Consequences of Metabolic Acidosis in Chronic Kidney Disease Patients

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Abstract

Metabolic acidosis is an inevitable complication associated with progressive loss of kidney function. It appears when glomerular filtration rate (GFR) falls below 25 ml/min/1.73 m². Metabolic acidosis arises from the difference between the excretion of hydrogen and the synthesis of ammonia ions. Damaged renal tubules cannot contribute in maintaining the acid base balance by reabsorbing the daily filtrated HCO₃⁻ and synthesizing new HCO₃⁻ ions. Although usually mild to moderate, it may lead to several metabolic complications.

Metabolic acidosis is one of the important causes of protein energy wasting (PEW) and can trigger muscle loss in patients dealing with chronic kidney disease (CKD). Furthermore, it contributes to the development of chronic kidney disease-metabolic bone disease by increasing the bone resorption and inhibiting the bone formation. It has been shown that the acidic environment could play an important role in regulation of the hepcidin homeostasis and thus, be one of the factors contributing to the etiology of the anemia of chronic disease. It is also known that metabolic acidosis can severely affect kidney function by causing progressive tubulointerstitial injury and decline in glomerular filtration rate.

All these metabolic effects are complex but can be successfully managed. Series of studies provide evidence that bicarbonate therapy is beneficial in these patients. It helps in achieving the balance between calcium and phosphate. Furthermore, it improves dietary protein intake and lean body mass and slows down the decline in glomerular filtration rate. Thus, metabolic acidosis needs to be monitored and carefully corrected.

Keywords: metabolic acidosis, chronic kidney disease, kidney transplantation, bone metabolism, anemia

Introduction

Maintaining the acid base homeostasis is one of the most important factors which contribute to normal protein function [1]. The extracellular fluid pH value of 7.4 is carefully protected. If an increase in acidity or alkalinity occurs, three lines of defence activate—the blood buffers, the respiratory system's control of CO₂ and the renal excretion of the excess acid or base [2]. The third defence line, kidney, is the most important in preserving this balance [3]. Metabolic acidosis is an inevitable complication associated with progressive loss of kidney function [4]. Its incidence and prevalence increase with declining kidney function [5]. When glomerular filtration rate (GFR) falls below 25 ml/min/1.73 m² kidney's capacity to synthesize new ammonia and excrete excess hydrogen ions significantly reduces [5-7]. Furthermore, damaged renal tubules cannot contribute in maintaining the acid base balance by reabsorbing the daily filtrated HCO₃⁻ and synthesizing new HCO₃⁻ ions [5,6]. Although metabolic acidosis is usually mild to moderate, it can have a major impact on bone and muscle metabolism, nutritional status and anemia [5,6,8]. It may negatively affect kidney allograft function and is also associated with an increased morbidity and mortality of these patients [4,6,9,10]. These metabolic effects are very complex but can be successfully managed [8].

We present an overview of clinical consequences of metabolic acidosis in patients with chronic kidney disease.

Metabolic acidosis and bone disease

Disorders of mineral and bone metabolism are common in patients with chronic kidney disease (CKD). Serum phosphate levels rise due to decreased renal phosphate excretion [11]. Moreover, the conversion of vitamin D to its active form is decreased leading to decreased serum calcium levels and reduced intestinal calcium absorption. The disturbed ion balance provokes the secretion of parathyroid hormone (PTH) in order to normalize the disturbed values [6,11]. Series of studies confirmed that metabolic acidosis contributed to the development of chronic kidney disease-metabolic bone disease [6]. Bone is considered to be an important buffering component since it is a reservoir of labile base in the form of alkaline salts of calcium [6,12]. Many studies suggested that a decrease of pH level and plasma bicarbonate concentration stimulate bone resorption and inhibit bone for-
Metabolic acidosis and malnutrition

It happens through activation of osteoclast’s and inhibition of osteoblast’s activity. In vitro studies provided evidence that a bone mineral base was released into the circulation when administering exogenous acid [12]. Furthermore, these studies provided evidence that metabolic acidosis could reduce vitamin D levels and stimulate PTH secretion. Not only does chronic metabolic acidosis stimulate PTH secretion but in the same time attenuates the cellular response to it [6]. If the acidification lasts long enough bone mineral content and bone mass progressively decline and osteoporosis occurs [12]. In children, uncontrolled metabolic acidosis can lead to stunted growth. This is not only the outcome of inhibited bone formation but happens also as the consequence of decreased cartilage production. The assumption is that metabolic acidosis could decrease growth hormone and insulin-like growth factor 1 (IGF-1) secretion and attenuate their actions on targeted tissues [6].

Metabolic acidosis and malnutrition

Malnutrition is a very frequent condition among patients with functioning graft. Chrusciel et al. showed in their study that malnutrition could be found in more than 20% of transplant recipients [13]. Both inadequate nutrient intake and ineffective nutrient utilization can contribute to nutritional disorders in CKD patients [14].

Protein energy wasting (PEW) is a disorder characterized by progressive loss of muscle and visceral protein stores, including albumin, which becomes noticeable in the advanced stage of kidney disease [15,16]. It is very common in patients with end-stage renal disease (ESRD) and can lead to increased debility and mortality, especially because PEW is strongly linked with an increased cardiovascular risk. Mechanisms responsible for muscle protein breakdown are complex and cannot be associated only with lower protein intake [16]. Uremic milieu leads to loss of appetite but uremia also inhibits the regenerative potential of skeletal muscle by acting on muscle stem cells [6,16]. 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 [16,17]. Inflammation markers such as CRP, IL-1 and IL-6 are often elevated in CKD patients. This happens due to the decreased excretory function of the kidneys but also during hemodialysis treatment which can activate microinflammation cascade through the exposure of the blood to dialysis membranes. Furthermore, oxidative stress arises from the difference between increased oxidant generation and insufficient anti-oxidant defence mechanisms. The presence of inflammation and generated free radicals results with tissue injury. It is a well-known fact that insulin is one of the most important factors in preserving lean body mass. However, it is not confirmed that disturbed insulin signaling, which can occur in these patients, could lead to muscle degradation [16].

Series of studies have suggested that metabolic acidosis was also one of the most important contributing factors of PEW [17]. Acidosis increases muscle catabolism through an 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 [6,16,17]. Studies in rats and humans indicated that the correction of metabolic acidosis raised both plasma and muscle protein levels by decreasing the transamination and decarboxylation in muscle [6].

Metabolic acidosis and anemia

A normochromic, normocytic anemia is very common in the advanced stages of CKD. About 50% of all ESRD patients and 30-40% of kidney transplant recipients deal with its consequences [14]. Not only does anemia increase the overall cardiovascular risk, but it also leads to progression of renal impairment due to tissue hypoxia [10,14]. Deficient erythropoietin synthesis, shortened erythrocyte half-life and iron deficiency are the most important causes of anemia associated with CKD [1]. Heparin is a recently discovered but very important central regulator of body iron homeostasis [18]. This 25-amino acid peptide is synthesized predominantly in the liver but it is also expressed in other cells, including microphages. If over-expressed, heparin is associated with anemia of inflammation, chronic kidney disease and iron-refractory iron deficiency anemia [19]. In their study Rivera et al. showed the potent role of heparin. When injected into mice it resulted in a dramatic drop of serum iron levels within an hour while the effect of a single dose lasted for 3 days even though heparin alone was rapidly cleared from plasma [20]. Heparin regulates cellular iron metabolism by binding to ferroportin, its receptor and the only known cellular exporter in mammals. This complex is degraded in lysosomes and iron cannot be released in the plasma [19]. Heparin is homeostatically regulated by iron and erythropoietic activity but interestingly enough, its transcription is also regulated by acid base status [19,21]. A recent study of Mizumoto and al. has shown that heparin levels were high in patients with ESKD and that acidic environment induced heparin transcription in the hepatoma cells. Thus, serum heparin levels are increased and could play a very important role in the etiology of the anaemia of chronic disease [21].

Metabolic acidosis, progression of CKD and effect on the kidney allograft

Even though CKD inevitably progresses to ESRD, this process might be attenuated. Series of factors contribute to this such as cardiovascular disease, anemia, microinflammatory state, oxidative stress [10]. Metabolic acidosis is also among the factors which affect the kidney. Furthermore, even mild metabolic acidosis may affect the function of kidney allograft. This happens possibly through the stimulation of adaptive mechanisms aimed at maintaining acid base homeostasis [4]. Increased ammonia and endothelin production may cause progressive tubulointerstitial injury and decline in glomerular...
filtration rate while the newly synthesized bicarbonate alkalizes the interstitium and encourages precipitation of calcium in the kidney [6,8,9]. Finally, studies performed on rats using the remnant kidney model of CKD indicated that GFR decline was mediated in part by the actions of excess aldosterone and endothelin stimulated through acid retention [8]. A limited number of studies performed on humans have also supported the potential role of metabolic acidosis in the progression of CKD [6]. Administration of bicarbonates to individuals with CKD of diverse etiology and metabolic acidosis not only slowed progression of CKD (GFR decline was less than half of the control group who received sodium chloride), but the number of individuals developing ESRD was significantly reduced [6]. Studies performed on rats provided evidence that bicarbonate therapy could decrease the severity of tubulointerstitial disease by preventing a development of interstitial inflammation and chronic fibrosis [8]. As previously mentioned, metabolic acidosis may also seriously damage the kidney allograft [4]. This is strongly associated with the use of immunosuppressive medications. These agents also contribute to the development of hyperkalemia, hyperchloremia and metabolic acidosis [22-24]. Immunosuppressive therapy is one of the cornerstones of successful kidney transplantation but we often neglect its negative effects on graft function [22,25]. 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. It is manifested with a decrease in allograft function at least 3 months after transplantation. Calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus contribute to CAN and are strong profibrotic agents. Most allografts show histopathologic signs of CNI toxicity 10 years after transplantation. Initiated fibrogenesis can in the end lead to organ failure thus making it difficult to achieve a successful long-term allograft outcome [26].

**Correction of metabolic acidosis with bicarbonate supplementation**

Metabolic acidosis is a very important clinical issue that needs to be monitored in patients suffering from CKD as well as in kidney transplant recipients. Its effects on kidney function, nutritional status, anemia and bone mass are complex and sometimes severe but can be successfully managed. There have been many studies showing benefits of the base therapy. It has been previously mentioned that metabolic acidosis supports the presence of mineral disturbance and thus aggravates bone disease. It provokes PTH secretion but attenuates the cellular response to it, reduces vitamin D plasma level, stimulates bone absorption and inhibits bone formation. Acidification encourages osteoclast activity while prohibiting the activation of osteoblasts. If this process lasts long enough, bone mass will be lost and osteoporosis will occur [12]. Sebastian et al. examined the influence of administering potassium bicarbonate on bone metabolism in postmenopausal women in their study in 1994. The study showed that supplementation with potassium bicarbonate had lowered urinary excretion of calcium and phosphorus thus inducing the increase in the balance of these minerals. Secondly, the serum osteocalcin concentration had also risen. In conclusion, the administration of potassium bicarbonate reduced the bone absorption and increased the bone formation. Studies performed in adult patients on chronic maintenance hemodialysis showed similar results-correction of acidosis by raising the dialysate base concentration attenuated the rise in PTH, reduced bone absorption and improved bone formation [7,27].

Metabolic acidosis is one of the major factors in the development of PEW disorder. This disorder is characterized by the increase in protein catabolism due to the upregulation of the ubiquitin-proteasome system, increased amino acid oxidation and decreased visceral protein synthesis. The presence of uremia is also a contributing factor, which leads to loss of appetite and blunts muscle regenerative potential. Ione de Brito-Ashurst et al. showed how bicarbonate therapy could be beneficial in fighting this specific disorder. They observed bicarbonate therapy action by comparing the difference between two groups of patients—one group received bicarbonate treatment while the other did not. First of all, the group which was given bicarbonate supplementation at a dosage of 1.82 ± 0.8 g/day showed a significant increase of serum HCO3− levels. Secondly, a significant improvement in dietary protein intake, lean body mass and an increase of albumin plasma levels was apparent in this group of patients [15]. Series of studies performed on animals and humans confirmed that metabolic acidosis is one of the risk factors for CKD progression [8]. It activates the alternative complement pathway and causes tubulointerstitial injury which leads to increased proteinuria, fibrosis and faster rate of decline in renal function [6,15]. There is also substantial evidence that bicarbonate therapy could slow the GFR decline. Administration of citrate or bicarbonate to rats with CKD slowed a decline in GFR and prevented tubulointerstitial inflammation and fibrosis. The results of the previously mentioned study of Ione de Brito-Ashurst and colleagues showed that the rate of loss of creatinine clearance was significantly lower in the treated group in comparison to control subjects. The observed decline in creatinine clearance was 5.93 ml/min/1.73 m2 in the control group compared with 1.88 ml/min/1.73 m2 in the treated group [15]. It needs to be emphasized that base therapy is not without risks. Possible adverse effects are volume overload, congestive heart failure and hypertension, all due to sodium retention. Thus, all of the patients receiving this therapy should be carefully monitored. It is recommended to give enough alkaline therapy in order to achieve normal serum HCO3− values [6].

**Conclusions**

In conclusion, metabolic acidosis is a complex but inevitable condition of CKD. It has a major impact on bone and muscle metabolism, nutritional status, anemia and kidney function and is also associated with an increased morbidity and mortality of these patients. All these complications clearly respond to base therapy. Therefore, all
patients in the state of metabolic acidosis should be monitored and treated in order to prevent complications and improve their health and quality of life.

Conflict of interest statement. None declared.

References