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Original Article

Evaluation of tests for microalbuminuria screening in patients with diabetes

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Abstract

Background. The first step in the diagnosis of diabetic nephropathy is to measure albumin in a spot urine sample. The aim of this study was to assess the accuracy of urinary albumin concentration (UAC), urinary albumin-to-creatinine ratio (UACR), and the Micral-Test II in a random urine specimen (RUS) for microalbuminuria screening in diabetes mellitus.

Methods. Two hundred and seventy-eight patients collected 24 h timed urine specimens followed by RUS. Albumin (immunoturbidimetry) and creatinine were measured in protein-negative (Combur-Test) urine samples. Samples were classified as normoalbuminuric [24 h urinary albumin excretion rate (UAER) $<20\,\mu g/min$; $n = 189$] and microalbuminuric (UAER = $20-199\,\mu g/min$; $n = 89$). Micral-Test II readings were performed in 130 RUS. Receiver operating characteristics (ROC) curves were constructed using UAER as the reference standard.

Results. The areas under the ROC curves were similar for UAC (0.934 ± 0.032) and UACR (0.920 ± 0.035; $P = 0.626$), but the Micral-Test II had lower accuracy to diagnose microalbuminuria (area = 0.846 ± 0.047) than UAC ($P = 0.014$). The first cutoff point with 100% sensitivity for UAC was 14.4 mg/l (specificity = 77.2%), and 15.7 mg/g for UACR (specificity = 73.0%). Concerning the Micral-Test II, sensitivity and specificity for the 20 mg/l cutoff point were 90.0 and 46.0%, respectively. The agreement between UAER and the Micral-Test II for microalbuminuria diagnosis was 55.8% ($\kappa = 0.22$; $P < 0.001$). The cost of diagnosing microalbuminuria was U$1.74 (UAC), U$2.00 (UACR) and U$4.09 (Micral-Test II) per patient.

Conclusions. Measurement of UAC in a RUS was the best choice for the diagnosis screening of microalbuminuria in diabetic patients, considering cost and accuracy.

Keywords: diabetes mellitus; diabetic nephropathy; Micral-Test II; microalbuminuria; screening tests; urinary albumin excretion rate

Introduction

Diabetic nephropathy (DN) should be detected and treated at the microalbuminuria stage, which is potentially reversible [1]. In addition to being the earliest stage of DN, microalbuminuria is associated with increased cardiovascular morbidity and mortality [2].

The first step in the screening for microalbuminuria should be the measurement of albumin in a urine sample by a reliable method: spot (first-morning or random sample), 24 h collection or timed collection [2]. Timed urine collection, although cumbersome, is considered the reference method, since it was used in the early studies [3–5], which established the predictive role of microalbuminuria for the development of overt nephropathy. The easiest way to screen for microalbuminuria is using a spot urine specimen [2]. When using a spot sample, the albumin-to-creatinine ratio is often determined [2,6–8]. Measuring albumin concentration alone in a spot urine sample has also been used by some [9] and recommended by others [6], but this method has been criticized [10]. We have previously observed that measuring albumin concentration in a random urine sample was as accurate as, and cheaper than, determining the albumin-to-creatinine ratio [9,11].

In clinical settings where a standard quantitative technique to measure urinary albumin is not available,

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a semi-quantitative test such as the Micral-Test II strip could be used to screen for microalbuminuria [2,12].

Therefore, the aim of this study was to evaluate the performance of urinary albumin concentration (UAC), urinary albumin-to-creatinine ratio (UACR) and albumin determination by the Micral-Test II strip in a random urine specimen (RUS) for the screening of microalbuminuria in patients with diabetes mellitus.

Subjects and methods

This is a study of diagnostic accuracy to evaluate three screening tests for microalbuminuria in a RUS. Measurements of timed 24 h urinary albumin excretion rate (UAER) were used as the reference standard.

Patients

Consecutive diabetic patients ($n = 531$) attending the Diabetes and Internal Medicine outpatient clinics at Hospital de Clínicas de Porto Alegre were prospectively recruited by one of the investigators (J. Incerti). Patients with proteinuria (positive Combur-Test in a random urine sample or proteinuria >500 mg/24 h), urinary infection (positive urine culture), clinical conditions causing dehydration (due to possibility of false positive results on albumin measurements) or any wasting diseases that could cause severe undernourishment were excluded. 278 patients were included in the final sample. Their main clinical features were as follows: 28 type 1 and 250 type 2 diabetic patients; 116 (41.7%) males; 57.3 ± 13.4 years of age (16–84 years); diabetes duration of 11.6 ± 7.7 years (1–45 years); BMI of 28.0 ± 11.1 kg/m^2; blood pressure levels of $139.8 \pm 23.5/81.8 \pm 11.9$ mmHg, and serum creatinine of 0.89 ± 0.26 mg/dl (0.5–2.0).

Informed consent was obtained from each patient and the Ethics Committee approved the protocol.

Urine samples and measurements

During their routine consultation, patients received written orientation for the collection of a 24 h timed urine sample. When patients returned to the clinic with the 24 h urine sample, a RUS was collected without any special recommendation. In this sample, a sediment analysis and a culture were performed, albumin and creatinine were measured, and Micral-Test II strip reading was carried out. Initially, 531 patients collected 531 24 h timed urine samples followed by 531 RUS collections. Both samples were excluded from the analysis if the RUS was not sterile ($n = 56$), if it was positive for total protein (Combur-Test positive) ($n = 50$), if more than five erythrocytes were observed per high-power field in the urinary sediment ($n = 0$), if sediment analyses were not performed ($n = 66$), if creatinine measurements were not performed ($n = 28$) or if the 24 h urine collection was considered to be incomplete (creatinine values <700 mg for women and <1000 mg for men; $n = 53$). Thus, 278 24 h and RUS samples were analyzed. The samples were classified as normoalbuminuric (UAER <20 μg/min) or microalbuminuric (UAER = 20–199 μg/min) according to UAER [2]. In addition, from the 278 RUS, 130 fresh urine samples were randomly selected and used for Micral-Test II strip readings, performed at room temperature by three investigators (J. Incerti, J. Lins Camargo and T. Zelmanovitz) blinded to the albumin content of the samples and to the patient's renal status. A subset of RUS ($n = 101$) was frozen (−20°C) for a repeated reading of Micral-Test II after 2 months.

Nineteen patients collected three 24 h timed urine samples followed by RUS to calculate intra-individual coefficients of variation (CVs) for urinary measurements.

Total protein measurement (semi-quantitative) was performed using the test strip Combur-Test (Boehringer Mannheim, Lewes, UK) read by an automated device (Meditron M; Boehringer Mannheim). Urinary albumin was measured in duplicate by immunoturbidimetry [MicroAlb SeraPak (Bayer, Tarrytown, NY) on Cobas Mira Plus (Roche)]. The mean intra- and inter-assay CVs were 4.5 and 7.6%, respectively. To control the quality of measurements, a subset of urines with known albumin concentration (90–112 mg/l) was simultaneously measured with all evaluated samples. The semi-quantitative test employed to measure albuminuria, Micral-Test II (Micral; Boehringer Mannheim GmbH, Mannheim, Germany), is a gold-labelled, optically read test strip. After 1 min reaction the colour result was visually compared with colour blocks on a chart attached to the vial, with colours representing 0, 20, 50 and 100 mg/l of albumin. According to the manufacturer, the colour corresponding to 20 mg/l indicates the presence of microalbuminuria. Creatinine in urine was measured by the Jaffé's reaction and the intra- and inter-assay CVs were 0.7 and 2.3%, respectively.

The cost (US currency) of microalbuminuria diagnosis per patient was calculated for UAC, UACR and the Micral-Test II, based on the cost of each test and the cost of diagnostic confirmation (UAER measurement).

Statistical analysis

The Receiver Operating Characteristic (ROC) curve approach was used to analyze the performance of the screening tests for microalbuminuria, considering the UAER as the reference standard. The true-positive rate (sensitivity) *vs* the false-positive rate (100-specificity) was plotted for each measurement. The estimated area under the fitted smooth curve ranges from 0.5 (no apparent accuracy) to 1.0 (perfect accuracy) as the ROC curve moves toward the left and top boundaries of the ROC graph. The first point with 100% sensitivity was chosen in each curve. Also, the point nearest to the intersection of the curve with the 100%-to-100% diagonal was determined. This represents the best equilibrium between sensitivity and specificity (point of equilibrium). In the curve constructed to analyze the performance of the Micral-Test II, the cutoff point of 20 mg/l (indicating presence of microalbuminuria) was considered. The κ coefficient was used to assess the agreement between Micral-Test II readings by different readers, and between the results of fresh and defrosted samples. $\kappa = 0$ defines no agreement and $\kappa = 1$ defines total agreement. ANOVA, followed by Bonferroni test or Kruskal–Wallis ANOVA, *t*-test or Mann–Whitney *U*-test (for albuminuria) were used as appropriate. Spearman's correlation coefficient was used for testing the relationships between albumin measurements in RUS and UAER, between albumin measurements and age. Intra-individual CVs for urinary albumin and creatinine measurements were calculated in 24 h urine specimens and RUS.

Data were shown as mean ± standard deviation and, to describe areas of the ROC curves, as mean ± standard error. Variables with a non-normal distribution were reported as median (range). The level of significance was set at 0.05. MedCalc for Windows (Mariakerke, Belgium) and SPSS 10.0 (SPSS, Chicago, IL) were used for the analyses.

Results

Among the 278 24 h urine samples, 189 were classified as normoalbuminuric [UAER = 6.2 (2.7–19.1) μg/min], and 89 as microalbuminuric [UAER = 60.8 (21.8–196.2) μg/min]. In the evaluation of the 130 urine samples submitted to the Micral-Test II, 100 of the respective 24 h urine collections were classified as normoalbuminuric [UAER = 6.47 (2.72–19.3) μg/min] and 30 as microalbuminuric [UAER = 53.38 (20.7–149.7) μg/min].

Correlation coefficients

The correlation coefficient (278 urine samples) was 0.76 for UAER *vs* UAC ($P < 0.0001$); 0.74 for UAER *vs* UACR ($P < 0.0001$); and 0.86 for UACR *vs* UAC ($P < 0.0001$). Age and 24 h creatinuria presented a negative correlation (278 patients; $r = -0.19$; $P = 0.002$). No correlation was observed between age and UAER ($r = 0.02$; $P = 0.74$), age and UAC ($r = 0.07$; $P = 0.22$) and age and UACR ($r = 0.11$; $P = 0.08$).

To evaluate the possible effect of ageing on 24 h creatinine, UAER, UAC and UACR, patients were divided according to age tertiles. The 24 h creatinuria was lower in the highest tertile (age ≥65 years) in relation to the first tertile (age <54 years) (1137.6 ± 313.7 *vs* 1294.9 ± 414.0 mg/24 h; ANOVA, $P = 0.037$; Bonferroni test for multiple comparisons, $P = 0.028$). On the other hand, the values of UAER [8.69 (2.72–173.4) *vs* 8.94 (3.12–196.17) μg/min *vs* 7.86 (3.16–163.59) μg/min; Kruskal–Wallis, $P = 0.587$], UAC [9.0 (4.8–245.8) *vs* 14.6 (5.0–565.3) *vs* 4.3 (5.0–568.0) mg/l; Kruskal–Wallis, $P = 0.56$], and UACR [14.7 (2.1–311.3) *vs* 16.7 (1.8–554.2) *vs* 17.8 (3.3–968.3) mg/g; Kruskal–Wallis, $P = 0.129$] did not differ among age tertiles.

Coefficients of variation

Intra-individual CVs for urinary measurements were calculated from sterile urine samples collected by eight normoalbuminuric (UAER = 6.15 (5.0–19.9 μg/min) and 11 microalbuminuric (UAER = 79.3 (24.4–192.0 μg/min) patients. Each patient collected three 24 h timed urine samples for UAER measurements and three RUS for UAC, UACR and creatinine measurements (57 timed urine collections and 57 RUS). The interval between collections was of 30.3 ± 11.8 days (6–69 days).

The intra-individual CVs for UAER, UAC and UACR were 32.1, 42.4 and 33.9%, respectively. The intra-individual CV for urinary creatinine measurements in RUS was 34.8%, and 11% in 24 h urine collection.

Table 1. Accuracy of UAC and UACR as screening tests for microalbuminuria in a random urine specimen in diabetic patients based on ROC curve analysis

	First cutoff point with 100% sensitivity	Point of equilibrium between sensitivity and specificity[a]
UAC	14.4 mg/l	29.7 mg/l
Sensitivity (%)	100	92.1
Specificity (%)	77.2	93.7
UACR	15.7 mg/g	32.0 mg/g
Sensitivity (%)	100	91.0
Specificity (%)	73.0	92.1
Men	15.7 mg/g	26.4 mg/g
Sensitivity (%)	100	92.0
Specificity (%)	75.8	87.9
Women	20.8 mg/g	32.0 mg/g
Sensitivity (%)	100	97.4
Specificity (%)	81.3	92.7

[a]Nearest point to the intersection of the curve with the 100%-to-100% diagonal in each ROC curve.

Performance of UAC, UACR and Micral-Test II in a RUS for the diagnosis of microalbuminuria

Table 1 shows sensitivity and specificity values of UAC and UACR based on ROC curve analysis ($n = 278$), considering two cutoff points for the diagnosis of microalbuminuria (first point with 100% sensitivity and point of equilibrium between sensitivity and specificity). The specificity of UAC and UACR was similar when considering the 100% sensitivity cutoff points. The sensitivity and specificity of the Micral-Test II strip for a 20 mg/l cutoff point (as indicated by manufacturer) on fresh urine samples based on ROC curve analysis ($n = 130$) were 90 and 46%, respectively. For defrosted samples ($n = 101$) the sensitivity was 85.2% and the specificity was 41.9%.

The comparison among the areas under the ROC curves for UAC, UACR and the Micral-Test II (Figure 1) took into account the individual results, for each single patient ($n = 130$), of the three screening methods being tested and of the reference test method (UAER). We observed a similar area under the UAC (0.934 ± 0.032) and UACR (0.920 ± 0.035) curves ($P = 0.626$). The area under the curve was smaller for the Micral-Test II (0.846 ± 0.047) than for UAC ($P = 0.014$).

ROC curves were also constructed to evaluate UACR performance to diagnose microalbuminuria in men ($n = 116$) and women ($n = 162$) resulting in a similar area under the two curves (0.967 ± 0.018 for men and 0.982 ± 0.015 for women). Also similar were the areas under the curves for the fresh and defrosted samples evaluated by Micral-Test II strip readings ($P = 0.158$).

The agreement between the Micral-Test II (values ≥20 mg/l) and UAER (values ≥20 μg/min) for the

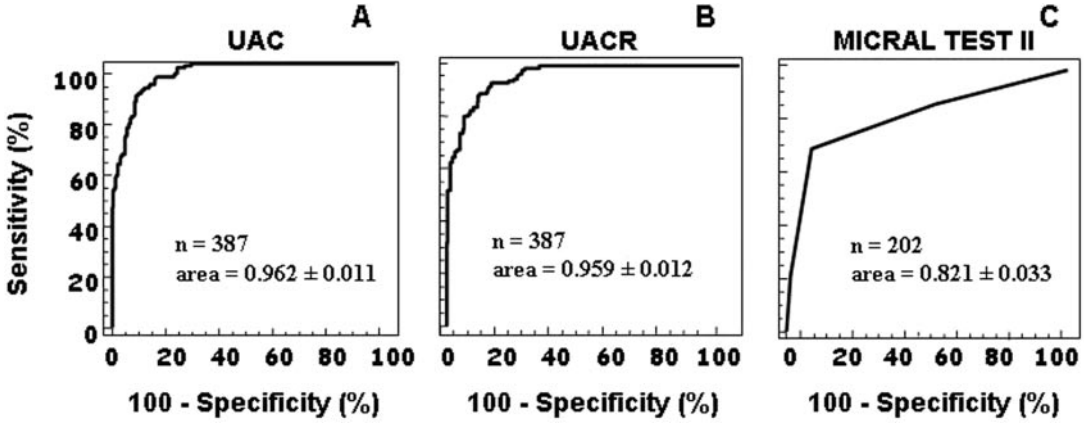

Fig. 1. ROC curves ($n = 130$) for (**A**) urinary albumin concentration (UAC = mg/l), (**B**) urinary albumin-to-creatinine ratio (UACR = mg/g) and (**C**) Micral-Test II (mg/l) performed in a random urine specimen as screening tests for microalbuminuria.

diagnosis of microalbuminuria was 55.8% ($\kappa = 0.22$; $P < 0.001$). The agreement between Micral-Test II readings (values ≥ 20 mg/l) for the three observers (390 readings) was 83.3%, and was considered as excellent (observer 1 and 2, $\kappa = 0.80$, $P < 0.0001$; observer 1 and 3, $\kappa = 0.83$, $P < 0.0001$; observer 2 and 3, $\kappa = 0.75$, $P < 0.0001$).

Cost of microalbuminuria diagnosis

The cost of microalbuminuria diagnosis based on the cost of each test was calculated taking into account the average time required to perform each test (albumin, 2.7 min; creatinine, 1.5 min; Micral-Test II, 1.1 min), the hourly rate of a technician (U$3.02) and the cost of the materials used (immunoturbidimetry for albumin, U$1.07; creatinine assay, U$0.16; Micral-Test II, U$3.23 per strip). Considering these variables, the cost per test was U$1.20 for UAC, U$1.43 for UACR and U$3.29 for Micral-Test II.

The cost of diagnostic confirmation (UAER measurements) was calculated based on the sensitivity (100% for UAC and UACR and 90% for the Micral-Test II) and specificity (77.2% for UAC, 73.0% for UACR and 46.0% for the Micral-Test II) of the cutoff points of each test as determined by ROC curves and on a prevalence of 25% for microalbuminuria [13]. The final cost per patient for the diagnosis of microalbuminuria was U$1.74 for UAC, U$2.00 for UACR (U$1.98 for men and U$1.93 for women), and U$4.09 for the Micral-Test II.

Discussion

In this study, it was observed that UAC and UACR measured in a RUS are accurate screening tests for microalbuminuria. A major advantage of these tests is that the urine sample can be collected during a medical visit. Moreover, UAC had the lowest cost for microalbuminuria diagnosis.

The excellent performance observed for UAC confirmed our previous observation with fewer patients [9]. The use of the 100% sensitivity point instead of the point of equilibrium to analyze accuracy is justified since the test was being evaluated for screening purposes [7]. Furthermore, the expected decreased specificity when compared with the point of equilibrium (77.2 *vs* 93.7%), did not significantly increase the final cost of microalbuminuria diagnosis (U$1.74 to 1.56 per patient; data not shown), with the advantage of fewer false-negative measurements.

Although in theory the measurement of albumin concentration in a spot sample could have been influenced by dilution of the urine, this was probably not relevant, since there was a strong correlation between UAC and UAER, as already described by others [10]. UAC in fasting morning urine samples is suggested for microalbuminuria screening by the European Diabetes Policy Group [6]. However, the accuracy of the recommended cutoff point of 20 mg/l is not given. Bakker [10], using a ROC curve for diagnosis of microalbuminuria, and selecting points of equilibrium in each curve, described higher sensitivity and specificity for UACR (94% sensitivity and 92–93% specificity) compared with UAC (89–90% for both sensitivity and specificity), but specific information concerning the areas of the ROC curves was not provided. In addition, since Bakker [10] used an aliquot of a timed overnight or 24 h urine collection to measure albumin, these results cannot be compared with the present study, in which a RUS was employed.

The use of sex-specific UACR values has been recommended [6,10,14,15], but is not a consensus [2,8,16]. In the present study, the use of a differentiated point for men and women improved the specificity when compared with a single point (75.8 and 81.3% *vs* 73.0%), at no additional cost. This suggests that when using UACR to screen DN, it is worth establishing different values for men and women.

Some authors suggest the use of age-specific UACR values [10,15], since the progressive reduction of muscle mass with age would reduce urinary creatinine

excretion, leading older individuals to present a higher UACR. The consequence would be more frequent false-positive results for microalbuminuria in these subjects. In the present study, although 24 h creatinine values were negatively correlated with age, there was no relationship between UACR and age, and also no difference in UACR values among age tertiles. We excluded women with creatinine <700 mg and men with creatinine <1000 mg to discard incomplete urine collections. As a consequence, some ageing patients with low muscle mass may have been left out. However, the mean age of patients excluded by this criterion (57.3 ± 13.4 years) was not different from the mean age of the studied patients (59.63 ± 10.63; $P = 0.167$).

In the present study the accuracy of the Micral-Test II as evaluated by ROC curves was lower than that of the UAC. In fact, the agreement between UAER and the Micral-Test II was poor. This was not related to the reading of the strips, since the agreement between readings was excellent, as observed by other authors [12]. The sensitivity of the point defined as indicating microalbuminuria by the manufacturer (20 mg/l) was 90.0%. A similar sensitivity (88%) has already been reported by others [17]. These values were lower than the minimum sensitivity value (95%) recommended for semi-quantitative tests to be used for microalbuminuria screening [7]. Mogensen *et al.* [12], in a large multicentric study, observed a sensitivity of 96.7% and a specificity of 71% for the diagnosis of microalbuminuria with the Micral-Test II. The reference standard for microalbuminuria diagnosis was the measurement of albumin concentration in a spot urine sample (20 mg/l) rather than a 24 h UAER determination. Furthermore, Micral-Test II readings were performed in the same urine aliquot. Adopting these criteria in our study would translate into higher sensitivity and specificity for strip readings: 95.2 and 53.4% (data not shown). In fact, even when urinary albumin measurements performed in timed urine collections are used as the reference criterion for microalbuminuria, the reading of strips to detect microalbuminuria in the same aliquot produces higher sensitivity and specificity values [17,18] than those observed in the present study. Other authors [19] have also described higher sensitivity (95.2%) and specificity (84.7%) for microalbuminuria diagnosis than those observed in the present study. This difference could be due to the performance of strip readings in first-morning urine specimens, in which the known diurnal variation in albumin excretion is not present as compared with a random urine specimen. Albumin measurements in a first morning urine specimen are more correlated with 24 h protein excretion than measurements in a random spot urine sample [2,20].

To calculate the cost of UAC, UACR and the Micral-Test II, beyond the average time to perform each test, the hourly rate of the technician, the material used, and the sensitivity and specificity for the diagnosis of microalbuminuria were also taken into account. The laboratory machines used were not included in this calculation because they are rented, and the rental amount depends on the number of tests performed. Furthermore, in our hospital this equipment is not used solely to perform these tests. Therefore, although the Micral-Test II appears to be unfavourable with respect to cost, it is important to consider that UAC and UACR can be performed only where there is a laboratory structure, whereas the Micral-Test II does not depend on any prerequisite. In this regard, immediate urine results using the Micral-Test II, despite its lower sensitivity and specificity [17], may represent an advantage, especially when a standard quantitative technique is not available. According to NKF/KDOQI guidelines [20], it is usually not necessary to obtain a timed urine collection for microalbuminuria evaluation, and albumin should be measured in a spot urine sample using either an albumin-specific dipstick or albumin-to-creatinine ratio. However, it is important to note that patients with a positive dipstick test should undergo confirmation of microalbuminuria by a quantitative measurement [20].

In conclusion, taking into consideration accuracy and cost, the measurement of UAC in a RUS, having 15 mg/l as the cutoff point for diagnosis, was the best choice for microalbuminuria screening in diabetic patients.

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Conflict of interest statement. None declared.

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