Research Article

Is Metabolic Acidosis a Novel Risk Factor for a Long-Term Graft Survival in Patients after Kidney Transplantation?

Damian Gojowy Katarzyna Skiba Magdalena Bartmanska
Aureliusz Kolonko Andrzej Wiecek Marcin Adamczak

Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland

Keywords

Metabolic acidosis · Kidney transplantation · Chronic kidney disease · Prognosis · Risk factor

Abstract

Background: Results of both experimental and clinical studies suggest that metabolic acidosis (MA) contributes to the progression of chronic kidney disease (CKD) and mortality in CKD patients. It is unknown whether the same relationship exists in kidney transplantation (KTx) patients. The aim of this observational study was to examine this relationship between MA and both mortality and renal outcomes in patients after KTx. **Methods:** Four hundred eighty-six (290 male; 196 female) patients aged 48 ± 12 years, at least 1 year after KTx, were analyzed. Blood HCO_3^- was measured, and patients were then observed over 3 years. MA was defined as the blood HCO_3^- concentration <22 mmol/L. The end points of survival analysis were death and initiation of dialysis therapy. In patients who did not reach the above-mentioned end points, the difference between final (after 3 years of follow-up) and initial estimated glomerular filtration rate (eGFR) was calculated. **Results:** MA was initially diagnosed in 57 (12%) patients after KTx. Three-year patient survival was 89.5% in the MA group and 97.4% in the non-MA group ($p = 0.001$). Three-year graft survival was 73.7% for patients with MA and 93.0% for patients without MA ($p < 0.001$). In patients with MA who did not reach study end points, blood bicarbonate concentration at baseline correlated positively with a change in eGFR ($R = 0.48$, $p = 0.002$, $n = 36$). Such a correlation was not found in patients without MA ($n = 388$). **Conclusions:** (1) MA significantly increases the risk of mortality in patients after KTx. (2) The intensity of MA may be associated with progression of transplanted kidney dysfunction in KTx patients.

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Published by S. Karger AG, Basel

Marcin Adamczak
Department of Nephrology
Transplantation and Internal Medicine, Medical University of Silesia
Francuska 20/24, PL-40-027 Katowice (Poland)
madamczak1@op.pl

Introduction

Metabolic acidosis (MA) is a common abnormality in patients with chronic kidney disease (CKD). The main cause of MA is the reduced ability of failing kidneys to adequately excrete metabolically produced acid, which accumulates and titrates body bicarbonate, thereby reducing its serum concentration. Healthy kidneys can perform proper net acid excretion, which includes new bicarbonate regeneration to replace the HCO_3^- titrate by the accumulated acid. The prevalence of MA in CKD patients is between 2 and 13% in stage 3 and 19–37% in stage 5. MA occurs more frequently among patients with an estimated glomerular filtration rate (eGFR) $<30 \text{ mL/min/1.73 m}^2$, even 10-fold higher than in individuals with normal renal function [1, 2].

It has been shown in many observational clinical and experimental studies that MA is an independent factor of CKD progression [3–7]. Observational studies have shown that the risk of CKD progression is significantly increased in patients with blood bicarbonate concentration $<22 \text{ mmol/L}$ [8, 9]. In the MESA study (Multi-Ethnic Study of Atherosclerosis), which included patients with eGFR $<60 \text{ mL/min/1.73 m}^2$, it has been shown that a lower serum bicarbonate concentration was associated with the extent of deterioration of kidney function, independently of baseline eGFR [10]. Experimental studies suggest that the main factors that are involved in the pathogenesis of decline of kidney function in CKD patients with MA are local increase in ammonium synthesis in kidney interstitial tissue, increased production of proinflammatory cytokines and increased tissue concentration of hormones like angiotensin II, aldosterone and endothelin-1 [3].

Di Iorio et al. [11], in a randomized clinical trial including 795 patients with CKD and MA, have shown that treatment with oral bicarbonate reduced CKD progression and decreased mortality. Results of a recent meta-analysis of 14 clinical trials have also suggested that MA treatment may slow CKD progression [12].

Moreover, large observational studies have shown that serum bicarbonate concentration $<22 \text{ mmol/L}$ is associated with increased mortality in CKD patients [13, 14]. A similar relationship was also shown in stage 3 CKD patients with serum bicarbonate concentration $<23 \text{ mmol/L}$ [15]. Based on results from the above-mentioned studies, the Working Group of the Polish Society of Nephrology suggests in their guidelines a correction of MA in this group of patients [16].

Taking into consideration the negative effect of MA on native kidney function and mortality in CKD patients, it seems reasonable to study such a relationship in patients after kidney transplantation (KTx). The results of available studies suggest that the prevalence of MA in patients after KTx ranges from 11 to 58% [17–22]. The results of the observational study from our site suggests that MA is less common in patients after transplantation than in the CKD group with similar eGFR (12.0 vs. 19.6%) [23]. However, there was a scarcity of data regarding the influence of MA on graft function. The recently published very first report showed worse patient survival and graft function in KTx patients with MA [24].

The aim of this clinical, single-center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in the long term after KTx.

Material and Methods

Four hundred eighty-six patients (290 male; 196 female), at least 1 year after KTx and not treated with alkalizing agents (sodium bicarbonate or citrate salts), were enrolled in this study. The mean age of the patients was 48 ± 12 years, and the mean time after KTx was 6.4 ± 4.4 years.

At baseline of observation, HCO_3^- , blood hemoglobin concentration and serum potassium concentration in venous blood were measured in all patients. Serum creatinine concentration was measured at baseline and subsequently every year during a 3-year follow-up period. eGFR was calculated using the MDRD formula.

MA was defined as blood HCO_3^- concentration <22 mmol/L. In patients who did not reach end points (death or graft loss), the difference between 3-year and initial eGFR (i.e., eGFR change) was calculated.

Due to significant differences in baseline eGFR between MA and non-MA groups, and to avoid bias, we performed an additional subanalysis, in which 57 patients with baseline MA diagnosis were matched with 57 patients without baseline MA by sex, age, baseline eGFR, time after transplantation and prevalence of diabetes.

Statistical analysis was performed using Statistica 12 software (StatSoft Inc., 1984–2014). The Shapiro-Wilk test was used to test the distribution of variables. Analyses of differences were done with χ^2 and Mann-Whitney U tests. Correlation analysis was done with the Spearman test. The analysis of the Kaplan-Meier survival curves was done using death or graft loss as end points; the log-rank test was used to compare survival curves. Multiple regression analyses were performed separately for patients with and without baseline MA, using baseline eGFR and baseline HCO_3^- as independent variables. Multivariable Cox regression analysis models were made with type of donor (live or cadaver), presence of diabetes mellitus in recipient, use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), regimen of immunosuppressive treatment and episode of acute rejection as qualitative predictors. As quantitative predictors in the model, baseline eGFR, blood bicarbonate concentration, systolic blood pressure, body mass index, recipient age and number of KTx were used. The data were presented as means and standard deviation. Relative risk was presented with 95% confidence interval. Differences were considered as significant when $p < 0.05$.

Results

Study Group Analysis

At baseline, MA was diagnosed in 57 (12%) patients after KTx. In a subgroup of patients with suboptimal function of the transplanted kidney (eGFR <30 mL/min/1.73 m²), MA was significantly more frequent than in patients with better graft function (37 vs. 7%, $p < 0.001$), and blood bicarbonate concentration significantly correlated positively with eGFR ($R = 0.45$, $p < 0.001$). In the whole study group, the mean eGFR at baseline and after 1, 2 and 3 years of observation was 51.8 ± 23.8 , 50.2 ± 22.9 , 51.1 ± 22.9 and 52.6 ± 23.3 mL/min/1.73 m², respectively. There were significant differences in baseline eGFR, blood hemoglobin concentration and serum potassium in patients with and without baseline MA (Table 1). Blood bicarbonate concentration correlated positively with blood hemoglobin concentration ($R = 0.39$, $p < 0.001$) and negatively with serum potassium concentration ($R = -0.33$, $p < 0.001$). HCO_3^- concentration did not correlate with recipient age or time after transplantation.

During a 3-year follow-up there were 6 deaths (10.5%) in the baseline MA group and 11 deaths (2.6%) in the non-MA group. Fifteen (26.3%) patients with baseline MA and 30 (7.0%) patients without MA lost their kidney graft function. Relative risks of death (RR 4.11 [1.58–10.67]) and graft loss (RR 3.58 [2.02–6.32]) were significantly higher in patients with baseline MA. Survival analysis showed significantly higher mortality (Fig. 1) and lower graft survival (Fig. 2) in patients with baseline MA as compared to those without MA ($p = 0.001$ and $p < 0.001$, respectively). The multivariable Cox regression analysis model with baseline eGFR, bicarbonate concentration, recipient age, systolic blood pressure, body mass index, coexis-

Table 1. Clinical characteristics of patients in the long term after kidney transplantation (KTx) with and without metabolic acidosis at baseline in the whole studied group

	Patients with metabolic acidosis (<i>n</i> = 57)	Patients without metabolic acidosis (<i>n</i> = 429)	<i>p</i> value
Age, years	50.2±11.4	49.1±12.1	ns
Time after KTx, years	6.8±5.0	6.4±4.3	ns
Male/female	32/25	258/171	ns
eGFR at baseline, mL/min/1.73 m ²	33.4±17.6	54.2±23.5	<0.001
Blood hemoglobin concentration, g/dL	12.1±2.2	13.7±1.7	<0.001
Serum potassium concentration, mmol/L	4.3±0.6	3.9±0.5	<0.001
Serum sodium concentration, mmol/L	140.6±3.2	139.9±3.1	ns
Systolic blood pressure, mm Hg	139.2±14.9	136.3±14.7	ns
Diastolic blood pressure, mm Hg	87.8±9.4	84.5±9.8	0.02
Body weight, kg	75.5±14.4	75.1±14.4	ns
Body mass index	27.4±4.4	26.2±4.4	ns
Antihypertensive drugs, <i>n</i>	2.3±1.0	2.0±1.2	ns
Main immunosuppressive agent, %			ns
Tacrolimus	49.1	48.0	
Cyclosporine A	47.4	46.6	
mTOR inhibitor	3.5	5.3	
Glucocorticoid therapy	42.1	48.0	ns
ACEI or ARB therapy	54.3	40.6	ns

eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ns, nonsignificant.

tence of diabetes mellitus, use of ACEI or ARB, cadaver donation, number of KTx, immunosuppressive regimen and episode of acute rejection has shown that systolic blood pressure (hazard ratio, HR, 1.03 [1.00–1.06], *p* = 0.03) was a predictor for initiation of renal replacement therapy. Baseline eGFR (HR 0.92 [0.89–0.96], *p* < 0.001), bicarbonate concentration (HR 0.90 [0.81–0.99], *p* = 0.04) and recipient age (HR 0.95 [0.92–0.99], *p* = 0.02) were negative predictors for initiation of renal replacement therapy. In a similar model, recipient age (HR 1.14 [1.05–1.25], *p* = 0.003) and number of KTx (HR 7.72 [1.15–51.64], *p* = 0.03) were predictors of death. Blood bicarbonate concentration (HR 0.79 [0.65–0.96], *p* = 0.01) and episode of rejection (HR 0.17 [0.03–0.89], *p* = 0.03) were significant negative predictors of death in this model. In the Cox regression model with both end points of the study, baseline eGFR (HR 0.96 [0.93–0.98], *p* < 0.001) and bicarbonate concentration (HR 0.88 [0.81–0.95], *p* = 0.002) were negative predictors.

In patients who did not reach the end points of the study after 3 years of follow-up, there still was an eGFR difference between patients with and without MA (38.5 ± 17.9 vs. 54.1 ± 23.3 mL/min/1.73 m², *p* < 0.001). After 3 years of follow-up, patients with baseline MA blood HCO₃⁻ concentration correlated positively with a 3-year eGFR change (*R* = 0.48, *p* = 0.002; Fig. 3) whereas no such correlation was seen in patients without MA (*R* = 0.02, *p* = 0.7).

Multivariate regression analysis in patients with baseline MA with a 3-year change in eGFR as dependent variable and initial eGFR and blood bicarbonate concentration as independent variables showed that the change in eGFR was independently influenced by both baseline eGFR (*β* = -0.47, *p* = 0.002) and blood HCO₃⁻ concentration (*β* = 0.47, *p* = 0.002). In patients without baseline MA, a 3-year eGFR change was influenced only by baseline eGFR (*β* = -0.34, *p* < 0.001), but not by blood bicarbonate concentration.

Fig. 1. Kaplan-Meier survival curves in which the end point was death (whole studied group analysis).

Fig. 2. Kaplan-Meier survival curves in which the end point was initiation of dialysis therapy (whole studied group analysis).

Fig. 3. Blood HCO_3^- concentration and change in eGFR in a 3-year follow-up in patients after kidney transplantation with metabolic acidosis who did not reach the end point of the study.

Table 2. Clinical characteristics of kidney transplantation (KTx) patients with and without metabolic acidosis at baseline in the case-controlled analysis

	Patients with metabolic acidosis (n = 57)	Patients without metabolic acidosis (n = 57)	p value
Age, years	50.2±11.4	50.0±4.4	ns
Time after KTx, years	6.8±5.0	6.8±4.4	ns
Male/female	32/25	32/25	ns
eGFR at baseline, mL/min/1.73 m ²	33.4±17.6	33.5±16.9	ns
Blood hemoglobin concentration, g/dL	12.1±2.2	12.8±1.7	ns
Prevalence of diabetes, %	33	33	ns
Serum potassium concentration, mmol/L	4.3±0.6	3.9±0.4	<0.001
Serum sodium concentration, mmol/L	140.6±3.2	139.9±3.2	ns
Systolic blood pressure, mm Hg	139.2±14.9	137.1±14.1	ns
Diastolic blood pressure, mm Hg	87.8±9.4	83.7±8.9	0.03
Body weight, kg	75.5±14.4	75.1±15.5	ns
Body mass index	27.4±4.4	26.2±4.6	ns
Antihypertensive drugs, n	2.3±1.0	2.1±1.2	ns
Main immunosuppressive agent, %			ns
Tacrolimus	49.1	61.4	
Cyclosporine A	47.4	31.6	
mTOR inhibitor	3.5	7.0	
Glucocorticoid therapy, %	42.1	52.6	ns
ACEI or ARB therapy, %	54.3	40.3	ns

eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ns, nonsignificant.

Case-Control Subanalysis

In a case-control analysis of 57 patients with and 57 subjects without baseline MA, patients were matched by sex, age, baseline eGFR, time after transplantation and prevalence of diabetes. The characteristics of patients with and without MA are given in Table 2. Three-year survival was significantly higher in the non-MA group (100 vs. 89.5%, $p = 0.007$; Fig. 4). Three-year graft survival tended insignificantly to be worsened in MA patients (84.2% in the non-MA vs. 73.7% in MA patients, $p = 0.12$; Fig. 5). The multivariable Cox regression analysis model with baseline eGFR, bicarbonate concentration, age of recipient, systolic blood pressure, body mass index, coexistence of diabetes mellitus, use of ACEI or ARB, number of KTx, immunosuppressive regimen and episode of acute rejection has shown that systolic blood pressure (HR 1.08 [1.02–1.14], $p = 0.01$) was a significant predictor and baseline eGFR (HR 0.84 [0.76–0.93], $p = 0.001$) was a significant negative predictor of initiation of renal replacement therapy. In a similar model, episode of rejection (HR 0.03 [0.00–0.87], $p = 0.04$) was and bicarbonate concentration (HR 0.62 [0.36–1.07], $p = 0.08$) tended to be a negative predictor of death. Recipient age (HR 1.30 [0.98–1.73], $p = 0.07$) tended to be a predictor of death in this model. In the Cox regression model with both end points of the study, systolic blood pressure (HR 1.05 [1.00–1.10], $p = 0.04$) was a significant predictor and bicarbonate concentration (HR 0.86 [0.76–0.96], $p = 0.007$), baseline eGFR (HR 0.92 [0.86–0.98], $p = 0.01$) and episode of rejection (HR 0.18 [0.04–0.77], $p = 0.01$) were significant negative predictors.

Fig. 4. Kaplan-Meier survival curves in which the end point was death (case-control subanalysis).

Fig. 5. Kaplan-Meier survival curves in which the end point was initiation of dialysis therapy (case-control subanalysis).

Discussion

The main finding of this study is the fact that MA observed in the long term after KTx significantly worsens graft function.

In the present study it is demonstrated that bicarbonate concentration in patients after KTx with MA correlates negatively with the degree of deterioration of transplanted kidney function. So far there is only one study analyzing such a relationship in patients after KTx [24]. Park et al. [24] have shown that MA may be a significant risk factor for graft failure and patient mortality, even after adjusting for eGFR. In the other observational study Djamali et al. [25] have shown that MA increases both the risk of cardiovascular events and mortality in kidney transplant recipients. In many experimental and clinical studies, it has been shown that MA significantly accelerates the progression of chronic native kidney disease [3–7]. In a large observational study including more than 5,000 patients, Shah et al. [8] demonstrated that patients with CKD with serum bicarbonate concentration <22 mmol/L are characterized by

a more pronounced progression of disease. In another large observational study including more than 3,500 individuals with a 6-year follow-up, it has been shown that those with a serum bicarbonate <22 mmol/L had a 2-fold increased risk of CKD progression [9]. In the MESA study, which included patients with a baseline eGFR <60 mL/min/1.73 m², a lower serum bicarbonate concentration was associated with a more rapid decline in kidney function, independently of baseline eGFR [10].

The major mechanism that affects the progression of CKD in patients with acidosis is the local increase in ammonium synthesis in the interstitial tissue of the kidney. In general, MA is characterized by decreased ammonium excretion. However, in patients with CKD there is a reduction in number of functioning nephrons, and ammonium excretion per nephron is substantially increased [26]. This local increased ammonium synthesis leads to the activation of an alternative complement pathway, increased inflammation and tubulointerstitial fibrosis [4, 27, 28]. There is a hypothesis that high concentrations of interstitial ammonia and activation of complement cause kidney fibrosis by increasing transforming growth factor- β_1 concentration [29, 30]. Moreover, an acidic environment enhances production of proinflammatory cytokines and chemokines, inducing oxidative stress [31, 32]. Another mechanism leading to CKD progression is the increased concentration of certain hormones and cytokines in the kidney tissue, a well-known role in CKD progression. It was demonstrated that acidosis increases the tissue concentration of angiotensin II [33]. It has been shown that upregulation of angiotensin II is associated with kidney infiltration by leukocytes [34–36]. A persistent increase in intrarenal angiotensin II concentration may enhance interstitial inflammation and in consequence lead to tubular atrophy and interstitial fibrosis [34, 35]. In addition, there are some observations that suggest that an acid-rich diet may increase production of endothelin-1, which leads to an increase in H⁺ secretion in proximal and distal kidney tubules and stimulates aldosterone production in adrenal glands [3, 28, 37]. A local renal increase in the concentration of aldosterone in kidney interstitial cells stimulates interstitial tissue inflammation and fibrosis, leading to progression of CKD.

The results of the current study suggest that MA significantly increased mortality in patients after KTx. So far there is only one study that assesses the impact of MA on outcome in patients after KTx. In a 5-year follow-up of over 2,000 patients, Park et al. [24] have shown that a total CO₂ concentration below 22 mmol/L is associated with an increased risk of graft failure and patient mortality. In patients with chronic disease of the native kidney, it has been demonstrated in observational studies that MA increases mortality. In a large clinical registry of CKD patients including more than 41,000 cases, it has been shown that a serum concentration of bicarbonate <23 mmol/L in CKD stage 3 individuals increases mortality [15]. Also, in 2 other large studies – the MDRD Study and NHANES III, it has been demonstrated that a serum bicarbonate concentration <22 mmol/L is associated with increased mortality in CKD patients [13, 14].

There are several factors that account for the increased mortality in patients with MA. The first, mentioned above, is progression of CKD. This involves both, the earlier initiation of renal replacement therapy as well as the negative impact of more advanced CKD upon survival. The second factor is the direct negative impact of MA on the cardiovascular system [38, 39]. It has been shown that MA increases the prevalence of hypertension in patients with CKD [40]. In addition, there is increased production of β_2 -microglobulin and thereby its accumulation in tissues, including the heart, in the form of amyloid in these patients [41]. Another factor worsening the prognosis in patients with CKD and MA is glucose intolerance, resulting from insulin resistance [42, 43]. It has also been demonstrated that MA may participate in the pathogenesis of the malnutrition-inflammation-atherosclerosis syndrome [39, 44]. MA lowers the plasma concentration of free insulin-like growth factor-1, increases the concentration of protein binding of insulin-like growth factor-1 and decreases growth

hormone concentration, which also participates in the pathogenesis of malnutrition [2, 45, 46].

In the present study, we have demonstrated that in patients with MA after KTx, the serum potassium concentration is significantly higher. It has been shown that the blood bicarbonate concentration correlates negatively with the serum potassium concentration independently of baseline eGFR. A similar relationship has been demonstrated in another study of MA in patients after KTx [47]. It is well known that in MA, potassium ions are repositioned from the intracellular to the extracellular space. Hyperkalemia, on the other hand, can induce intracellular alkalosis in Henle's thick ascending loop cells and decrease NH_4^+ concentration in the collecting tubule. Single-nephron ammoniogenesis increases as a compensation for the decreased functioning number of nephrons and leads to kidney fibrosis [48]. Additionally, hyperkalemia has a well-known arrhythmogenic effect, which can lead to increased mortality in this group of patients.

In this study of kidney transplant patients with MA, blood hemoglobin concentration was significantly lower than in the group of patients without MA. Blood hemoglobin concentration correlates positively with blood bicarbonate concentration independently of baseline eGFR. Analysis of the Transplant European Survey on Anemia Management study, involving 4,263 patients after KTx from 72 centers, showed a strong association between blood hemoglobin concentration and graft function impairment [49]. Yorgin et al. [50] showed a correlation between the plasma bicarbonate concentration and blood hemoglobin concentration in patients after KTx. One year after transplantation, the occurrence of anemia depended on the severity of MA (assessed by serum total pCO_2) and graft function impairment, while 5 years after transplantation it depended only on low serum pCO_2 .

Our study has some limitations. Except for its retrospective design, there is a lack of bicarbonate blood concentration measurement at the end of the 3-year follow-up period. On the other hand, the strength of this study is a case-controlled method in the subanalysis in which patients with MA were compared with patients without MA matched by age, sex, baseline eGFR and time after KTx.

In summary, our study suggests that MA worsens the kidney graft outcome in patients after KTx. To prove the effectiveness of MA correction, it is necessary, however, to do interventional prospective studies to determine the effectiveness of treatment of MA and its impact on prognosis in this group of patients. Therefore, the issue of MA in patients after KTx requires further studies.

Statement of Ethics

The current study was an observational retrospective study. The study does not need to be approved by the institute's committee on human research. There was also no need to get informed consent from patients. Results presented in the study are based on routine tests used in monitoring patients after KTx.

Disclosure Statement

The results presented in this paper have not been published previously in whole or part, except in abstract format. M.A. received a lecture fee from SANUM. The other authors declare no conflicts of interest for this study.

Funding Sources

This work was supported by the Medical University of Silesia in Katowice, Poland (KNW-1-051/N/8/K; to M.A.).

Author Contribution

D.G.: was involved in writing the manuscript, statistical analysis and literature review. K.S.: was involved in collecting data, writing the manuscript and literature review. M.B.: was involved in collecting data, statistical analysis and writing the manuscript. A.K.: was involved in collecting data and statistical analysis. A.W.: was responsible for planning the research, coordination and supervision of research, interpretation of results and writing the manuscript. M.A.: was involved in planning of the research, writing the manuscript, interpretation of results and supervision of research.

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