METABOLIC ACIDOSIS – AN UNDERESTIMATED PROBLEM AFTER KIDNEY TRANSPLANTATION?

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SUMMARY – Despite prolonged survival and better quality of life as compared to dialysis, kidney transplantation frequently presents with a complex set of medical issues that require intensive management to protect graft function. Metabolic acidosis has an impact on several metabolic complications such as mineral and muscle metabolism, nutritional status and anemia. It may also have an effect on graft function, possibly through the stimulation of adaptive mechanisms aimed at maintaining acid-base homeostasis. We investigated current practice in the evaluation of metabolic acidosis at one of the largest transplant centers in the Eurotransplant region. Adult renal transplant recipients having received allograft from January 2011 to August 2012 were included in the investigation. We recorded the frequency of measuring the parameters of venous blood gas analysis, as well as creatinine and urea levels, creatinine clearance, proteinuria, calcium, phosphate and potassium blood levels, body mass index and the time spent on dialysis prior to kidney transplantation. Out of 203 patients who had received renal allograft at our institution during the observed period, 191 (124 males and 67 females, age range from 18 to 77 years) were enrolled in the study. Of these, only 92 (48.167%) patients had parameters of venous blood gas analysis measured at some time after kidney transplantation. Acid-base status was determined more often in males (77 males *vs*. 22 females, p=0.001). Patients with pH/blood gas analysis performed were found to have significantly higher creatinine and urea levels and significantly lower creatinine clearance (p<0.001 both). Serum calcium levels were also significantly lower in this group of patients (p<0.001). Metabolic acidosis is a very important clinical issue that needs to be monitored in every transplant recipient. Its effects on graft function, nutritional status, anemia and bone mass are complex but can be successfully managed. Our study showed metabolic acidosis to be linked with significantly higher creatinine and urea levels, decreased creatinine clearance and lower calcium levels. Nevertheless, metabolic acidosis still stays a highly underestimated problem among nephrologists dealing with transplant recipients. We suggest regular determination of the acid-base status in renal transplant recipients.

Key words: *Acidosis; Kidney transplantation; Treatment outcome*

Introduction

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD)[1]. Although the quality of life improves significantly after transplantation, these patients frequently present with a complex set of medical issues that require intensive management to protect graft function[2,3]. One of the common but highly underestimated issues that can occur after transplantation is the presence of metabolic acidosis[4]. Metabolic acidosis is an inevitable complication associated with progressive loss of kidney function[5]. It appears when the glomerular filtration

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rate (GFR) falls below 25 mL/min/1.73 m^2 [6]. It arises from difference between the excretion of hydrogen and the synthesis of ammonia ions[7-9]. Damaged renal tubules cannot contribute to maintaining the acid-base balance by reabsorbing the daily filtrated HCO_3^- and synthesizing new HCO_3^- ions[6]. Metabolic acidosis is usually mild to moderate but can lead to several metabolic complications if not properly controlled[6,10]. It is one of the important causes of protein energy wasting (PEW) and may trigger muscle loss in patients with chronic kidney disease (CKD)[11]. Furthermore, it contributes to the development of chronic kidney bone disease by increasing bone resorption and inhibiting bone formation[6,12]. A recent study by Mizumoto *et al.* showed that acidic environment could play a very important role in regulating hepcidin homeostasis, thus being one of the factors contributing to the etiology of anemia of chronic disease[13]. It is also known that metabolic acidosis can severely affect graft function by causing progressive tubulointerstitial injury and a decline in GFR[5,8,10,14]. All these metabolic effects are complex but can be successfully managed[10]. Therefore, metabolic acidosis needs to be carefully monitored in every transplant recipient.

The aim of this study was to investigate current practice in the evaluation of metabolic acidosis at the Zagreb University Hospital Center (UHC).

Patients and Methods

Study design

All adult renal transplant recipients having received allograft from January 2011 to August 2012 were included in the study. Among them, only data on the recipients whose renal function remained stable for at least 3 months after transplantation were used in the analysis.

Study measurements

Laboratory and clinical data were collected from medical records and charts. We recorded the frequency of measuring parameters of venous blood gas analysis (acid-base status, ABS), as well as creatinine and urea levels, creatinine clearance, proteinuria, calcium, phosphate and potassium blood levels, body mass index, and the time spent on dialysis prior to kidney transplantation.

Statistical analysis

Statistical evaluation of the data was carried out using the SPSS statistical package, version 17.0 for Windows. Baseline data were reported using descriptive statistics. Normality of distribution for continuous variables was analyzed using Kolmogorov-Smirnov test. Normally distributed variables were described with mean and standard deviation (SD), while variables that were not normally distributed were described with median, minimum and maximum. Nominal variables were reported with absolute numbers and percentages. To compare characteristics of the two groups of patients, we used the parametric independent sample t-test for continuous variables and its corresponding nonparametric alternative Mantel-Haenszel or χ^2-test for categorical variables. The level of significance was set at $p<0.05$.

Results

Out of 203 patients transplanted at our institution during the observed period, 191 were enrolled in the study, while 12 patients were lost from follow up. Five patients died, four patients underwent graftectomy because of life threatening indications (pseudoaneurysm of the renal artery, mycotic aneurysm, pancytopenia with fungal infection and graft rejection, and retroperitoneal hematoma), one patient rejected the graft, and two patients continued follow up at another center.

There were 124 male (64.9%) and 67 female (35.1%) patients, mean age 51.04±12.23 years. The main etiology of CKD was chronic glomerulonephritis without performed biopsy (22.51%), followed by polycystic kidney disease (14.14%) and IgA nephropathy (7.33%). The mean time spent on dialysis prior to kidney transplantation was 44.11±29.07 months. The median body mass index (BMI) of our patients was 25.97 kg/m^2 (min 17.3 kg/m^2, max 43.04 kg/m^2). All patients received basiliximab induction, tacrolimus, mycophenolate mofetil or mycophenolate sodium, and steroids.

Only 92 of 191 (48.17%) study patients had parameters of venous blood gas analysis measured at some time after kidney transplantation. The mean determined pH value was 7.41 (range, 7.2-7.54). Forty-one (44.56%) patients were in the state of compensated metabolic acidosis, which means that their pH

values were within the reference range but their base excess was lower than -2 mmol/L. Three (3.26%) patients had moderate metabolic acidosis with pH values slightly under the reference interval and base excess ranging from -6 to -9 mmol/L. Moreover, we found that patients with performed pH/blood gas analysis had significantly higher creatinine, urea and serum calcium ($p<0.001$) levels, and lower creatinine clearance ($p<0.001$ all) (Table 1).

Comparison of BMI between these two patient groups yielded no significant difference. The median BMI of patients with performed blood gas analysis was 25.78 kg/m^2 (range, 17.3-43.04 kg/m^2), while the group without pH determination had median BMI of 26.06 kg/m^2 (range, 19.69-38.28 kg/m^2).

There was no between-group difference in serum potassium or sodium level. Episodes of acute rejection occurred in 20 patients, without significant difference between the groups.

Discussion

Metabolic acidosis is an important clinical problem that needs to be monitored in every kidney transplant recipient. Metabolic acidosis may have an impact on several metabolic complications, such as bone and muscle metabolism, nutritional status, and anemia[6,9,10]. It may also have an effect on graft function[5,8,14].

Results of our study suggested metabolic acidosis to be one of the highly underestimated issues among nephrologists dealing with transplant recipients. As shown by the statistics, only 92 (48.17%) of 191 patients included in the study had acid-base status determined at some time after kidney transplantation. These were mainly patients with much worse kidney graft function, which was the leading indication for acid-base status analysis. It is also very important to mention that 44 patients were found in the state of metabolic acidosis. Most of them (44.56%) were in the state of compensated acidosis. It is well known that mineral and bone metabolism disorders are common in patients with CKD[15]. Serum phosphate level rises due to decreased renal phosphate excretion[15]. Furthermore, the conversion of vitamin D to its active form is decreased, leading to decreased serum calcium levels and reduced intestinal calcium absorption[6,15]. The disturbed ion balance provokes the synthesis and secretion of parathyroid hormone (PTH) in order to normalize the disturbed values[6,15].

Metabolic acidosis also contributes to the development of chronic kidney bone disease[6]. The pH of extracellular fluid is closely protected[16]. Any increase in acidity or alkalinity activates three lines of defense, i.e. blood buffers, respiratory system control of CO_2, and renal excretion of excess acid or base[16]. Bone is considered to be an important buffering component[6,12]. Many studies have suggested that decreased pH level and low plasma bicarbonate concentration stimulate bone resorption and inhibit bone formation[6]. *In vitro* studies provided evidence that a bone mineral base was released into the circulation when administering exogenous acid[12]. If the acidification lasts long enough, the bone mineral content and bone mass progressively decline and osteoporosis occurs[12]. Analysis of our data showed significantly lower serum calcium levels in the group of patients with measured pH/blood gas values. Bearing in mind that most of these patients were in

Table 1. Statistical analysis of groups with acid-base status (ABS) analyzed and not analyzed

Parameter	ABS analyzed	ABS not analyzed	p value
Creatinine (μmol/L)	196 (87-638)	135 (85-489)	<0.001
Creatinine clearance (mL/min)	44.6 (1.3-88.7)	61.7 (12.7-126.7)	<0.001
Urea (mmol/L)	11.25 (4.6-40.4)	7.2 (2.9-39.5)	<0.001
Calcium (mmol/L)	2.46 (1.9-2.89)	2.53 (2.02-3.04)	<0.001
Proteinuria (g/dU)	0.31 (0.04-5.98)	0.37 (0.07-2.88)	0.147
Phosphorus (mmol/L)	1.02 (0.4-2.63)	1.84 (0.5-5.8)	0.348
Potassium (mmol/L)	4.15 (2.8-5.9)	4.28 (3.4-5.5)	0.323
Body mass index (kg/m^2)	25.7 (17.3-43.04)	26.19 (19.69-38.28)	0.709
Dialysis vintage (months)	37 (6-133)	46.41 (0-178)	0.256

Data are expressed as mean (range)

the state of acidosis with slightly reduced graft function, this could support the hypothesis that metabolic acidosis may be a major factor contributing to the development of kidney bone disease.

Malnutrition is a very frequent condition among patients with functioning graft[17]. In their study, Chruściel *et al.* showed that malnutrition could be found in more than 20% of transplant recipients[17]. PEW is characterized by a progressive loss of muscle and visceral protein stores[11]. It is very common in patients with ESRD and can lead to increased debility and mortality[11]. The mechanisms responsible for muscle protein breakdown are complex and cannot be associated only with lower protein intake[11]. Uremia inhibits the regenerative potential of skeletal muscle by acting on muscle stem cells[11]. Several abnormalities such as increased levels of circulating cytokines due to the presence of chronic inflammation, oxidative stress and endothelial damage, metabolic acidosis and disturbed insulin signaling also stimulate protein degradation and inhibit protein synthesis[11,18].

Series of studies suggested that metabolic acidosis was one of the most important contributing factors of PEW[18]. Acidosis increases muscle catabolism through upregulation of the ATP-dependent ubiquitin-requiring pathway[6,18,20]. It also reduces protein synthesis, especially of albumin, and enhances amino acid oxidation, especially degradation of valine[6,11,18]. Studies in rats and humans indicated that the correction of metabolic acidosis raised both plasma and muscle protein levels by decreasing transamination and decarboxylation in the muscle[6].

We did not find significant BMI difference between the two patient groups. Even when mild, metabolic acidosis may affect graft function. This happens possibly through stimulation of adaptive mechanisms aimed at maintaining acid-base homeostasis[5]. Increased ammonia and endothelin production may cause progressive tubulointerstitial injury and GFR decline, while the newly synthesized bicarbonate alkalinizes the interstitium and encourages precipitation of calcium in the kidney[6,8,10]. Finally, studies performed on rats using the remnant kidney model of CKD indicated that the decline in GFR was mediated in part by the actions of excess aldosterone and endothelin stimulated through acid retention[10]. A limited number of studies performed on humans also supported the potential role of metabolic acidosis in the progression of CKD[6]. Studies showed that the administration of bicarbonate to individuals with CKD of diverse etiology and metabolic acidosis not only slowed the progression of CKD (the decline in GFR was less than half of the control group who received sodium chloride), but the number of individuals developing ESRD was reduced significantly[6]. It is also very important to emphasize the impact of immunosuppressive therapy on graft function. This specific therapy is one of the cornerstones of successful kidney transplantation but we often neglect its negative effects on graft function[21,22]. Chronic allograft nephropathy (CAN) is the leading cause of graft loss one year after transplantation and is associated with a significant rise in morbidity and mortality[3,21]. Calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus contribute to CAN as strong profibrotic agents[22]. Most allografts show histopathologic signs of CNI toxicity 10 years after transplantation[3]. Initiated fibrogenesis can in the end lead to organ failure, thus making it difficult to achieve successful long-term allograft outcome[22]. These immunosuppressive agents also contribute to the development of metabolic acidosis[22,24,25]. According to statistical analysis of our data, the assumptions about metabolic acidosis affecting graft function may be correct. Our analysis showed that patients with determined acid-base status indeed had reduced graft function. This could be seen from the significantly higher median serum levels of creatinine and urea, as well as lower median values of creatinine clearance in this group of patients. However, this may have been the consequence of more frequent ABS evaluation in patients with less optimal graft function. Still, many patients without determined acid-base status had poor graft function.

In conclusion, the findings in this study indicate that metabolic acidosis is still a highly underestimated problem among nephrologists dealing with kidney transplant recipients. The awareness of acidosis and its effects on metabolism and graft function is clearly not raised because the majority of our patients with satisfactory graft function were found in the state of compensated or mild form of acidosis. By evaluating and correcting these metabolic disturbances, we could effectively protect and ameliorate graft function and the quality of life of our patients. In our further

studies, we plan to determine acid-base status in the whole population of kidney transplant recipients from our center in order to identify the actual prevalence of metabolic acidosis among this specific population.

We suggest regular acid-base status examination in renal transplant recipients.

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Sažetak

METABOLIČKA ACIDOZA – ZANEMARUJEMO LI JE NAKON TRANSPLANTACIJE BUBREGA?

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Metabolička acidoza je česta komplikacija vezana uz progresivan gubitak bubrežne funkcije. Njezin utjecaj na status uhranjenosti, razvoj anemije, koštanu masu i funkciju presađenog bubrega je vrlo složen, ali se može učinkovito spriječiti. Istražili smo koliko se određivanju i praćenju acidobaznog statusa (ABS) posvećuje pozornosti u jednom od najvećih transplantacijskih centara unutar organizacije Eurotransplant. U istraživanje su uključeni svi odrasli primatelji bubrega u razdoblju od siječnja 2011. do kolovoza 2012. godine. Tijekom promatranog razdoblja transplantirano je 203 bolesnika, a 191 bolesnik uključen je u istraživanje (124 muškarca i 67 žena, raspona dobi od 18 do 77 godina). Statistička analiza pokazala je da je u poslijetransplantacijskom razdoblju ABS bio određen samo u 92 (48,167%) bolesnika. ABS je češće određivan muškarcima (p=0,001). Bolesnici s određivanim ABS imali su značajno više vrijednosti kreatinina i ureje (p<0,001), kao i značajno niži klirens kreatinina (p<0,001). Ova skupina bolesnika imala je i značajno niže serumske koncentracije kalcija (p<0,001). Metabolička acidoza je važno kliničko pitanje koje je potrebno pažljivo razmotriti kod svakog primatelja bubrega. Naše istraživanje pokazalo je da je metabolička acidoza povezana sa značajno višim vrijednostima kreatinina i ureje, smanjenim klirensom kreatinina i nižim vrijednostima kalcija. Unatoč tome, metabolička acidoza ostaje uvelike zanemaren problem kod ove skupine bolesnika. Preporučamo redovito praćenje acidobaznog statusa svih bolesnika s presađenim bubregom.

Ključne riječi: *Acidoza; Transplantacija bubrega; Ishod liječenja*