Prevalence and predictors of severe metabolic acidosis in chronic kidney disease stage 3-5

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Abstract

Background and objective Metabolic acidosis is a common metabolic complication of chronic kidney disease with different frequencies across stages of CKD. The objective of the study was to estimate the prevalence and study predictors for development of severe metabolic acidosis in CKD stage 3–5.

Methods It was a cross-sectional study of patients aged > 18 years with metabolic acidosis and stage 3–5 CKD for 1 year at two medical centers in Iraq. The prevalence of severe metabolic acidosis and correlation with patients' characteristics were studied using Fisher exact test for categorical variables and nonparametric independent samples Mann-Whitney U T test. Predictors for severe metabolic acidosis was analyzed using multiple logistic regression.

Results Among 117 patients with CKD stage 3–5 and metabolic acidosis, severe metabolic acidosis was reported in 14.5%. It was more frequent in stage 5 CKD compared to stage 4 CKD (64.7% vs 35.3%). Correlation of severe metabolic acidosis was statistically significant with urinary tract obstruction, glomerular diseases, reduced cortical thickness on ultrasonography, anemia, hyperkalemia, hypocalcemia and hyperphosphatemia. By multivariate analysis, female sex, urinary tract obstruction and glomerular diseases were predictors for development of severe metabolic acidosis.

Conclusion Severe metabolic acidosis was common in stage 5 CKD. Female sex, urinary tract obstruction and glomerular diseases were predictors for development of severe metabolic acidosis.

Background

Metabolic acidosis is a common complication of chronic kidney disease (CKD) (1). Most early stages of CKD do not have metabolic acidosis because of compensatory increase in renal ammonia production and bone buffering (2-4). The prevalence of metabolic acidosis in CKD is 15% (1, 5). The most important risk factor for metabolic acidosis is reduced glomerular filtration rate (GFR) (1). Diets are also contributing factors for development of metabolic acidosis in CKD, high animal protein diet increase the risk while fruits and vegetables decrease the risk of metabolic acidosis (6). Renin-angiotensin-aldosterone blockers are risk factor for development of metabolic acidosis in CKD by inhibition of aldosterone action on the cortical collecting duct (7). Hyperkalemia by inhibition of renal ammoniagenesis may lead to development of metabolic acidosis (8). Smoking, anemia, albuminuria, hyperalbuminemia and diuretic use are also a risk factors for development of metabolic acidosis (1).

Little is known about prevalence and factors associated with development of severe metabolic acidosis in CKD. Some patients in clinical practice have severe metabolic acidosis and others have mild to moderate metabolic acidosis which may linked to certain demographics, clinical characteristics and laboratory parameters.

The objective of the study is to estimate the prevalence of severe metabolic acidosis in patients with CKD stage 3-5 and to assess the factors that predict its development.

Methods

Data source, study design and participants

The data were obtained from medical records of patients with chronic kidney disease and metabolic acidosis consulted the outpatient clinic and those who were admitted to the nephrology ward. This is a cross-sectional study conducted from May 1, 2019, to May 1, 2020 at two medical centers (Baghdad Medical City and Basra Teaching Hospital). The study was approved by Institutional Review Board of Ministry of Health and University of Basra. Patients > 18 years old with chronic kidney disease stage 3, 4 and 5 not on dialysis with metabolic acidosis were included in the study. Patients with acute kidney injury, CKD stage 1 and 2, CKD 5 on dialysis and kidney transplantation were excluded from the study.

Definitions And Measurements

Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 (9). Estimated GFR was calculated using CKD-EPI equation which is available in the smartphones and calculated using this equation: eGFR = 141 x min $(S_{Cr}/\kappa, 1)^{\alpha}$ x max$(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black] (10). CKD was classified into 5 stages according to eGFR (in ml/min/1.73 m2) values as follows: stage 1, eGFR > 90; stage 2, eGFR 60–89; stage 3, eGFR 30–59; stage 4, eGFR, 15–30, stage 5, < 15 (11). K/DOQI criteria was used for laboratory parameters definition; anemia with hemoglobin concentrations < 11 g/dL, metabolic acidosis with serum bicarbonate concentrations < 22 mmol/L, hyperkalemia with plasma potassium > 5 mmol/L, hyperphosphatemia with plasma phosphorus > 4.5 mg/dL, hypocalcemia with corrected plasma calcium < 8.4 mg/dL and hyperparathyroidism with plasma PTH > 450 pg/mL (12, 13). Mild to moderate metabolic acidosis was defined as serum bicarbonate levels of 12–22 mmol/L and severe metabolic acidosis was defined as serum bicarbonate levels < 12 mmol/L (14). Ultrasonographic criteria were as follows; Small-sized when the length is < 9 cm, decrease cortical thickness when the cortical thickness is < 4 mm, increased renal echogenicity when the kidneys are more echogenic than the liver (15). Data were available for all patients and the missing variables were as follows: 31.6% for uric acid, 3% for hemoglobin, 11% for calcium, 13.6% for phosphorus, 36.7% for PTH, 52% for albumin and 34% for albuminuria.

Covariates

Data were collected on patients' demographics, medical history of chronic diseases and duration of CKD. Laboratory workups include hemoglobin levels, basic metabolic panels and serum PTH. The following laboratory parameters were measured with the following methods: plasma creatinine by modified Jaffe colorimetric, plasma potassium by flame photometry, venous bicarbonate by specific electrode, plasma phosphorus by colorimetry, plasma calcium by colorimetry,serum PTH by second generation radioimmunoassay and UACR by immunonephelometry.

Ultrasonographic assessment include renal size, cortical thickness and echogenicity was performed by an expert dependable sonograph physician. Possible causes of CKD were labeled based on medical history of chronic diseases. Patients with hypertension, the CKD was assumed to be due to hypertension due to long history of hypertension preceding the CKD and ultrasonographic evidence of renal parenchymal disease. Patients with DM, presence of microvascular complications of diabetes such as retinopathy and neuropathy with or without proteinuria and history of uncontrolled diabetes was factor for labelling as diabetic kidney disease. Glomerular diseases were diagnosed based on proteinuria, hematuria with or without hypoalbuminemia, abnormal autoimmune serology or renal biopsy proven diagnosis. Urinary tract obstruction was diagnosed when there is bilateral hydronephrosis or hydroureteronephrosis or unilateral hydronephrosis or hydroureteronephrosis in single kidney. Durations of CKD was measured in months.

Outcomes

The outcome of the study was estimation of prevalence and predictors of severe metabolic acidosis in CKD stages 3–5.

Statistical analysis

Descriptive statistics were performed using means and standard deviations and proportions for categorical variables. Comparisons were made between severity of metabolic acidosis and patients' clinical characteristics using Fisher exact test for categorical variables and nonparametric independent samples Mann-Whitney U T test for continuous variables.

Comparisons were made between of severity of metabolic acidosis and laboratory parameters using independent samples Mann-Whitney U T test. The predictors for development of severe metabolic acidosis in relation to the study variables was analyzed statistically using multivariate regression analysis. All statistical tests were 2-sided, and a P value < 0.05 was considered statistically significant. Statistical analysis was done by SPSS version 25.

Results

One-hundred-seventeen patients with CKD and metabolic acidosis were studied. Table 1 illustrated the baseline demographics and clinical characteristics of the patients. The mean age was 64 ± 14 SDs, 53.8% were females, 17.9% were black, 48.7% were smokers, the mean BMI was 29.8 ± 5.8 SDs. Comorbidities were as follows: HTN in 84.6% and DM in 53%. Urinary tract obstruction was documented in 7.7% and glomerular diseases in 6%. Stages of CKD were as follows: stage 3 in 26.5%, stage 4 in 38.5% and stage 5 in 35%. Median durations of CKD were 12 months. Severe metabolic acidosis was reported in 14.5%. Small-sized kidneys were reported in 34.2%, decrease cortical thickness in 41% and increased echogenicity in 75.2%. regarding treatment, 61.5% were on ACEI or ARB and 63.2% were on diuretics.

Table 1. Baseline characteristics of the patients (n = 117).

Characteristics	Overall patients (n = 117)
Age (years)	64 ± 14
Female	63 (53.8)
Black race	21 (17.9)
BMI (kg/m2)	29.8 ± 5.8
Smoking	57 (48.7)
HTN	99 (84.6)
DM	62 (53)
UTO	9 (7.7)
Glomerular diseases	7 (6)
Stage 3 CKD	31 (26.5)
Stage 4 CKD	45 (38.5)
Stage 5 CKD	41 (35)
Duration of CKD	14 ± 7.5
Severe metabolic acidosis*	17 (14.5)
Small-sized kidneys	40 (34.2)
Decrease cortical thickness	48 (41)
Increased echogenicity	88 (75.2)
ACEI/ARB use	72 (61.5)
Diuretic use	74 (63.2)

Values were expressed as mean ± SDs and n (%).

*Severe metabolic acidosis, serum bicarbonate < 12 mmol/L.

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; CKD, chronic kidney disease; UTO, urinary tract obstruction; ACEI, angiotensin converting enzyme inhibitors; ABR, angiotensin receptor blockers.

Table 2 showed the correlations between clinical characteristics of the patients and severity of metabolic acidosis; urinary tract obstruction, glomerular diseases and decrease cortical thickness were statistically

correlated with sever metabolic acidosis.

Table 2. Baseline clinical characteristics of the patients by severity of metabolic acidosis status (n = 117).

Characteristics	Severe metabolic acidosisa	Mild-Moderate metabolic acidosisb	P valuec
Age (in years)	63 ± 15	62 ± 17	0.785
Female	12 (70.6)	49 (50)	0.187
Black race	4 (23.5)	17 (17.3)	0.511
BMI	29.5 ± 6	29.8 ± 5.8	0.641
Smoking	6 (35.3)	51 (52)	0.294
HTN	13 (76.5)	84 (85.7)	0.303
DM	7 (41.2)	54 (55.1)	0.101
UTO	6 (35.3)	3 (3.1)	<0.001
Glomerular disease	3 (21.4)	4 (4.9)	0.061
CKD duration	16.6 ± 8.6	14.5 ± 7.5	0.397
Small-sized kidneys	8 (47.1)	32 (32.7)	0.278
Decrease cortical thickness	12 (70.6)	36 (36.7)	0.015
Increased echogenicity	15 (88.2)	73 (74.5)	0.353
ACEI/ARB use	9 (52.9)	61 (62.2)	0.592
Diuretic use	9 (52.9)	63 (64.3)	0.421

Values were expressed as mean ± SDs and n (%).

aSevere metabolic acidosis, serum bicarbonate < 12 mmol/L.

bMild-Moderate metabolic acidosis, serum bicarbonate 12-22 mmol/L.

cComparisons were made between severity of metabolic acidosis and patients' clinical characteristics using Fisher exact test for categorical variables and nonparametric independent samples Mann-Whitney U T test for continuous variables.

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; CKD, chronic kidney disease; UTO, urinary tract obstruction; ACEI, angiotensin converting enzyme inhibitors; ABR, angiotensin receptor blockers.

Table 3 showed the correlation between laboratory parameters and severity of metabolic acidosis; all laboratory parameters were correlated with severe metabolic acidosis.

By multivariate regression analysis; female sex, urinary tract obstruction and glomerular diseases were predictors for development of severe metabolic acidosis (Table 4). All laboratory abnormalities were not predictors for development of severe metabolic acidosis by multivariate regression (Table 5).

Severe metabolic acidosis was more frequent in females (Figure 1) and severe metabolic acidosis was more frequent in stage 5 CKD (Figure 2).

Table 3. Baseline laboratory characteristics of the patients by severity of metabolic acidosis status (n = 117)

Laboratory characteristics	Severe metabolic acidosisa	Mild-Moderate metabolic acidosisb	P valuec
Hgb (g/dL)	9.7 ± 1.6	10.7 ± 2.3	0.036
Serum K (mmol/L)	5.3 ± 1	4.7 ± 0.9	0.016
Serum Ca (mg/dL)	8 ± 1.2	8.8 ± 1	0.015
Serum PO4 (mg/dL)	6 ± 1.8	4.7 ± 1.8	0.006
Serum PTH (pg/mL)	650 ± 597.9	271 ± 199.5	0.065

Values were expressed as mean ± SDs.

aSevere metabolic acidosis, serum bicarbonate < 12 mmol/L.

bMild-Moderate metabolic acidosis, serum bicarbonate 12-22 mmol/L.

Hgb, hemoglobin; K, potassium ions; Ca, calcium ions; PO4, phosphorus ions; PTH, parathyroid hormone.

cComparisons were made between of severity of metabolic acidosis and laboratory parameters using independent samples Mann-Whitney U T test.

Table 4. Multivariate logistic regression of predictors of severe metabolic acidosis per patients' characteristics.

Characteristics	Adjusted OR	P value	95% CI
Age (years)	0.99	0.910	0.96, 1
Female	0.08	0.03*	0.009, 0.79
BMI (kg/m2)	0.99	0.873	0.87, 1.1
Black race	0.4	0.369	0.075, 2.62
Smoking	0.862	0.581	0.182, 4
HTN	0.768	0.832	0.067, 8.75
DM	1.57	0.539	0.37, 6.67
UTO	0.018	0.003*	0.001, 0.25
Glomerular disease	0.07	0.019*	0.008, 0.643
ACEI/ARB use	1.2	0.780	0.32, 4.5
Diuretic use	0.684	0.572	0.18, 2.55
Small-sized kidneys	2.39	0.469	0.226, 25.4
Decrease cortical thickness	0.188	0.220	0.013, 2.7
Increased echogenicity	4.37	0.129	-.65, 29.4

OR, odds ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure; CKD, chronic kidney disease; UTO, urinary tract obstruction; ACEI, angiotensin converting enzyme inhibitors; ABR, angiotensin receptor blockers.

*Female, urinary tract obstruction and glomerular diseases were independent predictors for severe metabolic acidosis.

Table 5. Multivariate logistic regression of predictors of severe metabolic acidosis per patients' laboratory parameters.

Parameters	Adjusted OR	P value	95% CI
Anemia	1.43	0.737	0.18, 11.2
Hyperkalemia	1.16	0.846	0.26, 5.3
Hypocalcemia	2.6	0.244	0.52, 13.56
Hyperphosphatemia	1.79	0.504	0.33, 9.7
Hyperparathyroidism	2.67	0.218	0.56, 12.8

OR, odds ratio; CI, confidence interval.

All abnormal laboratory parameters were not predictors for development of severe metabolic acidosis

Discussion

In the present study, metabolic acidosis was common in CKD and occurred in 19% in stage 3, 38% in stage 4 and 43% in stage 5 (Stage 2 were excluded because all had normal serum bicarbonate concentrations). In Chronic Renal Insufficiency Cohort (CRIC) study, the prevalence of metabolic acidosis was 7% in stage 2, 13% in stage 3 and 37% in stage 4 (1).

Severe metabolic acidosis was reported in 14.5%. It occurred more frequently in females and stage 5 CKD compared to stage 4 CKD (64.7% vs 35.3%) (1). Glomerular diseases, urinary tract obstruction, decreased cortical thickness, anemia, hyperkalemia, hypocalcemia, hyperphosphatemia and hyperparathyroidism showed statistically significant correlation with severe metabolic acidosis. Hyperkalemia is associated with worsening of metabolic acidosis by inhibition of renal ammonia synthesis (8). Glomerular diseases associated with retention of uremic toxins and in severe cases cause severe anion-gap metabolic acidosis. Urinary tract obstruction cause type 4 renal tubular acidosis with degree of metabolic acidosis that is out of proportion to the degree of renal impairment (16). Anemia and hyperphosphatemia were predictor for development of metabolic acidosis in study by Raphael KL et al. but, in the present study, they were associated with severe metabolic acidosis (1). Smoking, use of ACEI/ARB or no use of diuretics were predictors for development of metabolic acidosis in study by Raphael KL et al. but, in the present study, they were not associated with severe metabolic acidosis (1). Regarding ultrasonographic findings of CKD, only decrease cortical thickness showed statistically significant correlation with severe metabolic acidosis. We hypothesized that the renal cortex contained more functioning nephrons which is responsible for adaptation to acid-base balance so, less cortical thickness equal to less functioning nephrons and more severe metabolic acidosis.

By multivariate analyses; female, urinary tract obstruction and glomerular diseases were independent predictors for development of severe metabolic acidosis. So, we need more alkali in for correction of severe metabolic acidosis in these predictors in order to retard CKD progression and preserve the bone.

Also, by multivariate analyses, all laboratory abnormalities were not predictors for development of severe metabolic acidosis.

The study has some limitations. First, it was a cross-sectional study so there may be missed cases of severe metabolic acidosis on follow up. Second, Dietary history was lacking in order to know the impact of diet on severity of metabolic acidosis. Third, cases of acute on chronic kidney disease were excluded from the study and we think these cases may be associated with severe metabolic acidosis.

Conclusions

Severe metabolic acidosis was common in stage 5 CKD. Female sex, urinary tract obstruction and glomerular diseases were predictors for development of severe metabolic acidosis.

Abbreviations

CKD, chronic kidney disease; GFR, glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; KDOQI, kidney disease outcomes quality initiative; PTH, parathyroid hormone; UACR, urine albumin:creatinine ratio; HTN, hypertension; DM, diabetes; BMI, body mass index; UTO, urinary tract obstruction; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; CRIC, chronic renal insufficiency cohort.

Declarations

Ethics approval and consent to participate

This study was approved by Institutional Review Board of Ministry of Health and University of Basra.

Consent to publish

All authors have consent to participate in this work.

Availability of data and materials

The data are available upon request after submission.

Competing Interest

All authors declare no conflict of interests.

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Author' contributions

Hayder Aledan, data collection and writing the manuscript; Jawad Rasheed, data collection and reviewing the manuscript.

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Figures

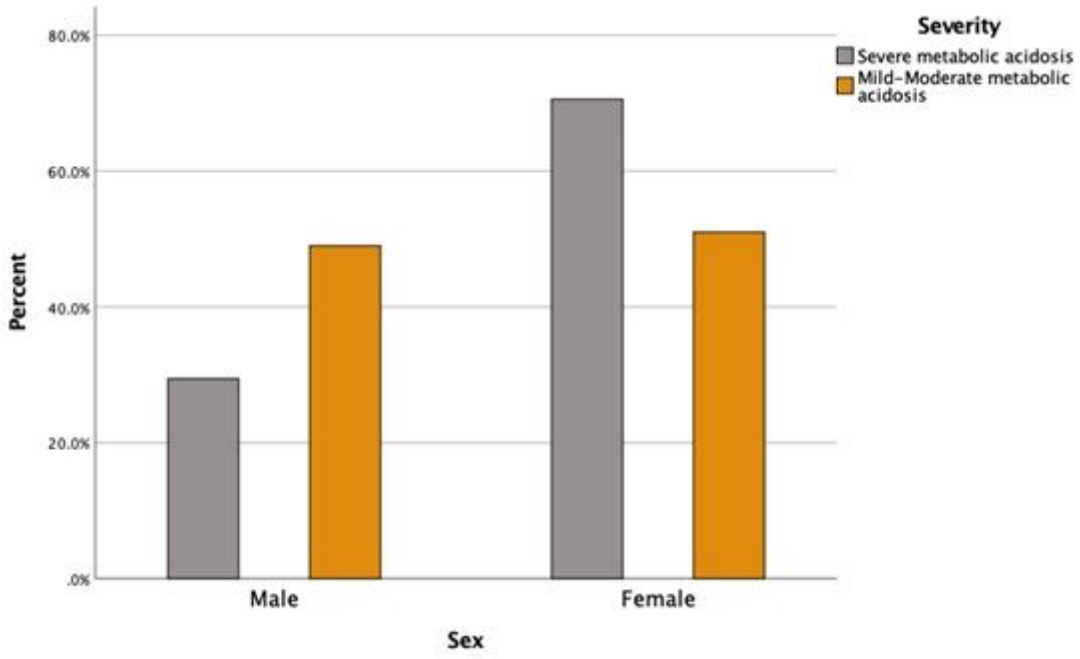

Figure 1

Proportion of severity of metabolic acidosis by sex status.

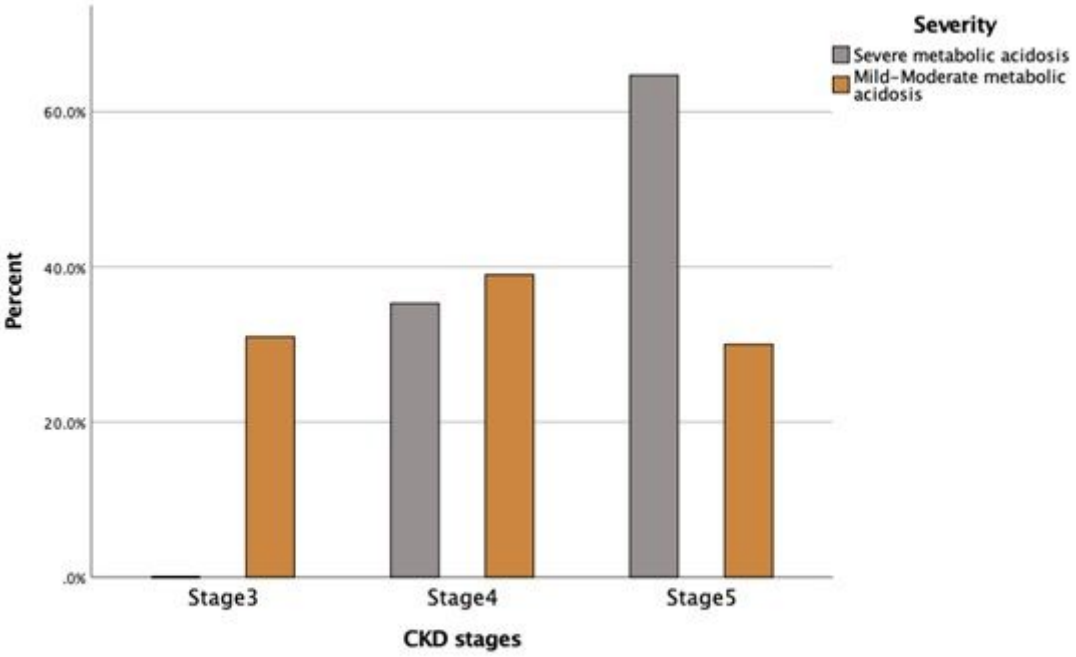

Figure 2

Proportion of severity of metabolic acidosis by CKD stages