Research Article

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Analysis of blood gas beyond bicarbonate in outpatients with stage 3–5 chronic kidney disease

[Evre 3–5 kronik böbrek hastalığı olanlarda bikarbonatin ötesinde kan gazı analizi]

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Abstract

Objectives: Metabolic acidosis is a common disorder seen in course of chronic kidney disease (CKD). In this study, we aimed to investigate the association of Base excess (BE), Anion gap (AG) and Delta Ratio with progression of CKD, renal replacement therapy (RRT) requirement and mortality in patients with stage 3–5 CKD.

Methods: A total of 212 patients with stage 3–5 CKD were included in this study. Patients were divided into two groups according to the baseline BE level. Patients were also grouped according to the delta ratio such as non- AG, High AG and mixed type.

Results: Mean BE level was significantly lower (-4.7 ± 4.0 vs. -3.3 ± 4.3 ; $p=0.02$) in patients with CKD progression. The patients in group 1 ($n: 130$) ($Be < -2.5$) revealed more CKD progression (%53 vs. %32; $p=0.002$), and RRT requirement (%35 vs. %15; $p=0.001$). Baseline BE < -2.5 (odds ratio, 0.38;

95% CI, 0.16 to 0.91; $p<0.05$) and baseline GFR (odds ratio, 0.94; 95% CI, 0.90 to 0.97; $p<0.001$) were independently related to RRT requirement. Delta BE was independently associated with mortality (odds ratio, 0.90; 95% CI, 0.85–0.96; $p<0.01$).

Conclusions: Low BE levels were associated with CKD progression and RRT requirement. BE change is associated with mortality during the follow-up of those patients.

Keywords: anion gap; base excess; chronic kidney disease; delta ratio; metabolic acidosis; mortality; progression; renal replacement therapy.

Özet

Giriş: Metabolik asidoz, kronik böbrek hastalığının (KBH) seyri sırasında sık görülen bir bozukluktur. Bu çalışmada, evre 3–5 kronik böbrek hastalarında Baz açığı (BA), anyon gap (AG) ve delta oranlarının hastalık progresyonu, renal replasman tedavi (RRT) ihtiyacı ve mortalite ile ilişkisini incelemeyi amaçladık.

Metod: Toplam 212 evre 3–5 kronik böbrek hastası çalışmaya dahil edildi. Hastalar bazal BA düzeylerine göre iki gruba ayrıldı. Hastalar ayrıca delta oranlarına göre anyon gap olmayan, yüksek anyon gapli ve karışık tip olarak da gruplandırıldı.

Sonuçlar: KBH progresyonu gösterenlerde ortalama BA seviyesi anlamlı şekilde (-4.7 ± 4.0 vs. -3.3 ± 4.3 ; $p=0.02$) düşüktü. Grup-1 ($n: 130$) ($Be < -2.5$) deki hastalar daha fazla KBH progresyonu (%53 vs. %32; $p=0.002$) ve RRT ihtiyacı (%35 vs. %15; $p=0.001$) gösterdi. Bazal BA seviyesi (odds ratio, 0.38; 95% CI, 0.16 to 0.91; $p<0.05$) ve bazal GFR (odds ratio, 0.94; 95% CI, 0.90 to 0.97;

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$p < 0.001$) RRT ihtiyacı ile bağımsız ilişkiliydi. Delta BA, mortalite ile (odds ratio, 0.90; 95% CI, 0.85–0.96; $p < 0.01$) bağımsız ilişkiliydi.

Tartışma: Düşük BA seviyeleri KBH progresyonu ve RRT ihtiyacı ile ilişkiliydi. BA değişimi hastaları takibi sırasında mortalite ile ilişkili bulundu.

Anahtar Sözcükler: anion gap; baz açığı; delta oranı; kronik böbrek hastalığı; metabolik asidoz; mortalite; progresyon; renal replasman tedavisi.

Introduction

Metabolic acidosis (MA) is common in the course of chronic kidney disease (CKD) [1]. MA generally accompany when the glomerular filtration rate (GFR) diminishes below 30 mL/min. MA is associated with both poor renal outcomes and high mortality rates in patients with CKD [2–5]. Chronic MA might be the result of pathophysiologic changes in cardiovascular system, nutritional status, inflammation and/or bone mineral metabolism [6–17]. Although for diagnostic evaluation of MA in CKD, bicarbonate levels are frequently used, there is no consensus in using it for either diagnose or treatment. Base excess (BE) is an important parameter which reflects the excess amount of acid or base in the plasma due to the defect of metabolic system. BE is a cheap and commonly used parameter which is also easy to evaluate. However, BE is a valuable parameter beyond bicarbonate levels in patients with both critically ill intensive care unit and acute kidney injury, in terms of predicting mortality [18].

On the other hand, there is no sufficient data in the literature about utilization of BE in evaluation of patients with stable coursed CKD.

Anion gap (AG) is used in MA to determine whether it is caused by accumulation of non-volatile acids (lactic acids, keto acids, etc.) (increased AG metabolic acidosis, normochloremic MA) or by loss of bicarbonate (normal AG MA, hyperchloremic MA). Both high AG MA and non-AG MA can be seen during the course in CKD. These conditions can also be seen simultaneously. Evaluation of delta ratio can be used in the differential diagnosis of those kinds of situations. There are no sufficient datas in the literature about the clinical importance of utilization delta ratio in CKD patients. In this study we aimed to investigate the association of BE, AG, delta ratio, and types of MA determined by these parameters with disease progression, renal replacement therapy (RRT) requirement and mortality in stable patients with stage 3–5 CKD.

Methods

The patients who admitted to the nephrology out patient clinic of our hospital between January 2009 and 2016 with estimated GFR level below 60 mL/min/1.73 m² but non-dialysis dependent, who have a minimum 12 month follow-up period and who was older than 18 years old were included in this study. Patients who were receiving RRT for acute kidney injury, pregnant, debility, end-stage liver disease, active infection, autoimmune diseases, active malignancy, end-stage dementia, chronic obstructive lung disease, using oral bicarbonate therapy and acute kidney injury were excluded from the study. GFR was calculated from MDRD formula. CKD progression was defined as equal and/or more than 25% kidney function loss and/or progression to the next stage [19]. Patients with bicarbonate levels were below 22 or receiving oral alkali therapy were accepted as having MA status. Patient's biochemical and blood gas studies were performed initially; at sixth month control and at the last control visit. BE, AG and delta ratios were calculated from the biochemical results and simultaneous venous blood gas samplings. AG was calculated from the following formula: $AG = \text{Sodium (Na}^+) - (\text{Chloride [Cl}^-] + \text{Bicarbonate [HCO}_3^-])$. AG above 12 was defined as high AG MA. Delta ratios (DR) of patients with high anion gap were also calculated from the following formula: $DR = \text{Delta AG (AG-12)} / \text{Delta Bicarbonate (24 - HCO}_3^-)$ [20]. Patients were divided into four groups as: normal AG acidosis (DR < 0.4); mixed type (normal and high) AG acidosis (DR: 0.4–1.0); isolated high AG acidosis (DR: 1.0–2.0) and metabolic acidosis with metabolic alkalosis (DR > 2.0). Patients were also divided into 2 groups depending on BE as group 1: BE < –2.5 and group 2: BE ≥ –2.5. Delta BE was calculated by subtracting BE at the first control visit from BE at the last control visit whereas, delta bicarbonate was calculated by subtracting bicarbonate at first visit from bicarbonate at last control visit. Patients were also divided into another two groups as patients with worsening delta BE (was defined as more negative than the first BE) and patients with stable delta BE (was defined as zero and/or more positive than the first BE). Serum urea, creatinine, uric acid, albumin, calcium, phosphorus, sodium, potassium and chloride tests were measured in Olympus 2700 biochemistry analyzer with the commercially available kits (Beckman Coulter Diagnostics Division Headquarters, Brea, CA, USA). The chemistry tests were measured photometrically while indirection selective electrodes (ISE) method was used for measurement of the electrolytes. Blood gas analysis was made using ABL 800 FLEX with commercially available kits (Radiometer Medical APS, 2700 Bronshøj, Denmark). The intra and interassay CVs of all tests were below 10% as mentioned in their kit inserts.

Statistical analysis

All analyzes were performed with SPSS 15.0 for Windows statistical package. The mean and SD of all values were calculated. Mean values of the 2 groups were compared using the Student's *t*-test or a non-parametric test if the data was not normally distributed. $p < 0.05$ was considered to be statistically significant. Clinical Outcomes (CKD progression, RRT requirement and mortality) were analyzed by Cox regression analysis. Overall survivals and RRT requirement rates were

analyzed with the Kaplan–Meier survival curve; the Cox proportional hazard model was used to identify independent predictors of outcomes. All statistical analyses were performed using SPSS, version 15 (Chicago, Ill., USA).

Results

Two hundred and twelve patients were included in the study. The average age was 66 ± 12 (30–89) and 54% were male. 51% were diabetic. 86% were hypertensive and 44% had history of cardiovascular disease. The etiologies of CKD were as follows: 80 patients (38%) with type-2 diabetes mellitus; 68 patients (32%) with essential hypertension; 24 patients (11%) with glomerulonephritis; 12 patients (6%) with obstructive uropathy; 7 patients (4%) with autosomal dominant polycystic kidney disease and 21 patients (9%) with unknown etiology. The average follow-up period was 28 ± 15 (12–73) months. The average GFR, bicarbonate and BE levels were 24 ± 11 mL/min; 21 ± 3.8 mmol/L; -3.95 ± 4.24 respectively. 59 patients (27.8%) were at CKD stage 3; 104 patients (49%) were at CKD stage 4; 49 patients (23.2%) were at CKD stage 5. The

average GFR, bicarbonate and BE levels at the last control visits were 23 ± 14 mL/min; 21 ± 4.2 mmol/L; -2.85 ± 5.24 respectively. MA ratio increased to 52.4% from 44.3% throughout the follow-up period. Initially 94 patients (44.3%) had MA. 59.5% (n=56) of them had high AG acidosis. According to delta ratio; 21 patients (37.5%) had non AG acidosis; 17 patients (30.3%) had mixed type AG acidosis; 13 patients (23.2%) had isolated high AG acidosis and 5 patients (9%) had both high AG acidosis and metabolic alkalosis. When delta ratio was calculated, the number of normal AG acidosis patients increased to 59 (38 + 21) from 38 eventually. The comparison of those patients are respresented at Table 2.

Outcomes for CKD progression and RRT requirement

Chronic kidney disease (CKD) progression and RRT requirement appeared 46 and 30% of patients during follow-up period, respectively. CKD progression rate (58 vs. 40%; $p=0.01$) and RRT requirement (44 vs. 20%; $p<0.001$) were significantly higher in patients with MA. Patients who

Table 1: Comparison of patients with BE and without BE.

	All patients (n=212)	With BE (BE<-2.5, n=130)	Without BE (BE≥-2.5, n=82)	p-Value
Age, year	66 ± 12	66 ± 12	66 ± 11	0.9
Gender (M/F), %	55	55	54	0.8
Diabetes mellitus, %	51	51	52	0.8
Hypertension, %	86	84	89	0.7
CVD, %	44	42	46	0.8
Serum urea, mg/dL	105 ± 51	111 ± 55	96 ± 43	0.03
Serum creatinine, mg/dL	3.0 ± 1.4	3.2 ± 1.7	2.7 ± 1.0	0.01
Glomerular filtration Rate(MDRD), mL/min/m ²	24 ± 11	23 ± 11	26 ± 11	0.06
Uric acid, mg/dL	8.0 ± 1.9	7.9 ± 2.0	8.1 ± 1.8	0.7
Serum sodium, mmol/L	136 ± 5.8	136 ± 5.7	136 ± 5.9	0.5
Serum potassium, mmol/L	4.89 ± 0.8	4.96 ± 0.8	4.78 ± 0.7	0.1
Serum calcium, mg/dL	9.0 ± 0.9	9.0 ± 0.8	9.1 ± 1.0	0.2
Serum phosphorus, mg/dL	3.9 ± 0.9	4.0 ± 0.9	3.8 ± 0.9	0.1
Serum chloride, mmol/L	104 ± 7.2	106 ± 6.8	101 ± 6.7	<0.001
Serum albumin, g/dL	3.9 ± 0.5	3.9 ± 0.6	4.0 ± 0.4	0.2
Hemoglobin, g/dL	11 ± 1.7	11 ± 1.6	12 ± 1.8	0.01
Serum bicarbonate, meq/L	20.8 ± 3.7	18.6 ± 2.6	24.4 ± 2.0	<0.001
Base excess	-3.9 ± 4.2	-6.5 ± 3.0	0.14 ± 2.1	<0.001
pH	7.34 ± 0.06	7.33 ± 0.06	7.37 ± 0.05	<0.001
Metabolic acidosis (+/-), %	44.3	63.1	14.6	<0.001
<i>End-points</i>				
RRT requirement	30	35	15	0.001
Progression of CKD	46	53	32	0.002
Mortality	19	21	17	0.5

$p<0.05$ is defined as significant in bold.

Table 2: Comparison of metabolic acidosis types.

	Without MA (n:118)	Normal AG MA (n:59)	High AG MA (n:35)			p- Value
			Mixed type (n:17)	Isolated high type (n:13)	Metabolic alkalosis (n:5)	
Age, year	66 ± 11	67 ± 11	59 ± 13	70 ± 12	62 ± 13	0.1
Gender (M/F), %	56	53	47	63	50	0.8
Diabetes Mellitus, %	55	48	47	38	40	0.9
Baseline serum urea, mg/dL	94 ± 43	109 ± 49	127 ± 30	162 ± 105	139 ± 69	0.001
Baseline eGFR, mL/ min/m ²	28 ± 11	22 ± 8.6	17 ± 7.4	16 ± 10	17 ± 9.2	0.001
Uric Acid, mg/dL	7.9 ± 1.7	7.5 ± 1.9	8.2 ± 2.2	9.2 ± 3.8	9.7 ± 1.8	0.04
Serum albumin, g/dL	4.0 ± 0.5	4.0 ± 0.5	3.8 ± 0.5	3.3 ± 0.4	3.7 ± 0.7	<0.01
Hemoglobin, g/dL	11 ± 1.8	10.9 ± 1.5	10.3 ± 1.2	10.7 ± 2.6	10.6 ± 1.8	0.04
Serum bicarbonate, meq/L	23 ± 2.8	18 ± 2.9	18 ± 2.8	16 ± 3.8	22 ± 2.0	<0.001
<i>End-points</i>						
RRT requirement, %	17	34	59	50	60	<0.001
Progression of CKD, %	34	50	82	63	100	<0.001
Mortality, %	21	12	29	43	10	0.1

p<0.05 is defined as significant in bold.

revealed CKD progression were younger (63 ± 1 vs. 68 ± 11 ; $p<0.01$); high rates of diabetes mellitus incidence (59 vs. 45% ; $p=0.04$) and GFR (22 ± 12 vs. 26 ± 11 mL/min/1.73 m²; $p=0.02$) were lower compared to the non-progressive group. On the other hand, there were no statistically significant difference between two groups in terms of initial bicarbonate levels (20.3 ± 3.6 vs. 21.3 ± 3.6 ; $p=0.06$); whereas the average BE level was much more lower in patients with CKD progression (-4.7 ± 4.0 vs. -3.3 ± 4.3 ; $p=0.02$) and the ratio of patients who has BE level below -2.5 was statistically significantly higher (73 vs. 52% ; $p=0.002$) in this group. Similar findings were reached for RRT requirement.

Comparison of patients in group 1 (n: 130) (BE< -2.5) and group 2 (n: 82) showed significantly higher rates of both CKD progression (53 vs. 32% ; $p=0.002$) and RRT requirement (35 vs. 15% ; $p=0.001$). Those parameters are represented at Table 1. In cox regression analysis (variables: age, gender, diabetes mellitus history, baseline GFR, bicarbonate level, BE< -2.5), only diabetes mellitus independently associated with CKD progression. However, in non-diabetic patients; BE< -2.5 was independently associated with CKD progression (odds ratio, 0.27; 95% confidence interval, 0.10–0.80; $p<0.05$). On the other hand, baseline BE< -2.5 (odds ratio, 0.38; 95% confidence interval, 0.16–0.91; $p<0.05$) and baseline GFR (odds ratio, 0.94; 95% confidence interval, 0.90–0.97; $p<0.001$) were independently related to RRT requirement. Kaplan Meier analysis of BE for RRT requirement is representing in Figure 1.

When comparison of patients with types of MA according to delta ratio; CKD progression and RRT requirement were significantly high in mixed type acidosis group. These ratios were found to be as followed: in acidosis group with mixed-type (n: 17; 82%, 59%); isolated high AG (n: 13; 63%, 50%), with non anion gap (n: 59; 50%, 34%); and both high AG acidosis and metabolic alkalosis group (n: 5; 100%, 60%). Comparison of demographics, laboratory values and outcomes of the patients according to MA Types are represented in Table 2. These ratios were 34 and 17% in non-MA group (n: 118), respectively ($p<0.001$).

Outcomes for mortality

Nineteen percentage of patients died during follow-up period. Comparison of patients with and without MA was not found statistically significant (21 vs. 15% ; $p=0.58$) for mortality. At the same time, there were no statistically significance between both BE groups and baseline blood gas parameters for mortality. Cardiovascular disease history, high baseline urea levels, low albumin levels and low hemoglobin levels were significantly correlated to mortality. On the other hand, both BE levels (-5.46 ± 5.61 vs. -2.19 ± 5.00 ; $p=0.002$) and bicarbonate levels (19.3 ± 5.09 vs. 21.6 ± 3.96 ; $p=0.01$) at the last control visit were lower in nonsurvivors patients during follow-up period. Also, delta bicarbonate (-1.0 ± 6.0 vs. 0.7 ± 4.8 ;

Figure 1: The renal replacement therapy rates according to BE groups (group 1: BE <-2.5 and group 2: BE ≥ -2.5) in Kaplan Meier analysis.

$p=0.10$) was not found to be statistically significant. However delta BE (-0.80 ± 6.7 vs. $+1.69 \pm 5.7$; $p=0.03$) was significantly lower in non-survivor patients. In cox regression analysis (variables: age, cardiovascular disease history, baseline urea, albumin, hemoglobin and delta BE) delta BE (odds ratio, 0.90; 95% confidence interval, 0.85 to 0.96; $p<0.01$) and baseline serum albumin levels (odds ratio, 0.40; 95% confidence interval, 0.21–0.77; $p<0.01$) were associated with mortality. In Kaplan Meier analysis, mortality was significantly high in delta BE decreasing group (Figure 2). There were no statistically significant

difference between types of MA according to delta ratio in terms of mortality.

Discussion

Evaluation of BE in outpatients with stage 3–5 CKD provides beneficial informations for predicting CKD progression and RRT requirement. BE is simple, cost-effective, and routinely used in critically ill patients for metabolic and hemodynamic assessment. Also, BE

Figure 2: The survival rates according to delta BE groups in Kaplan Meier analysis.

can provide beneficial informations beside the bicarbonate level in terms of metabolic assesment [21]. When the studies in the literature are evaluated, BE is stand out as a benefial survival marker especially in the early shock period of trauma patients. BE is found to be superior than lactate for prediciting shock and ressusitation risk in trauma patients at the study of Davis JW et al. [22]. BE is also found to be a predictor of mortality in patients with sepsis and septic shock [23]. On the other hand, there are no sufficient data in the literature of utilizing BE in stable CKD patients. A study in the literature, in which pregnancy related hypertension is evaluated, Cao et al. found significant relation between disease severity and BE in pregnancy related hypertension patients [24]. During follow-up period those parameters are found to provide useful information about fetal growth. Actually, the most common cause of chronic MA is CKD. It often occurs as a consequence of diminished renal acid excretion. MA leads to damage in various endocrine and vital organs by primarily causing cellular disfunction. MA can cause muscle mass loss, hypoalbuminemia, protein malnutrition, inflammation, changes in the metabolism of some molecules (like glucose, insulin, leptin, growth hormon etc.), disorders in bone mineral metabolism when the bicarbonate level is below 22 mmol/L. Those changes may appear even before pronounced MA occurs [7–17]. BE is a parameter which reflects excess acid or base in the blood that occurs as a consequence of an impairment in the metabolic system. Standard BE is readily available from most blood gase parameters. The benefit of this parameter is improved when combined with the AG. BE may reflect excess acid load in the early period beyond bicarbonate. In our study, 44% of patients were diagnosed as MA via using bicarbonate ($\text{HCO}_3^- < 22$), whereas the ratio raised to 61% if BE (< -2.5) was used for diagnosis. This finding suggest that BE may precede bicarbonate for diagnosis of MA. Actually, in the last five decades, bicarbonate based formulas had been used for evaluation of acid-base disorders. Those formulas are theoretically important, simple and cheap. However when evaluated just on a basis of bicarbonate, unacceptably different results might be found in patients with CKD because even if the main determinative of the acid-base balance is hydrogen ions, different types of acid might also be involved in the process. Therefore bicarbonate based formulas might be insufficient for determining the acid-base balance.

Base excess (BE) may stand out among those methods because of being simple, cost-effective, and routinely used in the field of nephrology. MA is common in the course of CKD [1]. In the mean while, there are conflicting results

about the type of the MA during the follow-up period. Delta ratio provides detailed information about the type of MA in high AG Acidosis (non-AG acidosis, high AG acidosis, mixed type). The non-AG acidosis is often accompanied in the early stages of CKD. During follow-up peiroad, as the CKD progresses and eGFR level diminishes below 15 mL/min, acids such as sulfate and phosphate accumulate and as a result, MA with high anion gap might be attached. In the literature there is no sufficient data about the clinical importance of this situation. In our study, the patients with non-AG acidosis were 2/3 of the all patients with MA. The eGFR of those patients were lower compared to those with high AG acidosis. Progression of CKD and RRT requirement of patients with non AG acidosis were also lower compared to those with high AG acidosis. Those findings were similar to those in the literature [24]. To conclude, determining the type of MA via using delta ratio provides beneficial informations about the severity, progression and the awareness in the patients with stable CKD.

The presence of MA is associated with increased mortality both in early and advanced stage of CKD [25, 26]. In the literature, the study of Kovesdy CP et al. in which 1,240 male pre-dialysis CKD patients were evaluated, serum bicarbonate level below 22 mmol/L were found to increase the mortality 1.3 times. Similarly, a study in which 41,749 male patients with stage 3–4 CKD had been evaluated, serum bicarbonate levels below 23 nmmol/L were found to increase mortality by 23%. Actually, in the literature, there are some studies about the relationship between serum AG and mortality in various patient populations such as CKD, coronary artery disease, aortic aneurysm and sepsis [27–31]. Abramowitz MK et al. have demonstrated that the higher levels of AG was a risk factor of mortality in cases with less advanced CKD [27]. In our study, mortality rate is highest the type of MA in isolated high AG Acidosis (43 vs. 12%) when compared with non-AG acidosis (Table 2).

In our study, while there were no relationship between baseline blood gase parameters such as bicarbonate, BE and Delta Ratio and mortality but significantly association between BE change and mortality was found during follow-up period. To conclude, BE change during the natural course of CKD is seem to be an important parameter beyond the baseline bicarbonate and BE for predicting mortality.

There are some limitations in this study. First of all, the number of patients were relatively low and there were not exist a control group. Secondly, in mixed type acidosis and metabolic alkalosis group patients, detailed evaluation of the etiologies could not be made. Thirdly, urine anion gap was not used in the differantial diagnosis of MA.

Base excess (BE) and delta ratio are simple, cost-effective parameters that provides beneficial informations in patients with stage 3–5 CKD. Low BE levels are associated with both CKD progression and RRT requirement. BE change is related to mortality during the follow-up period. Further large scaled studies are needed to clarify this issue.

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