sent to Diabetes Outpatient Clinics and Primary Care Settings across the Turkey, and the screening was carried out between June and September 2003. Twelve subjects per center were recruited from 101 Centers. Demographic features, the prevalence of albuminuria, clinical and laboratory variables as well as drug treatment in type 2 diabetic subjects without prior known albuminuria by randomized sampling were recorded.

Subjects were included using any one of the following criteria; 1- currently prescribed any diabetic treatment medication, 2- a fasting glucose ≥126 mg/dl or a random

glucose ≥200 mg/dl confirmed by a second test during the year before ascertainment, 3- a hospital discharge diagnosis of diabetes.

A Clinical Report Form (CRF) was filled in for every patient. Demographics (age, gender), clinical characteristics (height, weight, BMI, duration of diabetes, HbA1c and serum creatinine values within the last six months, presence and duration of hypertension and complications like diabetic retinopathy, diabetic foot lesion) were recorded.

For the evaluation of cardiovascular risk; family history, smoking, known hyperlipidemia, comorbidities, such as left ventricular hypertrophy, coronary artey disease, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, peripheral vascular disease were asked or identified from the medical records.

Medication use at the time of the study enrollment were recorded on the CRF. They were categorized as oral antidiabetic agents, insulin, or both for diabetes; diuretics, angiotensin-converting enzyme inhibitors (ACEI), AT_1-receptor blockers (ARBs), alpha blockers, beta blockers, calcium channel blockers for hypertension; statins for dyslipidemia; warfarin and aspirin as antiplatelet/anticoagulant. If the used drug was not categorized, it was mentioned under the others section.

Blood pressure was determined by a single recording wih an appropriate cuff after approximately 10 minutes rest in the sitting position.

Albuminuria was assessed by a single random urine albumin/creatinine (A/C) ratio measurement using Bayer reagent strip Multistix 10SG. This semiquantitive strip test has a sensitivity of 84% and specifity of 91% for the albumin/creatinine ratio according to its manufacturer. The cutpoint recommended by the ADA (23) and the National Kidney Foundation (24) (ACR >30 mg/g) was used to define albuminuria in random urine specimens. Albuminuria is considered only if confirmed by the Albumin/Creatinine (A/C) ratio as a chart below (Table 1) (19,20). The study protocol was approved by the local ethics committee and written informed consent was obtained from every patient.

Statistical Analyses

Statistical analyses were conducted to evaluate the distribution of covariates by the presence or absence albuminuria. A minimal multivariate model predicting the level of albuminuria (normal, microalbuminuria, or macroalbuminuria) was constructed using 'proportional odds' ordinal logistic models. Parallel models predicting the albumin/creatinine ratio (log transformed) as a continuous variable were built using ordinary linear regression models and gave comparable results. To build these models, independent variables were added to the model in the order in which they increased the total likelihood of the model, taken as a measure of explanatory power, until no further additions significantly ($p<0.05$). Statistical significance was determined using independent *t* test or ANOVA for continuous data and the χ^2 tests for categorical data. Data analyses were performed using SPSS 11.0, and $p<0.05$ values were considered as statistically significant.

RESULTS

A total of 1114 subjects were eligible for inclusion. Baseline characteristics of Turkish subjects with type 2

Table 1: Evaluation of the Albumin / Creatinine (A/C) ratio.

A C	10 mg/l	30 mg/l	80 mg/l	150 mg/l
10 mg/dl	100	300	800	1500
50 mg/dl	20	60	160	300
100 mg/dl	10	30	80	150
200 mg/dl	5	15	40	75
300 mg/dl	3	10	27	50

A1 Severely increased (macro-)

A2 Moderately increased (micro-)

FIN

A3 Normal to mildly increased

[A/C <30 mg/g: Normal to mildly increased, A/C within [30,300] mg/g: Moderately increased (micro-,microalbuminuria), A/C >300 mg/g: Severely increased [macro-, macroalbuminuria (nephropathy)], Exception: when (A,C) = (10,10), a second test is needed. This situation will be designated as F.I.N. (Further Investigation Needed]

diabetes mellitus are shown in Table 2. "The normal to mildly increased albuminuria" as normoalbuminuria, "moderately increased albuminuria" as microalbuminuria and "severely increased albuminuria" as macroalbuminuria were identified in 416 (37.3%), 536 (48.1%) and 63 (5.7%) subjects, respectively, further investigation was needed in 99 subjects (8.9%) (Figure 1).

In patients with microalbuminuria, the chronological age, the diseases duration of diabetes and hypertension, systolic and diastolic blood pressure, serum creatinine and HbA1c levels and the prevalence of hypertension were significantly higher than in patients with normoalbuminuria ($p<0.05$). In microalbuminuric patients, mean body weight was significantly higher and the ratio of family cardiovascular

Table 2: Baseline characteristics of Turkish subjects with type 2 diabetes mellitus.

Characteristics	Study population (n=1114)
Gender (Female/male)	649/465
Age (years±SD)	57.9 ± 10.5
Height (cm±SD)	164 ± 9
Weight (kg±SD)	75.5 ± 12.5
BMI (kg/m²±SD)	28.3 ± 4.7
Duration of diabetes (years±SD)	8.7 ± 6.6
HbA1c (%±SD)	8.0±2.3

(BMI, body mass index; HbA1c; glycated haemoglobin)

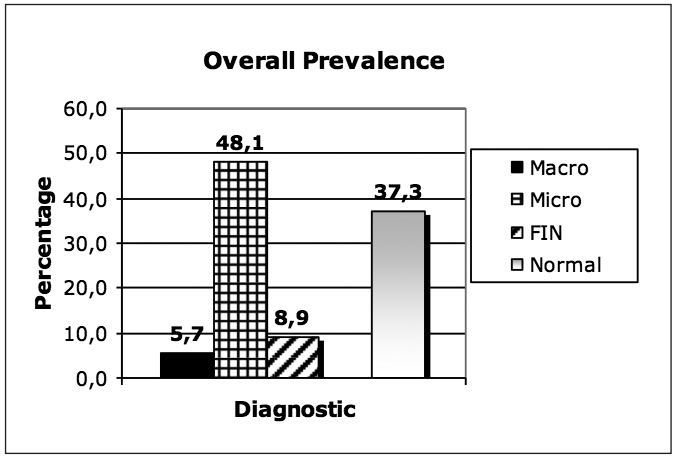

Figure 1: Overall prevalence of microalbuminuria in Turkish diabetic subjects (n=1114).

Table 3: Clinical and biochemical characteristics in subjects with type 2 diabetes according to albuminuria.

Parameters	Normo-albuminurics (n=416)	Micro-albuminurics (n=536)	Macro-albuminurics (n=63)
Chronologic age (year±SD)	56.2±10.9	59.1±9.9 *	58.8±9.9
Height (cm±SD)	164.0±9.0	164.0±8.9	164±8.8
Weight (kg±SD)	76.4±2.8 §	76.1±2.0 ‡	73.3±3.6
BMI (kg/m²±SD)	28.6±4.5	28.4±4.6	27.5±5.7
Duration of diabetes (year±SD)	7.7±6.3	9.3±6.9 *	10.5±6.5 §
History of smoking [n(%)]	127 (30.5)	157 (29.3)	25 (39.7) §
History of hypertension [n(%)]	269 (64.7)	362 (67.5) *	53 (84.1) §
Duration of hypertension(years±SD)	6.6±5.5	8.2±7.2 *	6.7±5.3
Known hyperlipidemia [n(%)]	180 (43.3)	214 (39.9)	33 (52.4) ‡
Family cardiovascular risk [n(%)]	168 (40.4)	162 (30.2)	30 (47.6) ‡
Family history of diabetes [n(%)]	264 (63.5)	289 (53.9)	42 (66.7)
Systolic blood pressure (mmHg±SD)	138.0±20.8	142.0±20.9 *	142.0±19.7 §
Diastolic blood pressure (mmHg±SD)	83.5±11.4	86.0±12.2 *	84.6±11.0
Serum creatinine (mg/dl±SD)	1.9±2.5	2.5±3.4 *	3.4±3.4 §
Urine albumin (mg/l±SD)	1.5±0.6	2.9±0.8*	3.3±0.9§‡
Urine creatinine (mg/dl±SD)	3.6±0.9*§	1.3±0.7‡	0.2±0.2§
HbA1c (%±SD)	7.4±1.7	8.0±2.3 *	8.7±2.9‡ §

Data are n (%) or mean (SD); BMI, body mass index; HbA1c, glycated haemoglobin. * $p<0.05$, microalbuminurics *vs.* normoalbuminurics; § $p<0.05$, macroalbuminurics *vs.* normoalbuminurics; ‡ $p < 0.05$, microalbuminurics *vs.* macroalbuminurics.

risk was significantly less than in macroalbuminuric patients (p<0.05). In patients with macroalbuminuria, duration of diabetes, history of hypertension and smoking, systolic blood pressure, serum creatinine and HbA1c were significantly higher than in normoalbuminurics, but the mean weight of the patients with macroalbuminuria was significantly less than patients with normoalbuminuria and microalbuminuria (p<0.05) (Table 3).

Comorbidities, left ventricular hypertrophy, coronary artery disease, diabetic foot lesions, other kidney disease beside diabetes, number of patients with one or two comobidities were significantly more prevalent in macroalbuminurics and microalbuminurics than normoalbuminurics (p<0.05). Congestive heart failure was more frequently seen in macroalbuminurics, and diabetic retinopathy in microalbuminurics than in normoalbuminurics (p<0.05). Number of patients with one co-morbidity, peripheral vascular disease, diabetic foot lesions, diabetic retinopathy, other kidney disease besides diabetes, chronic renal failure were significantly higher in macroalbuminuric than in microalbuminuric patients (p<0.05) (Table 4).

The treatment modalities of diabetic subjects grouped according to their level of albuminuria are presented in Table 5. Use of insulin, antihypertensives (especially ACE inhibitors), and antiaggregating agents (especially other than warfarin or aspirin) were significantly more frequent in macroalbuminurics and microalbuminurics than in normoalbuminurics. Diuretics were more oftenly used in patients with microalbuminuria than in normoalbuminuria, whereas patients with normoalbuminuria were more frequently treated with oral antidiabetic agents than patients with microalbuminuria and macroalbuminuria. Combined therapy with insulin and oral antidiabetic agents, calcium channel blockers, and aspirin were more frequently used in macroalbuminurics than in normoalbuminurics; whereas ATI-receptor blockers in normoalbuminurics than in subjects with macroalbuminuria (p<0.05).

Use of oral antidiabetic agents, and ATI-receptor blockers were more often in microalbuminuric- than in macroalbuminuric subjects; and antiaggregating therapy (especially with warfarin or aspirin) vice versa (p<0.05).

Macroalbuminuria was diagnosed in 5.2% of female, 6.5% of male subjects, the same rates for microalbuminuria were 48.0% vs 48.2%. The rates of microalbuminuria were significantly higher in subjects with hypertension (49.6 % and 41.1 % in hypertensive and non-hypertensive subjects, respectively and p<0.050). The serum creatinine were normal in 76.7% of subjects, elevated in 21.0%, and suggesting chronic renal failure in 2.3%.

Table 4: Complications and comorbidities in study population according to the albuminuria.

Complications	Normo-Albuminurics	Micro-Albuminurics	Macro-Albuminurics
Comorbidities [n(%)]	81 (19.2)	131 (24.4) *	25 (39.6) ‡§
LVH	21(5.1)	48 (8.9) *	10 (15.9) ‡ §
CAD	27 (6.5)	47 (8.8) *	9 (14.3) ‡§
MI	21(5.1)	28 (5.2)	8 (12.7) ‡§
CHF	12 (2.9)	21 (3.9)	5 (8.3) ‡§
Stroke, TIA	7 (1.7)	14 (2.6)	4 (6.4)
PVD	9 (2.2)	15 (2.8)	12 (19.1) ‡ §
1 co-morbidity	70 (16.8)	100 (18.7) *	44 (69.8) ‡ §
2 co-morbidity	12 (2.9)	27 (5.0) *	4 (6.4) §
3 co-morbidity	1 (0.2)	6 (1.1)	1 (1.6)
>3 co-morbidity	-	2 (0.4)	3 (4.8) ‡
Diabetic foot lesion [n(%)]	15 (3.6)	53 (9.9) *	13 (20.6) ‡§
Diabetic retinopathy [n(%)]	62 (14.9)	148 (27.6) *	26 (41.3) ‡§
Other kidney disease besides diabetes [n(%)]	12 (2.9)	30 (5.6) *	11 (17.5) ‡§
Chronic renal failure [n(%)]	29 (6.9)	51 (9.5)	15 (23.8) ‡§

LVH, left ventricular hypertrophy; CAD, coronary artery disease; MI, myocardial infarction; CHF, congestive heart failure; TIA, transient ischemic attack; PVD, peripheral vascular disease. * p<0.05, microalbuminurics vs. normoalbuminurics; § p<0.05, macroalbuminurics vs. normoalbuminurics; ‡ p < 0.05, microalbuminurics vs. macroalbuminurics.

DISCUSSION

There is strong evidence that hyperglycemia plays the key role in the pathogenesis of diabetic nephropathy. Some mechanisms such as metabolic (hyperglycemia, AGEs, poliol pathway), hemodynamic (systemic hypertension, glomerular hypertension) and signalization pathways (PKC, MAPK) and mediators (TGF-b1, CTGF, angiotensin II) have been suggested that link hyperglycemia to the functional and structural abnormalities of diabetic kidney disease (**25**). Subjects with diabetic nephropathy have a reduced life span, more comorbid events (such as more serious cardiac and peripheral vascular disease) than do diabetic subjects without nephropathy; events that significantly affect the subjects' lifestyle and ability to work. Management of diabetes and comorbidities, such as dyslipidemia, hypertension, anemia, and others, are important in preventing cardiovascular and renal events in patients with diabetic nephropathy. Microalbuminuria is an independent predictor of cardiovascular disease and all-cause mortality in both diabetic (26) and nondiabetic men and women (27). Screening for microalbuminuria is an important tool to identify people who are at high risk for cardiovascular events and progression of kidney disease, and who need more intensive therapy compared with subjects with normal albumin excretion rates (24). The ADA and the National Kidney Foundation define microalbuminuria as an A/C ratio of 30 to 300 μg/mg in both men and women (23,24). The A/C ratio is a more convenient test for subjects and may be less prone to errors due to improper collection methods and variations in 24-h protein excretion compared with a random urine specimen (24,28).

We report data in a large cohort of primary care subjects who have type 2 diabetes. Microalbuminuria which is the earliest detectable manifestation of diabetic kidney disease was determined approximately in two-third of the study population. There was one report about the prevalence of microalbuminuria in a small cohort from Turkey where overall prevalence of microalbuminuria was 21.7 % in a subgroup of diabetic patiens (29). Studies in the white UK population revealed a prevalence of microalbuminuria

Table 5: The treatment modalities in study population grouped according to the level of the albuminuria.

Parameters	Normo-Albuminurics	Micro-Albuminurics	Macro-Albuminurics
Anti-diabetic therapy [n(%)]			
Oral antidiabetic agents	343 (82.5) *§	385 (71.8) ‡	36 (56.5)
Insulin	43 (10.3)	104 (19.4) *	16 (29.7) ‡§
Both	16 (3.8)	26 (4.9)	4 (6.5) §
Anti-hypertensive therapy [n(%)]	270 (64.9)	410 (76.5) *	51 (80.9) §
Diuretics	57 (13.7)	83 (15.5) *	12 (18.8) §
ACE-inhibitör	121 (29.1)	214 (39.9) *	29 (45.8) §
Alpha-blocker	4 (1.0)	12 (2.2)	1 (1.6)
Calcium-channel blockers	60 (14.4)	92 (17.2)	15 (24.3) §
ATI – receptor blockers (ARBs)	95 (22.8) §	129 (24.1) ‡	11 (17.4)
Beta-blockers	27 (6.4)	34 (6.3)	4 (6.3)
Others†	3 (0.7)	8 (1.5)	1 (1.6)
Lipid therapy [n(%)]			
Statins	148 (35.6)	203 (37.9)	25 (39.6)
Others	22 (5.3)	22 (4.1)	2 (3.2)
Antiaggregating therapy [n(%)]	172 (41.4)	254 (47.4) *	40 (63.9) ‡§
Warfarin	-	3 (0.6)	3 (4.8) ‡
Aspirin	166 (39.9)	231 (43.1)	34 (54.2) ‡§
Other drugs	6 (1.4)	20 (3.7) *	3 (4.8) §

* p<0.05, microalbuminurics *vs.* normoalbuminurics; § p<0.05, macroalbuminurics *vs.* normoalbuminurics; ‡ p < 0.05, microalbuminurics *vs.* macroalbuminurics. † : ACEI + diuretic or ARB+ diuretic.

of 7%–9% (30,31), 31% in Mexican Americans (32), 26% in Pima Indians (33), 42% in Nauruans (34), and 35% in Hispanic Americans (35) in diabetes. The microalbuminuria prevalence in diabetic subjects varies among different ethnic groups, ranging from 19 to 36% in Caucasians (36,37), 26 to 64 % in Polynesians (38), and 25 to 36 % in African-Americans (39,40). Reported microalbuminuria prevalence in U.S. in those without diabetes has ranged from 3.4 to 13%, but these studies vary in the ethnic groups and age ranges studied (41,42).

The overall global prevalence of microalbuminuria, and macroalbuminuria are reported as 39%, and 10%, respectively in DEMAND Study (22). In the Turkish cohort the same parameters were 48.1% vs 5.7%, respectively. The prevelance of microalbuminuria in our population was seen higher than found globally in DEMAND Study.

In the present study, age, weight, duration of diabetes, history and duration of hypertension, systolic and diastolic blood pressure, serum creatinine levels, HbA1c are found as important clinical and metabolic characteristics of microalbuminuria. On the other hand, diabetic foot lesions, diabetic retinopathy and co-morbidities, especially LVH and CAD, are detected more often in microalbuminurics. Some studies have revealed duration of diabetes, male sex, and pre-existing retinopathy as major risk factors for microalbuminuria (10,32). Gupta *et al* reported HbA1c to be associated with microalbuminuria (43). John *et al* found male sex, older age, longer duration of diabetes, poor glycaemic control, and raised blood pressure as risk factors of microalbuminuria (44), while Vijay *et al* declared duration of diabetes, systolic and diastolic blood pressure, age of the patient, and serum creatinine to be associated with proteinuria (45). Age was reported as one of the risk factors in the Wisconsin Study (10), in a Danish population study (46), and in the Pima Indians (47). The association of glycaemic control with microalbuminuria has been well established by various studies (10, 32, 46, 47). Other factors which are reported to be associated with microalbuminuria are alcohol intake (10), foot ulcers (48), and smoking (49).

Microalbuminuria has also been reported to be associated with generalized vascular disease (50). Subjects with microalbuminuria who progress to macroalbuminuria (>300mg/24 h) are likely to progress to ESRD over a period of years (51,52). Microalbuminuria in diabetic subjects has not only been recognized as a predictor of progression of diabetic nephropathy but also as a powerful independent risk factor for cardiovascular disease (9, 53-57).

There is no doubt that poor glycemic control is associated with diabetic nephropathy. Levels of hemoglobin HbA1c are higher in subjects with microalbuminuria and macroalbuminuria than in those with normoalbuminuria (28), and in two longitudinal studies, the glycemic control predicted the future development of microalbuminuria in normotensive type 1 diabetic subjects with normoalbuminuria (56,58). The Diabetes Control and Complications Trial (DCCT), a prospective multicenter randomized clinical trial comparing the effect of intensive and conventional insulin therapy on the risk of development and progression of diabetic chronic complications in 1,441 subjects with type 1 diabetes. It has been demonstrated that a sustained improvement in HbA1c reduces the risk of development of diabetic nephropathy (59). Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) has shown that improved glycemic control is effective in the prevention of microalbuminuria in subjects with newly diagnosed type 2 diabetes (60). Thus, the prevention of elevated urinary albumin excretion is an important therapeutic target for the prevention of renal and cardiovascular events, and it continues to be important to explore modifiable factors that affect microalbuminuria. Combined beneficial effect of three factors - glycemia, blood pressure, and lipid profiles - on regression/remission of microalbuminuria has been shown (61). Thus, recommended therapeutic goals are clinically reasonable and effective reduction of elevated urinary AER in diabetic subjects. Subjects with microalbuminuria has been treated with insulin (19.4 %), antihypertensive drugs (76.5 %, ARBs 24.1 %, ACE-inhibitors 39.9 %), statins (37.9 %) and antiaggregants (47.4 %). These findings suggest that these therapeutic modalities are used in low rates. Thus, these may be among the responsible factors for developing microalbuminuria which is highly prevalent in our study population.

In conclusion, a high prevalence of microalbuminuria (48.1 %) associated with enhanced renal and cardiovascular risk, were detected in type 2 diabetic subjects without previously known nephropathy. A high level of urinary albumin appears to be related to general vascular dysfunction and particularly endothelial anomalies which allow macromolecules to leak through the endothelial barrier into the renal and retinal tissue. Microalbuminuria is undoubtedly the result of complex interactions between endocrine, metabolic, and hemodynamic factors.. Diabetic nephropathy is rarely seen in the first 3 years following the diagnosis of diabetes. It is usually detected after 5 to 15 years in subjects with type 1 diabetes (16); but the screening should begin at the time of diagnosis in subjects with type 2 diabetes because the actual duration of their disease is not known. This study suggest that early detection, monitoring of vascular complications and more aggressive multifactorial treatment aiming at renal and vascular protection are needed. Population-based screening and aggressive measures should be undertaken to lower the burden of microalbuminuria and diabetes mellitus in our country and others.

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APPENDIX

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