Diagnostic efficacy of random albumin creatinine ratio for detection of micro and macro-albuminuria in type 2 diabetes mellitus

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ABSTRACT

الأهداف: يعتبر إختبار إفراز الزلال في البول لمدة 24 ساعة الإختبار المثالي لتقييم الضرر الكلوي. وقد أجريت هذه الدراسة لتقييم فاعلية إختبار نسبة الزلال إلى الكرياتينين في البول العشوائي لتقييم الضرر الكلوي في المرضي الذين يعانون من النوع الثاني من داء السكري.

الطريقة: قد أجريت هذه الدراسةالإستعادية في الفترة ما بين مارس 2013و يونيو 2014 و تكونت الدراسة من مجموعة من مرضى الداء السكري النوع الثاني عددهم 122 (متوسط العمر 15±54 : 104 من الإناث و 18 من الذكور). مستوى الألبومين في البول الأقل من 30 مج / ج قد تم إعتباره طبيعي بينما قد تم إعتبار القيم التي تتراوح بين 300-30 و الأكبر من 300 مرضى ببيلة الألبومين الجزئي و الكلي بالترتيب.

النتائج: لوحظ التوافق بين كلا الإختبارين في 114 عينة (93.4%) و كانت حساسية إختبار إفراز الزلال في البول لمدة 24 ساعة 100%, ، وكانت النوعية 91.3% بقيمة التنبؤ الإيجابية 95%, وقيمة التنبؤ السالبة 100% في حالات بيلة الألبومين الجزئي. وفي حالات بيلة الألبومين الكلي كانت حساسية إختبار إفراز الزلال في البول لمدة 24 ساعة 100%،وكانت النوعية 94.1% وقيمة التنبؤ الإيجابية 76% وقيمة التنبؤ السالبة 100%. تحليل متلقى منحنى التشغيل باستخدام قيم القطع 40 ملغ / غ في حالات بيلة الألبومين الجزئي و 300 ملغ / غ لمرضى ببيلة الألبومين الكلي. في حالات بيلة الألبومين الجزئي كانت حساسية إختبار إفراز الزلال في البول لمدة 24 ساعة 100%، وكانت النوعية 97.5% بقيمة التنبؤ الإيجابية 95% وقيمة التنبؤ السالبة 100 مع 100% مساحة تحت المنحنى. وفي حالات بيلة الألبومين الكلي كانت حساسية إختبار إفراز الزلال في البول لمدة 24 ساعة 100%،وكانت النوعية 94% وقيمة التنبؤ الإيجابية 76% التنبؤ السالبة 100% السالبة 100% مع 98.2% مساحة تحت المنحنى.

الخاتمة: نتائج إختبار إفراز الزلال في البول العشوائي كانت متوافقة مع نتائج إختبار إفراز الزلال في البول لمدة 24 ساعة بإستثناء القصور الكلوي في المرضي الذين يعانون من النوع الثاني من داء السكري.

الكلمات الأساسية: الألبومين ، الكرياتينين ، داء السكري ، بيلة الألبومين الجزئي

Objectives: To compare a less cumbersome random albumin creatinine ratio (RACR) with 24-hour urinary albumin excretion (UAE) for detection of renal damage in patients with type 2 diabetes mellitus (T2DM).

Methods: This retrospective study performed between March 2013 and June 2014 at the Department of Pathology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia included 122 patients (mean age 54±15, 104 females and 18 males) with T2DM. Urine albumin levels of <30 mg/g was considered normal, from 30-300 mg/g considered as micro-albuminuria, and over 300 mg/g considered as macro-albuminuria.

Results: Concordance between the 2 assays was observed in 114 (93.4%) samples. The sensitivity of RACR assay was 100%, specificity was 91.3% with a positive predictive value (PPV) of 95%, and a negative predictive value (NPV) of 100% in micro-albuminuria range. For macro-albuminuria, RACR had a sensitivity of 100%, specificity of 94.1% with PPV of 94% and NPV of 100%. Receiver operating characteristic (ROC) curves analysis cut-off values of 40 mg/g-300 mg/g for micro- and >300 mg/g for macro-albuminuria revealed 100% sensitivity, 97.5% specificity, 95% PPV, and 100% NPV for micro-albuminuria, and 100% sensitivity, 94% specificity, 76% PPV, and 100% NPP for macro-albuminuria. The area under the curve for micro-albuminuria was 100% and 98.2% for macro-albuminuria.

Conclusion: Performance of RACR was comparable to 24 hour UAE assay particularly in excluding renal damage in T2DM.

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Diabetes related chronic kidney disease (CKD) is among the serious micro-vascular complications of type 2 diabetes mellitus (T2DM), and is a leading cause of end-stage renal disease.[1] Between 30-40% of patients with diabetes develop CKD that manifests as albuminuria, or decreased glomerular filtration rate.[2-4] The prevalence of diabetes-related CKD is increasing alongside the prevalence of diabetes all over the world.[5] Micro-albuminuria is a term used for a relatively small amount of albumin excretion in urine in the early stages of CKD in diabetics. This may progress to overt proteinuria in 20-40% of diabetics in 10 years culminating in end-stage renal disease in approximately 20% of patients.[6,7] The presence of diabetes, irrespective of new-onset, or previously diagnosed diabetes poses a 2.5 fold increased risk of albuminuria.[8] Screening for micro-albuminuria early in the disease particularly in T2DM is, therefore, critical in salvaging kidneys as it is a potentially reversible form of kidney injury.[9] The gold standard for assessment of albuminuria is the estimation of albumin concentration in a urine sample collected over 24-hours as the outcome will not be affected by the variations in protein excretion during the day.[10,11] This procedure, however, has several limitations, such as sample collection errors on part of the patient, poor compliance, extended duration of sample collection, and is not cost effective.[12-14] Since the excretion of creatinine and protein remains constant if the glomerular filtration is stable[15] measurement of protein to creatinine in a spot, or random urine sample would not be affected by the variations in protein and albumin excretion in urine samples.[16] Measurement of random urine albumin creatinine ratio (RACR) has been evaluated in a number of studies demonstrating a close relationship with 24-hour protein excretion.[17,18] The existing data, however, falls short of certainty with which RACR might be used to rule in, or rule out proteinuria. This study was performed to assess the performance of RACR against the gold standard estimation of 24-hour urinary albumin excretion (UAE) for detection of micro-albuminuria in Saudi patients with T2DM.

Methods. This retrospective study of 122 Saudi patients with T2DM was performed at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia between March 2013 and June 2014. Along with the demographic details data for 24 hours UAE, the RACR were extracted from patient records. This group of patients included 104 female and 18 male patients with the mean age of 54 ± 15 years. All the patients included in the study had been diagnosed as having diabetic CKD for at least one year and patients suffering from hematuria, acute infections particularly urinary tract infections, and pregnant females were excluded from the study. Out of the total, 110 (90%) patients were suffering from hypertension, and among them, 101 (92%) were receiving renin angiotensin aldosterone system suppressive therapy, and 9 (8%) patients were being treated with ß receptor blocking medicines. The mean systolic blood pressure of the patients was 135 ± 16 mm Hg, and the mean diastolic blood pressure was 74 ± 10 mm Hg. Hemoglobin A1c (HbA1c) level of the group was 8.6 ± 1.7% and the mean body mass index of the group was 31.1 ± 6.6 kg/m^2. The mean duration of illness was 13 ± 8 years. Random urine sample for assessment of albumin-creatinine ratio was collected as midstream urine sample at the time of patient visit to the clinic. For the collection of 24 hours urine specimen in the following 24 hours, all participants were instructed to begin collection after discarding first morning urine until the collection of first voided urine sample next morning in the receptacle provided. Patients were instructed to avoid strenuous muscular activity during the collection of 24 hours urine sample. Urine albumin and creatinine levels were determined by turbidimetric immunoassay and photometric assays respectively using Roach Cobas analyzer (Basal, Switzerland). Urine albumin level of less than 30 mg/g was considered normal, micro-albuminuria was defined as any value between 30 to 300 mg/g and albuminuria more than 300 mg/g was considered as macro-albuminuria. This study was approved by Institutional Review Board of the College of Medicine, King Saud University, Riyadh, King Saud University.

Statistical analysis. Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Version 19 for Windows was used for data analysis. The categorical data were summarized as numbers and percentages whereas continuous data were summarized as the mean and standard deviation. Group comparisons for continuous data were performed using t-test. The diagnostic accuracy of RACR was assessed by using sensitivity, specificity, positive predictive values and negative predictive values. A $p<0.05$ was considered statistically significant.

Results. Female preponderance was evident among the patients with 85.2% females and 14.8% males.

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Concordance between the 24 hours urine collection and RACR results was found in 114 (93.4%) samples. Discordant results were observed in 8 (6.5%) patients with RACR detecting micro-albuminuria in 5 patients and macro-albuminuria in 3 patients whereas 24-hour albumin excretion in these patients was normal and in micro-albuminuria range respectively. **Figure 1** show data for detection of micro and macro-albuminuria among the T2DM included in the study. Of the total 36 (29.5%) patients were found to have micro-albuminuria and 46 (37.7%) had macro-albuminuria when tested by both 24 hours UAE and RACR. A higher proportion of patients (16.3%) were found to have micro-albuminuria when tested by RACR compared to 24 hours urine albumin excretion (13.1%). Macro-albuminuria on the other hand was observed in higher proportion (16.3%) among patients tested by 24 hour UAE compared to those tested by RACR (13%).

Table 1 compares data for albumin estimation in 24 hours UAE urine samples and RACR with albumin concentrations of <30 mg/g, between 30-300 mg/g and above 300 mg/g. Below the cut-off level of <30 mg/g the mean urine albumin level detected by RACR (9.6 ± 7.1 mg/g) was significantly higher (p=0.03) than the mean urine albumin concentration detected in 24 hours urine samples (7 ± 5.4 mg/g). Between 30-300 mg/g range the mean urine albumin concentration measured by RACR was 80 ± 41 mg/g and in 24 hours urine sample it was 115 ± 73 mg/g which was devoid of any statistical significance (p=0.09). At the cut-off level of > 300 mg/g the means of urine albumin estimated by RACR (1615 ± 10 mg/g) and in 24 hours urine samples (1416 ± 85 mg/g) were no different (p=0.31). For the performance of RACR against 24 hours UAE data were analyzed using the predefined cut-off values of 30-300 mg/g for micro and >300 mg/g for macro-albuminuria and cut-off values of 40-300 mg/g for micro and >300 mg/g determined by receiver operating characteristic (ROC) curve analysis.

Figure 2 describes sensitivities and specificities of RACR using both cut-off levels. For the predefined cut-off levels of 30-300 mg/g RACR had a sensitivity of 100% and specificity of 91.3% whereas >300 mg/g RACR had a sensitivity of 100% and a specificity of 94.1%. Using the cut-off levels of 40-300 mg/g for micro and >300 mg/g for macro-albuminuria determined by ROC analysis the sensitivity of RACR for detection of micro-albuminuria was 100% and specificity was

Table 1 - Comparison of proteinuria among type 2 diabetes mellitus patients by random albumin creatinine ratio (RACR) and 24 hour urinary albumin excretion (UAE).

Albumin creatinine	Number of patients	Mean±SD	*P*-value
<30 cut-off level (mg/g)			0.039*
RACR	76	9.6±7.1	
24-hour UAE	80	7.0±5.4	
30-300 cut-off level (mg/g)			0.09
RACR	20	80±41	
24-hour UAE	22	115±73	
30-300 cut-off level (mg/g)			0.31
RACR	26	1615±10	
24-hour UAE	20	1416±85	

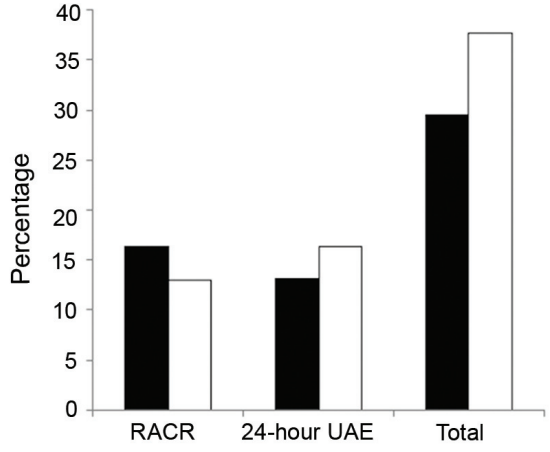

Figure 1 - Distribution of micro and macro-albuminuira among patients with type 2 diabetes mellitus assessed by random albumin creatinine ratio and 24 hour urine albumin excretion. RACR - random albumin creatinine ratio, 24 hr UAE - 24 hours urinary albumin excretion.

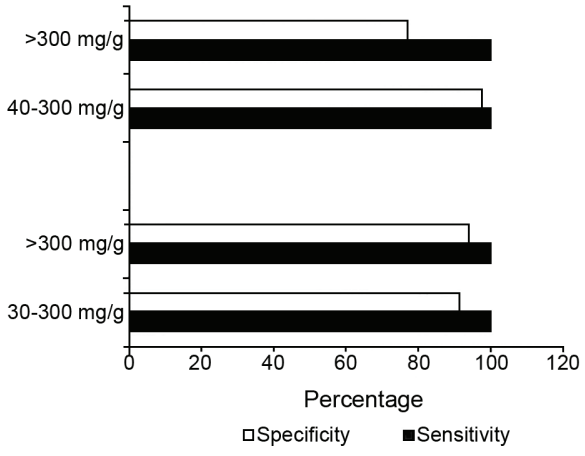

Figure 2 - Sensitivity and specificity of random albumin creatinine ratio method against 24 hour urinary albumin excretion assay in patients with type 2 diabetes mellitus with micro and macro-albuminuria using different cut-off levels.

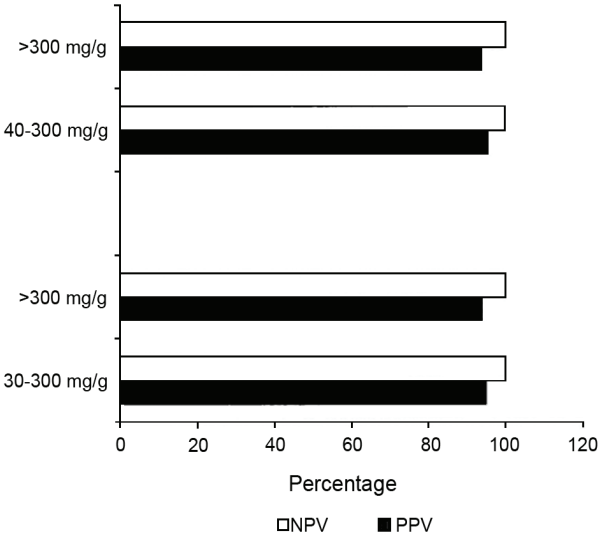

Figure 3 - Positive and negative predictive values for random albumin creatinine ratio method against 24 hour urinary albumin excretion assay in patients with type 2 diabetes mellitus with micro and macro-albuminuria using different cut-off levels.

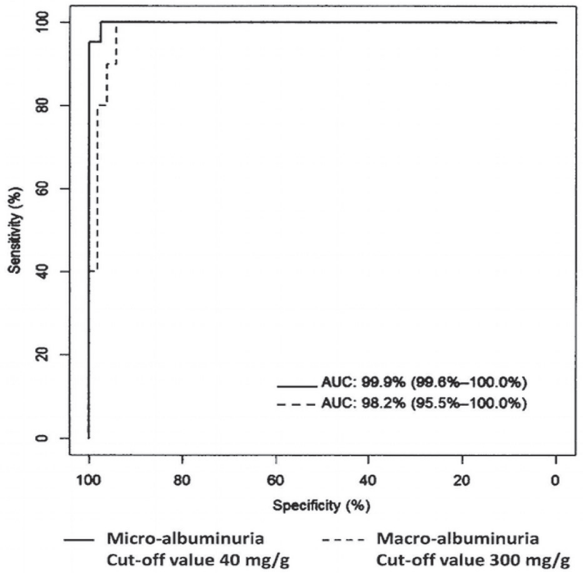

Figure 4 - Receiver operating characteristic curves analysis for the diagnostic accuracy of random albumin creatinine ratio of patients with T2DM.

97.5% whereas for macro-albuminuria the sensitivity was 100%, specificity was 76%.

Figure 3 shows positive and negative predictive values of RACR for both predefined and ROC analysis determined cut-off levels for micro and macro-albuminuria. RACR had a positive predictive value of 95% and negative predictive value of 100% between the range 30-300 mg/g and for albuminuria over 300 mg/g RACR had a positive predictive value of 94% and negative predictive value of 100%. RACR at a cut-off value of 40-300 mg/g had a PPV of 95% and NPV of 100% for micro-albuminuria and a PPV of 94% and NPV of 100% for macro-albuminuria. The area under the curve (AUC) for micro-albuminuria was 99.9% and for macro albuminuria the AUC was 98.2% (**Figure.** 4).

Discussion. A sizable proportion of patients with T2DM were found to have both micro (29.5%) and macro-albuminuria (37.7%) in the present study when tested by using both RACR and 24-hour UAE methods. Although the proportion of diabetics with micro-albuminuria in the present study was lower than the percentage of T2DM patients with micro-albuminuria (45.7%) observed in a recently published Spanish study, however, the concentration of urinary protein for micro-albuminuria was almost similar to that found in the present study.[19] The number of patients with micro-albuminuria and macro-albuminuria were comparable in the present study, however, in an Iranian study investigating proteinuria in T2DM, most of T2DM patients had macro-albuminuria compared to a rather small number of patients with micro-albuminuria detected by both RACR and 24 hours UA excretion.[20] These observations indicate racial and ethnic differences in occurrence of diabetic micro and macro-albuminuria. The presence of a number of confounding factors such as high prevalence rates of diabetes among various racial or ethnic populations,[21] differences in glycemic control[22] and the availability of healthcare facilities[23] are also believed to be among important factors contributing to racial and ethnic differences in diabetes related micro and macro-albuminuria. The cut-off level for micro-albuminuria (between 30-300 mg/g) and macro-albuminuria (>300 mg/g) used in the present study were similar to traditionally applied ranges.[24] Despite the general agreement of the cut-off levels the threshold of albuminuria has been under debate as the upper normal range of albuminuria much lower than the accepted lower cut-off value for micro-albuminuria has been considered as a strong predictor of cardiovascular complications frequently associated with T2DM.[25] Moreover, there is evidence that any degree of measurable albuminuria in patients with T2DM.[25] is a risk factor for cardiovascular morbidity and mortality.[26] Similarly urinary albumin-creatinine ratio of either equal to, or more than 5 mg/g a level traditionally not considered to be of any clinical relevance has also been shown to have an association with rapid decline

in cognitive functions.[27] Collectively these observations suggest that assessment of urinary albumin-creatinine ratio not only is useful for the classification of micro and macro-albuminuria, but may also be a very useful tool for monitoring the continuous variable.

The performance of RACR against the gold standard 24-hours UAE in this study was comparable both for micro and macro-albuminuria. A systematic review of 16 studies investigating proteinuria by comparing RACR and 24-hour UAE in renal diseases has revealed sensitivities between 69% and 96% and specificities between 41% and 97% of the tests with positive values ranging between 46% and 95%, and negative predictive values ranging between 45% and 98%.28 Using cut-off points applied in the present study, the RACR method has been shown to exhibit a sensitivity of 86% and specificity of 60% for micro-albuminuria, and sensitivity of 75% and specificity of 99% for macro-albuminuria screening in patients with T2DM.[20] The sensitivities of 100% both for micro and macro-albuminuria along with higher specificities detected in the present study were consistent with the previous reports supporting the efficacy of using RACR as an alternate, and a relatively simple test for assessment of proteinuria. In addition, the higher positive and negative predictive values for micro and macro-albuminuria using RACR as a screening test in the present study indicate the importance of this test in ruling-out proteinuria more confidently than ruling it in. This observation is in conformity with previously reported evidence[29] suggesting RACR performs better in ruling-out the presence of significant proteinuria.

The group of patients included in the present study comprised predominantly of female patients with T2DM. In an attempt to establish the normal upper limit of albumin-creatinine ratio female children were found to have a higher normal upper limit compared to the male children with an inverse correlation with age.[30] At 30 mg/g cut-off level sensitivities of both the tests appear to be lower in women compared with men necessitating a reduction in the existing thresholds that may compromise the specificity.[31] This was evident in the present study where a cut-off level of 40 mg/g for micro-albuminuria was associated with a higher specificity of 97.5%. A recent study investigating chronic kidney disease among patients with T2DM revealed that being female with T2DM is a significant risk factor for developing nephropathy.[32] Moreover, among women, abdominal obesity is considered as a predisposition for albuminuria irrespective of whether the obese women are hypertensive or diabetics suggesting that these individuals are at a higher risk for developing a renal or cardiovascular disease.[33] The preponderance of women in the present study could be primarily due to female predisposition to renal disease and the presence of diabetes.

The RACR method has been evaluated in a number of studies, and it has been recommended that it is a useful initial screening test for screening patients with diabetes with negligible omission rate as one in 8 patients will require 24-hour UAE estimation for confirmation of micro-albuminuria.[34] Moreover, RACR has been regarded as a best choice for diagnoses and screening of micro-albuminuria in patients with T2DM particularly for being an accurate and a cost effective test.[35] Collectively the existing evidence and the findings of the present study suggest that RACR appears to be a reliable and a useful tool for screening for proteinuria in T2DM, and is a less cumbersome method compared to 24-hour UAE estimation. This study was however limited by a small sample size and single evaluation in each patient. Moreover, most patients in the present study were females and the findings of this study may not be applicable to the male Saudi gender. Similarly, patients with orthostatic proteinuria could not be excluded from the study and may have contributed to discordant results observed in the present study. Large-scale studies are recommended addressing the limitations of the present study along with an assessment of at least 3 consecutive evaluations per patient for validation of the findings of the present study.

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