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RELATIONSHIP OF UREA, SODIUM AND CHLORIDE IN RENAL FAILURE PATIENTS

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ABSTRACT Blood urea nitrogen (BUN) values are inversely related with decline of renal function. The changes in the serum sodium and chloride concentration will contribute to metabolic acid base disturbances. The changes in serum osmolality are determined by changes in serum concentration of sodium, glucose and urea levels. In this current research study 122 cases of renal failure patients are included and classified into five groups based on urea levels like 48 to 70 mg/dl, 71 to 90 mg/dl, 91 to 120 mg/dl, 121 to 150 mg/dl and > 150 mg/dl. In each of these groups the serum sodium level is assessed, the relationship between sodium and urea in the calculation of serum osmolality is analysed and the ratio between serum sodium and chloride level is calculated. The study concludes that sodium/chloride ratio is reduced in these patients irrespective of serum sodium levels. This simple ratio that can be easily calculated at the bedside may serve as a marker in the management of metabolic acidosis in renal failure patients.

KEYWORDS : Sodium/Chloride Ratio, Urea, Osmolality, Tonicity

INTRODUCTION:

Blood urea nitrogen (BUN) denotes the nitrogen part of blood urea and its higher values are inversely related with the decline of renal function and were identified as a risk factor for progression of renal disease.[1] In chronic kidney disease (CKD), particularly in stages 4 and 5, the metabolic acidosis is very common where the serum sodium bicarbonate level is reduced. The Japanese Society of Nephrology suggested using the difference between serum sodium and chloride levels as a surrogate marker of metabolic acidosis.[2] The kidney plays a significant role in maintaining water, electrolyte, osmolality and acid base balance. Changes in serum osmolality are primarily determined by changes in the serum concentration of sodium with its associated anions, glucose and urea levels.[3]

Osmolality refers to the concentration of all the solutes but tonicity (effective osmolality) refers to the concentration of effective osmoles that contribute to water movement between the intracellular and extracellular compartment and so its value is less than osmolality.The effective solutes can create an osmotic pressure gradient across cell membranes which leads to osmotic movement of water. [3-6] The serum sodium is a major contributor to the effective serum osmolality, so hypernatremia is associated with hypertonicity. Hyponatraemia usually denotes low effective osmolality or hypotonicity but it may occur with isotonic or hypertonic serum if the serum contains increased effective osmoles such as glucose or mannitol. Urea is not an effective osmole because it easily crosses the cell membranes and attains equilibrium between extracellular fluid (ECF) and intercellular fluid (ICF). The normal range of serum osmolality is between 275 and 295 mOsm/KgH_2O. [3-6] Hyponatremia is usually defined as a serum sodium level below 135 mmol/L and it is classically divided into mild (130–134 mmol/L),moderate (125–129 mmol/L), and severe (<125 mmol/L) hyponatremia. The normal range of sodium is between 135 and 145 mmol/L.[7]

The volume of urine is due to both the clearance of water and clearance of osmoles which is caused by water diuresis and osmotic diuresis respectively. The osmolality of the urine reflects the ability of the kidneys to concentrate the urine. Urea readily crosses the cell membranes so it does not create an osmotic gradient.[3,8,9] If the urinary excretion rate of urea is high, all of it may not be reabsorbed and urea can act as an effective osmole in the inner medullary collecting duct which leads to water excretion. Urea is an ineffective urine osmole when there is a high rate of electrolyte excretion but acts as an effective osmole when there is a low rate of electrolyte excretion.[10]

In chronically uremic patients, urea equilibrates between blood, brain and other tissues reaching a steady state of hyperosmolality. Urea behaves like an ineffective osmole and no movement of water is associated with uremia because there is no osmotic gradient. But haemodialysis results in rapid removal of blood urea with greater speed than equilibration rate between the brain and bloodstream across the blood-brain barrier. This leads to an osmotic gradient resulting in movement of water into the brain causing cerebral oedema, raised intracranial pressure and symptoms of dialysis disequilibrium syndrome.[11,12]

Hypotonicity causes cellular oedema and Hypertonicity leads to shrinkage of cells but the rapidity of its development influences the severity.[8] The changes in serum sodium and chloride concentration will contribute to metabolic acid base disturbances. [13] In this current research study, the relationship between sodium and urea in the calculation of serum osmolality is compared and the ratio between serum sodium and chloride level is calculated for all these renal failure patients. The study concludes that sodium/chloride ratio is reduced in these patients irrespective of serum sodium levels.

MATERIALS AND METHODS:

This project was done under Sri Balaji Vidyapeeth (SBV) Short Term Studentship (STS) program conducted for the students. The student investigator for this project is Ms.Aishwarya Thakare, final year M.B.B.S Student, who is guided by Dr. Rajini Samuel. A total of **122 renal failure cases** with abnormal urea and creatinine with their electrolyte values are included in this study. They are divided into **five groups** based on **serum urea** values namely **48 to 70mg/dl (23** cases)**, 71 to 90 mg/dl (28** cases)**, 91 to 120 mg/dl (31** cases)**, 121 to 150 mg/dl (27** cases) **and > 150 mg/dl (13** cases). Blood urea nitrogen (BUN) values are calculated by using the following relation.[14]

Blood urea =2.14 * BUN

Many formulas are available for the calculation of Serum osmolality but usually it requires the values of serum sodium, glucose and urea.[5,6]

Serum Osmolality = 2 X Serum Sodium + BUN /2.8 + Glucose/18

In the above equation sodium is in mmol/L but the BUN and glucose are in mg/dl. The correction factors like **2.8** for **BUN** and **18** for **glucose** are used to convert them to mmol/L.[5,6] The serum sodium is the major contributor to osmolality, so serum sodium alone can be used to roughly calculate the serum osmolality.

Serum Osmolality based on sodium alone = 2 X Serum Sodium

If both serum sodium and urea (BUN) values are considered for calculation (without glucose levels) then the serum osmolality is calculated by the following formulae.

Serum Osmolality based on sodium and urea = 2 X Serum Sodium + BUN/2.8

In this study two serum osmolality values are calculated, one using both the serum sodium and urea(BUN) values and the other one is calculated using serum sodium alone. The blood glucose value is not included in this study.

Difference between these two Serum Osmolality = BUN/2.8
Each of the five groups based on urea levels are again divided into **5 subgroups** based on **serum sodium** levels (**111-120, 121-124, 125-129, 130-134 & 135 - 141**). The normal serum sodium level is between 135 and 145 mmol/L but in our study the highest sodium value seen is 141 so the group is taken as 135 to 141. Each of the five groups based on urea levels are again divided into **5 subgroups** based on the **ratio** between **serum sodium** and **chloride** levels (**1.08 to 1.14, 1.15 to 1.20, 1.21 to 1.25, 1.26 to 1.30 & 1.31 to 1.32**).

RESULTS:

The calculated Serum osmolality, ratio (Sodium+Potassium)/Chloride and Sodium/Chloride ratio in various groups based on serum urea values are clearly tabulated in **table 1**. The sodium levels and the Sodium/Chloride Ratio in various groups based on serum urea values are tabulated in **table 2** and **3** respectively.

Table 1: Calculated Serum osmolality, (Sodium+Potassium)/ Chloride Ratio & Sodium/Chloride Ratio in various groups based on serum urea values

S. NO	Number of Cases in Groups based on Serum Urea Values (mg/dl)				
	48 to 70 (23 cases)	71 to 90 (28 cases)	91 to 120 (31 cases)	121 to 150 (27 cases)	> 150 (13 cases)
1	Mean ± Std Dev of Serum Osmolality Calculated using Sodium and Urea levels :				
	271.43 ± 9.13	276.67 ± 9.65	283.67 ± 8.78	291.88 ± 8.99	293.31 ± 12.20
2	Mean ± Std Dev of Serum Osmolality Calculated using Sodium levels alone:				
	261.65 ± 9.02	263.64 ± 9.83	266.13 ± 8.44	269.19 ± 8.83	263.85 ± 13.10
3	Mean ± Std Dev of the Difference between these two Osmolality:				
	9.77 ± 1.12	13.02 ± 1.10	17.54 ± 1.33	22.69 ± 1.56	29.46 ± 3.33
4	Mean ± StdDev of Ratio Na^+/Cl^- Calculated using Sodium and Chloride levels:				
	1.20 ± 0.04	1.21 ± 0.05	1.18 ± 0.03	1.17 ± 0.02	1.18 ± 0.04
5	Mean ± StdDev of Ratio $(Na^+ + k^+) / Cl^-$ Calculated using Sodium, Potassium and Chloride levels:				
	1.24 ± 0.04	1.25 ± 0.05	1.22 ± 0.03	1.22 ± 0.03	1.22 ± 0.04

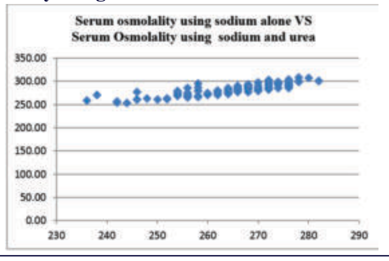
Table 2: Sodium levels in various groups based on serum urea values

Serum Sodium Levels	Number of Cases in Groups based on Serum Urea Values (mg/dl)					
	48 to 70 (23 cases)	71 to 90 (28 cases)	91 to 120 (31 cases)	121 to 150 (27 cases)	> 150 (13 cases)	Total (122)
111-120	0	0	0	1	1	2
121-124	1	4	1	0	1	7
125-129	9	2	6	2	4	23
130-134	7	12	14	9	0	42
135 - 141	6	10	10	15	7	48

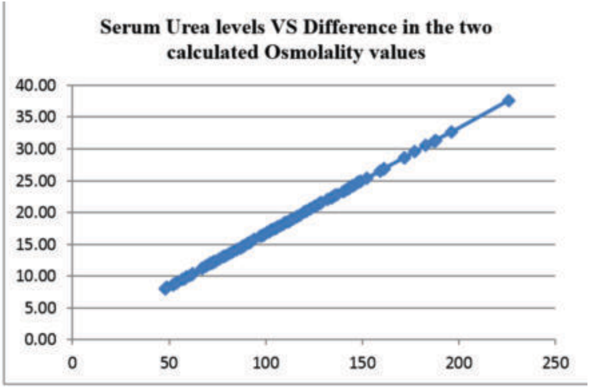
Table 3: Sodium/Chloride Ratio in various groups based on serum urea values

Ratio Na^+/Cl^-	Number of Cases in Groups based on Serum Urea Values (mg/dl)					
	48 to 70 (23 cases)	71 to 90 (28 cases)	91 to 120 (31cases)	121 to 150 (27 cases)	> 150 (13 cases)	Total (122)
1.08 to 1.14	0	2	5	1	1	9
1.15 to 1.20	12	13	21	23	8	77
1.21 to 1.25	10	7	4	3	4	28
1.26 to 1.30	0	4	1	0	0	5
1.31 to 1.32	1	2	0	0	0	3

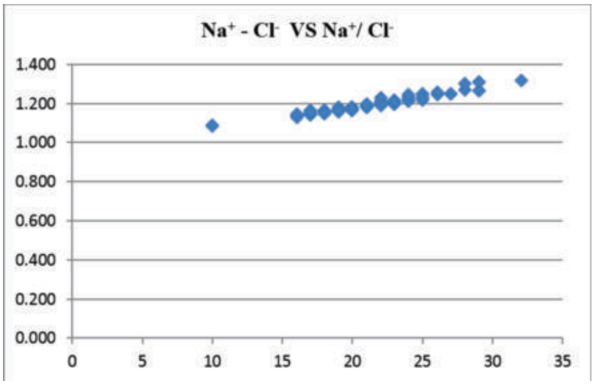
Graph 1: X: axis Serum osmolality using sodium alone VS Y: axis Serum Osmolality using both sodium and urea



Graph 2: X: axis Serum Urea levels VS Y: axis Difference in the two calculated Osmolality values



Graph 3: X: axis Difference between Serum sodium and chloride VS Y: axis Ratio between Serum sodium and chloride



DISCUSSION:

During hemodialysis, the plasma becomes hypotonic in relation to brain cells due to rapid decrease in serum urea level compared with the concentration in the brain cells. Equilibration of urea across the cell membranes takes several hours.This causes sudden water shift from the extracellular space to the brain cells resulting in edema. The rapid change in plasma solute level results in change of serum osmolality that occurs during or after hemodialysis is most likely to cause osmotic demyelination syndrome in patients with end stage renal disease.[11,12] In conditions of high blood urea concentration, all of it is not reabsorbed so urea behaves as an effective osmole leading to osmotic diuresis that can result in hypernatremia. Oral urea is used as a safe and effective agent for treatment of hyponatremia because it increases urinary free water excretion by acting as an osmotic agent.[8,15,16]

The relation between the two calculation of serum osmolality, one using sodium alone and other using both serum sodium and urea level is shown in the **graph 1**. The difference between these two calculated osmolality value is directly related with their serum urea levels which is shown in **graph 2**. The glucose value is not included in this study. Suppose if the blood glucose is **90 mg/dl** then the calculated osmolality will be higher by **5** and if the blood glucose is **180 mg/dl** then the calculated osmolality will be higher by **10**. (based on **glucose/18** in the formulae). [5,6] The sodium and glucose are effective osmoles that contribute to tonicity but urea is usually an ineffective osmole and do not contribute to tonicity but under certain circumstances urea can behave as an effective osmole increasing the tonicity. The serum osmolality (either calculated or measured) value should be properly correlated with the individual values of sodium, glucose and urea.

The difference between serum sodium and chloride is directly related to their ratio and these ratio values are lowered in these patients (shown in **graph 3**). The ratio between **sodium** of **140** mmol/L and **chloride** of **100** mmol/L will be **1.4**. The ratio is lowered if the serum sodium level is lowered or the chloride level is increased and the ratio will be higher if the serum sodium level is increased or the chloride level is decreased. Out of the **122** cases, **48** had **normal** serum sodium , **42** had **mild** hyponatremia, **23** had **moderate** hyponatremia and only **9** are considered as **severe** cases. In some of the previous studies they have mentioned that higher urea levels can induce osmotic diuresis that can increase the serum sodium level resulting in hypernatremia.[8.9] If this would have occurred in **these cases**, then the **sodium** levels in these patients **may be much lower** and the higher urea(**BUN**) values **may** have influenced the serum sodium levels.

The difference between serum sodium and chloride levels serve as a surrogate marker of metabolic acidosis.[2,13] In this study the ratio (sodium + potassium)/chloride and sodium/chloride are calculated and **their difference** is usually between **0.04 to 0.05**. The potassium being an intracellular ion, major changes in its concentration is not practically possible so **sodium/chloride ratio alone** is **sufficient** to serve as a marker. It is clearly seen that the **ratio** Na^+/Cl^- is **lowered in all** of these patients, **9 cases** had **lowest ratio** between **1.08** to **1.14, 77 cases** had ratio between **1.15** to **1.20**, **28 cases** had ratio between **1.21** to **1.25**, **5 cases** had ratio between **1.26** to **1.30** and **only 3 cases** had slightly lower ratio between **1.31** to **1.32**. It is always better to correlate the sodium and urea levels and also the sodium and chloride levels for effective management of these patients.

CONCLUSION:

The understanding of the relationship between sodium and urea plays a significant role in the management of osmolality. The simple ratio between serum sodium and chloride that can be easily calculated at the bedside may serve as a marker in the management of metabolic acidosis in renal failure patients.

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CONFLICT OF INTEREST:

NIL

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NONE

REFERENCES:

1. Seki et al. Blood urea nitrogen is independently associated with renal outcomes in Japanese patients with stage 3–5 chronic kidney disease: a prospective observational study BMC Nephrology (2019) 20:115
2. Yuichi Maruta et al. Association between serum Na–Cl level and renal function decline in chronic kidney disease: results from the chronic kidney disease Japan cohort (CKD-JAC) study Clinical and Experimental Nephrology (2019) 23:215–222
3. Goce Spasovski et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia Nephrol Dial Transplant (2014) 29 (Suppl. 2): ii1–ii39
4. Osmolarity, osmolality, tonicity, and the reflection coefficient deranged physiology 2021
5. MehdiRasouli Basic concepts and practical equations on osmolality: Biochemical approach clinical biochemistry 2016; 49(12): 936-941
6. Daniel K. Faria, Maria Elizabete Mendes, Nairo M. Sumita The measurement of serum osmolality and its application to clinical practice and laboratory: literature review J Bras Patol Med Lab, 2017; 53(1): 38-45
7. Sahoo S, Grover S. Hyponatremia and psychotropics. J Geriatr Ment Health 2016;3:108-22.
8. Sonali Vadi and Kenneth Yim Hypernatremia due to Urea-Induced Osmotic Diuresis: Physiology at the Bedside Indian J Crit Care Med. 2018 ; 22(9): 664–669.
9. Jesiree Iglesias Quadros Distenhreft et al. The role of urea-induced osmotic diuresis and hypernatremia in a critically ill patient: case report and literature review Braz. J. Nephrol. 2020;42(1):106-112
10. Manjula Gowrishankar et al Minimum urine flow rate during water deprivation: Importance of the permeability of urea in the inner medulla, Kidney International. 1998; 53:159–166
11. Kirtida Mistry Dialysis disequilibrium syndrome prevention and management International Journal of Nephrology and Renovascular Disease 2019:12 :69–77
12. Tarhan et al. Osmotic Demyelination Syndrome in End-Stage Renal Disease After Recent Hemodialysis: AJR:182, 2004: 809 -816
13. Durward A, Skellett S, Mayer A, Taylor D, Tibby SM, Murdoch IA. The value of the chloride: sodium ratio in differentiating the aetiology of metabolic acidosis. Intensive Care Med. 2001;27(5):828-35.
14. Suganya, Shanmuga Priya, Rajini Samuel, Balaji Rajagopalan A Study to Evaluate the Role of Bun/Creatinine Ratio as a Discriminator Factor in Azotemia Int. J. Pharm. Sci. Rev. Res.2016; 40(1): 131-134
15. Richard H. Sterns, Stephen M. Silver and John K. Hix Urea for hyponatremia? Kidney International (2015) 87, 268–270.
16. Helbert Rondon-Berrios et al. Urea for the Treatment of Hyponatremia Clin J Am Soc Nephrol 13: 1627–1632, 2018.