Kidney Medicine

Spot Versus 24-Hour Urine Osmolality Measurement in Autosomal Dominant Polycystic Kidney Disease: A Diagnostic Test Study

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Rationale & Objective: Arginine vasopressin (AVP) is an established driver of cyst growth in autosomal dominant polycystic kidney disease (ADPKD). Urine osmolality (osm) measures are surrogate markers of AVP activity. Both 24-hour and spot urine samples are used as indicators of AVP suppression. The agreement between these 2 measurements remains unclear.

Study Design: A retrospective cohort study.

Setting & Study Population: Three hundred and forty-nine patients with ADPKD with 839 urine samples from a tertiary care center.

Selection Criteria for Study: Patients with ADPKD with records of spot and 24-hour urine measurements.

Data Extraction: Consecutive patients' data from January 2018 to March 2023 were extracted from the quality assurance database of The Ottawa Hospital Cystic Kidney Disease Clinic.

Analytical Approach: Discordance assessed at target urine osmolality of 250 and 270 mmol/kg. Agreement assessed by Bland-Altman plots. The percentage of patients with difference in osmolality between the 2 measures for cutoff points of > 50, > 100, >150, and > 200 mmol/kg was calculated.

Results: The mean 24-hour urine osm was 364 mmol/kg, and the mean spot urine osm was 424 mosm/kg. Mean age of 46 years, 52% females, and 47 (13.5%) were on tolvaptan. Overall, in comparing spot urine osm to 24-hour urine osm, the discordance at 250 and 270 mmol/kg was 24% with poor agreement on Bland-Altman plots. The differences between the 2 measures at varying cutoff points were 53.9% at 50 mmol/kg, 35.8% at 100 mmol/kg, 24.1% at 150 mmol/kg, and 16.1% at 200 mmol/kg. Results were similar when only a single measurement from each patient was used for analysis.

Limitations: Total of 29% of patients did not have concurrent spot urine osmolality and 24-hour urine osmolality. The study was conducted at a single center. Limited number of patients were on tolvaptan.

Conclusions: In adults with ADPKD, important differences exist between the 24-hour urine osmolality and spot urine osmolality that preclude interchangeable use. The method employed may impact clinical decision-making. More research is needed to determine, which urine osm should be used when assessing AVP suppression.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of end stage kidney disease.[1] The PKD1 and PKD 2 genes code protein Polycystin 1 and 2 respectively, which are integral membrane proteins of the primary cilium. Pathogenic variants in the PKD gene lead to the formation of numerous fluid-filled cysts in the kidneys. These cysts expand continuously over time, leading to the displacement and obstruction of various intrarenal structures, ultimately resulting in atrophy and fibrosis of renal parenchyma.[2]

The pathophysiology of cyst development has been attributed to altered intracellular calcium homeostasis and increased levels of intracellular cyclic adenosine monophosphate.[3] Arginine vasopressin (AVP), which has an important role in osmoregulation, is also known to increase cyclic adenosine monophosphate in distal nephrons via V2 receptor and has a role in cystogenesis and disease progression of ADPKD. As a corollary, AVP suppression decreases the rate of cyst development and growth.[4] Increased water intake reduces urinary osmolality and suppresses AVP secretion.[5] Increasing water intake has been shown to retard disease progression in a polycystic kidney disease rat model.[6] Alternatively, V2 receptor antagonists such as tolvaptan are being used to retard cyst growth and decline in kidney function.[7]

Kidney function in patients with ADPKD typically starts to decline in the third decade. However, it has been noted that the ability to concentrate urine reduces much earlier, even in childhood.[3,8] This has also been corroborated in animal models of ADPKD.[9] Urinary osmolality (Uosm) reflects urinary concentrating ability and is used as a surrogate marker for AVP suppression. There is increasing emphasis on Uosm measurement in ADPKD patients given its role in cystogenesis. Urine osmolalities of 250 and 270 mmol/kg have been suggested as targets to achieve optimal AVP suppression.[10,11] Studies in ADPKD have used either spot urine osmolality or 24-hour urine osmolality.[11-14]

In clinical practice, Uosm can be measured from either a spot urine sample or from a 24-hour urine collection. Spot Uosm is convenient for patients; however, values obtained

PLAIN LANGUAGE SUMMARY

Urine osmolality measures are used clinically to dose tolvaptan in patients with adult polycystic kidney disease. We compared urine osmolality from 24-hour and spot urine samples. We found out that important differences exist between 24-hour and spot urine samples' osmolality. The method employed to determine urine osmolality may impact clinical decision-making in the management of patients with adult polycystic kidney disease.

vary according to the time of day and amount of fluid ingested in the few hours preceding the sample and is thus subject to significant fluctuations.[13,14] Twenty-four-hour Uosm samples are more likely to accurately represent daily physiology but can be subject to over or under collection or may get altered by significant deviation from one's usual dietary habits.[15] At this time, there are no guidelines to suggest which method is preferred in patients with ADPKD. Also, no studies have shown whether spot Uosm values are comparable to 24-hour Uosm values in ADPKD patients. We undertook this study to determine if spot Uosm and 24-hour Uosm correlate in patients with ADPKD. The protocol was approved by Ottawa Health Science Network Research Ethics Board (protocol number 20220359). Informed consent requirements were waived owing to the retrospective nature of the study.

METHODS

The study was performed at The Ottawa Hospital Cystic Kidney Disease Clinic. The Ottawa Hospital is a 1,150-bed academic tertiary care center with a catchment area of ~1.3 million people. The Ottawa Hospital Cystic Kidney Disease Clinic is a speciality nephrology clinic designed to provide comprehensive, multidisciplinary care for patients with cystic kidney disease, predominantly ADPKD, and is the sole such program within the catchment area. At each visit, patients are seen by a nurse, dietitian, and a nephrologist. In this clinic, each patient is routinely educated on 24-hour urine collection and asked to provide both 24-hour urine sample collected at home and a spot urine sample collected at the clinic at each clinic visit. Blood work is also performed at that time. There was no set time for the clinic visit, and it varied during the day. A comprehensive quality assurance database has been maintained for these patients since the inception of the clinic (January 2018). This database is regularly audited for accuracy. The study cohort was derived from this database, and consecutive patients' data from January 2018 to March 2023 were included.

Urine osmolality was measured by freezing point depression osmometry on the Advanced Instruments Model 3320. The coefficients of variation were 0.95% at 305 mmol/kg, 0.6% at 448 mmol/kg, and 0.75% at 818 mmol/kg.

Continuous variables are reported as mean (± SD) if normally distributed and median (IQR) if non-normally distributed; categorical variables are reported as numbers (%). Discordance was assessed by calculating the percentage of samples where urine osmolality values from 24-hour urine samples and spot urine samples were compared against target thresholds of 250 and 270 mmol/kg. For each target, if both the 24-hour urine and spot urine results were either below, at, or above the target, the sample was considered concordant. If the results differed between the 2 methods (one below and one above the target), the sample was considered discordant. We choose the target osmolality of 250 and 270 mosm/kg as they are the suggested targets in patients with ADPKD. The mean difference in urine osmolality was calculated by spot urine osmolality minus the 24-hour urine osmolality. Analysis was performed for all samples and for individual patients. Separate analysis was also performed for patients who were and were not prescribed tolvaptan. The percentage of patients with differences in osmolality between 24-hour urine osmolality and spot urine osmolality for cutoff points of > 50, > 100, >150 and, > 200 mmol/kg were calculated. Bland-Altman Plots were also constructed to assess the agreement between spot urine osmolality and 24-hour urine osmolality.

RESULTS

There were a total of 514 patients seen in the clinic during the time frame. One hundred and sixty-five patients (32%) who did not have pertinent data (did not have 24-hour urine osmolality or spot urine osmolality) were excluded from the analysis. The final analysis contained 839 urine samples from 349 patients. Demographics are presented in Table 1.

The mean ± SD age of the cohort was 46 ± 15 years. Fifty-two percent were females. The vast majority of patients were of self-reported White race. Many of the patients were classified at high risk of progression by Mayo classification, Mayo Class 1C or above, (Table 1; https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). The median (P25-P75) serum creatinine for the group was 1.09 (0.87-1.47) mg/dL. The mean ± SD urine osmolality was 364 ± 162 mosm/kg.

The group treated with tolvaptan (n = 47 [13.5%] were younger, mean ±SD age of 43 ± 11.4 years versus 46.6 ± 15.9 years and tolvaptan group had a lower number of females (42.6% vs 53%). As expected, urine osmolality was lower in the tolvaptan treated group (195 mosm/kg vs 372 mosm/kg) and urine volume was higher (4.7 L vs 2.5 L, Table 1). The median serum creatinine was higher in the group treated with tolvaptan (1.36 vs 1.09 vs mg/dL, Table 1).

Table 1. Demographics

	All Patients (n = 349)	Patients on Tolvaptan (n = 47)	Patients not on Tolvaptan (n = 302)
Age (y), mean ± SD	46.2 ± 15.4	43 ± 11.4	46.6 ± 15.9
Female (n, %)	180 ± 51.6	20 ± 42.6	160 ± 53
Race (n, %)			
White	237 (67.9)	38 (80.9)	199 (65.9)
Black	13 (3.7)	2 (4.3)	11 (3.6)
East Asian	25 (7.2)	3 (6.4)	22 (7.3)
Indian sub-continent	18 (5.2)	-	18 (6)
Other	56 (16.1)	4 (8.5)	52 (17.2)
Age at diagnosis of PKD (y), mean ± SD	33.4 ± 17.1	26.4 ± 12.3	34.4 ± 17.5
Mayo Class n = 181, (n, %)			
1A	18 (10.1)	-	18 (12)
1B	43 (24)	1 (3.5)	42 (28)
1C	67 (37.4)	16 (55.2)	51 (34)
1D	26 (14.5)	3 (10.3)	23 (15.3)
1E	25 (14)	9 (31)	16 (10.7)
Serum creatinine mg/dL, median (P25-P75)	1.09 (0.87-1.47)	1.36 (1.09-2.34)	1.04 (0.86-1.37)
Serum urea nitrogen, mg/dL, median (P25-P75)	17.4 (13.2-25.5)	21.3 (14.3-32.2)	17.1 (13.2-23.8)
Urine albumin to creatinine ratio mg/g, median (P25-P75)	21.2 (10.6-58.4)	44.3 (22.1-80.5)	20.4 (9.7-58.4)
24-Hour urine volume (L), mean ± SD	2.65 ± 1.23	4.7 ± 2.2	2.5 ± 1.1
24-Hour urine osmolality (mmol/kg), mean ± SD	364 ± 162	195 ± 94	372 ± 161
24-Hour urine sodium (mmol/d), mean ± SD	150 ± 67	161 ± 67	148 ± 67
24-Hour urine potassium (mmol/d), mean ± SD	65 ± 26	63 ± 27	66 ± 26
24-Hour urine creatinine (mg/d), mean ± SD	1,504 ± 577	1,403 ± 600	1,493 ± 577
24-Hour urine urea (mmol/d), mean ± SD	388 ± 157	370 ± 181	382 ± 153
Spot urine osmolality (mmol/kg), mean ± SD	424 ± 202	211 ± 121	434 ± 201

There was significant discordance at treatment targets of 250 and 270 mmol/kg (24% and 24%, respectively) for all samples (Figure 1). Results were similar when only the first sample from each patient was analyzed (Figure 2). A similar difference was observed in patients treated with tolvaptan (Figures S1 and S2).

The mean difference in urine osmolality and differences of 50, 100, 150, and 200 mmol/kg between spot and 24-hour urine osmolality are shown in Table 2. Across the entire population and considering all spot urine samples (n = 839), more than half (53.9 %) exhibited a difference of >50 mmol/kg between spot urine samples and 24-hr urine samples, while around 16 % displayed a difference exceeding 200 mmol/kg between the 2 categories. In the subset of patients treated with tolvaptan, 36.5% had a difference exceeding 50 mmol/kg between the spot and 24-hr urine samples, and 6.5% exhibited a difference surpassing > 200 mmol/kg between the 2 samples when considering all the available urine samples (n = 122).

Figures 3 and 4 display the Bland-Altman plots of the difference in osmolality. A discernible and consistent divergence between the 2 measurements is evident across the entirety of spot urine samples (n = 839), particularly at higher values of urine osmolality (Figures 3 and 4). This discrepancy is characterized by a wide dispersion spanning the spectrum of mean urine osmolality. Similarly, Figures 5 and 6 showcase a comparable pattern within the subgroup of individuals with 1 urine sample per patient. Within the tolvaptan treated cohorts (Figures S3-S6), a similar systematic bias is observable, albeit with a more confined distribution.

DISCUSSION

Our study reveals that in patients with ADPKD, clinically significant differences exist between spot and 24-hour urine osmolality that precludes interchangeable use. Clinical decision-making therefore should take into consideration the urine osmolality measurement method employed. Urine osmolality measurement has an important place in the management of patients with ADPKD. A post hoc analysis of the TEMPO 3:4 trial showed that the baseline urine osmolality in ADPKD is associated with female sex (biological sex), higher age, presence of hypertension, lower estimated glomerular filtration, and higher total kidney volume[16] indicating that it may be helpful as a prognostic marker. In addition, treatment with tolvaptan reduced Uosm by 200-300 mmol/kg and greater reduction in baseline Uosm was associated with slower decline in kidney function.[17] A feasibility trial of high water intake in patients with ADPKD used Uosm ≤ 270 mmol/kg as target[10] and Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease suggested a urine osmolality target of < 250 mmol/kg in the tolvaptan treated group.[11]

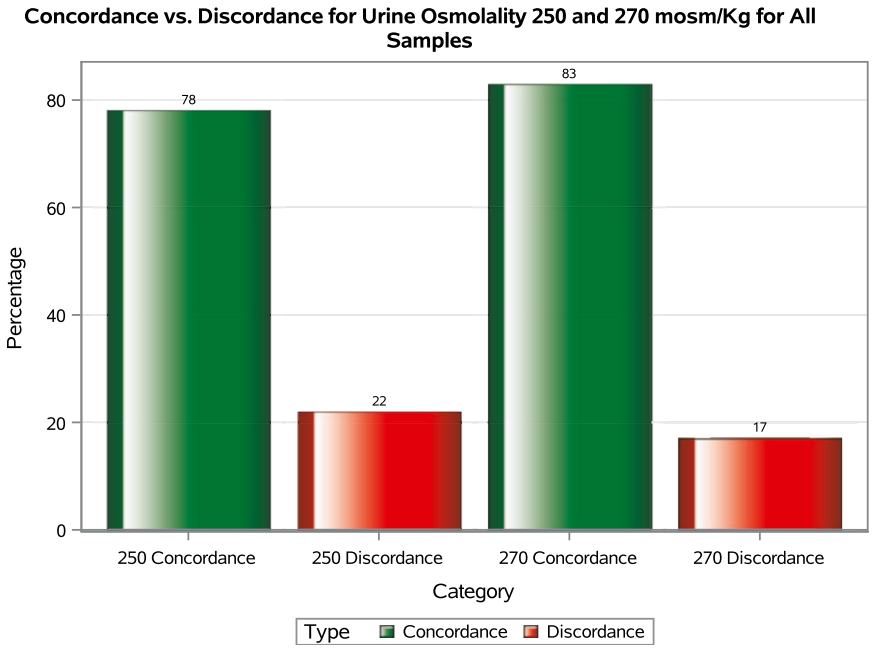

Figure 1. Concordance versus discordance for urine osmolality at 250 and 270 mosm/kg for all samples. This bar chart compares the percentage of concordance and discordance in urine osmolality at thresholds of 250 and 270 mosm/kg across different categories. The green bars represent concordant samples, whereas the red bars indicate discordant samples. The percentages are displayed above each bar.

Important studies in the field of ADPKD have been split on the methods used to assess Uosm. The TEMPO 3:4 and REPRISE studies reported spot urine osmolality. In these studies, 24-hour urine collections were not done because of concern that the urine collections could lead to unblinding.[7,16,18] In contrast, the PREVENT-ADPKD trial reported on 24-hour urine osmolality.[19] Gobburu et al showed that spot urine osmolality in controls versus those

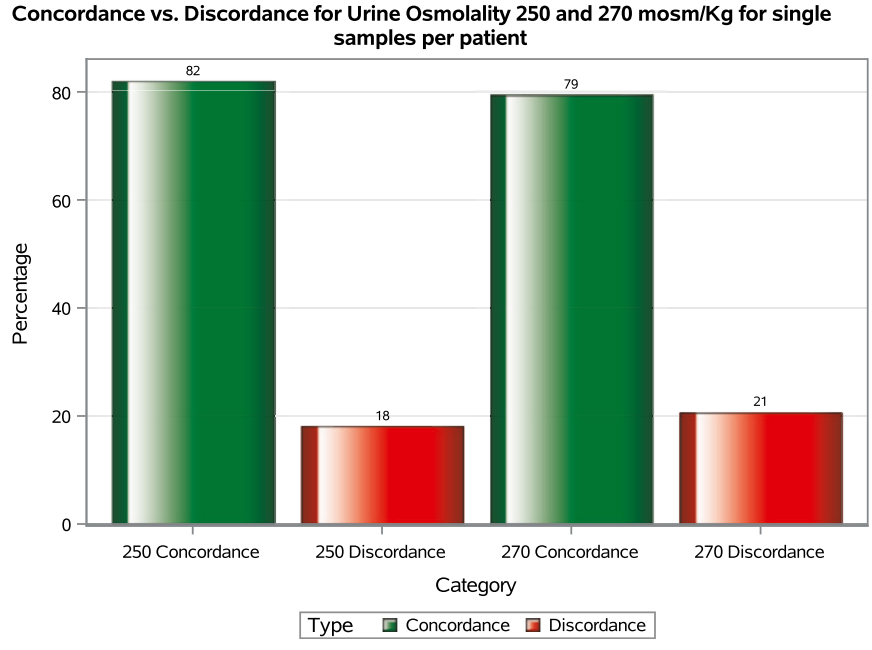

Figure 2. Concordance versus discordance for urine osmolality at 250 and 270 mosm/kg for Induvial Patients. This bar chart compares the percentage of concordance and discordance in urine osmolality at thresholds of 250 and 270 mosm/kg across different categories. The green bars represent concordant samples, whereas the red bars indicate discordant samples. The percentages are displayed above each bar.

Table 2. Osmolality Result Difference Between Spot and 24-Hour Urine Collection

	Mean difference ± SD, mmol/kg	Difference in osmolality > 50 mmol/kg, (n, %)	Difference in osmolality > 100 mmol/kg, (n, %)	Difference in osmolality > 150 mmol/kg, (n, %)	Difference in osmolality > 200 mmol/kg, (n, %)
All measurements n = 839	61 ± 139	452 (53.9%)	300 (35.8%)	202 (24.1%)	135 (6.1%)
Individual patients n = 349	61 ± 153	196 (56.2%)	147 (42.1%)	102 (29.2%)	69 (19.8%)
All measurements of patients on tolvaptan n = 122	37 ± 92	45 (36.6%)	30 (24.4%)	15 (12.2%)	8 (6.5%)
Individual patients on tolvaptan n = 47	15 ± 96	20 (41.7%)	12 (25%)	6 (12.5%)	3 (6.3%)

treated with tolvaptan does not reflect the 24-hour blockade of vasopressin activity in the kidney.[20] To our knowledge, only the DRINK feasibility trial reported both spot and 24-hour urine osmolality; however, no comparison was made between the 2 measurements.[12]

Our study compared spot Uosm measurements to 24-hour urine Uosom measurements in patients with ADPKD. We found significant discordance in urine osmolality at treatment targets of 250 and 270 mmol/kg between spot urine osmolality and 24-hour urine osmolality. The discordance was present in all analyses that we performed (all samples, first available samples, patients on treatment with tolvaptan and patients not on tolvaptan). We noted a difference of more than 50 mmol/kg between spot and 24-hour measurements in 56% of our total study population, with 20% showing difference of more than 200 mmol/kg. This significant difference between spot Uosm and 24-hour urine Uosm was also noted in patients on tolvaptan therapy. In our study, tolvaptan treated patients had a median 24-hour urine osmolality value of 211 mmol/kg. Thus, even in patients with fairly dilute urine, a significant discordance between 24-hour urine osmolality and spot urine osmolality were present. We would consider these differences clinically significant as they may lead to different therapeutic interventions. For example, if urine osmolality was 300 mmol/kg by spot urine osmolality in a patient on tolvaptan where 24-hour urine osmolality was not performed, the clinician might increase dose of tolvaptan but the same patient on 24-hour urine osmolality may have urine osmolality of 240 mmol/kg, which would be at target and no intervention would be needed. Our study clearly indicates that spot Uosm measurements cannot be used interchangeably with 24-hour Uosm measurements.

The limitations of our study include the following: (1) the retrospective study design of the study and we had to

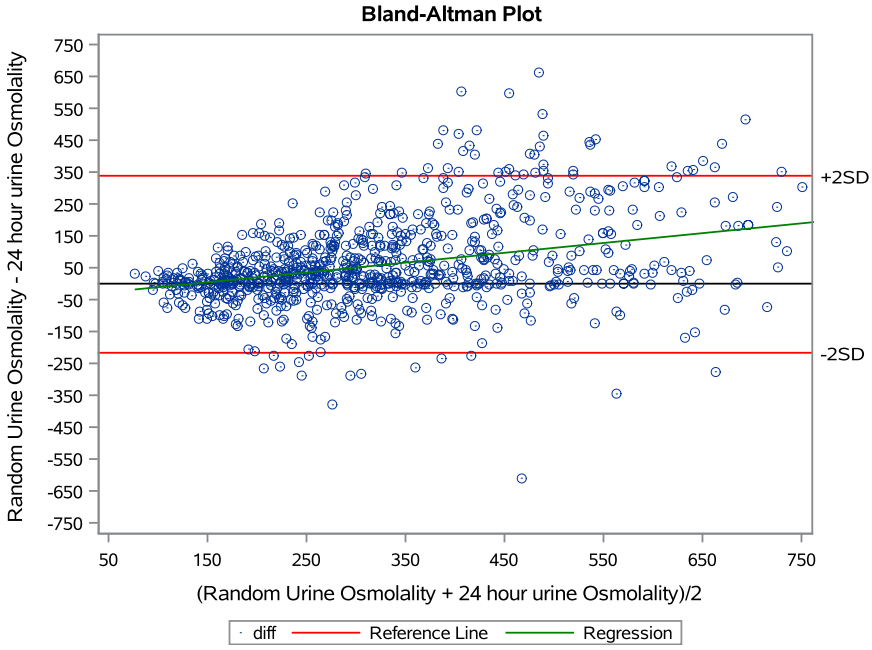

Figure 3. Bland-Altman plot comparing random and 24-hour urine osmolality for all samples. The plot shows the differences between random and 24-hour urine osmolality versus their mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

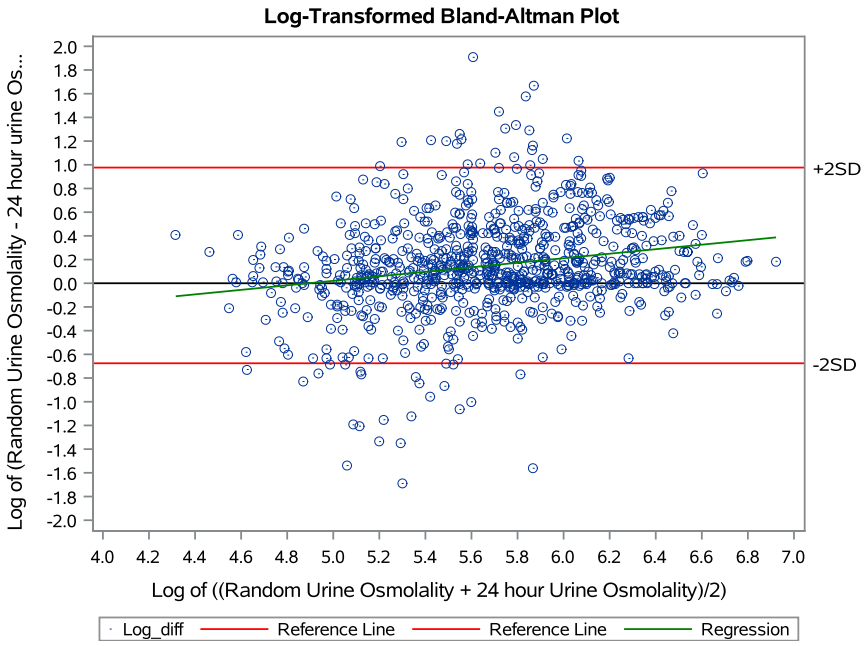

Figure 4. Log-transformed. Bland-Altman plot comparing random and 24-hour urine osmolality for all samples. The plot shows the log-transformed differences between random and 24-hour urine osmolality versus their log-transformed mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

exclude patients that did not have concurrent spot urine osmolality and 24-hour urine osmolality but still our sample size is quite large for this population; (2) the study was conducted at a single center but should be generalizable as standardized techniques were used for measurement of urine osmolality; (3) majority of the patients being of self-reported White race; (4) limited number of patients being on tolvaptan; and (5) we did not

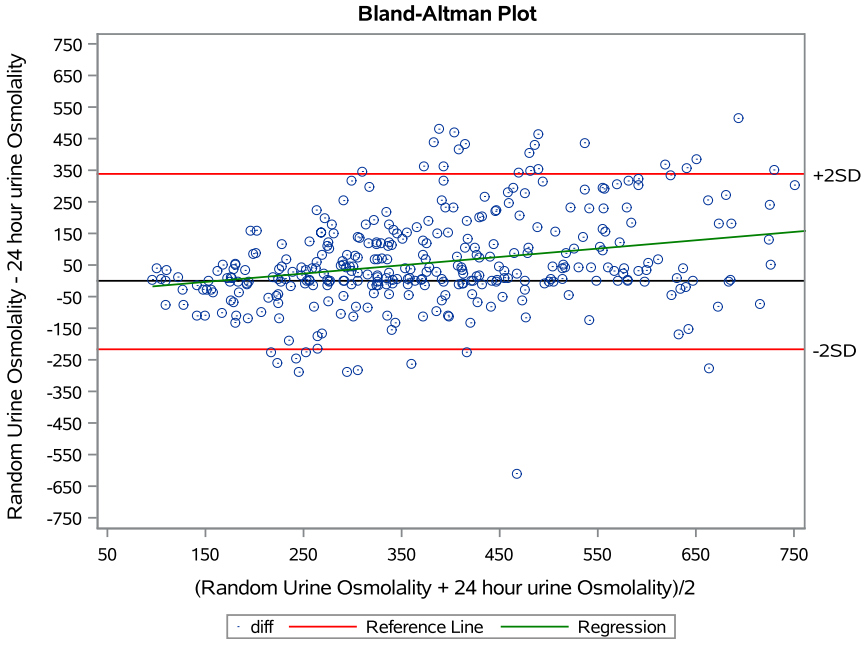

Figure 5. Bland-Altman plot comparing random and 24-hour urine osmolality for individual patients. The plot shows the differences between random and 24-hour urine osmolality versus their mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

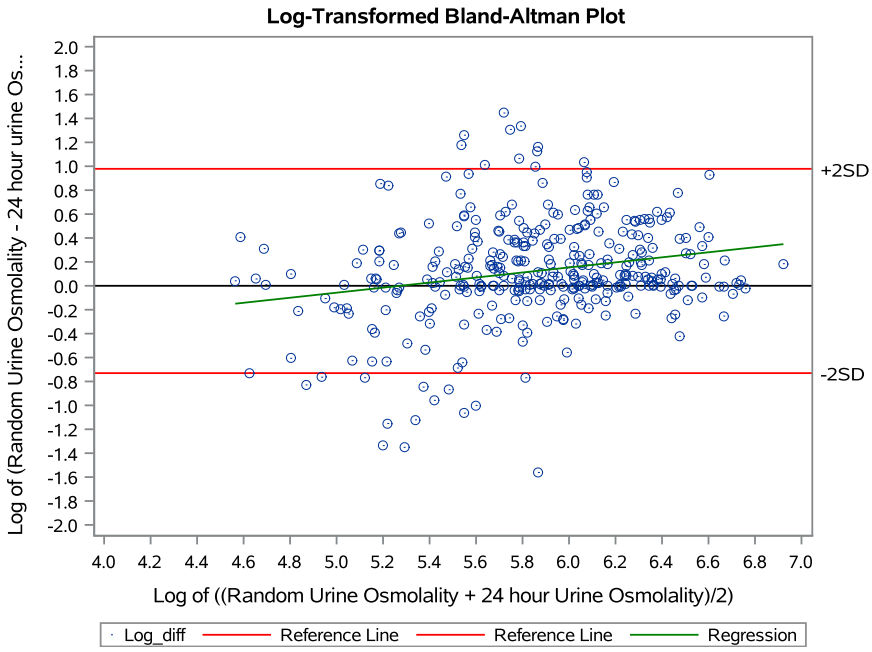

Figure 6. Log-transformed Bland-Altman plot comparing random and 24-hour urine osmolality for induvial patients. The plot shows the log-transformed differences between random and 24-hour urine osmolality versus their log-transformed mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

collect spot urine samples at a particular time. Urine osmolality has circadian variation. Study by Bottin et al indicated that voids between 14:00 to 20:00 approximated 24-hour urine sample.[21]

In summary, our study showed significant discordance between spot and 24-hour urine sample measurements. We demonstrated that there is a significant, clinically relevant difference in the results of spot urine osmolality and 24-hour urine osmolality. Caution should be used when comparing different studies reporting on Uosm, as not all studies use a consistent approach. Routine testing for 24-hour urine may be cumbersome. For patients on tolvaptan, an early morning low urine osmolality may be favorable; however, robust evidence is needed to establish individualized therapeutic objectives for patients with ADPKD. Further studies are required to determine which method should be considered preferable and eventually adopted as the standard of care. Future clinical practice guideline should specify the type of sample to be used for Uosm benchmarks.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Concordance versus discordance for urine osmolality at 250 and 270 mosm/kg for all samples on patients on tolvaptan. This bar chart compares the percentage of concordance and discordance in urine osmolality at thresholds of 250 and 270 mosm/kg across different categories for patients on tolvaptan. The green bars represent concordant samples, whereas the red bars indicate discordant samples. The percentages are displayed above each bar.

Figure S2: Concordance versus discordance for urine osmolality at 250 and 270 mosm/kg for induvial patients on tolvaptan. This bar chart compares the percentage of concordance and discordance in urine osmolality at thresholds of 250 and 270 mosm/kg across different categories for patients on tolvaptan. The green bars represent concordant samples, whereas the red bars indicate discordant samples. The percentages are displayed above each bar.

Figure S3: Bland-Altman plot comparing random and 24-hour urine osmolality for all samples on patients on tolvaptan. The plot shows the differences between random and 24-hour urine osmolality versus their mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

Figure S4: Log-transformed Bland-Altman plot comparing random and 24-hour urine osmolality for all samples on patients on tolvaptan. The plot shows the log-transformed differences between random and 24-hour urine osmolality versus their log-transformed mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

Figure S5: Bland-Altman plot comparing random and 24-hour urine osmolality for individual on patients on tolvaptan. The plot shows the differences between random and 24-hour urine osmolality versus their mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

Figure S6: Log-transformed Bland-Altman plot comparing random and 24-hour urine osmolality for individual on patients on tolvaptan. The plot shows the log-transformed differences between random and 24-hour urine osmolality versus their log-transformed mean. Open circles represent individual specimen. The black line at zero indicates perfect agreement, whereas the red lines show the limits of agreement (±2 SD from the mean difference). The green regression line indicates any potential bias between the 2 measurements.

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