IJCIM

International Journal of Complementary and Internal Medicine

RESEARCH ARTICLE

Urine Albumin-to-Creatinine Ratio (ACR) in the First Morning Void: Influence of Collection time and Urine Retention time

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Received: January 31, 2023 **Published:** February 19, 2023

Citation: CB Maluf. Urine Albumin-to-Creatinine Ratio (ACR) in the First Morning Void: Influence of Collection time and Urine Retention time. Int J Complement Intern Med. 2023;4(1):127–135. DOI: 10.58349/IJCIM.1.4.2023.00119

Abstract

Albuminuria has been linked to the onset and progression of chronic kidney disease (CKD) and adverse cardiovascular outcomes. The Within-subject biological variability for albuminuria is estimated to range from 4% to 103%, this variability is largely dependent on the type of urine sample and the circadian proteinuria's. To determine the effect of time of day of sample collection of first morning voids, we analyzed the equivalence of the albumin dosage and Albumin-to-creatinine ratio (ACR) in a 12-h urine sample with the ACR in a first morning urine sample collected at different times of day, which were collected between 3:50 and 5:59 a.m., 6:00 and 6:29 a.m., and 6:30 and 8:15 a.m. 123 adult participants from ELSA-Brasil cohort were asked to provide both a 12-h urine sample and a first morning urine sample and to record their collection times. Statistical analysis was performed using the intraclass coefficient correlation (ICC), Pearson's r correlation coefficient, the Lin's concordance correlation coefficient, and the Bland-Altman agreement method. Compared to ACR obtained from 12-h overnight urine samples, ACR in samples collected between 6:30 and 8:15 a.m. of first morning void urine yielded the highest correlation coefficients (Lin's > 0.95, Pearson's r > 0.97, ICC >0,98) and agreement by the Bland-Altman method. The albuminuria is affected by the circadian rhythm and our results suggest that albumin and ACR measurements were significantly affected by the hour of sample collection of morning, whose collection, when it occurred between 06:30 and 08:15, showed the best agreement.

Keywords: Urine, Preanalytical phase, Albuminuria, Albumin-to-creatinine ratio (ACR), ELSA-Brasil

Introduction

Albuminuria, generally defined as urine albumin excretion above 30 mg/day, has been linked to the onset and progression of Chronic kidney Disease (CKD) and an increased risk of adverse cardiovascular outcomes.[1-3] When detected on at least two occasions over a period of 3 months, albuminuria may be indicative of glomerular structural kidney alterations, being one of the diagnostic criteria for CKD according to the Chronic Kidney Disease Epidemiology Collaboration (KDIGO CKD).[4] Albuminuria can be detected by random urine collections or by 12-h or 24-h timed urine samples. The 24-h timed is the gold standard, however it is time consuming and prone to collection error up to 47%.[5] The use of the albumin-to-creatinine ratio (ACR) from a random urine collection seems to provide a reproducible measure of albumin excretion, thus, being a suitable alternative to the cumbersome 24-hour urine collection. Studies comparing the ACR in a first morning urine sample and 24-h urine albumin excretion rate (AER) have reported a sensitivity of 88% to 100% and specificity of 81% to 100% .[6] Either, the Laboratory Working Group of the National Kidney Disease Education Program and the Working Group for Standardization of Albumin in Urine recommends reporting urine albumin measurements from first morning void urine samples because they provide lower within-subject biological variability and compare well with 24-h urine excretion values.[7-9] Estimates of within-subject biological variability for albumin excretion of 4%–103% have been reported from different studies.[7] This variability is largely dependent on the period over which the samples were collected (days, weeks, months) and the type of urine sample used (first morning, random urine collections or by 12-h or 24-h timed urine samples 24 h).

Circadian Rhythms are functional biological oscillations, self-sustaining on a daily cycle, which suggests the ability to anticipate the geophysical rhythms. The kidneys present a greater urine's volume during the day compared with the night. Several renal functions, including glomerular filtration rate and diuresis, have circadian rhythms. Albuminuria follows a circadian rhythm, which excretion's peak occurs at around 4 p.m. and its nadir is at 03:00 a.m. the glomerular filtration rate (GFR) measured by inulin and creatinine clearance reaches the peak during the day, around 2–3 p.m., and a minimum in the middle of the night.[10,11]

The 12-hour overnight urine samples are used in ELSA's study, after validated.[12,13] There are few studies comparing first morning urine ACR and 12-h overnight urine AER and most of them didn't describe in sufficient detail how the random urine samples were collected to allow meaningful understanding of the differences.[14-16]

This study aimed to determine the agreement between the ACR in 12-h overnight and first morning urine samples and whether this agreement varies with urine retention time and time of first morning urine void.

Methods

Setting and Population

This cross-sectional study evaluated a convenience subsample consisting of 123 participants, 66 women (54%), 57 men (46%) from one of the participating centers (Minas Gerais) in the second wave of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

ELSA-Brasil is a multicenter cohort study of active and retired public servants employed at higher education institutions and research centers from six Brazilian states. ELSA-Brasil baseline data were collected between 2008 and 2010 from civil servants aged 35–74 years at baseline assessment and the second wave of data were collected between 2012 and 2014. The study was approved by the Research Ethics Committees at the participating institutions and by the National Research Ethics Commission (CONEP). All participants provided written consent to participate in the study. Detailed information about the ELSA-Brasil design and cohort profile can be found elsewhere.[17,18]

Sample Collection

All ELSA-Minas Gerais second-wave participants were invited to participate in this study to achieve a minimum sample size of 100 participants at a 1:1 sex ratio, as recommended by Bland (2004).[19] Participants who were using topical agents in the genital area, and women who were menstruating were excluded. Individuals who agreed to participate were asked to provide a 12-h urine sample and a first morning urine sample. Participants received written and verbal instructions on how to collect urine samples and were given a form where urine collection times for the 12-h overnight and first morning urine samples should be recorded. Participants were provided with two plastic urine sample bottles (one large and one small) with wide mouth and screw-on lid appropriately labeled for the 12-h and first morning urine samples, respectively.

Participants were instructed to start the 12-h urine collection in late afternoon or early evening, after discarding the first urine, record the collection time, starting the collection period from the initial collecting time until the same hour at the next morning, completing 12 hours, and should collect all urine into sample bottle 1, which should be kept refrigerated, and record the collection times. Participants were asked to write a reminder of the procedure in the bathroom. The next morning, when waking up, the next urine sample should be collected into bottle 2, which was labeled "first morning urine," and record the hour of

collection. Every discharge inside the 12h limit time apart from the first urine in the morning should be added to bottle 1. Sample bottles 1 and 2 were delivered together with the recording form at the research unit to laboratory staff, who validated the collection process.

The urine volume of each sample bottle was determined. After homogenizing the sample bottle 2, a 2mL aliquot was removed and the remaining volume was transferred to sample bottle 1, completing the total volume of 12-h urine sample, which was homogenized and 2mL aliquot was removed. Urine aliquots were stored in a freezer at −80 °C until analysis.

To determine the effect of time of day of sample collection of first morning voids, we analyzed the equivalence of the albumin dosage and ACR in a 12-h urine sample (ACR12) with the ACR in a first morning urine sample (ACRM) collected at different times of day. Urine samples collected between 3:50 and 5:59 a.m., 6:00 and 6:29 a.m., and 6:30 and 8:15 a.m. were referred to as ACRM1, ACRM2, and ACRM3, respectively, and urine samples collected between 6:00 and 8:15 a.m. (ACRM2+ACRM3) were referred to as ACRM4. These time intervals were chosen with the intention of grouping similar n and evaluate the impact of the circadian rhythm.

To determine the effect of urine retention time on ACR measurements, we grouped participants according to urine retention time prior to first morning void urine collection as follows: ≤ 2-h urine samples, hereafter referred to as ACRMR2h; > 2-h to ≤ 4-h samples, ACRMR2–4h; > 4-h to ≤ 6-h samples, ACRMR4–6h; > 6-h to ≤ 8-h samples, ACRMR6–8h; and > 8-h to ≤ 9-h50min samples, ACRMR8–10h. These time intervals were chosen considering the second urine in the morning whose time interval is between 2 to 4 hours.

Laboratory Methods

Measurements were performed with strict internal and external quality control at the Central Laboratory of the Clinics Hospital, Federal University of Minas Gerais (UFMG), in Belo Horizonte, state of Minas Gerais. Urinary albumin concentration (UAC) and creatinine concentration were determined by an immunoturbidimetric assay (bromocresol green) and a two-point colorimetric kinetic method (amidinohydrolase/Oxidase), respectively measured by Vitros® 5600 integrated system (Ortho Clinical Diagnostics, Raritan, NJ, USA). Urine measurements were made on average three months after sample collection. Urine samples were removed from the freezer (−80 °C), thawed completely at room temperature, homogenized by rotating the tubes, and visually checked for turbidity before analysis. Both urine samples from each participant were analyzed in the same analytical run. The intra-assay coefficient of variation (CV) for urine albumin and creatinine was 4.3% and 5.0%, respectively.

The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation was not corrected for race in accordance with the results from validation studies of the equation performed in Brazil.[20,21] Diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) ≥ 126 mg/dL, or 2-h post-load (75 g anhydrous glucose) plasma glucose ≥ 200 mg/dL, or glycated hemoglobin (HbA1c) ≥ 6.5%, or by self-report of previous diagnosis of DM and/or use of insulin or oral hypoglycemic agents. Blood pressure (BP) was determined from three measurements taken in a quiet, temperature-controlled (20–24 °C) environment after participants had sat undisturbed for 5 min.[17]

Statistical Analysis

The equivalence between the albumin and ACR in 12-overnight urine samples and first morning void samples was examined using the Pearson's r correlation coefficient, the intraclass correlation coefficient (ICC), the average of differences between the measurements by the Bland-Altman method, and the Lin's concordance correlation coefficient. Normality of the difference mean values of The Bland-Altman test, was validated by cubic root transformation. Statistical analyses were performed using STATA statistical software package version 14.1 and R statistical software package version 3.5.3.

Results

Table 1 shows the characteristics of the ELSA-Brasil in Minas Gerais subsample, consisting of 123 participants (57 men, 66 women). In total, 4% of subjects were diabetics and 9.7% used diuretics. The mean creatinine concentration was 0.69 ± 0.15 mg/dL (mean ± SD) with an eGFR defined by the CKD-EPI equation > 90 mL/min/1.73 m² for all participants. The mean urine albumin concentration for the entire population was 7.85 ± 24.9 mg/L in the 12-h overnight urine sample and 5.05 ± 10.95 mg/dL in the first morning urine sample. Mean ACR for the entire population was 12.95 ± 8.63 mg/g and 7.93 ± 22.71 mg/g in the 12-h overnight urine sample and first morning urine sample, respectively.

Table 2 shows the results of agreement analysis between the ACR in 12-h overnight urine samples (ACR12) and first morning urine samples (ACRM). In addition, results for the ACRM from urine samples with different retention times are also presented. Correlation coefficients were highest in 2–4-h first morning urine samples, however the Bland-Altman limits of agreement ranged from −20.83 to 25.44.

Table 1. Characteristics of the 123 second-wave ELSA-Brasil participants stratified by gender

	Total (n=123)	Women (n=66)	Men (n=57)
Age (years), mean ± SD	54 ± 8.7	54.84 ± 8.61	52.82 ± 8.42
SBP (mmHg), mean ± SD	118.0 ± 13.0	115.32 ± 14.25	121.39 ± 12.46
DBP (mmHg), mean ± SD	77.0 ± 9.0	75.84 ± 9.27	78.58 ± 9.05
Weight (kg), mean ± SD	74.0 ± 15.5	67.1 ± 12.63	81.39 ± 14.15
Diabetes, n (%)	5 (4.0%)	2 (3.0%)	3 (5.2%)
Use of diuretics, n (%)	12 (9.7%)	8 (12.0%)	4 (7.0%)
Creatinine (mg/dL), mean ± SD	0.69 ± 0.15	0.59 ± 0.095	0.79 ± 0.14
Urinary volume (mL), mean ± SD	1041.0 ± 511.0	1083.0 ± 473.0	993.0 ± 553.0
*eGFR (mL/min/1.73 m²), mean ± SD	133.0 ± 32.0	133.47 ± 34.76	133.15 ± 29.87
Alb12 (mg/L), mean ± SD	7.85 ± 24.9	9.09 ± 32.24	6.4 ± 12.04
AlbM (mg/L), mean ± SD	5.05 ± 10.95	4.73 ± 10.56	5.43 ± 11.47
ACR12 (mg/g), mean ± SD	12.95 ± 8.63	15.78 ± 43.0	9.67 ± 32.94
ACRM (mg/g), mean ± SD	7.93 ± 22.71	7.25 ± 12.4	8.71 ± 30.73

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; Alb12: 12-h overnight urine albumin concentration; AlbM: first morning urine albumin concentration; ACR12: 12-h overnight urine albumin-to-creatinine ratio; ACRM: first morning urine albumin-to-creatinine ratio. *eGFR: estimated glomerular filtration rate defined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation uncorrected for gender

Table 2. Correlation and agreement for albumin-to-creatinine ratio (ACR) from 12-h overnight urine samples and first morning urine samples with different urine retention times

	N	ICC		Correlation coefficients			Bland-Altman	
				Lin's	Pearson's r	Average of differences	Standard deviation	Limits of agreement
ACR12 vs. ACRM	123	0.561		0.559	0.647	5.05	29.54	−52.84–62.96
ACR12 vs. ACRMR2h	15	0.819		0.788	0.822	1.46	3.08	−4.58–7.50
ACR12 vs. ACRMR2–4h	41	0.960		0.959	0.974	2.30	11.80	−20.83–25.44
ACR12 vs. ACRMR4–6h	28	0.000		-0.016	−0.094	16.8	59.45	−99.77–133.29
ACR12 vs. ACRMR6–8h	30	0.578		0.562	0.596	1.03	3.29	−5.42–7.48
ACR12 vs. CRMR8–10h	9	0.855		0.778	0.844	0.61	0.96	−1.27–2.46

ICC: intraclass coefficient correlation; ACR12: 12-h overnight urine albumin-to-creatinine ratio; ACRM: first morning urine albumin-to-creatinine ratio; ACRMR2h: ≤ 2-h first morning urine albumin-to- creatinine ratio; ACRMR2–4h: 2–4-hfirst morning urine albumin-to-creatinine ratio; ACRMR4–6h: 4–6-h first morning urine albumin-to-creatinine ratio; ACRMR6–8h: 6–8-h first morning urine albumin-to-creatinine ratio; ACRMR8–10h: 8–10-h first morning urine albumin-to-creatinine ratio.

Table 3 shows the results of agreement analysis between 12-h overnight urine ACR (ACR12) and first morning urine ACR (ACRM) from first morning samples collected at different times of day. First morning urine ACR from samples collected between 6:30 and 8:15 a.m. (ACRM3) showed the highest correlation coefficients (ICC=0.994, Lin's=0.995, Pearson's r=0.998) and the narrowest limits of agreement (−7.61 to 9.61). However, analysis of urine samples collected at an extended collection period between 6:00 and 8:15 a.m. (ACRM4) showed worse correlation coefficients and limits of agreement.

Table 3. Correlation and agreement for albumin-to-creatinine ratio (ACR) from 12-h overnight urine samples and first morning urine samples collected at different times of day

	N	ICC	Correlation coefficients		Bland-Altman		
			Lin's	Pearson's r	Average of differences	Standard deviation	Limits of agreement
ACR12 vs. ACRM1	47	0.560	0.214	0.415	10.76	45.29	−78.01–99.55
ACR12 vs. ACRM2	50	0.213	0.089	0.127	1.82	13.64	−24.91–28.55
ACR12 vs. ACRM3	26	0.994	0.995	0.998	0.95	4.41	−7.61–9.61
ACR12 vs. ACRM4	76	0.958	0.606	0.883	3.22	17.83	−31.74–38.18

ICC: intraclass coefficient correlation; ACR12: 12-h overnight urine albumin-to-creatinine ratio; ACRM1: first morning urine albumin-to-creatinine ratio from samples collected between 3:50 and 5:59 a.m.; ACRM2: first morning urine albumin-to-creatinine ratio from samples collected between 6:00 and 6:29 a.m.; ACRM3: first morning urine albumin-to-creatinine ratio from samples collected between 6:30 and 8:15 a.m.; ACRM4: ACRM2+ACRM3.

In addition, we also determined the agreement between 12-h overnight urine albumin concentration. First morning urine from samples collected between 6:30 and 8:15 a.m. showed the highest concordance and correlation coefficients (Lin's=0.986, Pearson's r=0.987) and the narrowest Bland-Altman limits of agreement (−5.96 to 4.44).

Table 4. Correlation and agreement for albuminuria from 12-h overnight urine samples and first morning urine samples collected at different times of day

	N	ICC	Correlation coefficients		Bland-Altman		
			Lin's	Pearson's r	Average of differences	Standard deviation	Limits of agreement
Alb12 vs. AlbM1	47	0.560	0.154	0.268	6.48	36.65	−65.40–78.26
Alb12 vs. AlbM2	50	0.213	0.089	0.139	1.28	6.04	−10.56–13.13
Alb12 vs. AlbM3	26	0.994	0.986	0.987	-0.75	2.65	−5.96–4.44

Alb12: 12-h overnight urine albumin concentration; AlbM1: first morning urine albumin concentration from samples collected between 3:50 and 5:59; AlbM2: first morning urine albumin concentration from samples collected between 6:00 and 6:29 a.m; AlbM3: first morning urine albumin concentration from samples collected between 06:30 and 08;15 a.m.

Discussion

ACR above 30 mg/g has been associated with all-cause mortality in the general populations, cardiovascular disease, and progression to end-stage renal disease. The mortality risk might vary by comorbidities, socioeconomic status, women, and younger population. (ACR mortality)

The Albumin excretion presents a circadian rhythm, which excretion's rate is higher in the afternoon and lower in the night and depends on factors as posture, physical activity, diet and hydration an even. So, the ACR should be measured on a sample taken at a specific time. Our study showed that ACR and albumin measurements were significantly affected by time of day of sample collection in first morning urine samples. First morning samples collected between 6:30 and 8:15 a.m. yielded the highest correlation coefficients (Lin's and Pearson's) and the narrowest Bland-Altman limits of agreement, both for albumin measurements and the albumin-to-creatinine ratio (ACR). These findings can be explained by the circadian rhythm of albumin excretion, which shows a variation over 24 h and reaches the lowest point at 3:00 a.m. and it is independent of the GFR.[10] Otherwise, creatinine excretion rate only shows a 9.4% variation over 24 h.[23] Thus, the dosage of albuminuria has a greater impact on this equation. The use of the ACR in a random urine sample is effective in correcting urine albumin concentration due to differences in urine volume, but some authors suggest that even ACR measurements in 12-h or 24-h urine collections can correct for possible collection errors, including urine loss and inadequate fluid intake during the collection period.[24]

Results like ours were reported in other studies. Koopman analyzed the circadian rhythm of proteinuria and the consequences of the use of the ACR on 24-h proteinuria estimates. In their study, the best estimate was obtained with 3-h urine samples collected between 6:00 and 9:00 a.m. The authors concluded that because of the circadian rhythm of proteinuria, the ACR would only be useful for estimation of proteinuria if the random urine samples were collected at a fixed time of day.[25] Cowell, founded the highest correlation on first morning sample collected until 09:00 a.m., when looked the relationship between 24-h urinary albumin excretion and the albumin on first morning and on the same samples and considered the intervals 09.00h to 13.00 h, 13.00h to 18.00h, 18.00 to 23.00h to random samples.[26]

Chitalia compared proteinuria estimates from 24-h urine samples and first morning urine samples collected at 8:00 a.m. and obtained good correlation (r^2=0.97) and precision of agreement.[27] Differences between measurements were smaller than the biological variability of proteinuria, which is 35.5% in 24-h urine collections and 36% in first morning urine samples.[28] Witte compared measurements of urinary albumin concentration or ACR in a first morning void and in a spot urine sample (collected between 8:00 and 11:00 a.m.) with 24-h urine collections and showed that first morning voids agreed better with 24-h urine collections than spot urine samples.[29] Some of these studies did not assess urinary retention time and did not provide collection times for first-morning voids.

Using early morning sample ACR instead 24-hour sample to stage albuminuria in clinical practice leads to a small number of individuals CKD misclassifications, and the albuminuria must be confirmed in another sample. (ACR or 24 h)

The ACR is recommended and widely used as a reliable method in screening for albuminuria in patients with diabetes, hypertension, and increased risk for chronic kidney disease. The absence of standard methods for collecting samples and of an international reference method for urinary albumin measurement is an important limitation to the utility of the ACR in clinical settings.[6,30,31]

Even though a first morning urine void sample is recommended for estimation of urinary albumin excretion in screening for kidney disease[32] and different studies have shown concordance between ACR in the first morning urine and 24-h urine collections with good specificity and sensitivity,[13,23,25,33-35] the ACR measured on random urine samples appears to overestimate the prevalence of albuminuria[36] and, in some cases, its presence must be confirmed by a 24-h urine collection.[32] We highlight the need for the standardization of random urine samples, which are easier and simpler to collect, store, and transport but are subject to great variability if time of day of sample collection is not observed. The biological variation of urinary protein excretion throughout the day is influenced not only by its circadian rhythm, but also by diet, posture, and exercise, which can be avoided by the overnight sample.[26,37] The Nation Kidney Disease Education Program Laboratory Working Group (NKDEPLWG) recognizes that urine albumin measurements may show marked variability between laboratories, mainly due to the absence of standardized preanalytical and analytical procedures.[38]

This study has some limitations. We used 12-h timed overnight urine samples in the comparison with random urine samples because it was the standardized ELSA sample choice. Nevertheless, previous studies showed good correlation between urinary protein and creatinine concentrations in 12-h and 24-h urine samples[10,39] although the albumin excretion rate is on average 25% lower compared to 24 h urine sample.[14-16] Sensitivity and specificity analyses of first morning urine samples and 12-overnight urine samples were not performed because of the small number of cases with high ACR values.

The Albuminuria is affected by the circadian rhythm and our results suggest that albumin measurements were significantly affected by the hour of sample collection of first morning void and not by the urine retention time. Samples collected between 6:30 and 8:15 a.m. showed the best agreement. However, more studies are necessary due to the necessity of reproducibility for standardization of first void test in regard of ACR measurement.

Acknowledgement

The authors thank the staff and participants of the ELSA study for their important contributions. The study was supported by the Brazilian Ministries of Health (DECIT) and of Science and Technology (FINEP/CNPq). SMB is a research fellow of the National Research Council (CNPq, grant nº 300159/99-4).

Conflicts of Interest

Authors declare that there is no conflict of interest.

Funding

The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (FINEP, Financiadora de Estudos e Projetos and CNPq, National Research Council), grant 01 06 0278.00 MG.

Comment

This manuscript was reviewed by a professional science editor and by a native English-speaking copy editor to improve readability.

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