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Usefulness of A Random Spot Urine Proteins-to-Creatinine Ratio to Screen for Increased Albuminuria in Patients with Type 1 Diabetes

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Abstract

Background: Moderately increased albuminuria is a biomarker for early onset diabetic nephropathy. The aim of this study was to evaluate the performance of use proteinuria-to-creatininuria ratio (UPCR) at different cut-off to screen for increased albuminuria using albuminuria-to-creatininuria ratio (UACR) as a gold standard.

Methods: This was a cross-sectional study. A random spot urine sample was collected from patients with type 1 diabetes to measure albuminuria and total proteinuria using respectively an immunoturbidimetric and a colorimetric assay. Albuminuria was expressed as UACR and proteinuria as UPCR. The area under the curve (AUC) method and the kappa coefficient were used to compare UPCR and UACR.

Results: In 150 diabetic patients, moderately increased albuminuria was detected in 33.3% using UACR and 35.3% using UPCR at 272 mg/g. UPCR thresholds of 130, 150, 180 and 200 mg/g yielded higher detection rates than UACR. However, all UPCR cut-offs showed low diagnostic accuracy (AUC < 70%), and agreement with UACR was mild (kappa < 0.40).

Conclusion: The level of agreement between UPCR and UACR was moderate. It is not sufficient for UPCR to replace UACR to screen for increased albuminuria in patient with type 1 diabetes.

Keywords: Albuminuria, Diabetes, Diabetic Nephropathyn, Kidney Diseases, Proteinuria.

Introduction

Diabetes mellitus, or simply diabetes, is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized and over-produced, resulting in chronic hyperglycemia (1).

Diabetes is the leading non-infectious epidemic affecting humanity, with 537 million diabetics in 2021. If current trends continue, the number of diabetics will reach 643 million in 2030 and 783 million in 2045 (2). In Senegal, the prevalence of diabetes is believed to have reached 10.4% (3). Diabetes that is not properly managed can lead to chronic complications. Diabetes is a leading cause of chronic kidney disease (CKD) and kidney failure worldwide (4,5). Reports of incidence and prevalence of diabetic nephropathy (DN) vary by demographics and geographical locations. DN affects 30 to 40% of patients worldwide and 31.27–42.95% in Africa (6–8).

DN generally develops 10 years after the diagnosis of type 1 diabetes. Annual testing for albuminuria and estimated glomerular filtration rate should be performed in patients with type 1

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diabetes of ≥ 5 years duration regardless of treatment status (1). DN is clinically diagnosed by a persistent increased urine albumin excretion (defined as at least two abnormal specimens within a 3- to 6-months period) and by a decreased estimated glomerular filtration rate (eGFR). In most cases, kidney biopsies are not used to establish the presence of DN (1,7,9). In the absence of proper management, DN leads to end-stage CKD of which it is the leading cause worldwide (7). In Senegal, the overall prevalence of CKD is estimated at 4.9%, including 12.7% of diabetics (8).

Moderately increased albuminuria, also known as grade A2 albuminuria or microalbuminuria (discouraged term) is an early biomarker of DN at a reversible stage of the affection, enabling progression to renal failure to be delayed using ACE inhibitors (1,10). The urinary albumin assay needed to screen for moderately increased albuminuria is performed using an albumin-specific monoclonal antibody. This method which is the gold standard is not widely available in countries where financial resources are limited (11). Therefore, Kidney Disease: Improving Global Outcomes (KDIGO) have suggested the use of Urinary Protein to Creatinine Ratio (UPCR) at a threshold of 150 mg/g as an alternative to the use of Urinary Albumin to Creatinine Ratio (UACR) to screen for increased albuminuria, including moderately increased albuminuria and severely increased albuminuria or grade 3 albuminuria or macroalbuminuria (discouraged term) (12). Several other thresholds to define increased albuminuria from UPCR are also listed (130, 180, and 200 mg/g) (1, 13–17). It is in this context that the present work was carried out with the aim of evaluating the performance of UPCR, at different threshold values, to screen for increased albuminuria in patients with type 1 diabetes using UACR as the gold standard.

Materials and Methods

Ethical considerations

The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Cheikh Anta Diop Ethics's Committee (0312/2018/CER/UCAD). Free and informed consent was obtained from all adult participants. Parental or guardian approval was necessary to recruit minors.

Study design and patient population

This was a cross-sectional analytical observation study. Subjects were recruited on a systematic random basis from type 1 diabetes care centers in Dakar notably at the Albert Royer National Hospital of Children and at the Abass Ndao Hospital.

All children, adolescents and young adults living with type 1 diabetes who have been followed up in the targeted recruitment centers were eligible for inclusion in the study. Type 1 diabetic patients with fever, known hypertension or symptoms of urinary tract infection were not included in this study.

Demographic data collection and Specimen sampling

Demographic data, including age and sex, were extracted from medical records. Venous blood samples were collected in three specialized tubes: EDTA (ethylene diamine tetra-acetatic acid) tubes for glycated hemoglobin (HbA1c) analysis, fluoride tubes for blood glucose measurement, and plain tubes for serum urea and creatinine determination. Additionally, random spot urine samples were collected for concurrent analysis of creatininuria, proteinuria, and albuminuria.

Biochemical Methods

All biochemical tests were performed using materials previously described, except for HbA1c for which the HemoCue HbA1c 501 system (HemoCue, Serris, France) was used (17). Blood glucose, urea, and creatinine (serum and urinary) were quantified using standardized enzymatic assays, while urinary total proteins were analyzed via the non-enzymatic pyrogallol red molybdate method. Albuminuria levels were determined via an immunoturbidimetric assay to ensure high specificity for albumin detection. Glycated hemoglobin (HbA1c) was measured using an

affinity chromatographic assay. Glomerular filtration rate (GFR) was estimated using age-specific formulas: the Schwartz and Counahan-Baratt formulas (18-19).

Albuminuria Stratification

Patients were stratified into two groups based on albuminuria levels: group 1 (normal/mildly increased albuminuria), defined by UACR <30 mg/g or UPCR <150 mg/g, and group 2 (moderately/severely increased albuminuria), defined by UACR ≥30 mg/g or UPCR ≥150 mg/g. To refine diagnostic accuracy, UPCR thresholds were systematically adjusted to 130, 150, 180, 200, and 272 mg/g, with the latter identified as the optimal cut-off of the study cohort using Liu's method (14–18,20.

Statistical analysis

The statistical analysis has been described previously in (16). The diagnostic performance of UPCR was evaluated using receiver operating characteristic (ROC) curves i.e. area under the curve (AUC) analysés, while agreement between UPCR and the gold standard UACR was assessed via Cohen's kappa (κ) coefficient. The optimal UPCR threshold for detecting albuminuria was derived using Liu's method.

Results

Baseline characteristics of the study population

One hundred and fifty (150) type 1 diabetic patients were included in this study (Table 1). Mean age was 15.21±4.42 years. Male sex was present at a frequency of 51.33%. Half of the patients had HbA1c levels between 7.6% and 12.6% and three-quarters (¾) of the study population had poor glycemic control as the 25th percentile of HbA1c was 7.6%.

Table 1. Baseline characteristics of the study population.

Parameters	Mean±SD	25th percentile	75th percentile	Minimum	Maximum
Age (years)	15.21±4.42	13	19	2	24
Male sex, % (n)	51,33% (77)	XXX	XXX	XXX	XXX
Glycemia (g/l)	2.01±0.93	1.19	2.78	0.63	4.7
HbA1c (%)	10.20±3.28	7.6	12.6	4.3	15.5
Uremia (g/l)	0.23±0.09	0.16	0.29	0.09	0.59
Creatininemia (mg/l)	8.82±2.13	7.18	10.13	3.03	13.9
GFR-Schwartz (ml/min/1.73m^2)	76.17±22.66	61.64	85.4	41.22	184.01
GFR-Counahan-Baratt (ml/min/1.73m^2)	79.30±23.59	64.10	88.92	42.92	191.58
Craatininuria (g/l)	0.67±0.64	0.19	1.04	0.01	3.55
UACR (mg/g)	68.20±141.00	4.99	38.87	0.06	735.9
UPCR (mg/g)	487.10±866.61	58.6	461.02	6.56	5636.36

SD = Standard Deviation; HbA1c = Glycated Hemoglobin; GFR = Glomerular Filtration Rate; UACR = Urinary Albumine / Creatinine Ratio; UPCR = Urinary Proteins / Creatinine Ration.

Frequencies of Increased Albuminuria

No severely increased albuminuria was observed. The frequency of moderately increased albuminuria was 33.33% (n = 50) according to UACR. This frequency was significantly low ($p < 0.05$) compared with that recorded with UPCR at the thresholds of 130, 150, 180, 200 mg/g or 272 mg/g (Fig. 1)

Comparison of Proteinuria and Albuminuria Using AUC

The number of false negatives increased with increasing UPCR threshold value. In contrast, the number of false positives decreased with increasing UPCR threshold value (Table 2).

The UPCR sensitivity, specificity and AUC values show that, when the UPCR threshold

value was increased, sensitivity and specificity varied inversely (Table 3). In other words, if the threshold value was increased, the sensitivity of UPCR decreased while the specificity increased. The UPCR cut-off value of 272 mg/g showed the best compromise in terms of sensitivity and specificity *i.e.* the maximum sum of sensitivity and specificity. This suggested that UPCR 272 mg/g was the best cut-off value for our series.

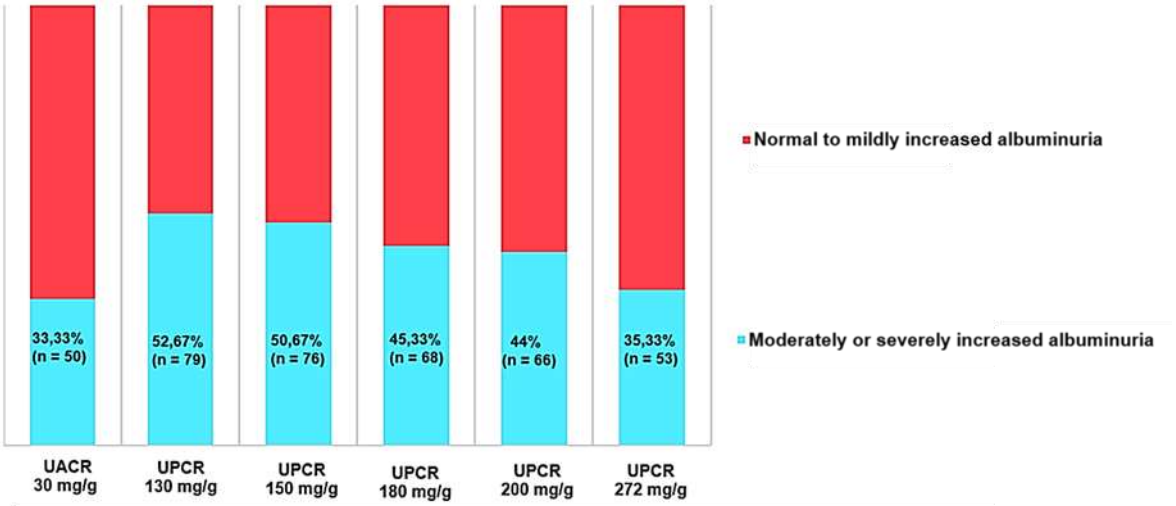


Fig. 1. Prevalences of pathological albuminuria according to UACR and UPCR at various cut-off values.

Table 2. Screening of increased albuminuria using UPCR versus UACR.

UPCR cut-offs (mg/g)	True positives n (%)	False positives n (%)	True negatives n (%)	False negatives n (%)
130	33 (41.77%)	46 (58.23%)	54 (76.06%)	17 (23.94%)
150	32 (42.11%)	44 (57.89%)	56 (75.68%)	18 (24.32%)
180	30 (44.12%)	38 (55.88%)	62 (75.61%)	20 (24.39%)
200	29 (43.94%)	37 (56.06%)	63 (75.00%)	21 (25.00%)
272	27 (50.94%)	26 (49.06%)	74 (76.29%)	23 (23.71%)

UPCR: Urinary Proteins / Creatinine Ratio. UACR: Urinary Albumin / Creatinine Ratio.

Table 3. Sensitivity, specificity and area under the curve at various UPCR thresholds with UACR as a gold standard.

UPCR cut-offs (mg/g)	Sensitivity (%)	Specificity (%)	AUC (95% CI)
130	66	54	0.6000 (0.517 – 0.682)
150	64	56	0.6000 (0.517 – 0.683)
180	60	62	0.6100 (0.526 – 0.693)
200	58	63	0.6050 (0.521 – 0.689)
272	54	74	0.6400 (0.558 – 0.722)

UPCR: Urinary Protein / Creatinine Ratio. UACR: Urinary Albumin / Creatinine Ratio. AUC: Area Under the Curve. CI: Confidence Interval.

The receiver operating characteristic curve (ROC curve) for UPCR versus the gold standard (UACR) shows the Area Under the Curve (AUC) was 66.13% (95%CI: 56.52 - 75.74%) (Fig. 2). Application of Liu's method revealed that UPCR = 272 mg/g was, in fact, the optimal cut-off for the series (21). The AUC of UPCR at different cut-off values versus UACR are shown in Figure 3. It shows that the AUCs were all below 70% making UPCR unreliable whatever the UPCR cut-off value considered. AUCs were all around 60% even for the UPCR threshold of 150 mg/g proposed by KDIGO or for the UPCR threshold of 272 mg/g (12,20).

Comparison of Proteinuria and Albuminuria Using Kappa Coefficients

The level of agreement between UPCR at different cut-off values and UACR indicated that the UPCR 272 mg/g threshold showed the highest agreement coefficient and kappa coefficient, especially compared with those of UPCR of 150 mg/g, although the agreement demonstrated was only a mild one with a kappa coefficient between 0.20 and 0.40 (Table 4).

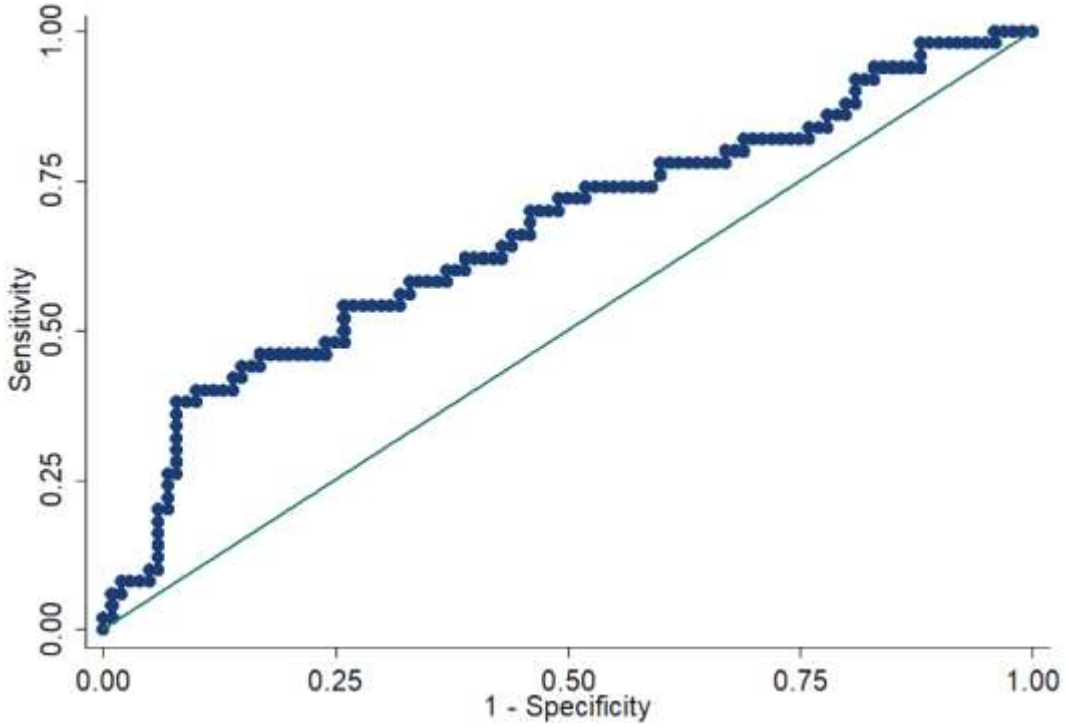


Fig. 2. Receiver operating characteristic curve (ROC curve) of UPCR in screening for moderately increased albuminuria with UACR as a gold standard. Curve analysis shows an area under the curve (AUC) of 66.13% (95% CI: 56.52% - 75.74%).

Table 4. Agreement between UPCR and UACR at various UPCR thresholds.

UPCR cut-offs (mg/g)	Agreement coefficient (%)	Cohen's kappa coefficient (95 % CI)	p-value
130	49.11	0.175 [0.030 – 0.320]	0.0104*
150	49.78	0.177 [0.029 – 0.325]	0.0105*
180	51.56	0.202 [0.048 – 0.355]	0.0054*
200	52.00	0.194 [0.039 – 0.349]	0.0073*
272	54.89	0.276 [0.116 – 0.436]	0.0004*

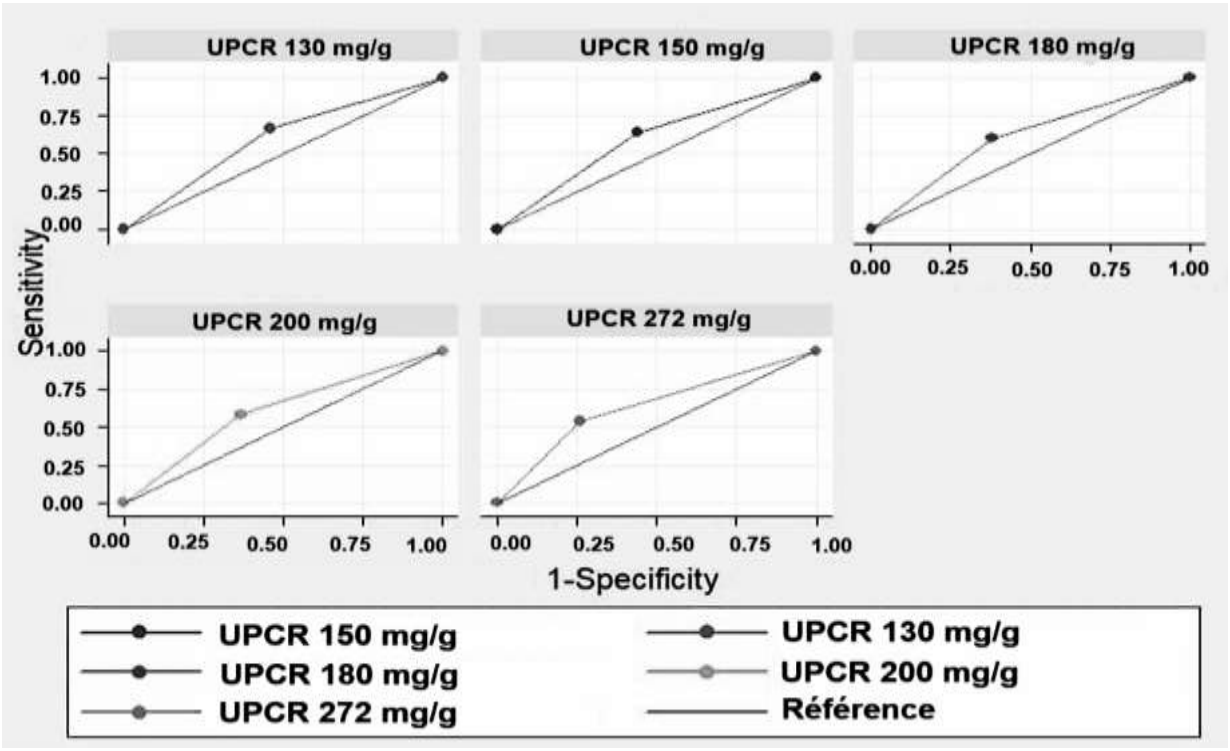


Fig. 3. Receiver operating characteristic curve (ROC curve) of UPCR at various thresholds with UACR as a gold standard.

Discussion

The result of this study shows that UPCR results are not sufficiently in agreement with those of the UACR to replace it to screen for increased albuminuria in patients living with type 1 diabetes. This was not expected because using UPCR as an alternative to UACR to estimate albuminuria is a recommendation of KDIGO (12). It would facilitate early diagnosis of diabetic nephropathy especially in countries with limited financial resources where albuminuria testing using immunochemical assays is expensive and not easily accessible (11,12). Moreover, in a previous study in patients living with sickle cell anemia our results showed a good agreement between UPCR and UACR making UPCR a reliable tool to estimate albuminuria in this setting (16). In a study where UPCR was compared not to UACR but to 24h-proteinuria, authors concluded that UPCR was reliable to diagnose and manage proteinuria in patients with type 2 diabetes (21). In contrast and in line with our results, a study conducted in patients with type 1 diabetes where UACR was also compared to 24 h-proteinuria and not to UACR, authors recommended caution in applying overconfidence to the values obtained with UPCR to manage proteinuria (22).

As implementing this recommendation of KDIGO should follow an evaluation of the performance of UPCR and as patients with type 1 diabetes often develop increased albuminuria, we conducted this work (12). Three-quarters (¾) of the patients included in this series had poor glycemic control since the 25th percentile of HbA1c was 7.6% whereas the target glycemic range for patients with type 1 diabetes is 6.5 – 7 % Table I (23). This poor glycemic control leads to the early onset of diabetic nephropathy, so that abnormal albuminuria consisting exclusively of moderately increased albuminuria according to UACR was present in 1/3 patients despite their young age Figure 1, Table I. This frequency is within the range of the overall estimated prevalence of moderately increased albuminuria in patients with diabetes in Africa, which ranges from 31.27% to 42.95% (6). A comparable moderately increased albuminuria frequency was reported by Ellis D. et al. in Denmark (33%), in Ethiopia (32%) and in Nigeria (34%) (24–26). But lower frequencies

were described in the literature, notably in the study by Rissassi J.R. et al. in Kinshasa (21.9%), Mathiesen E. R. et al. (20%), Moayeri H. et al. (19.5%) and Zahra Razavi et al. (14.3%) in Iran, Al-Agha et al. in Saudi Arabia (11.3%), Lutale et al. in Tanzania (12%) and Ismail et al. in Egypt (9.6%) (27–33). The frequency of moderately increased albuminuria in patients with type 1 diabetes is low and vary between 9.7 and 14.9% in Western countries (34,35). The frequency of moderately increased albuminuria in our series is therefore higher than those observed in developed countries, particularly in the West. This could be explained, on one hand, by the generally late diagnosis and therapeutic management of diabetes in our context and, on the other, by the low social, economic and intellectual standards, as well as by the lack of pediatric physicians, which is likely to hinder the therapeutic observation of the patients as well as rigorous regular follow-up.

A non-negligible frequency of moderately increased albuminuria, a biomarker of diabetic nephropathy, was noted in patients with type 1 diabetes. To screen for moderately increased albuminuria in this group of patients, UACR remains the only suitable test despite its limited availability and high cost, given that neither UPCR threshold proposed by KDIGO (150 mg/g) nor UPCR thresholds of 130, 180 or 200 mg/g found in the literature, let alone the UPCR threshold of 272 mg/g determined from our series of patients, have shown results that have an acceptable level of agreement with the UACR results. The KDIGO proposal to replace UACR with UPCR in screening for increased albuminuria in countries with limited financial resources would certainly be relevant but not applicable in patients with type 1 diabetes.

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Conflicts of interest

All authors declare they have no conflicts of interest.

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