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Correlation of Urinary Foam with Proteinuria in Patients with Chronic Kidney Disease

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Abstract

Background: Foamy urine is often reported to be associated with proteinuria and kidney diseases. There is no objective measure on the nature and correlation of this relationship. Literature reviews revealed very few studies that can confirm or refute this relationship. This study hypothesized that the severity and persistence of urinary foam were associated with the degree of proteinuria (as determined by urine protein-creatinine ratio and dipstick).

Methods: We analyzed urine samples of patients from our chronic kidney disease (CKD) clinics for urine protein and foam. The urine samples were shaken in a standardized way and heights of resting foam (in millimeters) were measured after a pre-determined resting time. The foam heights were correlated with clinical variables including proteinuria, stages of CKD, gender, age, co-morbidities and urine specific gravity.

Results: A total of 160 urine samples were analyzed. Greater foam height was significantly associated with advanced CKD stages (p=0.015), urine dipstick protein (p<0.001), urine PCR (p=0.005) and diabetes mellitus (p=0.013). Urine specific gravity (p=0.053) and hypertension (p=0.91) did not achieve statistically significant results with foam height. Further analyses were performed on 54 urine samples with no or low protein level (defined as urine PCR of less than <100 mg/mmol AND urine protein dipstick result of ≤ 1+). In these samples, there was no statistically significant relationship between foam height and CKD stages (p=0.403), specific gravity (p=0.564), diabetes mellitus (p=0.909) and hypertension (p=0.08).

Conclusion: Our study showed that urinary foam can be used as a rudimentary surrogate marker for proteinuria in patients with CKD. It provides extra leverage to the age-long assumptions that urinary foam is associated with kidney disease and proteinuria. More research will be needed to ascertain and investigate the nature of this relationship.

Keywords: Urine foam; Urine froth; Chronic kidney disease; Proteinuria

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Introduction

Foamy or frothy urine is often associated with proteinuria. Most clinicians and laymen will associate the presence of foam in the urine with some form of kidney diseases. It is often advocated that patients with this condition should consult nephrologists for further evaluations. However, there is no evidence to correlate nature or degree of foaming with clinically proven proteinuria. Our literature review revealed a dearth of reports or research on the subject matter, likely due to the absence of an accepted clinical definition for the condition and a validated approach for assessing foam.

The identification and quantification of urinary protein are important investigations in the management of renal diseases. These investigations play an important role in determining the diagnosis and prognosis of various renal pathologies. There are many methods of estimating and quantifying proteinuria. A 24-hour urine collection for protein estimation is the gold standard

for proteinuria quantification but this is usually cumbersome and time consuming. Urine Protein Creatinine Ratio (PCR) and urine protein dipstick are two common methods of assessing proteinuria. Even though there are issues with sensitivity and specificity [1-3], these methods are universally used because they are convenient and expeditious. In our clinics, we frequently shook urine samples to assess the degree and persistence of foam formation. We recognized that this was not a validated or evidence-based approach but it provided a rapid prediction and estimate on the presence and severity of proteinuria in the absence of laboratory equipment or analyzers.

We hypothesized that the severity and persistence of urine foam were associated with the degree of proteinuria (measured through urine dipstick and PCR). We took the opportunity to correlate clinical factors (severity of renal disease, urine concentration, presence of co-morbid conditions [diabetes mellitus and hypertension]) with the pattern of foam formation.

Materials and Methods

All early morning urine samples sent for urine protein creatinine ratio (PCR) from the chronic kidney disease (CKD) clinics during a three-month time frame were included in the study. The urine samples would have been sent as part of the routine management of chronic kidney disease and not deliberately as part of this research. For this purpose of this study, the urine samples were divided into two parts. The first part was subjected to the usual PCR examination via the automated analyzer. The second part (to contain 10mls in a standard urine bottle) was given to our investigators for urine dipstick test and physical examination for foam. Our investigator manually performed and interpreted the urine dipstick test on each sample. In addition, he examined for the presence of foam by physically shaking the urine bottle twice and allowing the foam to settle for 10 seconds. The amplitude of the shake and the amount of urine in the bottle were standardized by the investigator. The height of the foam head (in millimeters) were measured by a measuring tape.

Demographic data of the patients were collected from case notes and computerized records. The information collected were age, gender, diagnosis, presence of diabetes mellitus and hypertension, and serum creatinine. Research data on urine foam height, PCR, dipstick and specific gravity were recorded and collated with demographic data into an Excel worksheet.

We tested our hypothesis by assessing the relationship of urinary foam height with the relevant clinical variables. In order to eliminate urinary protein as a potential confounding variable, we compared urine samples with no or low level of protein with the same clinical variables. This was defined as urine PCR of less than <100 mg/mmol AND urine protein dipstick result of ≤1+. The data was analyzed through the Statistical Package for Social Sciences (SPSS, Version 16.0, Chicago, IL USA) program with Pearson's correlation being used to compare the categorical variables and Mann-Whitney non-parametric test to compare the continuous variables.

Results

A total of 160 urine samples were analyzed, of which 30 were from Stage 1 CKD, 39 Stage 2 CKD, 37 Stage 3 CKD, 25 Stage 4 CKD and 29 Stage 5 CKD patients. The male to female gender ratio was 1.7. 47% (n=75) and 79% (n=127) of patients were diabetic and hypertensive respectively. The mean and median ages were 55.333 ± 13.947 and 58 years respectively. Advanced CKD stages and diabetes mellitus were significantly associated with increased age, dilute urine and higher level of serum creatinine and urinary protein. The basic demographic comparative data were presented in **Table 1**.

Table 2 demonstrated the relationship between foam height and clinical variables. Greater foam height was significantly associated with advanced CKD stages (p=0.015), urine dipstick protein (p<0.001), urine PCR (p=0.005) and diabetes mellitus (p=0.013). Urine specific gravity (p=0.053) and hypertension (p=0.91) did not achieve a statistically significant relationship with foam height.

Table 3 showed the relationship between foam height and clinical variables in patients with no or low level of proteinuria (defined as urine PCR of less than <100 mg/mmol AND urine protein dipstick result of ≤ 1+). A total of 54 urine samples satisfied the criteria for no or low level of proteinuria. There was no statistically significant relationship between foam height and CKD stages (p=0.403), specific gravity (p=0.564), diabetes mellitus (p=0.909) and hypertension (p=0.08).

Discussion

Hippocrates made the observation that foaming of urine is associated with kidney diseases [4], likely through the presence of urinary albumin. Foaming occurs because albumin has a soap-like effect that decreases the surface tension of urine [5]. Expulsion of urine causes interaction of the electrostatic forces between molecules within the liquid and surface, leading to the formation of bubbles as a result of dispersion of air in the urine liquid. Persistence of bubbles is strongly influenced by the presence of tensioactive substances (protein, bile salts, etc) within the urine. These substances lower the surface tension, causing the formation of bubbles that often do not break [6]. Our PubMed search for 'foamy' or 'frothy' urine revealed only one publication reporting on clinical significance of subjective foamy urine [5]. Kang et al. reported that 16% of 72 nephrology patients who complained of foamy urine had overt proteinuria (defined as spot urine PCR >200 mg/g). A sub-analysis of 38 patients who had albumin creatinine ratio readings showed that 31.6% showed microalbuminuria or overt proteinuria. The same study showed that diabetes, poor renal function, increased serum phosphate and increase serum glucose were associated with overt proteinuria. Kang et al. also acknowledged a Korean language article that reported no dipstick-positive proteinuria among 45 healthy patients complaining of foamy urine [7]. Similar literature search was conducted through Medline and google scholar but no other study addressing this subject was identified. Unverified non-scientific reports have reported the presence of foaming with rapid urination, concentrated urine,

Table 1 Demographic data.

		N	Age (years)	p value	Serum Creatinine (mmol/l)	p value	Urine PCR (mg/mmol)	p value	Urine Specific Gravity	p value
All	Mean		55.333 ± 13.947		267.913 ± 229.435		235.965 ± 248.926		1.018 ± 0.056	
	Median		58		172		150		1.02	
Gender	Male	107	56.146 ± 13.903	0.366*	263.361 ± 227.835	0.757*	255.251 ± 207.744	0.225*	1.019 ± 0.053	0.167*
	Female	63	54.095 ± 14.034		274.921 ± 233.538		206.270 ± 209.417		1.017 ± 0.059	
CKD	Stage 1	30	43.967 ± 13.283	< 0.001**	78.233 ± 24.811	< 0.001**	120.517 ± 204.152	< 0.001**	1.021 ± 0.041	< 0.001**
	Stage 2	39	55.000 ± 15.548		121.795 ± 47.008		148.754 ± 224.420		1.018 ± 0.052	
	Stage 3	37	57.135 ± 13.147		216.351 ± 90.267		267.852 ± 256.901		1.019 ± 0.046	
	Stage 4	25	57.440 ± 11.143		338.040 ± 130.340		340.040 ± 295.229		1.015 ± 0.069	
	Stage 5	29	63.714 ± 6.531		665.965 ± 173.069		342.276 ± 182.191		1.013 ± 0.035	
Diabetes Mellitus	Yes	75	56.716 ± 11.454	0.245**	383.173 ± 270.452	< 0.001**	317.961 ± 231.336	< 0.001**	1.016 ± 0.054	< 0.001**
	No	85	54.129 ± 15.771		166.212 ± 113.472		166.212 ± 113.472		1.019 ± 0.053	
Hypertension	Yes	127	58.087 ± 11.750	< 0.001**	298.843 ± 239.779	< 0.001**	235.370 ± 235.284	0.953**	1.018 ± 0.057	0.152**
	No	33	44.818 ± 16.652		148.879 ± 129.478		238.255 ± 299.839		1.019 ± 0.050	

** Pearson's correlation
* Mann-Whitney test

Table 2 Correlation of urinary foam height with clinical factors (n=160).

Clinical factors		N	Foam Height (mm)	Correlation coefficient	P-value
CKD	Stage 1	30	8.567 ± 2.254	0.192	0.015*
	Stage 2	39	9.820 ± 3.523		
	Stage 3	37	10.811 ± 3.213		
	Stage 4	25	12.600 ± 4.743		
	Stage 5	29	9.828 ± 3.433		
Urine Dipstick	Negative	21	9.095 ± 4.218	0.358	< 0.001*
	1+	55	8.909 ± 10.879		
	2+	66	10.879 ± 3.426		
	3+	18	13.389 ± 4.448		
Urine PCR	≤100	66	9.394 ± 3.200	0.223	0.005*
	101-200	35	10.514 ± 3.221		
	201-300	16	9.813 ± 4.520		
	≥300	43	11.523 ± 3.921		
Urine specific gravity	< 1.015	33	10.181 ± 3.917	-0.153	0.053*
	1.015-1.019	39	12.132 ± 4.319		
	1.020-1.024	46	9.478 ± 2.787		
	≥1.025	43	9.465 ± 3.042		
Diabetes Mellitus	Yes	75	10.918 ± 3.824	-0.196	0.013**
	No	85	9.493 ± 3.286		
Hypertension	Yes	127	10.339 ± 3.681	0.048	0.91**
	No	33	9.909 ± 3.600		

* Using Pearson's correlation
** Using Mann-Whitney test

semen in urine and certain drugs.

Our study is unique because it assessed and correlated the degree of foaming (through foam height) with various clinical factors. We believe that our method is an innovative, simple and practical way of assessing the severity and persistence of foam. This method is easily replicable in settings where there is no immediate facility to assess proteinuria. We validated our hypothesis by confirming a significant association between foam height and proteinuria. This theory holds true because albumin is usually confined in the form of colloidal mixtures in the urine [8,9] and vigorous shaking disrupts the bond that holds the molecules within the colloid leading to electrostatic interactions with surface molecules and affecting surface tension equilibrium. Presumably larger quantities of urinary protein will reduce the threshold for colloidal dispersion of gas in the urine specimens leading to greater foam production.

There were interesting relationships between increased foam height with advanced kidney disease and diabetes mellitus. We

Table 3 Correlation of foam height in samples with no or low level of proteinuria (n=54).

Clinical factors		N	Foam height (mm)	Correlation Coefficient	P-value
CKD	Stage 1	19	8.105 ± 1.997	+0.116	0.403*
	Stage 2	23	9.130 ± 3.507		
	Stage ≥3	12	8.917 ± 2.451		
Urine specific gravity	≤1.015	13	8.538 ± 2.332	+0.078	0.564*
	1.015-1.025	19	8.722 ± 2.653		
	≥1.025	22	8.826 ± 3.055		
Diabetes Mellitus	Yes	11	8.791 ± 2.833	-0.016	0.909**
	No	43	8.454 ± 2.622		
Hypertension	Yes	39	8.923 ± 2.650	+0.243	0.08**
	No	15	8.200 ± 3.098		

* Pearson's Correlation
** Mann-Whitney test

suspected that this relationship was clouded by the fact that advanced CKD and diabetic patients were more likely to have proteinuria, hence contributing to increased foam height. The sub-analysis of samples with no or low level of proteinuria helped us to refute these relationships and jettison the possibility of other causes specific to diabetes and CKD that may have contributed to urinary foam. This strengthened our hypothesis that proteinuria may be the main determinant for urinary foaminess in patients with chronic kidney disease.

Urine specific gravity is the ratio of the density of urine to water and is dependent on the number and weight of solute particles (urea, chloride, sodium, potassium, phosphate, uric acid and sulfate) and on the temperature of the sample [10]. The concept of hyposthenuria (low urine specific gravity) was first observed and introduced by Sandor Koranyi in the early 19th century when he made the astute observation that deterioration of renal function was associated with characteristic changes in the freezing point depression of urine [11]. These observations by Koranyi led to the view that impaired kidney excretory function can lead to decreased excretion of sodium, chloride, phosphate and urea in the urine. This was consistent with our observation that advanced CKD stages were related to decreasing levels of urine specific gravity. Interestingly, we did not observe a relationship between urine concentration and urine foam. We suspect that this could be related to the discordance between the factors that are associated with dilute urine in our patient population. On the one hand, it would be expected that dilute urine (seen in advanced CKD stages) will be associated with a greater degree of proteinuria due to greater kidney damage. On the other hand, dilute urine has less particles that are osmotically active and less likely to disrupt surface tension equilibrium [12,13]. Both these factors may have conflicted resulting in a non-significant relationship between urinary foam and specific gravity.

We believe that more research is needed to investigate the relevance of urinary foam. There is a dearth of suitable and scientifically proven literature on this subject matter. Kalantar-Zadeh [14] highlighted this issue in his article and recommended research on the 'rising epidemic of foamy urine' in which he raised important questions on causes and consequences of foamy urine. A recent abstract from the International Continence Society in 2011 speculated that many possible causes of the frothing of urine may exist but no research has yet been published on why urine can froth [15]. Is the size and intensity of foam a helpful feature for the differential diagnoses? Can different types of urinary protein presents with different foam patterns? Judging by the ubiquitousness of this common condition, we feel that these are pertinent research questions that should be addressed by more research in the future.

The strength of this study lies with the fact that we can estimate or confirm proteinuria through rudimentary means without resorting to quantification via equipment or laboratory means. This can be especially useful in home or outpatients settings (with limited resources) where a rough estimate or prediction can be given to patients, whilst waiting for further time-consuming confirmatory tests. We also feel that this study can provide extra weight and leverage to the common age-long public assumptions that urinary foam is related to diseased kidneys and protein leakage.

This study was limited by our reliance on urine PCR and dipstick as the main determinants of proteinuria. We would have liked to use 24 hour urine protein collections as the yardstick in determining the presence of proteinuria, which would have enabled us to estimate sensitivity and specificity. However, through personal experience with 24 hour urine collections, we foresaw many incomplete and inaccurate collections that would have affected the accuracy of results. We would have like to compare our patients with controls with no renal impairment, but we only had ethical approval to recruit patients from our CKD clinics. Similarly, we were not able to correlate other potentially important serum biochemistry results (glucose, bilirubin, phosphate) with foam formation because the majority of these tests were not performed routinely in the CKD clinics.

Conclusion

Height of urinary foam was associated with proteinuria as determined by urine PCR and dipstick quantification. This effect appeared to be independent to stages of CKD, urine concentration and diabetes mellitus. We also concluded that hyposthenuria was seen in patients with advanced chronic kidney disease, despite the presence of proteinuria. Further studies are needed to assess the impact of other factors (diet, exercise, temperature, sampling time, drugs) on height of urinary foam.

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