Metabolic acidosis in hemodialysis patients: a review

Acidose metabólica em pacientes em hemodiálise: uma revisão

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Abstract

Metabolic acidosis is highly prevalent in hemodialysis patients. The disorder is associated with increased mortality and its deleterious effects are already present in the predialysis phase of chronic kidney disease. Metabolic acidosis has been linked to progression of chronic kidney disease, changes in protein and glucose metabolism, bone and muscle disorders and cardiovascular disease. At present, the control of metabolic acidosis in hemodialysis is mainly focused on the supply of bicarbonate during dialysis session, but further studies are needed to set the optimum target serum bicarbonate and the best concentration of the bicarbonate dialysate. The present study reviews pathophysiological and epidemiological aspects of metabolic acidosis in hemodialysis patients and also addresses its adverse effects and treatment.

Keywords: acidosis; renal dialysis; bicarbonates.

Resumo

A acidose metabólica é altamente prevalente em pacientes em hemodiálise. A doença está associada com mortalidade aumentada e os seus efeitos deletérios já estão presentes na fase pré-diálise da doença renal crônica. A acidose metabólica tem sido associada a progressão da doença renal crônica, alterações no metabolismo das proteínas e da glicose, doenças ósseas e musculares e enfermidades cardiovasculares. Atualmente, o controle da acidose metabólica em hemodiálise está voltado principalmente para o suprimento de bicarbonato durante a sessão de diálise, porém, mais estudos são necessários para definir o bicarbonato sérico alvo ideal e a melhor concentração de bicarbonato do banho. O artigo revisa os aspectos fisiopatológicos e epidemiológicos da acidose metabólica em pacientes em hemodiálise e também aborda seus efeitos adversos e tratamento.

Palavras-chave: acidose; diálise renal; bicarbonatos.

Introduction

End-stage renal disease (ESRD), which can be treated by either dialysis or transplantation, is a worldwide public health problem. Its incidence has increased in recent years, causing substantial economic burden to health care systems in the world.[1,2] Of note, the mortality of dialysis patients remains elevated compared to general population with approximately half of the patients dying from cardiovascular disease.[3]

In Brazil, for example, according to the Brazilian Survey of Chronic Dialysis of 2014, the estimated total number of dialysis patients was 100,397. National estimates of the rates of prevalence and incidence of dialysis were 499 and 170 patients per million people, respectively. The annual rate of crude mortality was 17.9%. The absolute number of dialysis patients has increased 3% annually over the past three years.[4]

The presence of metabolic acidosis and its association with mortality in patients on dialysis has been the subject of several publications[5-8] as summarized in Table 1. The real extent of this problem in Brazil is unknown because, in 1996, the national regulatory agency for the dialysis procedure has published an ordinance in which the mandatory measurement of bicarbonate in patients on renal replacement

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Table 1 Selected studies evaluating the impact of metabolic acidosis on mortality in dialysis patients

	Study design	Effects on mortality (Yes/No)	Main results
Vashistha *et al.*[5]	Observational, retrospective, multicentric, n = 121,351 (Database: DaVita)	Yes	Increase 15-35% in the risk of mortality for patients with bicarbonate < 22mEq/L.
Bommer *et al.*[7]	Observational, prospective, multicentric, n = 7,140 (Database: DOPPS I)	Yes	Up to 48% increase in mortality risk for patients with pre-dialysis serum bicarbonate in a midweek session < 18mEq/L or ≥ 27mEq/L.
Yamamoto *et al.*[7]	Observational, retrospective, multicentric, n = 15,132 (Database: Japanese Renal Data Registry)	No	36% increase in mortality risk for patients with predialysis pH > 7.40. No association was found between the levels of serum bicarbonate before or after dialysis with mortality.
Tentori *et al.*[8]	Observational, prospective, multicentric, n = 17,031 (Database: DOPPS II)	Yes	Average 30% increase in mortality risk for patients with serum pre-dialysis bicarbonate ≤ 17mEq/L.

therapy (RRT) was withdrawn.[9] The most recent Brazilian government guidelines recommend measurement of bicarbonate every six months (stage 4) or quarterly (stage 5), but only for patients undergoing conservative treatment,[10] keeping measurement of this parameter in patients on RRT not mandatory.

Pathophysiology of metabolic acidosis

Metabolic acidosis can be defined as a pathological condition characterized by an absolute or relative increase in body concentration of hydrogen ions with a reduction in serum bicarbonate. The adult human body produces 1 mEq/kg body weight of endogenous free acids daily (in children the value is 2-3 mEq/kg of body weight).[11] The acid balance in the body depends crucially on the quality and quantity of acids (mainly derived from proteins) and alkalis (sourced from fruits and vegetables) consumed in the diet and also on the amount of eliminated acids.[12] The excretion of the acid produced by the metabolism is mainly accomplished by two pathways: the lungs, responsible for eliminating volatile acids; and the kidneys, for the non-volatile acids.

Produced endogenous acids are neutralized by the body buffers, including bicarbonate, which is reabsorbed by the glomeruli, assisting in maintaining the acid-base balance. The kidney's ability to excrete acid and reabsorb bicarbonate is impaired when glomerular filtration rates (GFR) is below 40-50 ml/min, a point in which the installation of systemic metabolic acidosis generally initiates.[13-15]

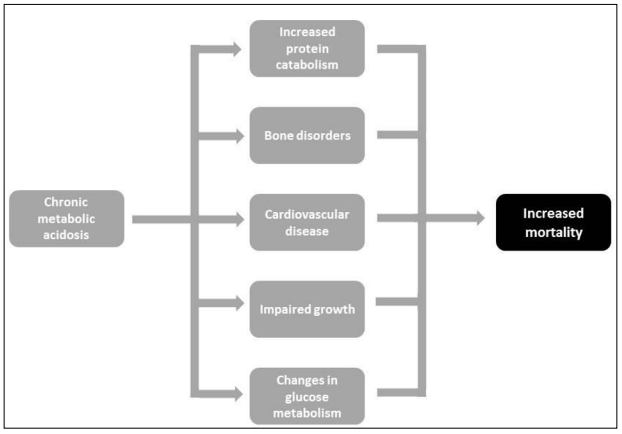
Metabolic acidosis can be triggered by three major mechanisms: an increase in the generation of acid, bicarbonate loss, and decreased renal acid excretion. In ESRD patients, the major mechanism involved is the decrease in the renal excretion of hydrogen ions.[16]

In hemodialysis, the factors that can conceivably contribute to the worsening of metabolic acidosis include: low gain of bicarbonate in dialysis (caused by inadequate level of bicarbonate in the dialysate, inadequate dialysis schedule or absenteeism), high protein intake or gastrointestinal loss of bicarbonate.[17,18]

Disorders related to metabolic acidosis

The deleterious effects of metabolic acidosis are already present in the predialysis phase of chronic kidney disease. Although beyond the scope of the present review, it is noteworthy that a number of studies have posed metabolic acidosis as a nephrotoxic factor implicated in the progression of chronic kidney disease.[19-22] The mechanism is thought to involve increased interstitial generation of ammonia (with activation of the complement pathway), augmented local production of endothelin, and activation of the RAAS. These players would promote renal interstitial fibrosis and acceleration of the nephron loss. Perhaps more important are the reports that the presence of metabolic acidosis is already associated with higher mortality even in the predialysis stage of CKD.[23] The adverse effects of chronic metabolic acidosis are summarized in Figure 1.

Figure 1. Long-term consequences of chronic metabolic acidosis.



Bone disorders

The changes that occur in bone mineral composition in the presence of metabolic acidosis suggest that it actively acts as a proton buffer. Consistent with this view, there is reduction of sodium and potassium bone (indicating exchange of protons), bone carbonate reduction (suggesting consumption of this buffer), and increased serum calcium.[24]

Also, increased calciuria is found without a parallel increase in intestinal calcium absorption suggesting that the bone is the source of the excreted calcium. *In vitro* studies indicate that during acute metabolic acidosis the initial bone calcium efflux is caused by physicochemical dissolution, whereas after 24 to 48 hours, it is predominantly mediated by cells. There is an increased concentration of prostaglandins, which stimulates the activity of osteoclasts and inhibits osteoblastos.[25] Acidosis can also contribute to the mineral and bone disease of chronic kidney disease.[26]

In children, chronic metabolic acidosis can cause growth retardation. This phenomenon is not completely understood but may involve perturbation of the growth hormone/IGF-1 axis, whose serum levels are diminished, resulting in reduction of the protein anabolismo.[27,28]

Effects on protein catabolism

Metabolic acidosis is also associated with increased protein catabolism and a consequent decrease in muscle mass, which can be associated with increased morbidity and mortality in hemodialysis patients.[29-31] In this regard, increased protein catabolism seems to play a more important role than decreased protein synthesis.[32] The main mechanism underlying muscle degradation in metabolic acidosis involves the ubiquitin-proteasome pathway. Physiologically, this system is the major pathway degrading protein in skeletal muscle. In the presence of acidosis there is increased expression of mRNA ubiquitin, elevation in the number of proteasome subunits, and over activation of the system leading to increased protein degradation.[33-35]

Another factor that appears to contribute to sarcopenia is the enhanced endogenous production of glucocorticoids in patients with chronic metabolic acidosis.[36] Glucocorticoids bind to phosphatidylinositol 3-kinase, leading to suppression of phosphorylation of Akt protein (essential for the intracellular signaling protein synthesis).[37] With the decrease in Akt phosphorylated proteins, there is a reduction in protein synthesis and consequent muscle loss.

Still within this context, insulin has an anabolic action by increasing glucose intake by muscle cells and inhibiting proteolysis. Recent studies suggest that the presence of metabolic acidosis can inhibit the anabolic effects of insulin which could contribute to the reduction of muscle mass in patients with chronic kidney disease. This insulin resistance is independent of the body fat content and can be a risk factor for developing type 2 *diabetes mellitus*.[38-40]

Hemodynamic effects

Metabolic acidosis directly affects heart function. The precise mechanism by which acidosis perturbs the inotropic state of the heart remains unknown. Reductions in pH to values below 7.2 inhibit the Na^+/K^+ ATPase transporter and cause a reduction in the cardiomyocytes action potential, which result in a decrease of muscle contractile force and heart failure.[41]

Another mechanism triggered by acidosis that is also implicated in heart failure involves the calcium: hydrogen ions compete with these ions by binding to troponin in myocardial cells; in the presence of high concentrations of hydrogen a smaller percentage of calcium binds to troponin, disturbing the interaction between actin and myosin and causing reduction of cardiac contractile.[42]

Other hemodynamic event directly associated with acidosis is the vasodilation due to increased serum levels of nitric oxide.[43] Nitric oxide induced vasodilation is exacerbated by the direct influence of the low pH in peripheral vascular resistance and in the response of the vessels to cathecolamines.[42]

Systemic inflammation and atherosclerosis

Chronic metabolic acidosis is associated with the onset of systemic inflammation and its deleterious

consequences for the human body: anorexia, malnutrition, accelerated atherogenesis, and increased incidence of cardiovascular disease.[3,44,45] Macrophages in acidic environment begin to produce greater quantities of tumor necrosis factor alpha and interleukins, which triggers an inflammatory reaction.[46] Furthermore, the renal failure by itself is associated with increased circulating cytokines, also contributing to the development of the inflammatory process.[47]

Chronic metabolic acidosis may be the trigger for most of the mechanisms underlying the malnutrition/inflammation/atherosclerosis syndrome, which is known to affect hemodialysis patients.[44] Patients with chronic metabolic acidosis show increased endothelial permeability and a more rapid development of atherosclerosis. Autopsies[48] and clinical studies[49] have shown that atherosclerotic plaques in coronary arteries are higher in hemodialysis patients when compared to the general population. In an experimental study, it was found that acidotic rabbits had increased endothelial permeability[43]. This increase in endothelial permeability leads to retention of oxidized LDL-cholesterol in the intima of arteries and can contribute to progression of atherosclerosis.[50]

Management

The mainstay in the treatment of chronic metabolic acidosis in end-stage renal failure patients is the supply of exogenous bicarbonate. This is usually provided by the dialysate containing bicarbonate during the dialysis sessions and, if necessary, orally. The target serum bicarbonate recommended by the KDOQI[51] is at least 22 mEq/L immediately before a hemodialysis session, but the recommendation does not specify if the number refers to the first dialysis session of the week or a midweek one. A recent review on the Subject,[52] based on a large observational study,[6] commentates that the best survival was found with bicarbonate before the mid-week session between 18 and 21 mEq/L.

Hemodialysis is currently the main way to supply bicarbonate and control of acidosis. Sixty-five percent of the dialysate bicarbonate crosses the membrane in one pass through the filter. This high value is responsible for the rapid increase in serum bicarbonate in the first two hours of dialysis; for the remainder of the hemodialysis session the serum bicarbonate only increases slightly or remains stable. At the end of the treatment alkalinity is about 4 to 7 mEq/L smaller than the bicarbonate dialysate. The probable cause for this stabilization at the end of HD is the reduction in bicarbonate concentration gradient and perhaps increased production of organic acids due to the rapid increase of álcalis.[53,54]

Theoretically, the prescription of the bicarbonate dialysate should be individualized according to the serum levels of bicarbonate of each patient. This strategy is indeed adopted in some centers especially in developed countries,[8] but it does require a more personalized attention by the care team and is difficult to apply as a routine procedure. In fact, the reality for the majority of dialysis centers is a standard prescription that is considered acceptable for the average population of each clinic. However, taking the differences in diet and catabolic state of each patient in consideration, it is unlikely that a single pattern is able to adequately treat all patients.

At the present, the limitations of the dialysis treatment in the control of metabolic acidosis results in a high frequency of this disorder in ESRD patients. Possible strategies to increase the performance of the dialysis treatment regarding control of the metabolic acidosis include increasing the concentration of bicarbonate in the dialysate,[54,55] and more frequent or longer dialysis sessions.[56] A modeling process in which the dialysate bicarbonate concentration varies along the session has been tested, however, no clear benefits over traditional hemodialysis was found.[54,57]

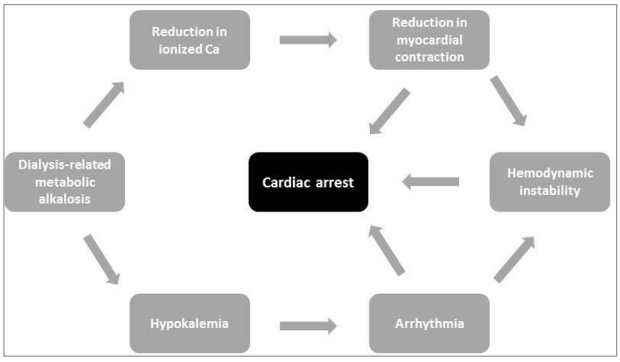
There is a wide variation in the dialysate bicarbonate concentration between countries with values ranging from 32.2 ± 2.3 mEq/L in Germany to 37.0 ± 2.6 mEq/L in the United States.[8] The increase in the dialysate bicarbonate concentration has been much discussed as the main way to control acidosis in hemodialysis patients as an inexpensive and easy method.

However, the adoption of this practice still demands more conclusive studies since the resultant metabolic alkalosis carries the potential to be as harmful as metabolic acidosis. A recent study showed an association between an 8% increase in overall mortality of dialysis patients for each increase of 4 mEq / L in the dialysate bicarbonate concentration.[8] The best concentration of dialysis bath bicarbonate is yet to be established.

Several mechanisms may be involved with the disputable increase in mortality related to metabolic alkalosis per or post-dialysis, such as: reduction in the ionized fraction of calcium and consequent reduction

in myocardial contraction,[58] hypokalemia,[59] changes in ventricular repolarization,[60,61] hemodynamic instability[62,63] and cardiopulmonary arrest (Figure 2).[64-66]

Figure 2. Possible pathways of the presumed adverse effects of dialysis-induced metabolic alkalosis.



Oral supplementation of sodium bicarbonate in the interdialytic period may also be considered in order to individualize the bicarbonate replacement. However, one should take into consideration that many of these patients regularly use a substantial amount of oral medications that can hinder adherence to prescription. Also, one should always be alert to the possible risk of sodium overload with the use of this supplement.[67,68]

The proper management of metabolic acidosis in patients on hemodialysis should also include the control of causative factors, such as inadequate hemodialysis and excessive intake of protein. The ancillary tools in this regard include: dialysis prescription optimization; surveillance for the prescription to be fulfilled; and encouragement to reduce absenteeism.

Although excessive intake of proteins can be harmful by aggravating acidosis, maintain adequate nutrition and preventing protein catabolism is of great importance in ESRD patients. Therefore, a protein intake around 1.2g/kg/day is required and excess acid production may be offset by increased supply of bicarbonate as opposed to dietary restriction.[67-69]

Conclusion

Chronic metabolic acidosis is closely related to chronic kidney disease and ESRD. Its presence in patients undergoing hemodialysis has been associated with mortality.

Much has been discussed about the best strategy to approach this acid-base disturbance since the metabolic alkalosis during and after the dialysis, caused by an increase in supply of bicarbonate by hemodialysis, may be potentially harmful to the patient.

A cutoff value for predialysis blood bicarbonate that would provide the lowest mortality is not yet clearly established, but it seems to seat between 18 and 22 mEq/L. Similarly, the most effective value of the dialysate bicarbonate concentration in this regard is also uncertain.

The obstacles to establishing a standard for the dialysate bicarbonate concentration probably stems from differences in the diet and biophysical profiles of patients, which are the main determinants of their alkali needs. Oral supplementation would allow easier customization of the individual requirements. However, this practice comes up against the difficulty of joining the prescription and the risk of salt and water retention.

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