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Original Research Article

A case control study of asymptomatic hyponatremia in patients with chronic kidney disease

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ABSTRACT

Background: This study has been conducted to assess the association between asymptomatic hyponatremia with cognitive dysfunction, bone health, quality of life and various inflammatory markers in non-dialysis chronic kidney disease patients.
Methods: A single centre hospital based observational case-control study conducted at a tertiary care hospital in eastern India. Non dialysis chronic kidney disease patients with (case) or without (control) asymptomatic hyponatremia were included in the study after proper assessment of inclusion and exclusion criteria. Relevant clinical and laboratory parameters were recorded. C reactive protein and interleukin 6 were measured and T score was assessed by dual-energy X-ray absorptiometry (DEXA) scan at lumbar vertebra (L1 to L4). For cognitive function assessment, Bangla adapted mental state examination (BAMSE) score was calculated and activities of daily living (ADL) score was also recorded.
Results: 38 patients in the control group and 37 patients in the case group came for follow-up visit. Significant positive correlation was found between serum sodium levels with the DEXA scan (T-scores). On the other hand, significant negative correlation was found between serum sodium with C-reactive protein (CRP) and interleukin-6 (IL-6) levels. Though BAMSE scores and ADL scores showed a positive correlation with serum sodium levels, the result was not statistically significant.
Conclusions: We conclude that asymptomatic hyponatremia in non-dialysis chronic kidney disease patients has significant association between DEXA scan T score and various inflammatory parameters like C reactive protein and interleukin 6. This may indicate possible role of prevention and treatment of this common electrolyte abnormalities to avoid effect of poor bone health and chronic inflammation in such a vulnerable population.

Keywords: Chronic kidney disease, Asymptomatic hyponatremia, DEXA score, BAMSE, ADL, IL-6, CRP

INTRODUCTION

Hyponatremia is the most common electrolyte disorder in clinical medicine and can be encountered in a variety of diseases.[1] Complications associated with hyponatremia that is more severe (<125 mmol/l) and evolves rapidly (over hours), can include seizures, coma, and cardiopulmonary arrest, and can be life threatening.[2] Asymptomatic hyponatremia is usually associated with mild to moderate chronic hyponatremia (<125-135 mmol/l). These patients do not present with any overt symptoms and is commonly missed in day-to-day practice. Symptoms of asymptomatic hyponatremia often include lethargy, restlessness, disorientation, headache, nausea and vomiting, muscle cramps and depressed neural reflexes, are rather non-descript. Chronic kidney disease (CKD) is known to affect the ability of the kidneys to regulate water homeostasis, and hence the risk of both hypo- and hypernatremia can increase with advancing stages of CKD.[3]

It has been seen in various studies that asymptomatic chronic hyponatremia is associated with functional and cognitive decline, alteration of gait and increased tendency to falls, loss of bone mineral density and low dual-energy

X-ray absorptiometry (DEXA) scores leading to increased risk of fractures.[4-7] All these have a direct bearing on the quality of life this people live. Hyponatremia is also associated with an increase in levels of various inflammatory biomarkers.[8] CKD is known to be associated with chronic inflammatory state, early cognitive dysfunction, low bone mineral density and increased tendency to falls.

Unfortunately, there is lack of data regarding impact of asymptomatic hyponatremia in CKD population. We had conducted this study to find association of asymptomatic hyponatremia with cognitive dysfunction, bone health, quality of life and various inflammatory markers in non-dialysis CKD patients. This kind of data is lacking in the community.

METHODS

This is a single centre hospital based observational case-control study study conducted at Institute of Postgraduate Medical Education and Research (IPGME&R), Kolkata, one of the largest tertiary care centres of Eastern India from September 2021 to February 2023. Patients presenting in the Nephrology Department of IPGME&R with CKD stages II-IV during the study period and meeting the criteria for cases or controls were enrolled after informed written consent.

Case was defined as the participant with asymptomatic hyponatremia i.e., sodium less than or equal to 135 meq/l and without any overt symptoms of hyponatremia in non-dialysis dependent CKD population. Control was defined as patients with sodium levels between 135-145 meq/l in non-dialysis dependent CKD patients.

Patients having overt symptoms of hyponatremia (like nausea, vomiting, headache, confusion, loss of energy, drowsiness, fatigue, restlessness, irritability, muscle weakness, spasms, cramps, seizures, or coma), women with pregnancy or lactating women, deranged liver function tests, severe disabling or life-threatening symptoms related to chronic kidney disease, hypothyroidism, adrenal dysfunction and serum sodium levels less than 125 meq/l and more than 145 meq/l were excluded from the study.

All participants underwent a detailed clinical evaluation and findings were entered in a case record form. Medical history included age, sex, associated comorbidity, particularly diabetes and hypertension, chronic kidney disease etiology and duration. Serum sodium levels were estimated using EasyLyte REF2120 Na/K analyzer. Serum calcium and phosphate estimations were done with Transasia EM 360 using cooled reagent position. The concentration of creatinine in serum was analyzed on an automated analyzer using the Roche/Cobas CREJ2 assay based on Jaffe's method. CRP and IL-6 were measured by nephelometry and enzyme linked immunosorbent assay (ELISA) respectively. NT Pro BNP was also measured once only at baseline and data recorded in pg/ml.

T score was assessed by DEXA scan at lumbar vertebra (L1 to L4). T score of less than –2.5 was classified as osteoporosis and a T score between –1 to –2.5 was classified as osteopenia according to World Health Organization (WHO) criteria. For cognitive function assessment, Bangla adapted mental state examination score (BAMSE) was calculated based on the pre formed proforma available. Scoring was allotted out of 30. Activities of daily living (ADL) score was also recorded once at baseline with the help of Katz index of independence in activities of daily living. The total score was given out of 6.

Statistical analysis

Data were collected in Microsoft excel sheet and all data were analyzed using statistical package for the social sciences (SPSS). All data were expressed as mean±SD, median or proportions. Independent samples t-tests were computed for all recorded variables of BAMSE score, ADL scores, DEXA scans, inflammatory biomarkers, and biochemical data between groups of "normonatremia" and "asymptomatic hyponatremia". Multivariate t-tests of mean comparisons adjusting for comorbidity and epidemiology had been computed using independent samples t-tests. All tests were two sided, with alpha error of 0.05. A multivariable linear regression model was used to examine associations between BMD and hyponatremia, controlling for comorbidities and diuretics. Results were expressed as 't' values with 95% confidence intervals (CIs).

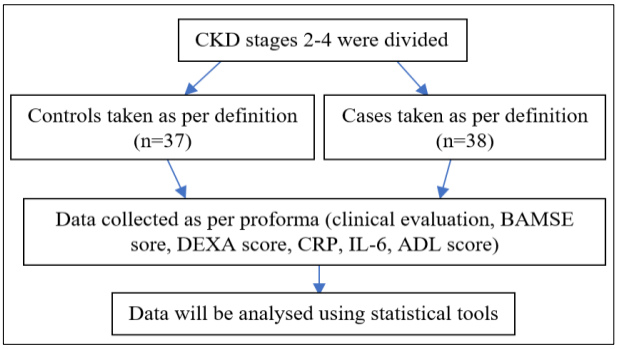

Figure 1: The methodology of the study.

RESULTS

In this study, 41 patients were recruited into the case and control group each; patients were advised to follow up with the test results. 38 patients in the control group and 37 patients in the case group came for follow-up visit. Among the cases, 16 (43.3%) were female and 21 (56.7%) were male. Number of female and male in the control group were respectively 16 (42.1%) and 22 (57.9%). Most of the patients based on socioeconomic status in the case group belonged to upper middle class and lower middle-class

group (29.7%) and in the control group to the lower middle-class group (34.2%). In the case group; 46% had stage 4 CKD, 30% had stage 3b CKD, 16% had stage 3a CKD and rest 8% had stage 2 CKD. In the control group; 42% had stage 4 CKD, 26% had stage 3b CKD, 19% had stage 3a CKD and rest 5% had stage 2 CKD. 45% (34) of the patients of the total study group were on loop diuretics; 47.4% (18) of the control group and 43.2% (16) of the cases group were on loop diuretics. 42.1% (16) of the controls and 48.6% (18) of the cases were on angiotensin converting enzyme (ACE) inhibitors.

On comparing the serum sodium levels with different parameters of interest (BMI, BAMSE score, ADL score, CRP level, eGFR, IL-6, NT-Pro BNP, DEXA score) by applying linear regression analysis and using the unpaired 't' test between cases and controls; CRP value, IL-6 levels DEXA score were found to be significantly associated with chronic asymptomatic hyponatremia.

Comparing the serum sodium levels with the DEXA scan (T-scores), a positive correlation was found and the association was statistically significant (F change= 0.005739). These two parameters were compared between the cases and controls and the result was found to be significantly different between the two (p=0.012). The data was analysed between 16 cases and 14 controls as all the participants did not undergo DEXA scan.

Serum sodium levels when compared with C-reactive protein levels and interleukin-6 levels both the data were found to show a negative correlation and the result was statistically significant (significant F change was 0.001 and 0.001 respectively). These parameters when compared between the cases and controls also showed a statistically significant result (p=0.001 and p=0.001 respectively).

By making a multilinear regression model based on available data; results of coefficient were obtained adjusting to for other independent variables. BAMSE scores, ADL scores, eGFR and NTPROBNP all showed a positive correlation with serum sodium levels but the result was not statistically significant. BMI showed a positive correlation with the serum sodium levels with the coefficient being 0.235 and it was statistically significant (p=0.026). CRP and IL-6 levels showed a negative correlation with the serum sodium levels with the coefficients being -0.428 and -0.308 and it was found to be statistically significant (p=0.001 and p=0.004).

Table 1: Baseline characteristics of the cases and controls.

Characteristics	Cases		Controls	
	Mean	SD	Mean	SD
Age (years)	43.03	16.329	41.71	15.801
Height (cm)	144.27	6.818	146.58	8.976
Weight (kgs)	53.35	6.533	55.32	10.113
BMI (kg/m^2)	25.697	3.1631	25.832	4.44
HB (g/dl)	9.954	1.4955	10.497	1.259
Creatinine (mg/dl)	2.432	0.8090	2.421	0.9724
Sodium (meq/l)	130.65	2.017	139.5	3.335
GFR (ml/min/1.73m^2)	34.81	16.821	36.66	17.507
CRP (mg/dl)	30.7086	12.195	25.58	15.318
IL6 (ng/ml)	5.097	2.0603	3.279	1.9984
NT PRO BNP (pg/ml)	2280.30	2898.254	2724.89	3301.792
DEXA (T scores)	-2.18569	-0.70172	-1.49871	0.70268
BAMSE	26.43	1.725	27.03	1.910
Activities of daily living (ADL) score	5.59	0.686	5.76	0.490

Table 2: Native kidney disease distribution in the cases and controls.

Native kidney disease (NKD)	Cases		Controls	
	Frequency	Percentage	Frequency	Percentage
Chronic glomerulonephritis (CGN)	12	32.4	12	31.6
Chronic interstitial nephritis (CIN)	9	24.3	13	34.2
Obstructive uropathy	6	16.2	4	10.5
IgA nephropathy	2	5.4	2	5.3
ANCA	1	2.7	1	2.6
Diabetic kidney disease (NKD)	6	16.2	6	16.2
Thrombotic microangiopathy (TMA)	1	2.7	0	0
Membranous nephropathy (MN)	0	0	1	2.6
Focal segmental glomerulosclerosis (FSGS)	0	0	1	2.6
ADPKD	0	0	1	2.6

Table 3: Association of different parameters with serum sodium levels using unpaired T score.

Parameters	Cases		Controls		P value
	Mean	SD	Mean	SD	
BAMSE score	26.43	1.725	27.03	1.910	0.162
ADL score	5.59	0.686	5.76	0.490	0.223
CRP level	30.7086	12.1952	18.6211	8.95509	0.001
eGFR	34.81	16.821	36.66	17.507	0.643
IL-6	5.097	2.0603	3.279	1.9984	0.001
NT-Pro BNP	2280.30	2898.254	2274.89	3301.792	0.538
DEXA score	-2.18560	0.701725	-14.9871	0.702678	0.012

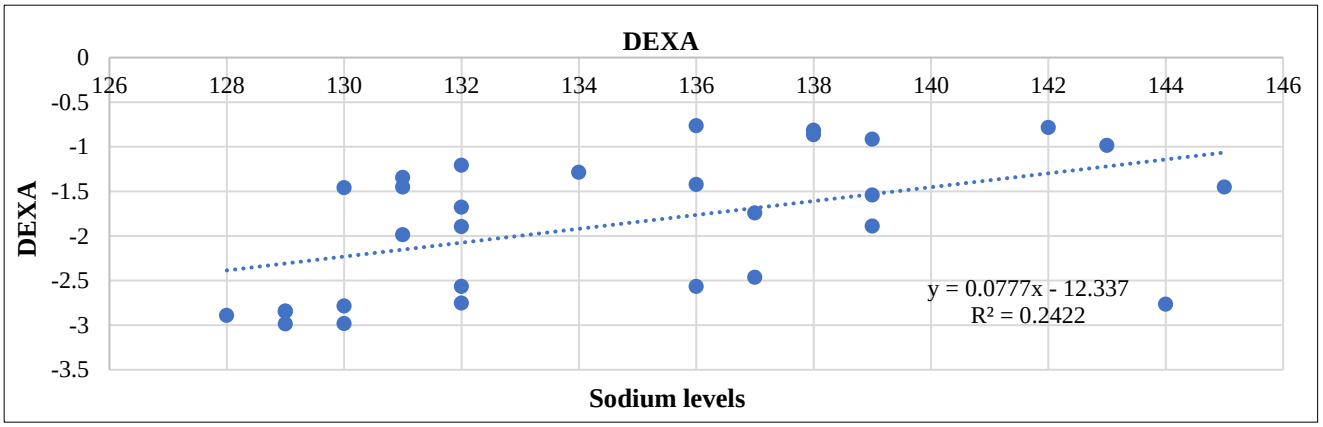

Figure 2: Linear distribution of the DEXA scan levels with serum sodium levels in the study population.

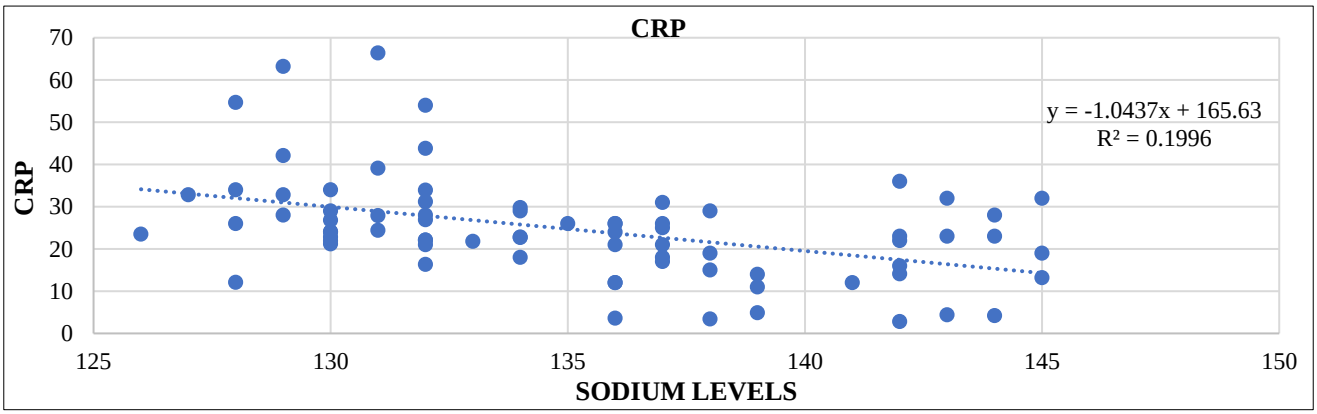

Figure 3: Linear distribution of the C-reactive protein along with the serum sodium levels.

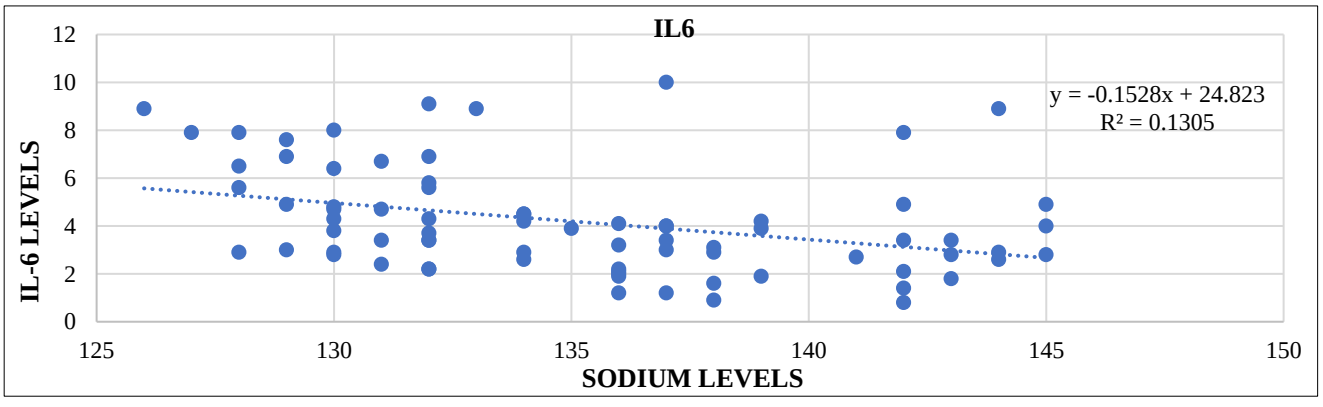

Figure 4: Linear distribution of the interleukin-6 levels and serum sodium levels in the study population.

Table 4: Multinominal linear regression between cases and controls for sodium levels.

Independent variables	Standardized coefficients beta	'T' value	'P' value	95% CI
BMI	0.235	2.277	0.026	0.40 0.603
BAMSE	0.026	0.218	0.828	-0.612 to 0.763
ADL	0.098	0.757	0.452	-1.403 to 3.116
GFR	0.041	0.356	0.723	-0.057 to 0.082
CRP	-0.428	-4.121	0.001	-0.272 to -0.095
IL6	-0.308	-2.961	0.004	-1.218 to -0.237
NT PRO BNP	0.101	0.822	0.414	0.001 to 0.317

DISCUSSION

The objective of the study was to look at the BAMSE scores in patients with and without hyponatremia; to assess the quality of life using ADL; to determine the T scores using DEXA scan and to compare the inflammatory markers between the said defined groups.

On comparing the serum sodium values individually with BAMSE scores, ADL scores, eGFR, BMI and NTPROBNP levels there was a positive correlation between the two but without any statistical significance. Comparison of the same parameters between the cases and controls there were no statistical significance between the two.

In a previous study, Xiong et al showed that a correlation analysis between serum sodium, level of education, CVD history, BMI, hsCRP all correlated significantly with all cognitive function measures.[9] In our study we found a correlation between serum sodium levels and BAMSE score but it was not statistically significant; this may be due to small sample size of the study group. Also, in a prospective study of 56 chronic dialysis patients it was found that mild hyponatremia was associated with functional and cognitive decline; but we did not have similar results maybe since our patients were not dialysis dependent and none of our patients has end stage renal disease.[4]

In the present study, a significant correlation was found between serum sodium levels and DEXA scan T scores. When comparing between hyponatremic and normonatremic patients; hyponatremic patients were more at risk of both osteopenia (T score less than -1.5) and osteoporosis (T score less than -2.5). Analysis of NHANES 3 found that the adjusted odds of osteoporosis were significantly higher among participants with hyponatremia than among those with normonatremia.[10] Hyponatremia increases risk of osteoporosis at both hip and lumbar spine. Another study by Kruse et al concluded that hyponatremia can be used as a screening tool and marker of osteoporosis.[11]

In our study we found that serum sodium levels had a positive correlation with ADL score and there was no significant difference between cases and controls. In a study published by Chou et al; they found that patients with dysmetria at the time of admission had worse ADL scores and it was statistically significant.[12] This fact maybe due to the sample size being less and that we had excluded patients with symptomatic hyponatremia.

In the recently published; CRIC study have found hyponatremia to be more associated with higher GFR levels in CKD population whereas our findings differ.[13] This may be because the study was done in different population groups with different dietary habits. Native kidney disease profile was also different between the two studies.

In our study, strong negative correlation and significant association were found between serum sodium levels and inflammatory markers like CRP and IL-6. Chronic inflammation accelerates the progression of CKD not only by aggravating kidney injury, but also by initiating its complications, especially the cardiovascular disease (CVD). Elevated levels of serum IL-6 and IL-1β are found in inflammatory diseases, and their levels are higher in patients with hyponatremia.[12] Hyponatremia is associated with inflammatory states and it is already known that inflammatory conditions are associated with increase in IL-6 levels and other proinflammatory markers. Chronic Kidney disease is an inflammatory state. This study was undertaken with the perspective of looking into the association between CKD, hyponatremia, and their effect on IL6 levels.

Limitations

In spite of every sincere effort, this study has lacunae. The study was conducted with a small sample size. Cases and controls were not matched to remove bias. There was lack of data to establish causality and to better characterize hyponatremia. Also, chronicity of the hyponatremia could not be evaluated. DEXA scan (T scores) not available for the entire study population. Inability to generalize the results of our study is another limitation.

CONCLUSION

In our study we found an association between osteopenia or osteoporosis and mild hyponatremia in non-dialysis dependent CKD patients. This could have an implication on the treatment of osteoporosis. We did not investigate the association of correction of hyponatremia and

improvement in DEXA (T scores), neither did we establish the chronicity of hyponatremia; which could be analyzed if a prospective study is undertaken in the future.

We found a strong negative correlation between serum sodium and inflammatory markers like CRP and IL-6 which would mean inflammation but causal association cannot be analyzed in this study. Further studies with proper adjustment for confounding factors are required to establish causation and its implication on treatment of mild asymptomatic hyponatremia.

We conclude that, presence of asymptomatic hyponatremia in non-dialysis CKD population may be an indirect indicator of poor bone health and presence of chronic inflammation, which is strongly associated with disease progression. Further research is required at a large scale to address the impact of correction of asymptomatic hyponatremia on these factors.

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REFERENCES

1. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant. 2006;21(1):70-6.
2. Schrier R. Does 'asymptomatic hyponatremia' exist? Nat Rev Nephrol. 2010;6:185.
3. Barstow C, Braun M. Electrolytes: Calcium Disorders. FP Essent. 2017;459:29-34.
4. Shavit L, Mikeladze I, Torem C, Slotki I. Mild hyponatremia is associated with functional and cognitive decline in chronic hemodialysis patients. Clin Nephrol. 2014;82:313-9.
5. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med. 2006;119(1):71.
6. Kruse C, Eiken P, Vestergaard P. Hyponatremia and osteoporosis: insights from the Danish National Patient Registry. Osteoporos Int. 2015;26(3):1005-16.
7. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM. 2008;101(7):583-8.
8. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56(12):519-22.
9. Xu R, Pi HC, Xiong ZY, Liao JL, Hao L, Liu GL, et al. Hyponatremia and Cognitive Impairment in Patients Treated with Peritoneal Dialysis. Clin J Am Soc Nephrol. 2015;10(10):1806-13.
10. Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, et al. Hyponatremia-induced osteoporosis. J Bone Miner Res. 2010;25(3):554-63.
11. Kruse C, Eiken P, Vestergaard P. Hyponatremia and osteoporosis: insights from the Danish National Patient Registry. Osteoporos Int. 2015;26:1005-16.
12. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56(12):519-22.

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