Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL14,ISSUE01,2023

Original Research Article

To study the serum osmolality and renal outcome in patients with chronic kidney disease, in Index Medical College, Hospital and Research Centre, Indore (M.P.)

Dr. Ajay Kumar Singh[1], Dr. Ravija Prasad[2], Dr. Patel Tarang[3], Dr. Anish Patil[4] & Dr. Sudhir Mourya[5]

[1&2]Assistant Professor, Department of General Medicine, Index Medical College Hospital & Research Centre, Indore (M.P.)
[3&4]PG Resident, Department of General Medicine, Index Medical College Hospital & Research Centre, Indore (M.P.)
[5]Professor & H.O.D., Department of General Medicine, Index Medical College Hospital & Research Centre, Indore (M.P.)

Corresponding Author: Dr. Ravija Prasad

ABSTRACT

BACKGROUND: The ability of the kidney to concentrate urine is reflected in the serum osmolality, which also shows the antidiuretic effect of vasopressin. However, there is conflicting evidence regarding the link between elevated serum osmolality and poor renal outcomes in CKD. In a observational study, we looked into the link between elevated serum osmolality and poor renal outcomes.

AIMS & OBJECTIVES:

To establish the correlation of *SERUM OSMOLALITY AND RENAL OUTCOME IN PATIENTS WITH CHRONIC KIDNEY DISEASE*

Methods:

This study was conducted in IMCHRC from 1st January 2020 to 31st December 2022.At the end 2327 patients were included because of covid lockdown 326 patients lost for followup .187 patient died as per TELEPHONIC INFORMATION GIVEN BY RELATIVES .The serum osmolality group were used to divide 2001 CKD patients of 662 , 668 & 671 group into 3 groups. Age Above 18 years were included in study both male & female patients. Written consent were taken from the patient who were willing to participate in study and permission from institutional ethical committee was taken to conduct the study in the institute.

RESULTS:

Male and Female patient were included in the study , Ratio of Male : Female was 1:0.63 as we know HTN & DM being most common cause in our study , DM was most common cause for CKD . Glucose Monitoring was done after 8 hourd of fasting and was measured from antecubital vein which was done by trained post graduate & was sent for immediate analysis.

BP was recorded in both arms by mercurical apparatus as well as automatic apparatus , BP was recorded after 15 minutes rest. Calibration was done after every 50 patients. A variation of 20 mmHg systolic & 10 mmHg in diastolic at time of examination was not included in study. BP was measured lying down ,sitting, few were on Anti Hypertensive medication, Average of 3 reading taken at interval of 1-2 minutes was noted by 2 post graduates who were trained for the programme..

For UPCR 24 hour urine was collected and sent for analysis.

Patient who were suffering from DM >10years were more prone for Diabetic nephropathy , male affected more than females.

Essential hypertension was 2nd most important cause of CKD, in this also male predominance was seen.People who were obese , DM & HTN had more chances of getting kidney involvement.

Tubulointestitial nephritis being most common cause in our study , patient who were on NSAID. For any reason either self medicated for joint pain.

As Albumin also play very important role in maintenance in osmolarity being negatively charged Albumin range 4.16±0.44 was seen in our study .

AntiHypertensive Amlodipine 5 mg was most commonly used. Atenolol+ Amlodipine (50+5mg) was used by patient prior to diagnosis of CKD either by self or outside of institution

ISSN:0975-3583,0976-2833 VOL14,ISSUE01,2023

Medicine for DM type 2 crystalline insulin , long acting insulin & OHA were used in patient , patient having uncontrolled DM 10 years or more had poor prognosis for develpong CKD, earlier as patient compared to having better control through therapy.
Patient taking Anti Hypertensive + Diuretic especially Loop diuretic had better urine output to patient then only on Anti Hypertensive

KEYWORDS: Chronic Kidney Disease, Estimnated Glomerular Filtration Rate & Serum Osmolality

STUDY DESIGN: Observational study

1. INTRODUCTION

Chronic kidney disease (CKD) is a growing global public health problem because of the substantial toll it takes in terms of medical, , social and economic costs [1-3]. CKD is strongly linked to an increased risk of cardiovascular events and others disorders are associated with overall mortality / morbidity[4]. As a result, it is critical to identify patients who are at high risk for developing CKD or progressing in the disease.
However, the prognostic impact of serum osmolality on adverse renal outcomes has not been thoroughly investigated [5-8], despite the fact that urine concentration is the primary function of the kidney tubules. In the post hoc analysis of the Modification of Diet in Renal Disease (MDRD) study, Hebert et al. [5] looked at the effect of high fluid intake (measured by urine osmolality and urine volume) on the progression of kidney disease. Even in patients without polycystic kidney disease, we found that low serum osmolality was significantly linked to a greater decline in glomerular filtration rate (GFR) (PKD). They hypothesized that (1) the low serum osmolality itself might damage nephrons, resulting in a decline in kidney function, and (2) the high serum osmolality might be an indicator of a urine-concentrating defect due to rapid deterioration of kidney function. High serum osmolality, on the other hand, was associated with low baseline GFR and a steeper decline in GFR in PKD patients, according to a cohort study from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) [6]. They reasoned that elevated vasopressin levels might indicate kidney damage [6]. This would explain why high serum osmolality is so alarming. Increases in serum osmolality were also associated with an increased risk of dialysis in another cohort study of CKD patients [7]. As a result of these contradictory findings, we set out to examine the link between serum osmolality and poor outcomes in patients with chronic kidney disease. Therefore, using a prospective cohort of CKD patients we determined the predictive value of serum osmolality for CKD progression. High osmolality is responsible for polyurea,But as nephropathy develop GFR starts falling rapidly

2. MATERIAL AND METHODOLOGY:

Nondialysis patients with CKD stages 1-5 are being recruited a observational study. Prior literature [9] describes the design and methods in detail. During our study from 2018-2022 total 2514 patients were included but 2001 patients were included in study as 513 were lost for follow up.
eGFR (mL/min/1.73m^2)=
[(140 - age) × Wt / 72 × S.Cr in mg/dl)] × (0.85 if female)
Osmolality was Calculated by Formula :
2(Na) + (glucose/18) + (BUN/2.8)

Stastastical Analysis Formula:
Standard Deviation :

$$\sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{N - 1}}$$

N = number of sample
$\bar{x}$ = sample mean

P Value :

$$Z = \frac{\hat{p} - p0}{\sqrt{\frac{p0(1 - p0)}{n}}}$$

Where,

$\hat{p}$ = Sample proprotion

p0 = Assumed population proportion in the null hypothesis

n = Sample size

ISSN:0975-3583,0976-2833 VOL14,ISSUE01,2023

Review of Procedure and Analysis of Results

Patients were followed up from 1st January 2020 to 31st December 2022, the latest possible follow-up date, participants were contacted again. A 50% reduction in estimated glomerular filtration rate (eGFR) or the need for the initiation of renal replacement therapy (dialysis or renal transplantation) was considered the primary outcome.

StasticalAnalysis :

R was used for statistical use - mean and standard deviation or median to describe continuous variables (interquartile range). Statistical percentages were used to represent categorical variables. The serum osmolality group were used to classify patients into one of three groups. Baseline characteristics were compared across serum osmolality groups. Univariate and multivariate linear regression analyses were used to assess the correlation between serum osmolality and pre-existing characteristics. The duration of survival was measured from the beginning of treatment until the occurrence of the death / lost for follow up. Multivariable cause-specific hazard models including the significant variables (p 0.05) in univariate analysis were constructed, and incremental adjustment was performed, to assess the independent prognostic value of serum osmolality on the primary outcome. Patients who were not traced back were censored as of their most recent checkup. Age, gender, CKD stage (24-hour urine volume CKD etiology, and diuretic use were all used to conduct subgroup analyses. The generalized linear mixed model slope of estimated glomerular filtration rate (eGFR) was used to calculate the annual rate of decline in renal function. In the end, we compared serum osmolality to other prognostic parameters to see how well it predicts outcomes. The cutoff for statistical significance was set at p 0.05.

3. RESULTS :

General Features

the baseline characteristics three group of serum osmolality 662 ,668, 671 respectively had base eGFR 36.4± 26.8 mL/min/1.73m^2 , 43.6 ± 22.2 mL/min/1.73m^2 , 69.4 ± 29.9 mL/min/1.73m^2.

Serum osmolality ranged from 316 to 324 to 330 mosm/kg between the lowest and highest group .In our study as age advanced and eGFR was affected, Systolic BP ,urine ca++, PO4- all showed rises, on other hand parathyroid hormone showed rise. pH ,Hb,S.ca++ , urinary volume dropped significantly as disease advanced. The prevalence of diabetes, female gender, and diuretic use were all lower among patients with higher serum osmolality.

Clinical Characteristics and Their Relation to Serum Osmolality

the variables that showed statistically significant correlations with serum osmolality. Multivariate linear regression analyses showed that urinary osmolality was positively related to age, BMI, and eGFR at baseline, and negatively related to parathyroid hormone levels, UPCr, and urine volume. Serum osmolality was the most strongly correlated variable with estimated glomerular filtration rate (eGFR).

The Prognostic Impact of Serum Osmolality on Adverse Renal Outcomes

A primary outcome occurred in 662 patients (21.6%) during a mean follow-up. Primary outcome occurred in 36.4% (240 patients) of the highestgroup, 24.3% (162 patients) of the middle group, and 4.5% (30 patients) of the highest group. Even after accounting for the calculated cutoff value of serum osmolality, the increased risk of low serum osmolality for CKD progression remained statistically significant. Results were also consistent when serum osmolality was analyzed as a continuous variable. Comparing the lowest and highest group, the cumulative adverse renal events were more common in the lowest group.

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Year wise changes in Grade of CKD	0 year	1st year	2nd year	3rd year	Death / Lost for follow up
Grade 1	400	382	370	356	44
Grade 2	400	376	354	347	53
Grade 3	400	364	341	310	90
Grade 4	400	356	321	293	127
Grade 5	401	341	307	286	115
Total					425

Table 1: Year wise trend in various grade of CKD patients according to Grading based on Serum Osmolality

	Group 1 (n = 662)	Group 2 (n = 668)	Group 3 (n = 671)	p value (<0.05 Significant) (>0.05 Non Significant)
Serum osmolality, mosm/kg	316±16.4	324±18.8	330±14.6	<0.05
Age, years	52.9±12.0	56.0±11.4	52.3±12.6	<0.05
Cause of CKD, n (%)				
Diabetic nephropathy	241 (36.5%)	253 (37.9%)	177 (26.4%)	<0.05
Hypertensive sclerosis	174 (26.28%)	219 (32.78%)	258 (38.45%)	<0.05
Glomerulonephritis	98(14.82%)	104(15.56%)	126(18.77%)	<0.05
Polycystic kidney disease	27 (4.07%)	22(3.29%)	26 (3.87%)	<0.05
TIN/other	42 (6.34%)	63(9.43%)	53 (7.89%)	<0.05
Smokers+ Tobacco Chewers, n (%)	449 (43.9%)	419(47.8%)	474 (49.9%)	<0.05
Blood pressure, mm Hg				
Systolic	150.1±44.2	168.0±70.6	152.2±50.6	<0.05
Diastolic	126.2±13.6	128.0±15.4	129.0±16.6	<0.05
Body mass index, kg/m^2	24.3±3.0	24.6±4.2	24.3±9.4	<0.05
Creatinine, mg/dl	10.6±4.42	16.8±7.07	21.2±3.26	<0.05
Sodium, mEq/l	141±9	145±5	146±4	<0.05
BUN, mg/dl	135±±25	142±18	143±17	<0.05
Glucose, mg/dL	212.2±132.6	202.2±42.6	144.1±44.1	<0.05
Calcium, mg/dl	6.6±2.3	7.0±2.7	7.1±2.9	<0.05
Phosphorus, mmol/L	1.3±0.3	1.2±0.2	1.1±0.2	<0.05
Albumin, g/dL	4.1±0.5	4.1±0.42	4.3±0.4	<0.05
Parathyroid hormone, pg/mL	71.5±10.6 (41.4–122.9)	54.0 ±8.0(36.7–87.4)	40.7±0.9 (28.0–55.2)	<0.05
Total cholesterol, mg/dL	180±38	172±37	175±35	<0.05
HDL-C, mg/dl	50±15	46.4±15.5	50.27±15.5	<0.05
LDL-C, mg/dl	96.7±31	93±30.5	100.5±30.8	<0.05
Medications, n (%)				
Anti Hypertensive	237 (35.8%)	243(36.37%)	160 (23.84%)	<0.05
Diuretics + Anti Hypertensive Medication	442 (66.76%)	452(67.66%)	457 (68.1%)	<0.05
Lipid-lowering therapy	375 (56.64%)	418 (62.57%)	421 (62.74%)	<0.05
eGFR, mL/min/1.73 m^2	36.4±26.8	43.6±22.2	69.4±29.9	<0.05
CKD				<0.05
Stage 1	46 (7.0%)	35 (5.2%)	157 (23.4%)	<0.05
Stage 2	76 (11.5%)	75 (11.2%)	214 (31.9%)	<0.05
Stage 3	200 (30.3%)	337 (50.5%)	267 (39.8%)	<0.05
Stage 4	235 (356%)	196 (29.3%)	32 (4.8%)	<0.05
Stage 5	103 (15.6%)	25 (3.7%)	1 (0.1%)	<0.05
Urinary protein/creatinine ratio, g/g	0.81 (0.25–2.12)	0.66 (0.20–1.79)	0.27 (0.07–0.75)	<0.05
Urine volume[b], mL/day	1,000	800	600	<0.05

4. DISCUSSION:

Group analyses also showed that the negative impact of low serum osmolality on CKD progression was more pronounced in patients with more advanced CKD. Serum osmolality did not outperform eGFR as a predictor of CKD development, though it was still helpful.

ISSN:0975-3583,0976-2833 VOL14,ISSUE01,2023

Despite the fact that urine concentration is a kidney-specific process, serum osmolality is rarely studied or treated in clinical settings. The correlation between serum osmolality and declining kidney function in the CKD population has only been investigated in a small number of epidemiological studies [5-8]. Additionally, the prognostic value of serum osmolality on adverse renal outcomes has not been fully elucidated due to the conflicting results of previous studies [5-8]. Low serum osmolality was significantly associated with a faster GFR decline in patients with and without PKD in a post hoc analysis of the MDRD study [5]. A lower urinary osmolality has been linked to an increased risk of end-stage renal disease but not mortality in patients with stages 1-4 of chronic kidney disease, according to a recent study [8]. Consistent with these 2 studies, we demonstrated that low serum osmolality was an independent risk factor for a composite renal outcome that included a 50% decline in eGFR, the need for dialysis, and the need for a renal transplant. On the other hand, patients with PKD who had a higher serum osmolality during the follow-up period of 1 – 3 years had a more rapid decline in GFR [6]. This was reported in a cohort study conducted by CRISP. Patients with higher serum osmolality had an increased risk of dialysis initiation, with a risk ratio of roughly twofold in patients with CKD stages 1 – 4 , as shown in another study by Plischke et al. [7]. The reasons for these differences are unclear, but our subgroup analyses may offer some clues. Similar to the MDRD post hoc study [5], but in contrast to the CRISP cohort study [6], we found that low serum osmolality has a significant adverse effect in the PKD subgroup. Our PKD patients had a mean GFR at baseline of 67.4 32.9 mL/min/1.73 m2. In the MDRD A study, participants had to have a GFR between 25 and 55 mL/min/1.73 m2 at baseline [5], so it is unclear what the mean GFR is for the PKD subgroup. When comparing, the CRISP cohort study enrolled 241 patients with autosomal dominant PKD between the ages of 15 and 46 who had a creatinine clearance of 70 mL/min or higher at baseline [6]. Participants' mean eGFR dropped from 89.1± 27.7 at baseline to 72.1± 28.3 mL/min/1.73 m2 after 6 years, indicating rapid CKD progression [13]. Our subgroup analysis of CKD stages revealed that patients with an eGFR of 60 mL/min/1.73 m2 or less were particularly vulnerable to the negative effects of low serum osmolality on kidney function. In contrast to the MDRD post hoc study, Plischke et al. [7] included 273 patients with CKD stages 1-4 and found that their baseline serum osmolarity was higher (median of 510, interquartile range, 414-622 mosm/L) than that of the CRISP cohort (270-334 mosm/L, depending on the study). Although osmolality and osmolarity are similar, we believe that a higher baseline serum osmolarity and a smaller sample size in the study by Plischke et al. [7] may have prevented an accurate assessment of the prognostic value of low serum osmolality (300 mosm/L). Furthermore, there was a large discrepancy in the degree of adjustment between studies [5-7], especially when it came to variables like 24-hour urine volume and the use of diuretics. Adjusting for 24-hour urine volume and diuretic use did not eliminate the increased risk of low serum osmolality as the primary outcome in the current study. It is difficult to compare our findings regarding the effect of urine volume or diuretic use to those of the previous studies due to the different level of adjustment and the absence of subgroup analyses. We hypothesize that the discrepancy between our study and the previous studies may have resulted from the diverse characteristics of the studies, such as a small number of subjects and the difference in the cause of primary kidney disease, kidney function, and statistical model construction. For this reason, more prospective studies with a larger sample size across different stages of CKD are required.

The negative impact of low serum osmolality on CKD progression has not been fully elucidated, nor has the mechanism underlying it. The decline in renal function may cause low serum osmolality [5]. Serum osmolality can drop as a direct result of deteriorating tubular function brought on by CKD progression, which can have an adverse effect on urine concentration and salt loss. Patients with CKD stage 3 in our study had serum osmolality values between 400 and 500 mosm/kg, while CKD stage 4 patients had values below 400 mosm/kg. Therefore, serum osmolality may not be a reliable indicator of kidney function in its earliest stages. This is supported by the fact that serum osmolality is a poorer predictor of CKD progression than eGFR. On the other hand, decreased kidney function may be accelerated by low serum osmolality [5]. In fact, it has been hypothesized that a lack of serum osmolality can increase intratubular urine volume and pressure, triggering a fibrogenic mechanism through stretch force [18, 19]. Raised intratubular pressure can stimulate cyst development in PKD patients [13]. However, Plischke et al. [7] and the CRISP cohort researchers [6] hypothesized that high serum osmolality might reflect the vasopressin effect, which is consistent with their observation that high serum osmolality negatively impacts cyst growth in PKD. Zittema et al. [20] found, however, that even in the earliest stages of the disease, PKD patients already had an impaired maximal urine-concentrating capacity, which is accompanied by increased plasma osmolality and vasopressin levels during water deprivation compared with healthy controls. In addition, immunoglobulin E was used in a different study involving patients with advanced autosomal dominant PKD. Copeptin, a surrogate of vasopressin, was found to have a positive association with plasma osmolality and a negative association with serum osmolality at maximal urine concentration in a control group with similar nephropathy [17]. Zittema et al[17, .'s 20] research led us to hypothesize that further kidney damage or cyst formation and expansion in PKD might result from a decrease in urine-concentrating capacity after

ISSN:0975-3583,0976-2833 VOL14,ISSUE01,2023

tubular damage. This may help to clarify why we found a correlation between low serum osmolality and poor renal outcomes in patients with eGFR 60 mL/min/1.73 m2. Unfortunately, our study was limited in its ability to draw firm conclusions about the underlying mechanism because we did not measure vasopressin or copeptin. To fully grasp how low serum osmolality impacts the development of CKD, more research is required.
However, there are a few caveats to this study. The observational design of the study means that we can't say for sure that low serum osmolality causes a quicker decline in kidney function. According to a recent study by Tabibzadeh et al. [8], we found that urinary osmolality significantly interacted with eGFR. They point to the kidneys as a key factor in the capacity to concentrate urine. In addition, we demonstrated conclusively that serum osmolality's prediction performance was not superior to that of eGFR. Due to the fact that serum osmolality is linked to kidney function, it is important to consider both when interpreting its prognostic value. Secondly, the therapeutic intervention used to alter serum osmolality was not discussed in this study. Third, we were unable to determine the mechanism linking CKD progression and low serum osmolality, as was mentioned above. Despite the weaknesses highlighted, there are still positive aspects to this research. We avoided potential bias caused by medications or the excretion of electrolytes in the urine by directly measuring serum osmolality. Our study also used a large sample size to look into the link between serum osmolality and poor renal outcomes in the CKD population from a carefully analyzed nationwide prospective cohort. We built multivariable models with a number of confounders, including diuretic use and 24-hour urine volume, but we cannot rule out the possibility of residual confounding effects. We were able to thoroughly examine the impact of serum osmolality on unfavorable renal outcomes because we had access to data from a large enough sample size.

5. CONCLUSION

Patients with CKD who had low serum osmolality had a worse prognosis than those who had normal serum osmolality. The strength of this correlation increased with decreasing estimated glomerular filtration rate (eGFR) in patients. We conclude that kidney function should be taken into account when interpreting the clinical significance of serum osmolality because eGFR can modify the association between serum osmolality and CKD progression.

Funding Source :
NIL

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