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Authors: Katarzyna Skiba, Damian Gojowy, Magdalena Szotowska, Magdalena Bartmańska, Aureliusz Kolonko, Lech Cierpka, Andrzej Więcek, Marcin Adamczak

Article type: Original article

Received: June 29, 2018.

Accepted: August 31, 2018.

Published online: September 12, 2018.

ISSN: 1897-9483

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Metabolic acidosis in patients after kidney transplantation

Katarzyna Skiba, PhD, MD, Damian Gojowy, MD, Magdalena Szotowska PhD, MD, Magdalena Bartmanska, MD, Aureliusz Kolonko, PhD, MD, Lech Cierpka, prof. PhD, MD, Andrzej Wiecek, prof., PhD, MD, Marcin Adamczak prof., PhD, MD

1Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland, 2Department of General, Vascular, and Transplant Surgery, Medical University of Silesia, Katowice, Poland

Address for correspondence:
Prof. dr hab. med. Marcin Adamczak
Oddział Nefrologii, Transplantologii i Chorób Wewnętrznych
Śląski Uniwersytet Medyczny w Katowicach
ul. Francuska 20-24, 40-027 Katowice
Tel: + 48 32 2591451
Fax: + 48 32 2553726
E-mail: madamczak1@op.pl

Conflict of interest: none declared.
Abstract:

**Introduction**: Metabolic acidosis (MA) may accelerate the progression of chronic kidney disease (CKD) and is an important risk factor for increased mortality in CKD patients. The clinical value of MA in kidney transplant patients (KTP) was not intensively studied so far.

**Objectives**: The aim of this clinical, single-center, cross-sectional, case-control study was to assess the prevalence of MA in KTP in comparison with CKD patients and to identify factors which participate in the pathogenesis of MA in KTP.

**Patients and Methods**: Venous blood concentration of bicarbonate ([HCO₃⁻]) and blood hemoglobin (Hb) concentration were measured in 500 KTP and 500 CKD patients matched by sex, age and eGFR. None of these patients received alkalizing treatment before entering into this study. MA was diagnosed in KTP with [HCO₃⁻] lower than 22 mmol/l.

**Results**: The prevalence of MA was significantly lower in KTP than in CKD patients (12.0% vs 19.6% respectively; P=0.001) and in both groups its prevalence significantly increased with the advancement of CKD stages (P<0.001 for trend). The prevalence of MA in KTP and CKD patients was significantly higher in patients with anemia. Multivariable analyses showed that Hb concentration correlates independently with eGFR and [HCO₃⁻] in KTP (β=0.314, P<0.001; β=0.274, P<0.001; respectively) Similar correlations were observed in CKD patients (β=0.273, P<0.001; β=0.123, P=0.006; respectively).

**Conclusions**: 1. In this single-center, cross-sectional, case-control study, the prevalence of MA in KTP was lower than in CKD patients. 2. In KTP, blood concentration of bicarbonate is related to kidney function and blood hemoglobin concentration.

**Key words**: chronic kidney disease, kidney transplantation, metabolic acidosis,
Introduction

Metabolic acidosis (MA) is a common consequence of chronic kidney disease (CKD). There is limited data about the prevalence and pathogenic factors of MA in patients after kidney transplantation (KTx) [1]. MA in CKD patients is mainly caused by insufficient production of bicarbonate in comparison to the endogenous acids production and acid intake [2].

MA has negative impact on quality of life and contributes to numerous systemic disorders in CKD patients. It has been shown that MA plays an important role in pathogenesis of malnutrition-inflammation-atherosclerosis syndrome (MIA) by the increased protein catabolism [3-7]. Furthermore, in some studies it has been shown that MA impairs the calcium-phosphate homeostasis in CKD patients [1]. MA reduces the sensitivity of the calcium receptor by reducing intracellular pH and as a result stimulates the parathyroid glands to secrete parathyroid hormone (PTH). It was also observed that MA is associated with an increased risk of bone mass reduction in patients after kidney transplantation [8]. It has also long been known that decreased bicarbonate blood concentration adversely affects skeletal muscle mass [9,10].

Several observational studies suggest that reduced blood concentration of bicarbonate below 22 mmol/l is an independent risk factor for CKD progression [11-14]. Moreover, results of observational studies in CKD patients suggest that MA is associated with a higher risk of mortality [15, 16]. Increased mortality was observed in patients with blood concentration of bicarbonate already below 23 mmol/l [16]. Results of above cited observational studies suggest that the target value of the bicarbonate blood concentration in patients with CKD should be higher than 22 - 23 mmol/l. Renoprotective properties of alkalizing agents such as NaHCO₃, sodium citrate, and the so-called alkaline diet have been shown in many clinical studies in CKD patients [17-24]. To our knowledge, there is only one
study assessing the impact of MA on mortality and long-term graft function in patients after KTx [25].

The aim of this study was to assess the prevalence of MA in kidney transplantation patients (KTP) in the late post-transplant period in comparison with CKD patients and to analyze factors related to MA in these subjects.

**Materials and methods**

The study included 500 randomly selected KTP at least 12 months after transplantation (transplanted in years 1987 – 2010). The control group consisted of 500 patients with CKD, matched by sex, age and the current estimated glomerular filtration rate (eGFR), as estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which was validated in patients after KTx [26]. Patients of both groups did not receive alkalizing agents and have been treated in outpatient clinic.

In all patients, the bicarbonate concentration in venous blood [HCO₃⁻] was measured by potentiometric method using a GEM 3500 Premier analyzer. The MA was diagnosed in studied patients when the actual [HCO₃⁻] was below 22 mmol/l [15,16]. Diabetes mellitus (DM) was assessed on the basis of medical records. The presence of proteinuria was detected using a semi-quantitative reagent strips with sensitivity threshold 30 mg/dl. Blood hemoglobin concentration (Hb) was determined by fluorescence flow cytometry (Sysmex XT-2000I) while anemia was defined according to the KDIGO guidelines: (Hb <13 g/dl for males and Hb <12 g/dl for females) [27].

In the study group, the immunosuppressive regimen was analyzed as well as the treatment with the angiotensin converting enzyme inhibitors, angiotensin receptor blockers as well as the presence of DM.

Statistical analysis was performed using Statistica 10.0. To assess the distribution, the
Shapiro-Wilk test was used. Correlation coefficients were calculated according to Spearman analysis. The differences between groups were tested with nonparametric ANOVA and Mann-Whitney tests. In addition, multivariable regression analysis was performed. Results are presented as a means values with SD or 95% confidence intervals. Differences between the values were considered significant when P<0.05.

Results

There were 298 men (59.6%) in each group. In KTP group, the mean (SD) time since KTx was 76.2 (51.9) months. Most common causes of kidney disease in CKD patients were: chronic glomerulonephritis (37.6%), arterial hypertension (29.4%), DM (4.8%) and lupus (3.6%). In 11.8% the cause of CKD was unknown. More details concerning studied population are presented in Table 1. Immunosuppressive agents and main co-medications used in both groups are shown in the Table. 2.

In KTP group, the mean (95% CI) blood cyclosporine through concentration (C₀) was 106.4 (102.4-110.5) ng/ml and mean (95% CI) tacrolimus through concentration was 7.1 (6.8-7.4) ng/ml. C₀ was lower in patients with MA (95.4 (86.9-103.8) ng/dl vs 108.1 (103.6-112.6) ng/dl, respectively; P=0.02). There was similar blood concentration of tacrolimus in patients with or without MA.

There was a slight, but statistically borderline difference in [HCO₃⁻] in patients after KTx and patients with CKD (25.38 (25.09-25.67) vs. 24.98 (24.66-25.31) mmol/l, P=0.056). In both groups, there was a trend to decrease [HCO₃⁻] with the progression of renal impairment (Figure 1). There were no significant differences in [HCO₃⁻] between men and women in both studied groups.

MA occurred less frequently in KTP than in CKD patients (12.0% vs. 19.6% respectively, P=0.001). In both groups, the incidence of MA increased along with impaired
kidney function (Figure 2). Additionally, significant positive correlations were found between eGFR and \([\text{HCO}_3^-]\) (for CKD: \(R = 0.443, P<0.001\); for KTP: \(R = 0.357, P<0.001\)). Of note, in both study groups no significant correlations were found between age and \([\text{HCO}_3^-]\). There were also no significant differences in the prevalence of MA between men and women in KTP and in CKD patients.

Anemia was diagnosed in 28.8% of KTP and 41.4% of CKD patients (\(P<0.001\)). The mean Hb concentration was significantly higher in KTP than in CKD patients (13.4 (13.3-13.6) vs. 12.8 (12.8-13.0) g/dl, \(P<0.001\)). In both study groups \([\text{HCO}_3^-]\) and eGFR were significantly lower in patients with concomitant anemia (KTP: 23.57 (22.99-24.15) vs 26.11 (25.80-26.42) mmol/l, 37.71 (34.89-40-53) vs 55.94 (53.54-58.34) ml/min/1.73m\(^2\); CKD: 24.22 (23.68-24.76) vs 25.52 (25.13-25.92) mmol/l, 42.50 (39.28-45.73) vs 57.75 (55.03-60.47) ml/min/1.73m\(^2\), respectively; \(P<0.001\) for all). The prevalence of MA was higher in patients with anemia in both groups (KTP: 25.0% vs 6.7%; CKD: 27.1% vs 14.3%, \(P<0.001\) for both). Significant correlations were found between blood Hb concentration and \([\text{HCO}_3^-]\), both in KTP and CKD patients (\(R = 0.387, P<0.001\) and \(R = 0.196, P<0.001\), respectively).

There were more subjects with proteinuria in CKD group (65.6%) in comparison with KTP group (23.8%) (\(P<0.001\)). Moreover, proteinuria was significantly higher in CKD patients than in KTP (136.1 (116.9-155.2) vs. 22.3 (12.3-28.3) mg/dl, respectively, \(P<0.001\)). Both eGFR (\(P<0.001\)) and \([\text{HCO}_3^-]\) (\(P<0.001\)) were significantly lower in proteinuric KTP, while no significant differences were noted in CKD patients with or without proteinuria. Of note, MA was diagnosed more frequently in proteinuric subjects, both in KTP and CKD groups (\(P<0.001\)).

DM was present in 23.4% KTP and 22.4% CKD (\(P=0.7\)). There were no significant differences in eGFR, \([\text{HCO}_3^-]\) and prevalence of MA in patients with without DM in both study groups. It is also worth noting that, there was a higher prevalence of DM in KTP
subgroup treated with tacrolimus in comparison to tacrolimus-free patients (28.1% vs 19.6%, P=0.03).

There were no significant differences between [HCO$_3$]$^-$ and prevalence of MA in KTP treated or not treated with tacrolimus (25.35 (24.88-25.83) vs 25.40 (25.04-25.76) mmol/l, P=0.8 and 11.6% vs 12.3%, P=0.8; respectively) Moreover, in KTP treated with cyclosporine eGFR, blood concentration of bicarbonate and the prevalence of MA was similar to patients treated with tacrolimus. There were no significant correlations between blood [HCO$_3$]$^-$ and the blood calcineurin inhibitors trough levels (cyclosporine or tacrolimus) in KTP group.

There was no significant difference in the prevalence of DM prevalence of KTP between patients treated with or without treatment with prednisone. However, mean [HCO$_3$]$^-$ was significantly higher in KTP treated with prednisone (25.7 (25.3-26.1) vs. 25.1 (24.7-25.5) mmol/l; P=0.03), while no differences were noted regarding eGFR or MA prevalence. One hundred sixty-three (32.6%) of KTP received angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, but there were no differences in [HCO$_3$]$^-$ or prevalence of MA in group of patients treated and not treated with that drugs.

In multivariable analysis with hemoglobin blood concentration as the dependent variable, and with the independent variables such as eGFR and [HCO$_3$]$^-$, it has been shown that blood hemoglobin concentration is related to glomerular filtration and [HCO$_3$]$^-$ in patients after kidney transplantation and in patients with CKD (respectively in kidney transplant patients: $\beta = 0.314$, P<0.001 and $\beta = 0.274$, P<0.001; and in patients with CKD: $\beta = 0.273$, P<0.001 and $\beta = 0.123$, P=0.006).

Discussion

Our paper presents results from a single center, cross-sectional, "case - control" study including 500 KTP at least one year after KTx and 500 patients with CKD matched by age,
sex and eGFR. Considering the potential benefits of alkali therapy in patients after KTx, it is important to estimate the number of such patients, in whom MA is present and to identify risk factors of MA.

The prevalence of MA in KTP was lower than in patients with CKD (12.0% vs 19.6% respectively). The descriptive nature of the study made it impossible to determine the causes of the lower prevalence of MA in patients after KTx than with CKD. However, some of possible explanations of such a difference might be postulated. Bicarbonate synthesis occurs in the tubulointerstitial compartment of the kidney. Kim et al. in experimental study on mice showed that renal denervation prevented interstitial inflammation (neutrophils and macrophages infiltration), reduced myofibroblasts number (α-SMA) and decreased of interstitial fibrosis extend after unilateral ureter obstruction procedure [28]. In the other study, it was shown that renal denervation protected from the above-mentioned abnormalities in mice exposed to kidney injury due to ischemia and reperfusion [29]. Transplanted kidneys in contrast of native kidneys are not innervated. Therefore, taking into account results of above mentioned experiments by Kim et al., speculated that tubulointerstitial damage is less pronounced in transplanted non-innervated kidney than in CKD patients matched according to eGFR with their innervated native kidneys. Another line of evidence suggested that MA is more specific to the interstitial damage than to glomeruli dysfunction may be the fact of high prevalence of MA in childhood and adolescent CKD patients, where interstitial damage is more frequent than in adults with similar eGFR [30]. The observation that anemia due to insufficient erythropoietin synthesis by cells in interstitium of kidneys in KTP is less frequent than in CKD patients is also in line with this hypothesis.

In adults, metabolic complications of CKD including MA occurs mostly in stage 4 and 5 of CKD [31, 32]. Results obtained in this study confirmed that in KTx patients as well as in
patients with CKD the prevalence of MA increases with the degree of kidney impairment and it is the most frequent in stage 5 CKD (58.3% in patients after KTx in stage 5 and 62.5% of patients with stage 5 CKD) (Figure 2).

Clinical studies have shown that post-transplant anemia is diagnosed in 30 - 40% of patients [33-37]. In the current study, the percentage of patients after KTx diagnosed with anemia was comparable and it was 28.8%. Analysis by Transplant European Survey on Anemia Management (TRESAM), showed a strong association between blood hemoglobin concentration and graft function impairment [34]. In the current study, MA occurred more frequently in patients with anemia in both KTP and patients with CKD. Multivariable analysis showed that in post-transplant period hemoglobin blood concentration is related to eGFR and [HCO₃⁻]. Similary, Yorgin et al. showed a significant relationship between the MA and anemia in KTx recipients [38]. Due to cross-sectional nature of current study we are not able to establish if anemia is the cause or consequence of MA. This issue need further interventional studies.

In the current study, we were able to demonstrate that MA occurred more often in patients with proteinuria. These findings result particularly due to the fact that in KTP with proteinuria (23.8% of patients after KTx), eGFR rate was significantly lower than in KTP without proteinuria. It is assumed that the greater the severity of graft dysfunction in KTP with proteinuria, the lower [HCO₃⁻] and more frequently MA occurred.

Previously published studies have shown that in patients with CKD MA development regardless of eGFR depends among other on DM and younger age at onset of the disease (<65 years vs >65 years) [34]. Long-term DM is associated with hyporeninemic hypoaldosteronism, tubular acidosis and acidosis related to hypermetabolic state [3]. Surprisingly, in the present study, DM did not affect the increase in the incidence of MA. However, these observations are consistent with the results of Caravaca et al., who have
shown that in patients with stage 5 CKD and DM less severe MA than in ones without DM occurred [39].

Patients with CKD were recruited from tertiary nephrology outpatient clinic therefore the distribution of the most common causes of CKD were different than expected in general CKD population (i.e. DM only in 4.8% but glomerulonephritis in 37.6% of patients). As a consequence of high prevalence of glomerulonephritis number of patients treated with steroids was closer to KTP. In KTP and CKD patients treated with prednisone the blood bicarbonate concentration was significantly higher than in patients without glucocorticoids treatment. Estimated GFR and the prevalence of MA was similar in both groups. It is assumed that the small increase in the blood bicarbonate concentration might be caused by the hypokalemic effect of glucocorticoids.

Renal tubular acidosis (RTA) which has been observed in previous studies in 13 - 17% of patients after KTx in early stages of kidney disease may contribute to low bicarbonate concentration [40,41]. Due to nature of present study it was impossible to determine the frequency of RTA in our cohort. Calcineurin inhibitor nephrotoxicity, acute and chronic rejection of the transplanted kidney and ischemic tubular injury are known factors contributing to the occurrence of RTA [42, 43]. In the eighties of the last century Stahl et al. observed a dose-dependent role of cyclosporine A in the pathogenesis of MA in patients after KTx [44]. Mohebii et al. elucidated the mechanism of action of tacrolimus on transport of proteins in the kidney playing a key role in the regulation of acid-base balance and causing MA [45]. In one study, the decreased HCO$_3^-$ concentration was observed significantly more frequent in patients after KTx treated with cyclosporine with corticosteroids than with azathioprine [46]. In another study, it was found that in patients in the late post-transplantation period and with eGFR > 40 ml/min/1.73m$^2$ RTA incidence was higher in patients treated with tacrolimus than with cyclosporine A [47]. Taking into account the above
mentioned findings it could be expected that due to chronic immunosuppressive therapy, the prevalence of MA in KTx recipients should be higher than in patients with CKD. Results of present study, however, did not confirm this statement. In the current study, the majority of patients after KTx (96.8%) were treated with a calcineurin inhibitor. Therefore, assessment of the frequency of MA in patients not treated with these drugs was impossible. Nevertheless, it has been shown, that the eGFR, blood bicarbonate concentration and the prevalence of MA in KTP did not depend on the type of calcineurin inhibitor. There was also no significant correlations between the \([\text{HCO}_3^-]\) and blood concentration of immunosuppressive agents in these patients.

Due to the risk of bleeding and local complications associated with arterial puncture as well as the need to spare arteries for the future access for hemodialysis, the acid-base balance parameters were measured not in arterial but in venous blood only, which seems to be an important limitation of the study. However estimation of \([\text{HCO}_3^-]\) in venous blood only seems to be sufficient for clinically useful diagnosis of MA.

Finally, considering the fact that KTP are characterized by higher prevalence of MA, and that in patients with CKD alkalizing treatment exerts renoprotective effect, it seems reasonable to carry out further studies in order to clarify whether or not MA correction will affect renal function and severity of anemia also in KTP.

**Authors’ Contributions**

KS was involved into collecting data, statistical analysis, writing manuscript and literature review. DG was involved into writing manuscript, statistical analysis and literature review. MB was involved to collecting data, statistical analysis and writing manuscript. MS was involved into statistical analysis and interpretation of results. AK was involved into collecting data and statistical analysis. LC was involved into interpretation of results. AW was
responsible for planning of the research, coordination and supervision of research, interpretation of results and writing manuscript. MA was involved into planning of the research, writing manuscript, interpretation of results and literature review. All authors edited and approved the final version of the manuscript.

**Acknowledgements**

This work was supported by Medical University of Silesia in Katowice, Poland.

**References**


Table 1. Characteristics of the study groups

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>n</th>
<th>F/M</th>
<th>Age, year</th>
<th>eGFR, ml/min/1.73m²</th>
<th>HCO₃⁻, mmol/l</th>
<th>n</th>
<th>F/M</th>
<th>Age, year</th>
<th>eGFR, ml/min/1.73m²</th>
<th>HCO₃⁻, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>11/11</td>
<td>45.4 (39.33-51.47)</td>
<td>111.81 (98.52-125.11)</td>
<td>26.46 (25.21-27.71)</td>
<td>29</td>
<td>13/16</td>
<td>42.9 (38.1-47.6)</td>
<td>111.48 (103.40-119.57)</td>
<td>27.14 (25.77-28.51)</td>
</tr>
<tr>
<td>2</td>
<td>126</td>
<td>49/77</td>
<td>49.5 (47.28-51.72)</td>
<td>71.56 (70.13-72.99)</td>
<td>27.01 (26.58-27.43)</td>
<td>127</td>
<td>48/9</td>
<td>48.4 (46.0-50.7)</td>
<td>73.37 (71.82-74.93)</td>
<td>26.20 (25.72-26.69)</td>
</tr>
<tr>
<td>3a</td>
<td>127</td>
<td>43/84</td>
<td>52.81 (50.68-53.35)</td>
<td>26.69 (25.60-26.57)</td>
<td>127</td>
<td>47/80</td>
<td>50.0 (47.4-52.5)</td>
<td>51.81 (51.08-52.54)</td>
<td>25.53 (24.90-26.16)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>139</td>
<td>61/78</td>
<td>52.81 (50.68-53.35)</td>
<td>26.69 (25.60-26.57)</td>
<td>127</td>
<td>47/80</td>
<td>50.0 (47.4-52.5)</td>
<td>51.81 (51.08-52.54)</td>
<td>25.53 (24.90-26.16)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>33/41</td>
<td>52.2 (49.55-54.76)</td>
<td>23.72 (22.81-24.63)</td>
<td>22.79 (21.91-23.68)</td>
<td>70</td>
<td>32/38</td>
<td>53.1 (50.2-56.0)</td>
<td>22.45 (21.48-23.41)</td>
<td>22.97 (21.95-23.99)</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>5/7</td>
<td>48.7 (43.81-53.52)</td>
<td>12.78 (11.74-13.81)</td>
<td>20.82 (17.97-23.67)</td>
<td>16</td>
<td>6/10</td>
<td>49.4 (43.4-55.4)</td>
<td>12.11 (11.06-13.15)</td>
<td>21.49 (19.06-23.92)</td>
</tr>
<tr>
<td>All stages</td>
<td>500</td>
<td>202/298</td>
<td>50.0 (48.9-51.0)</td>
<td>50.69 (48.66-52.71)</td>
<td>25.38 (25.09-25.67)</td>
<td>500</td>
<td>202/298</td>
<td>50.1 (48.9-51.3)</td>
<td>51.44 (49.26-53.61)</td>
<td>24.98 (24.66-25.31)</td>
</tr>
</tbody>
</table>

Abbreviations: CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate, F – female, HCO₃⁻ - blood bicarbonate concentration, M - male
Table 2. Immunosuppressive agents and co-medications used in kidney transplant recipients and chronic kidney disease patients.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>KTP</th>
<th>CKD patients</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>261 (52.2%)</td>
<td>35 (7.0%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>223 (44.6%)</td>
<td>0 (0.0%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Mycophenolate mofetil or mycophenolate sodium</td>
<td>393 (78.6%)</td>
<td>17 (3.4%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>28 (5.6%)</td>
<td>0 (0.0%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Everolimus or sirolimus</td>
<td>23 (4.6%)</td>
<td>0 (0.0%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Prednisone</td>
<td>235 (47.0%)</td>
<td>181 (36.2%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Metformin</td>
<td>14 (2.8%)</td>
<td>33 (6.6%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Erythropoiesis stimulating agents</td>
<td>26 (5.2%)</td>
<td>14 (2.8%)</td>
<td>P=0.052</td>
</tr>
</tbody>
</table>

Abbreviations: CKD – chronic kidney disease, KTP – kidney transplant patients
Figure 1. Blood bicarbonate concentration in different stages of chronic kidney disease in patients with chronic kidney disease and in patients after kidney transplantation

Figure 2. The prevalence of metabolic acidosis in different stages of chronic kidney disease in patients with chronic kidney disease and in patients after kidney transplantation