Progression of Metabolic Acidosis in Chronic Kidney Disease

Masayuki Tanemoto^{a, b}

^aDepartment of Internal Medicine, Shin-Kuki General Hospital, Kuki, Japan; ^bDivision of Nephrology, Department of Internal Medicine, International University of Health and Welfare School of Medicine, Atami, Japan

Keywords

Acid-base disorder · Chronic kidney disease · Disease progression · Kidney failure · Metabolic acidosis

Abstract

Background: Metabolic acidosis, which is classified into either high anion gap type (high-AGMA) or non-anion gap type (non-AGMA), is a common complication in chronic kidney disease (CKD), but its development in CKD is obscure.

Methods: Records of venous blood gas at a general hospital (2015–2017) were assessed by the physiological approach. Excluding records of primary respiratory disturbances, parameters of high-AGMA and non-AGMA (Δ AG and Δ Δ, respectively) were compared with the estimated glomerular filtration rate (eGFR). **Results:** Δ AG correlated with eGFR negatively ($r = -0.397$, $p < 0.001$), but Δ Δ did not correlate with eGFR ($p = 0.51$). Among the records grouped by the CKD stage (either G1–3, G4, or G5), Δ AG in G5 (0.9 ± 2.7) was higher than those in G1–3 (-2.2 ± 2.6 , $p < 0.001$) and in G4 (-2.0 ± 2.1 , $p < 0.001$). Δ Δ in G4 (4.0 ± 4.1) was higher than that in G1–3 (1.5 ± 3.7 , $p = 0.056$). Between the subgroups in G5 (either G5a: eGFR 10–15, G5b: eGFR 5–10, or G5c: eGFR < 5 mL/min/1.73 m²), Δ AG in G5c (3.8 ± 2.1) was higher than that in G5b (0.8 ± 2.4 , $p < 0.001$), which was higher than that in G5a (-0.9 ± 1.8 , $p < 0.001$). Δ Δ in G5a (5.6 ± 4.1) was higher than those in G4 ($p = 0.041$) and in G5b (3.2 ± 3.9 , $p = 0.001$), which

was higher than that in G5c (0.8 ± 3.8 , $p = 0.006$). **Conclusion:** High-AGMA developed and progressed in CKD stage G5. Non-AGMA generally progressed before the early phase of CKD stage G5 and regressed thereafter.

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Introduction

Metabolic acidosis, a group of acid-base disorders with decreases in serum bicarbonate concentration (HCO_3^-), is classified into either high anion gap type (high-AGMA), where accumulation of titratable acid decreases HCO_3^- , or non-anion gap type (non-AGMA), where accumulation of chloride (Cl^-) decreases HCO_3^- [1, 2]. The kidney participates in the pathophysiology of both high-AGMA and non-AGMA [3, 4]. It filters bicarbonate at the glomeruli and reabsorbs it at the renal tubules. It also filters titratable acid at the glomeruli and excretes ammonium at the renal tubules. Thus, both high-AGMA and non-AGMA develop by renal dysfunction, and metabolic acidosis is a common complication in chronic kidney disease (CKD) [5, 6].

Adversely affecting several organs, metabolic acidosis associates with mortality in CKD [7, 8]. Amelioration of metabolic acidosis slows CKD progression [9, 10]. However, there is inadequate information on the development

and progression of metabolic acidosis in CKD [3–6, 8, 11]. In the present study, development and progression of high-AGMA and non-AGMA were examined by using clinical records of blood gas analysis.

Materials and Methods

Design and Setting

This study was a retrospective analysis of clinical records at a general hospital in a metropolitan suburb. Records of patients managed in the Department of Nephrology from April 2015 to September 2017 were reviewed. The data of venous blood gas analysis performed simultaneously with measurement of serum concentrations of sodium (Na^+), Cl^- , albumin (Alb), and creatinine (Cr) were collected from the records. The records of either primary respiratory acidosis ($\text{pH} < 7.36$ and $\text{pCO}_2 > 48$ mm Hg) or primary respiratory alkalosis ($\text{pH} > 7.38$ and $\text{pCO}_2 < 43$ mm Hg) were excluded. The study was approved by the Ethics Committee of the hospital.

Laboratory Measurement and Definition

Blood gas analysis, which includes measurement of pH, HCO_3^- , and lactate concentration (Lac), was performed by the GEM premier 4000 analyzer (Instrumentation Laboratory Company, MA, USA). Serum chemistry measurement was performed by the TBA-c8000 analyzer (Canon Medical Systems, Tochigi, Japan). Estimated glomerular filtration rate (eGFR) was calculated from Cr, age, and gender by a modified Modification of Diet in Renal Disease Study equation [12].

Anion gap (AG) was calculated as “ $\text{AG} = \text{Na}^+ - \text{Cl}^- - \text{HCO}_3^-$ ” [1, 2]. Based on the finding that 1 g/dL Alb accounts for a negative charge of 2.5 mEq/L [13–15], AG was adjusted by Alb (AG_{adj}) as “ $\text{AG}_{\text{adj}} = \text{AG} + 2.5 \times (4 - \text{Alb})$.” Average value of AG_{adj} in the records with neither acidemia nor alkalemia ($\text{pH} 7.36\text{--}7.38$) was used as its reference (AG_{ref}), and 25 mmol/L was used as the reference of HCO_3^- ($\text{HCO}_3^-_{\text{ref}}$) [1].

Diagnosis of Metabolic Acidosis

By using $\text{HCO}_3^-_{\text{ref}}$ and AG_{ref} , metabolic acidosis was diagnosed according to the physiological approach [1, 2]. High-AGMA excluding lactic acidosis was diagnosed by using AG_{adj} ; the AG_{adj} subtracted by AG_{ref} and Lac (ΔAG) was used to indicate the magnitude of high-AGMA. $\Delta\text{AG} > 0$ was used to indicate the existence of the High-AGMA excluding lactic acidosis. Non-AG was diagnosed by using $\text{HCO}_3^-_{\text{ref}}$; $\text{HCO}_3^-_{\text{ref}}$ was subtracted by HCO_3^- (ΔHCO_3^-), and the value of the ΔHCO_3^- subtracted by ΔAG ($\Delta\Delta$) was used to indicate the magnitude of non-AGMA. $\Delta\Delta > 0$ was used to indicate the existence of non-AGMA.

Statistical Analysis

Continuous variables were calculated as the mean $\pm$ SD and were compared using analysis of variance. A correlation between parameters was analyzed using Pearson's correlation test. A linear regression between parameters was also built, and r of the prediction model was obtained. All statistical analyses were performed using SPSS software package (IBM Corp., Armonk, NY, USA). A p value of < 0.01 was considered statistically significant.

Table 1. Laboratory measures and calculated parameters of records

Measure	$n = 269$
pH	7.31 ± 0.06
pCO_2 , mm Hg	42.6 ± 4.6
Bicarbonate, mmol/L	21.6 ± 4.0
Sodium, mmol/L	139.5 ± 3.8
Chloride, mmol/L	107.7 ± 5.4
Albumin, g/dL	3.45 ± 0.73
Creatinine, mg/dL	5.18 ± 2.79
Lactate, mmol/L	1.28 ± 0.99
eGFR, mL/min/1.73 m^2	14.1 ± 15.3
AG_{adj}	11.6 ± 3.1
ΔAG	0.1 ± 2.9
ΔHCO_3^- , mmol/L	3.4 ± 4.0
$\Delta\Delta$	3.3 ± 4.2

Data are presented as mean $\pm$ SD. AG_{adj} , anion gap adjusted by albumin; eGFR, estimated glomerular filtration rate; ΔAG , AG_{adj} subtracted by its reference and lactate; ΔHCO_3^- , bicarbonate subtracted from its reference; $\Delta\Delta$, ΔHCO_3^- subtracted by ΔAG .

Results

Laboratory Measures and Calculated Parameters

Overall, 269 records were included in the study. Fifty-one records had pH 7.36–7.38, and the average value of AG_{adj} among them was 10.2. Table 1 shows the summary of laboratory measures and calculated parameters in them; pH, pCO_2 , HCO_3^- , Lac, and Cr ranged from 7.10 to 7.45, from 26 to 54 mm Hg, from 9.9 to 34.2 mmol/L, from 0.5 to 11.7 mmol/L, and from 0.27 to 13.05 mg/dL, respectively. eGFR, AG_{adj} , and ΔHCO_3^- ranged from 2.6 to 165.6 mL/min/1.73 m^2 , from 4.8 to 24.6, and -9.2 to 15.1 mmol/L, respectively. ΔAG and $\Delta\Delta$ ranged from -6.7 to 8.6 and from -9.7 to 16.8, respectively.

Development of Metabolic Acidosis in CKD

Figure 1 shows correlations of HCO_3^- , ΔAG , and $\Delta\Delta$ with eGFR. There was a positive correlation between eGFR and HCO_3^- ($r = 0.333$, $p < 0.001$; Fig. 1a) and a negative correlation between eGFR and ΔAG ($r = -0.397$, $p < 0.001$; Fig. 1b), but there was no correlation between eGFR and $\Delta\Delta$ ($r = -0.040$, $p = 0.51$; Fig. 1c). There were negative correlations between ΔAG and HCO_3^- ($r = -0.289$, $p < 0.001$; Fig. 2a) and between $\Delta\Delta$ and HCO_3^- ($r = -0.747$, $p < 0.001$; Fig. 2b).

The records were grouped by the CKD stage (either G1–3: eGFR ≥ 30 mL/min/1.73 m^2 , G4: eGFR 15–30 mL/min/1.73 m^2 , or G5: eGFR < 15 mL/min/1.73 m^2), and the

Fig. 1. Scatter plots comparing HCO_3^- (a), ΔAG (b), and $\Delta\Delta$ (c) with eGFR. There was a positive correlation between eGFR and HCO_3^- ($r = 0.333$, $p < 0.001$) with a linear approximation of $y = 0.087x + 20.4$ (a) and a negative correlation between eGFR and ΔAG ($r = -0.397$, $p < 0.001$) with a linear approximation of $y = -0.076x + 1.13$ (b). c There was no correlation between eGFR and $\Delta\Delta$ ($r = -0.040$, $p = 0.51$). eGFR, estimated glomerular filtration rate; HCO_3^- , bicarbonate concentration; ΔAG , AG_{adj} subtracted by its reference and lactate; $\Delta\Delta$, HCO_3^- reference subtracted by HCO_3^- and ΔAG .

Fig. 2. Scatter plots comparing ΔAG (a) and $\Delta\Delta$ (b) with HCO_3^- . There were negative correlations between ΔAG and HCO_3^- ($r = -0.289$, $p < 0.001$) with a linear approximation of $y = -0.395x - 21.6$ (a) and between $\Delta\Delta$ and HCO_3^- ($r = -0.747$, $p < 0.001$) with a linear approximation of $y = -0.708x - 24.0$ (b). HCO_3^- , bicarbonate concentration; ΔAG , AG_{adj} subtracted by its reference and lactate; $\Delta\Delta$, HCO_3^- reference subtracted by HCO_3^- and ΔAG .

levels of HCO_3^- , ΔAG , and $\Delta\Delta$ were compared between the groups (Table 2). The levels of HCO_3^- in G5 were significantly lower than those in G1–3 and in G4 ($p < 0.001$ between G5 and G1–3 and between G5 and G4). The levels in G4 were generally lower than those in G1–3 ($p = 0.012$). The levels of ΔAG in G5 were significantly higher than those in G1–3 and in G4 ($p < 0.001$ between G5 and G1–3 and between G5 and G4). However, the levels in G4 were not significantly different from those in G1–3 ($p = 0.93$). Although the levels of $\Delta\Delta$ were not significantly different between G1–3, G4, and G5 ($p = 0.056$, 0.12 , and 0.65 between G1–3 and G4, between G1–3 and G5, and between G4 and G5, respectively), its levels in G4 were generally higher than those in G1–3.

The records of G5 were further grouped by eGFR (either G5a: eGFR 10–15 mL/min/1.73 m², G5b: eGFR 5–10 mL/min/1.73 m², or G5c: eGFR <5 mL/min/1.73 m²), and the levels of HCO_3^- , ΔAG , and $\Delta\Delta$ were compared between these subgroups (Table 3). The levels of HCO_3^- were not significantly different between the subgroups ($p = 0.52$, 0.99 , and 0.62 between G5a and G5b, between G5a and G5c, and between G5b and G5c, respectively). The levels of ΔAG in G5c were significantly higher than those in G5b and in G5a, and its levels in G5b were significantly higher than those in G5a ($p < 0.001$ between G5c and G5b, between G5c and G5a, and between G5b and G5a). The levels of $\Delta\Delta$ in G5a were generally higher than those in G4 ($p = 0.041$). However, in contrast to the

Table 2. Comparison of HCO_3^- , ΔAG , and $\Delta\Delta$ between the CKD stages

Measure	CKD stage			<i>p</i> value
	G1–3 (<i>n</i> = 23)	G4 (<i>n</i> = 55)	G5 (<i>n</i> = 191)	
HCO_3^-	25.7±3.7	23.1±3.9	20.1±3.6	<0.001
ΔAG	−2.2±2.6	−2.0±2.1	0.9±2.7	<0.001
$\Delta\Delta$	1.5±3.7	4.0±4.1	3.4±4.3	0.069

Data are presented as mean ± SD. CKD, chronic kidney disease; HCO_3^- , bicarbonate concentration; ΔAG , albumin-adjusted anion gap subtracted by its reference and lactate; $\Delta\Delta$, ΔHCO_3^- (bicarbonate subtracted from its reference) subtracted by ΔAG .

levels of ΔAG , its levels in G5b were significantly lower than those in G5a, and its levels in G5c were significantly lower than those in G5b and in G5a ($p = 0.001$, 0.006 , and <0.001 between G5b and G5a, between G5c and G5b, and between G5c and G5a, respectively).

Discussion

The present study revealed progression of metabolic acidosis in CKD. High-AGMA other than lactic acidosis developed in CKD stage G5 and progressed by a further decline of renal function in this stage. Non-AGMA generally progressed by a decline of renal function before the early phase of stage G5, but it regressed thereafter.

In the present study, an indicator of high-AGMA, ΔAG , had generally negative values before the early phase of stage G5 and began to present positive values thereafter. These findings support the notion that the renal ability to excrete titratable acid is preserved until renal function is impaired severely [3]. Furthermore, the present study also found that ΔAG increased as renal function declined in stage G5. Thus, the findings indicated that high-AGMA other than lactic acidosis developed and progressed in CKD stage G5.

Non-AGMA is presumed to progress from the early CKD stages, since the renal ability to reabsorb bicarbonate and to excrete ammonium is impaired as renal function declines [3, 4, 11]. Supporting this notion, an indicator of non-AGMA, $\Delta\Delta$, increased gradually before the early phase of stage G5. However, $\Delta\Delta$ decreased rather than increased thereafter. These findings indicated that non-AGMA regressed rather than progressed by a renal

Table 3. Comparison of HCO_3^- , ΔAG , and $\Delta\Delta$ between the subgroups of stage G5

Measure	Subgroup; eGFR, mL/min/1.73 m ²			<i>p</i> value
	G5a; 10–15 (<i>n</i> = 55)	G5b; 5–10 (<i>n</i> = 98)	G5c; <5 (<i>n</i> = 38)	
HCO_3^-	20.3±3.4	21.0±3.8	20.4±3.4	0.46
ΔAG	−0.9±1.8	0.8±2.4	3.8±2.1	<0.001
$\Delta\Delta$	5.6±4.1	3.2±3.9	0.8±3.8	<0.001

Data are presented as mean ± SD. HCO_3^- , bicarbonate concentration; ΔAG , albumin-adjusted anion gap subtracted by its reference and lactate; $\Delta\Delta$, ΔHCO_3^- (bicarbonate subtracted from its reference) subtracted by ΔAG ; eGFR, estimated glomerular filtration rate.

function decline in stage G5. Bicarbonate would have begun to accumulate during the progression of renal dysfunction in stage G5. The levels of HCO_3^- , which did not increase despite the ΔAG increase in stage G5, also indicated the accumulation of bicarbonate at this stage. Severe renal impairment would decrease not only tubular reabsorption of bicarbonate but also its glomerular filtration, which would facilitate accumulation of bicarbonate in CKD stage G5.

The leading cause of lactic acidosis is tissue hypoxia, and lactic acidosis develops irrespective of CKD progression [16]. Hence, we excluded lactic acidosis as the high-AGMA developing in CKD. Ketoacidosis also develops irrespective of CKD progression; diabetic ketoacidosis is the most common, followed by fasting ketoacidosis and alcoholic ketoacidosis [17]. Therefore, development of ketoacidosis might have caused the present increase in ΔAG in CKD stage G5. However, it is unlikely that either diabetic, fasting, or alcoholic ketoacidosis generally developed and progressed in CKD stage G5. Thus, inclusion of ketoacidosis in the analysis of high-AG would not have significantly influenced the present finding of CKD-associated development of high-AGMA.

In the physiological approach, a time-honored tool to diagnose acid-base disturbances, increment of AG_{adj} from its reference (AG_{ref}) is used to indicate the degree of titratable acid accumulation [1, 2, 13–15]. As the AG_{ref} , which is the value of AG without abnormal ions in the serum, we used the average AG_{adj} of the records with neither acidemia nor alkalemia. Since these records might have had AG disturbances, the value of AG_{ref} used in the present study might not have been appropriate. However, ΔAG change by eGFR is independent of the value of

AG_{ref}. Thus, titratable acid except lactate would have accumulated in CKD stage G5 as found in the present study, even if AG_{ref} values were inappropriate.

The present study has several limitations. Firstly, possible inclusion of ketoacidosis, which generally develops irrespective of CKD progression, in high-AGMA could have influenced the development of high-AGMA. However, as mentioned above, this possible inclusion of ketoacidosis would not have influenced the high-AGMA development significantly. Secondly, a limited number of records in a single center, which included only a few records of CKD stage G1 and G2, was analyzed, and the study might be limited by the possibility of selection bias. Thirdly, several samples were from patients receiving multiple medications including diuretics and gastric acid secretion inhibitors. These medications could have influenced the acid-base disturbances that developed in CKD. Thus, further studies with large sample sizes and analyses with measurement of ketones and grouping by differences in treatment are required to confirm the present findings.

To conclude, the present study revealed progression of metabolic acidosis in CKD. High-AGMA other than lactic acidosis develops in CKD stage G5 and progresses by a further decline in renal function at this stage. Non-AGMA progresses before the early phase of stage G5 but regresses thereafter.

Statement of Ethics

The study was approved by the Ethics Committee of the Shin-Kuki General Hospital.

Disclosure Statement

The author has no conflicts of interests to declare.

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