Journal of Medical and Scientific Research

JMSR
www.jmsronline.com

Prakashiny S et al. J Med Sci Res. 2023; 11(4):270-274
http://dx.doi.org/10.17727/JMSR.2023/11-50

ORIGINAL RESEARCH OPEN ACCESS

Application of delta gap equation for the assessment of metabolic acidosis in renal failure patients

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Abstract

Introduction: Metabolic acidosis is commonly encountered in chronic kidney disease (CKD) which contributes to its progression. The metabolic acidosis in chronic kidney disease is presumed to be due to accumulation of unmeasured anions leading to a high anion gap (AG). The aim of the study was to assess the metabolic acidosis in renal failure patients using the calculation of delta gap.

Methods: 100 renal failure cases were included. Their abnormal urea and creatinine values were utilized to calculate the BUN/creatinine ratio for all the cases. Based on the dipstick urine testing grading, proteinuric renal diseases were identified. The urine and serum osmolality were calculated in these renal failure patients. Serum osmolality was calculated using the values of serum sodium and urea. Urinary density which is also called urine specific gravity was used for indirect calculation of urine osmolality. Modified delta gap equation was applied for quick evaluation of mixed metabolic acid-base disorders

Results: Out of the 100 cases, 41 were proteinuric renal disease cases and 59 were non-proteinuric renal disease cases. High anion gap metabolic acidosis were seen in 65% of the total 100 cases. In 33% of the total cases, non-anion gap metabolic acidosis was also seen in addition to the high anion gap metabolic acidosis as it is evidenced by the delta gap value of less than -6 mmol/L.

Conclusions: Earlier identification of the type and causative mechanism of metabolic acidosis in these patients may help to decrease the morbidity and mortality of these patients. The delta gap that can be easily calculated using this quick and short equation at the bedside may serve as a marker in the management of metabolic acidosis in renal failure patients.

Keywords: delta gap; modified quick equation; metabolic acidosis; renal failure

Introduction

Metabolic acidosis is commonly encountered in chronic kidney disease (CKD) which contributes to its progression. Japan cohort study evaluated the serum sodium chloride difference as a risk factor for renal function decline among the chronic kidney disease patients [1]. The metabolic acidosis in chronic kidney disease is presumed to be due to accumulation of unmeasured anions leading to a high anion gap (AG). Another study emphasizes the importance of considering both the stages of chronic kidney disease and the magnitude of the elevation of anion gap in these patients suggesting that normal anion gap metabolic acidosis may play a critical role in the acid base

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Received 17 May 2023; *Revised* 21 August 2023; *Accepted* 29 August 2023; *Published* 1 September 2023

Citation: Prakashiny S, Saranya N, Samuel TR, Prasad KH. Application of delta gap equation for the assessment of metabolic acidosis in renal failure patients. J Med Sci Res. 2023; 11(4):270-274. DOI: http://dx.doi.org/10.17727/JMSR.2023/11-50

disturbances observed in these steady state chronic kidney disease patients [2].

Uraemia is a marker of kidney function and it causes an elevated serum anion gap. Higher levels of anion gap present in less advanced kidney disease individuals are associated with increased risk of mortality [3]. Metabolic acidosis is classified into either high anion gap type (high-AGMA) or non-anion gap type (non-AGMA) and it is a common complication in chronic kidney disease (CKD), but its development in CKD is not well known [4]. High anion gap type metabolic acidosis developed and progressed in stage 5 of CKD but non-anion gap metabolic acidosis generally progressed before the early phase of stage 5 of CKD and regressed thereafter [4].

Acute kidney injury (AKI) is a common complication in critically ill patients and is usually associated with poor outcomes. In critically ill patients, both high and low serum osmolality were independently associated with an increased risk of development of acute kidney injury [5]. Urine osmolality is dynamic as the body corrects temporary water imbalance and can help evaluate renal concentrating ability, and fluid balance between fluid intake and fluid loss. Diuresis due to water, glucose, urea and sodium can affect the urine osmolality. If higher urine osmolality is due to hypovolemia, dehydration or inadequate water intake then urine output decreases. If urine osmolality is high but urine output increases, then it could be due to osmotic diuresis. Urine osmolality can be calculated from urinary density which is the specific gravity of urine [6].

Delta gap is used to assess elevated anion gap metabolic acidosis and to evaluate for the presence of mixed acid base disorder. Its value is used to find the additional presence of non-anion gap metabolic acidosis [7, 8]. The aim of the present study was to assess the metabolic acidosis in renal failure patients using the calculation of delta gap.

Materials and methods

This study was an interdepartmental research study conducted by the Department of Pathology, Biochemistry and Anaesthesiology at Shri Sathya Sai Medical College and Research Institute. The study was conducted for one year during the period April 2021 to March 2022 after obtaining approval from the institutional ethical committee. A total of 100 renal failure cases were included as convenience samples in this study. Their abnormal urea and creatinine values were utilized to calculate the BUN/creatinine to differentiate the pre renal, renal and post renal causes [9]. Their electrolyte values were noted. Blood urea nitrogen (BUN) values were calculated from blood urea. Serum sodium and BUN values were used to calculate serum osmolality. Blood urea =2.14X BUN**.**

Calculated serum osmolality

Many formulas are available for the calculation of serum osmolality. In our study, the values of serum sodium and urea were considered for its calculation. The serum sodium is measured in mmol/L but the value of BUN is given in mg/dl. So the correction factor 2.8 for BUN is used to convert it to mmol/L [10-12]. Serum osmolality based on sodium and urea = 2X; serum sodium + BUN/2.8

Dipstick urine testing

Based on the dipstick urine testing, proteinuric renal diseases were identified by grading as 1+, 2+, 3+ and 4+ in the urine test for protein. The reliability of the allocation of dipstick urinalysis to negative, trace and positive result that indirectly reflect the levels of urine albumin creatinine ratio had been reported in previous research studies [13-15].

Calculated urine osmolality

Urinary density (also called urine specific gravity) was used for indirect calculation of urine osmolality. The calculation was different for clean samples and samples with proteinuria or glucosuria. For samples with proteinuria or glucosuria, the correction factor 32,000 was applied and for clean samples, the correction factor 35,000 was utilized to calculate the urine osmolality from urine density. The formulae to calculate the urine osmolality is mentioned below [16].

For clean samples: Calculated urine osmolality = 35,000 X [Urinary density - 1]

For samples with proteinuria or glucosuria: Calculated urine osmolality = 32,000 X [Urinary density - 1]

Calculated delta gap

Delta gap is used to assess elevated anion gap (AG) metabolic acidosis and to evaluate for the presence of mixed acid base disorder. It helps to identify the additional presence of non-anion gap metabolic acidosis. The normal reference range for delta gap is from -6 to +6 mmol/L and it denotes high anion gap metabolic acidosis. If the value is <-6 mmol/L, it denotes the additional presence of non-anion gap metabolic acidosis. If the value is >+6 mmol/L, it denotes the additional presence of metabolic alkalosis [7, 8].

Delta Gap= $\Delta AG - \Delta HCO_3^-$

ΔAG = Calculated Anion Gap - Normal Anion Gap

$\Delta AG = Na^+ - (Cl^- + HCO_3^-) - 12$

$\Delta HCO_3^- = 24 - HCO_3^-$

Delta Gap = $Na^+ - Cl^- - 36$

Delta Gap = $\{Na^+\} - \{Cl^-\} - 36$

The above equation was used to calculate the delta gap. It is much easier and quicker to calculate delta gap from this simple equation that exists in literature.

Results

Out of the 100 cases, 41 were proteinuric renal disease cases and 59 were non-proteinuric renal disease cases. Based on the dipstick urine testing, 41 cases were identified as proteinuric renal diseases (1+: 12 cases, 2+: 7 cases, 3+: 20 cases, 4+: 2 cases). Among 100 cases, 41 proteinuric renal disease cases were seen and 7 cases with glucosuria were seen in 59 non proteinuric renal disease cases. So, 52 samples were considered as clean samples and the remaining were 48 samples. The mean and standard deviation of BUN/ creatinine ratio, calculated urine osmolality, calculated serum osmolality, sodium chloride difference and calculated delta gap were calculated for proteinuric and non-proteinuric cases and the results were shown in the table 1. Delta gap was calculated for all the cases using this short and quick equation. The metabolic acidosis in both proteinuric and non-proteinuric cases were assessed using the delta gap values and shown in the table 2.

Table 1: Calculated renal parameters in proteinuric and nonproteinuric renal diseases.

Parameters	*Proteinuric renal disease cases*		*Non-proteinuric renal disease cases*	
	Mean	*Std Dev*	*Mean*	*Std Dev*
BUN/ creatinine ratio	7.24	2.39	8.42	2.33
Calculated urine osmolality	480.00	211.66	408.17	211.64
Calculated serum osmolality	286.76	14.76	288.81	12.14
Sodium chloride difference	30.66	5.57	31.98	4.97
Calculated delta gap	-5.34	5.57	-4.02	4.97

Discussion

There is a clinical paradigm shift in the understanding of renal insufficiency caused by diabetic patients [17]. Over the last decades, it has been noticed that diabetic patients without proteinuria could also have progressive renal insufficiency. This has changed the diagnostic criteria for diabetic kidney disease (DKD) including both proteinuric and non-proteinuric kidney diseases. The dipstick testing has low sensitivity for renal dysfunction yet it is frequently used to detect the urinary excretion of protein because of its simplicity and cost effective for mass application in community [17-19].

Table 2: Assessment of metabolic acidosis in proteinuric and nonproteinuric renal disease

S.No.	Delta gap	Proteinuric renal disease cases total: 41		Non proteinuric renal disease cases total: 59		Total cases: 100
		No of cases	% cases	No of cases	% cases	
1	< -6	13	31.7	20	33.90	33
2	-6 to +6	27	65.9	38	64.41	65
3	>+6	1	2.4	1	1.69	2

The loss of renal function in kidney disease is due to decrease in the number of functional nephrons. Nonproteinuric kidney disease is characterized by decreased estimated glomerular filtration rate in the absence of proteinuria and the estimated glomerular filtration rate (eGFR) is below 60 mL/min/1.73 m^2. The absence of proteinuria denotes urinary albumin creatinine ratio (UACR) less than 300 milligram of albumin per gram of creatinine. There is no association between loss of renal function and albuminuria level in these patients. Some of these non-proteinuric renal disease patients may progress to advanced or end stage renal disease in a decade but with lower progression compared with proteinuric kidney diseases. In the latest update it has been mentioned that proteinuria is not a marker of nephropathy but it is an indicator of glomerular lesions in chronic kidney disease (CKD). This may be due to the improvements in glycaemic control and the widespread use of antagonists of the renin angiotensin system [19 -20].

Chronic kidney disease patients demonstrated that low urine osmolality was associated with a higher risk of kidney impairment. The changes in urine osmolality occur in renal failure but it is highly variable and not superior to the estimated glomerular filtration rate (eGFR). Low urine osmolality was an independent prognostic factor for disease progression in patients with chronic kidney disease (CKD). Low urine osmolality was also an independent risk factor for adverse renal outcomes in CKD patients. Urine osmolality may be useful to suggest a fluid imbalance when renal concentrating ability is intact, but it does not identify the cause. In adults with chronic kidney disease, urine osmolality can be used as a prognostic marker of deteriorating renal function but

the interpretation of urine osmolality should be done with other laboratory findings and clinical history.

Low urine osmolality might be the result of a decline in renal function. Tubular injury from progression of CKD can directly lead to decreased urine osmolality due to an impairment in the urine-concentrating function or salt wasting. Low urine osmolality may also accelerate the decline in kidney function by increasing the intratubular urine volume and pressure which increases the stretch force leading to a fibrogenic mechanism. Conversely, damage to tubular cells in CKD might result in a decrease in urine osmolality and an increase in vasopressin, leading to progression of CKD. The concentrating ability of the kidney can be compromised by older age which is commonly observed in chronic kidney disease patients [21]. The urine osmolality is different in different stages of the chronic kidney disease patients. A previous study had reported that in stage 3 of CKD, the value of urine osmolality was relatively well maintained at 400 to 500 mosm/kg in patients and as the renal disease is progressed to stage 4, the urine osmolality value was found to be lowered below 400 mosm/kg in those patients [21]. Another study had reported that higher urine osmolarity was independently associated with a higher risk of initiating dialysis in all the 4 stages of chronic kidney disease patients [22].

The prevalence of metabolic acidosis was higher in patients with advanced CKD and it also increases as it progresses from stage 4 to stage 5 of the chronic kidney disease. In addition, patients with high anionic gap (AG) metabolic acidosis showed an increase in renal function decline. The prevalence of High AG metabolic acidosis also increases as the disease progresses from stage 1 to stage 5 of chronic kidney disease [23]. Metabolic acidosis is one of the most common complications in chronic kidney disease (CKD) patients and is also associated with cardiovascular outcomes and mortality in CKD patients. It has been associated with bone demineralization, insulin resistance, muscle protein proteolysis and cognitive impairment [24]. Chronic metabolic acidosis is closely related to chronic kidney disease and end stage renal disease (ESRD). Its presence in patients undergoing haemodialysis has been associated with mortality. The increased use of bicarbonate in haemodialysis may be potentially harmful to the patient as it can cause metabolic alkalosis during and after the dialysis [25].

BUN/creatinine ratio will serve as a guide in differentiating the different prerenal, renal and postrenal failure patients. Usually the value of BUN/creatinine ratio is <10 for renal failure patients [9]. In our study, 41 proteinuric renal disease cases and 59 non-proteinuric renal disease patients were found among the 100 renal failure patients. The increase in the number of cases of non-proteinuric kidney diseases was obviously seen in this study. The calculated renal parameters in proteinuric and nonproteinuric renal disease cases were tabulated and shown in the table 1. The high variability of both serum and urine osmolality values in renal failure patients were clearly shown in the table 1.

The sodium chloride difference was lowered in all the renal failure patients indicating metabolic acidosis in these patients. In our study, high anion gap metabolic acidosis were seen in 65.9% of the proteinuric renal disease cases. In 31.7% of the proteinuric renal disease cases, non-anion gap metabolic acidosis was also seen in addition to the high anion gap metabolic acidosis as it was evidenced by the delta gap value of less than -6 mmol/L. High anion gap metabolic acidosis were seen in 64.41% of the nonproteinuric renal disease cases. In 33.90% of the nonproteinuric renal disease cases, non-anion gap metabolic acidosis was also seen in addition to the high anion gap metabolic acidosis as it was evidenced by the delta gap value of less than -6 mmol/L. In total cases of the renal diseases, 65% of high anion gap metabolic acidosis were seen. In 33% of the total cases, non-anion gap metabolic acidosis was also seen in addition to the high anion gap metabolic acidosis. Metabolic acidosis is one of the most common complications in chronic kidney disease (CKD) patients associated with increased cardiovascular outcomes and mortality. The application of this simple delta gap calculation will easily enable us to find the additional presence of non-anion gap metabolic acidosis.

Limitations: The present research study was done in limited number of patients and data was collected in tertiary care centre which do not precisely reflect the disease profile of the community. Therefore multi-centre research study involving more number of patients is required to provide precise results and conclusive data.

Conclusion

Delta gap is used to assess elevated anion gap metabolic acidosis and to evaluate for the presence of mixed acid base disorder. The delta gap that can be easily calculated using this quick and short equation at the bedside may serve as a marker in the management of metabolic acidosis in renal failure patients. Earlier identification of the type and causative mechanism of metabolic acidosis in these patients may help to decrease the morbidity and mortality of these patients.

Conflicts of interest

Authors declare no conflicts of interest.

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