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Can Urinary Total Protein-to-Creatinine Ratio Determine the Presence of Micro albuminuria in Patients with eGFR> 60 ml/ml/min/m²?

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Abstract

Objective

To determine the relationship between spot urine total protein-to-creatinine ratio (TPCR) and albumin-to-creatinin ratio (ACR) in diabetic and/or hypertensive patients with estimated glomerular filtration rate (eGFR) greater than 60 ml/min/m² and to determine the optimal TPCR value that can predict microalbuminuria.

Methods

190 diabetic and/or hypertensive patients who had eGFR ≥ 60 ml/min/1.73 m² were studied. Urine dipstick test, spot urine TPCR and ACR values of the patients were evaluated.

Results

A strong positive correlation was found between ACR and TPCR ($p<0.001$; $r=0.565$). The optimal cut-off value for TPCR was 119 mg/g. Sensitivity, specificity and AUC for this cut-off value were 83%, 69% and 0.811, respectively. According to the dipstick test, only 20.9% of the patients had microalbuminuria in the urine protein negative group.

Keywords: Microalbuminurial; Proteinuria; Estimated glomerular filtration rate

Introduction

Microalbuminuria is an independent risk factor for cardiovascular diseases and renal complications and assessment of urinary albumin excretion is recommended in patients with risk factors for hypertensive, diabetic and cardiovascular disease [1-3]. In addition, the presence of micro albuminuria is associated with an increased incidence of cardiovascular disease in the general population [4,5]. Reduction of albuminuria by using renin angiotensin system (RAS) blockade improves renal and cardiovascular outcomes [6].

Albuminuria is more reliable than proteinuria in showing the presence of renal damage [7]. Measuring the amount of albumin/protein in 24 h urine is the gold standard in assessing albuminuria/proteinuria [7]. However, this method is difficult and impractical. Guidelines recommend that the ratio of urinary total protein or albumin to urinary creatinine is the optimal method [7,8]. The urine dipstick test is a cheap, fast and widely used test. However, the ability of dipstick test to detect proteinuria/albuminuria has not been adequately evaluated.

Micro-albuminuria measurement is a preferred method compared to measuring urinary total protein creatinine ratio, but it limits the use of this test because it is time consuming and costly [9,10]. The association between proteinuria and albuminuria has been shown in many studies [11-15]. The cut-off value that predicts the micro-albuminuria of TPCR has been determined only in a limited number of studies [14,15].

The aim of this study was to determine the relationship between TPCR and microalbuminuria in diabetic and/or hypertensive patients with eGFR greater than 60 ml/min/m² and to determine the TPCR value that can predict micro-albuminuria.

Materials and methods

Patients who admitted to our nephrology outpatient clinic during the six-month period (01.01.2016-31.06.2016) and who had spot urinary total protein creatinine ratio, spot urine albumin creatinine ratio and dipstick test were retrospectively analyzed. Patients with a glomerular filtration rate below 60 ml/min/m² were not included in the study. Patients with 3+ protein in the dipstick test and patients with urinary tract infection (pyuria and/or hematuria in dipstick test) were excluded from the study. Patients with an ACR value above 300 mg/g or with a TPCR value above 1000 mg/g were also excluded from the study.

Patients' laboratory (serum creatinine, eGFR, serum albumin, TPCR, ACR) and demographic characteristics (age, gender,

presence of diabetes mellitus and hypertension) were recorded. According to the results of dipstick protein, patients were divided into 4 groups as negative, trace, 1+ and 2+. TPCR and ACR values were expressed as milligrams per gram of creatinine. The microalbuminuria was defined as an ACR of 30-300 mg/g. Normoalbuminuria was defined as an ACR less than 30 mg/g, and macroalbuminuria was defined as an ACR greater than 300 mg/g. The eGFR was calculated using the 4-variable MDRD Formula [16].

Statistical analysis was performed using the SPSS 15 program. Continuous variables were expressed as mean ± SD, and intermittent variables were expressed as number (%). The comparison of the frequency of albuminuria between groups was done by chi-square test. Spearman correlation analysis was used to determine the relationship between ACR and TPCR. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal TPCR value to predict microalbuminuria. Sensitivity and specificity were calculated according to the Likelihood ratio test. A value of $p<0.05$ was considered statistically significant.

Results

Microalbuminuria was detected in 76 (40%) of the 190 patients studied. The proportion of diabetic patients was 57.4%. The frequency of microalbuminuria in diabetic and non-diabetic patients was 45.9% and 32.1%, respectively. The demographic and laboratory characteristics of the patients in the study (Table 1).

The microalbuminuria and normoalbuminuria frequency of patients who were divided into 4 groups by the dipstick test protein results are shown in Table 2. According to the dipstick test, only 20.9% of the patients had microalbuminuria in the urine protein negative group, but this ratio increased with dipstick test protein level, and microalbuminuria was observed in all of the patients in group 4.

There was a strong positive correlation between ACR and TPCR ($p<0.001$; $r=0.565$). According to the ROC analysis, the optimal cut-off value for TPCR predicting microalbuminuria was 119 mg/g. Sensitivity, specificity and AUC for this cut-off value were 83%, 69% and 0.811%, respectively (Figure 1). At the 150 mg/g cut-off value suggested in the guidelines, the sensitivity value decreased to 59% but the specificity value increased to 79%.

Table 1: General Characteristics of Patients (GFR: Glomerular Filtration Rate; TPCR: Total Protein-to-Creatinine Ratio; ACR: Albumin-to-Creatinine Ratio).

Characteristic	N:190
Age (years)	51.1 ± 13.2
Gender (female/male)	133/57
Albuminuria Microalbuminuria (%) Normoalbuminuria (%)	40 60
Serum creatinine (mg/dl)	0.82 ± 0.14
GFR (ml/dk/1.73 m²)	88.48 ± 17.96
TPCR (mg/g)	158 ± 117
ACR (mg/g)	52.3 ± 70.9
Serum albumin (g/dl)	4.5 ± 0.3
Diabetes mellitus (%)	57.4
Hypertension (%)	56.3
Dipstick protein Negative (%) Trace (%) 1+ (%) 2+ (%)	73.7 13.7 9.5 3.2

Table 2: Albuminuria Distribution in Dipstick Protein Groups* (*$p<0.001$).

	Negative (N:140)	Trace (N:26)	1+ (N:18)	2+ (N:6)
Normoalbuminuria (N:114)	111 (%79.3)	2 (%7.7)	1 (%5.6)	0 (%0)
Microalbuminuria (N:76)	29 (%20.7)	24 (%92.3)	17 (%94.4)	6 (%100)

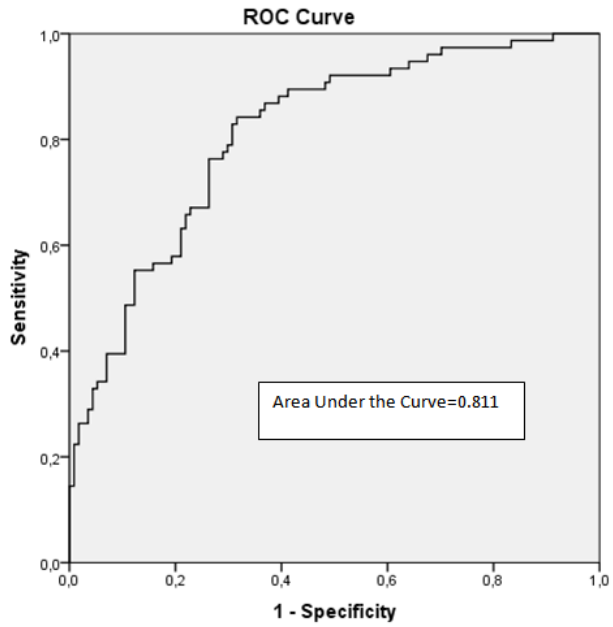

Figure 1: ROC curve analysis for the total urinary protein-to-creatinine ratio and albuminuria.

Discussion

In this retrospective study, it was found that there was a strong positive correlation between ACR and TPCR in diabetic and/or hypertensive patients with eGFR greater than 60 ml/min/m², and TPCR were predictive of microalbuminuria. The optimal cut-off value for predicting microalbuminuria for TPCR was found to be 119 mg/g creatinine. Various studies have reported positive correlation between TPCR and ACR [13-15]. For the first time, the study of Yamamoto et al. [15] has shown that TPCR measurement in diabetic patients predisposes to the presence of microalbuminuria. Similarly, in a study involving diabetic or non-diabetic patients with risk factors for cardiovascular disease, a strong positive correlation was found between TPCR and ACR, and it was shown that the presence of microalbuminuria could be detected by measuring TPCR [14]. Optimal TPCR cut-off values predicting microalbuminuria in these studies were 91 mg/g creatinine and 84 mg/g creatinine, respectively [14,15].

Because urinary albumin excretion shows circadian rhythm, measuring the amount of albumin in 24-hour urine is the gold standard for the determination of albuminuria [7]. However, the 24-hour urine collection is a test that is both impractical and questionable if it is collected correctly. Easier and more practical alternatives are the use of morning urine or spot urine specimens. It is suggested by the guidelines that the correction of spot urinary total protein/albumin with urine creatinine is the optimal method for the determination of proteinuria/albuminuria [7,8]. In a study in which diabetic patients were included and in which 24 h urine albumin levels were compared with spot urine ACR values, it was shown that ACR can diagnose microalbuminuria with high sensitivity and specificity and can be used to diagnose diabetic nephropathy in clinical practice [17].

The normal upper limit of urinary total protein excretion for adults is 150-200 mg/day [18]. According to the KDIGO/CKD guidelines, 150 mg/g creatinine for TPCR equals 30 mg/g creatinine for albuminuria [19]. In this study, the sensitivity and specificity of optimal cut-off value of 119 mg/g creatinine determined for TPCR according to ROC analysis were 83% and 69%, respectively. The sensitivity and specificity of the 150 mg/g cut-off value suggested in the guidelines for TPCR in predicting microalbuminuria in this study population were 59% and 79%, respectively.

Routine dipstick test is a cheap, quick-acting and widely used test, but microalbuminuria cannot be detected with this method. The clinical significance of trace protein in the dipstick test is unclear. Several studies have suggested that trace proteinuria may be a significant marker of albuminuria in diabetic patients [20,21]. It has been reported that presence of trace protein in the dipstick test may be useful in demonstrating microalbuminuria in the general population, especially in those with risk factors for cardiovascular disease [22,23]. Similarly, in this study 92.3% of patients with trace protein in the urine dipstick test were found to be microalbuminuric. However, a positive urinary dipstick test shows the presence of microalbuminuria with high specificity but low sensitivity [24]. For this reason, the dipstick test alone is not a suitable method for determining renal damage.

The limitations of this study were that the number of patients was low, TPCR and ACR values were evaluated by one measurement, and repeated measurements were not performed for proteinuria/microalbuminuria.

Conclusions

The presence of microalbuminuria can be determined by TPCR measurement in the majority of diabetic and / or hypertensive patients whose eGFR is > 60 ml/min/m². To find the optimal TPCR cut-off value to determine microalbuminuria, additional studies with a high number of cases are needed.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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