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Disturbances in Acid-Base Balance in Patients on Hemodialysis

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http://dx.doi.org/10.5772/52442

1. Introduction

The prevalence of metabolic acidosis increases in Chronic Kidney Disease (CKD) patients according to the fall in glomerular filtration rate (GFR). In early stages of renal dysfunction acid retention is mainly due to the reduced tubular ammonium (NH^{4+}) secretion. As GFR declines retention of organic acids (HSO_4^{-s}, HPO_4^{-}) is also observed. The acid load resultant from diet and protein catabolism was believed to be the main responsible for acidosis in hemodialysis patients, however recent studies have shown an increasingly important role of hyperchloremia in the genesis of metabolic acidosis and pathophysiological disorders associated with it [1]. This finding was made possible through the use of Stewart´s [2] physico-chemical approach for diagnosis and classification of acid base disorders. This new approach not only enables the identification and classification of acid-base disorders and allows the quantification of the magnitude of each component to the disorder genesis [3,4].

The current K/DOQI recommendation for the treatment of metabolic acidosis in the patients on hemodialysis therapy is for maintaining a serum bicarbonate of at least 22 mEq/l [5]. Although consensus recommendation, the studies on metabolic acidosis in these patients showed that hemodialysis fail to raise the levels of serum bicarbonate to the desired value. Santos et al. [6] in a study of metabolic acidosis ($HCO_3^- < 22$ mEq/L) in dialysis patients found a 90% prevalence of metabolic acidosis. Libório et al. found an average level of serum bicarbonate in dialysis patients of 18 to 19 mEq/L in their trials [1,7].

The deleterious effects of maintaining metabolic acidosis in this population of individuals are well known, endocrine disorders and anorexia leading to catabolism of endogenous proteins and changes in bone mineral metabolism all these contributing to increased morbidity and mortality in these patients [8].

CKD related acidosis is associated with several life-threatening conditions. Adequate treatment of this condition might be associated with better outcomes in the dialysis population as shown in some studies reporting improvement in nutritional status with oral bicarbonate supplementation or higher dialysis solution bicarbonate [6]. Data on involvement of chloride as cause of acidosis and its implication on acidosis complications are scarce.

In this chapter we intend to approach the importance of metabolic acidosis for dialysis patients, discuss the possible pathophysiological mechanisms involved in the genesis of the acidosis and the consequences that this disorder brings to these individuals, using quantitative physicochemical approach. We propose to conduct a literature review about the therapeutic alternatives as well as dialysis treatment modalities that could be used for the correction of this disorder.

2. The acid–base equilibrium: Henderson–Hasselbalch

The Henderson–Hasselbalch equation is still the standard method for interpreting acid–base equilibrium in clinical practice [9]. It is based in the following equation:

$$pH = pK1' + log\ HCO^{3-} / (Sx\ PCO_2) \tag{1}$$

This equation describes how plasma CO_2 tension, plasma bicarbonate (HCO^{3-}) concentration, the apparent dissociation constant for plasma carbonic acid (pK) and the solubility of CO2 in plasma interact to determine plasma pH. The magnitude of the metabolic acidosis is generally quantified by the base deficit or base excess, which is defined as the amount of base (or acid) that must be added to a liter of blood to return the pH to 7.4 at a partial pressure of carbon dioxide (PCO_2) of 40 mmHg [10].

3. Stewart model for acid base disorders

The traditional approach has been criticized as being descriptive rather than mechanistic in nature and limited in scope and therefore unable to make complete diagnosis in patients with complex disorders. In contrast, proponents of Stewart's approach believe it to be mechanistic in nature and comprehensive in scope, able to detect important hidden disorders [10,11]. The fundamental underpinning of Stewart's approach is the concept of independent and dependent variables in acid-base homeostasis. According to Stewart, "Independent variables in any system are those which can be directly altered from outside the system without affecting each other" and "...dependent variables in a system can be thought of as internal to the system. Their values represent the system's reaction to the externally imposed values of the independent variables." [12].

On the basis of Stewart's definition, H^+ and bicarbonate are dependent variables whose concentrations are determined by the three independent variables, Strong Ion Difference (SID),

PCO_2, and total concentration of weak acids (ATOT), mainly composed of albumin and phosphate [12]. In Stewart's approach, similar to the traditional approach, respiratory disorders are those that are due to a primary alteration in PCO_2. Metabolic disorders, however, are due to primary alterations in SID or ATOT and not bicarbonate. By the law of electroneutrality [4]:

$$([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) - ([HCO_3^-] + [A^-]) = 0 \qquad (2)$$

This formula can be rearranged as follows:

$$([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) = [HCO_3^-] + [A^-] \qquad (3)$$

Therefore,

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate + other\ strong\ anions]) = [HCO_3^-] + [A^-] \qquad (4)$$

Under normal conditions, concentration of lactate and other strong ions is very low and can be ignored. The formula could therefore be simplified to

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-]) = [HCO_3^-] + [A^-] \qquad (5)$$

SID therefore can be calculated as the difference between fully dissociated cations and anions or sum of bicarbonate and A^- where A^- represents total charges contributed by all nonbicarbonate buffers, primarily albumin, phosphate, and, in whole blood, hemoglobin. SID is therefore the same as buffer base concept introduced by Singer and Hasting more than five decades ago. When an abnormal anion is present, a gap will appear between SID calculated by the difference between strong ions (the so-called "apparent SID", SIDa) and calculated by the addition of bicarbonate and nonbicarbonate buffers (so called "effective SID" SIDe) (Figure 1). This difference, named strong ion gap (SIG), is a marker for the presence of an abnormal anion. Anion gap (AG) is also calculated on the basis of the principal of electroneutrality as shown as follows [4]:

$$([total\ cations] - [total\ anions]) = ([measured\ cations] + [unmeasured\ cations]) - ([measured\ anions] + [unmeasured\ anion]) = 0 \qquad (6)$$

This can be rearranged as:

$$([measured\ cations] - [measured\ anions]) = ([unmeasured\ anions] - [unmeasured\ cations]) = AG \qquad (7)$$

In normal state, plasma unmeasured anions reflect charges contributed by the nonbicarbonate anions (A^-), primarily albumin and phosphate. The unmeasured cations are primarily made up of calcium, magnesium, and, depending on the formula used, potassium. AG, the

difference between the abnormal and normal (or baseline) AG, represents the amount of abnormal anion(s) present in plasma. SIG, as pointed out already, also represents the amount of abnormal anion(s) present in plasma and is expected to be mathematically equal to ΔAG (Figure 1) [4].

This relationship could have been even stronger if ΔAG were calculated in a more precise manner by using actual baseline values for AG in each patient rather than the mean value of 12 [13]. It should be clear that specific components of Stewart's formulas, such as SID and SIG, are conceptually and mathematically closely related to specific components of traditional formulas such as bicarbonate, AG, and ΔAG[4].
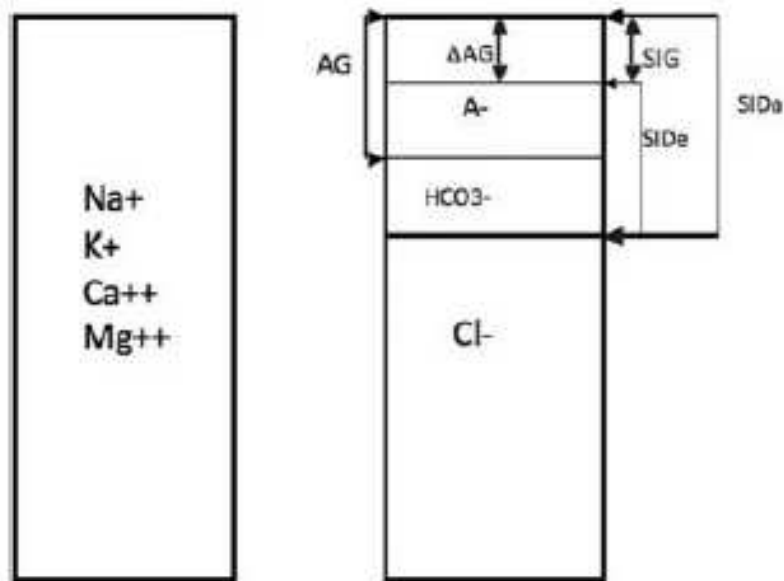

Figure 1. Relation between Strong Ion Gap (SIG) and ΔAG [4]

4. Classical X Stewart´s approach

One important goal of any method used to analyze acid base disorders is to develop a clinically useful classification. The traditional approach, using a robust body of empirical observations, has developed a classification that contains six primary disorders: Metabolic acidosis, metabolic alkalosis, acute and chronic respiratory acidosis, and acute and chronic respiratory alkalosis. Metabolic acidosis can further be classified as anion gap or hyperchloremic acidosis. In addition, by using compensatory formulas as well as ΔAG, the traditional approach is capable of diagnosing complex acid-base disorders [14].

In Stewart's approach, classification of acid base disorders is based on changes in the three "independent" variables (Table 1) [15]. Respiratory disorders, as in the traditional approach, are due to a change in PCO_2, whereas metabolic disorders are due to alterations in either SID or ATOT. SID is decreased in metabolic acidosis and increased in metabolic alkalosis. By

calculating SIG, one can further classify metabolic acidosis. In hyperchloremic metabolic acidosis, both effective and apparent SID decrease equally, as the increase in chloride is counterbalanced by an equal decrease in the bicarbonate concentration. SIG therefore remains at or near zero. In AG metabolic acidosis, apparent SID does not change (as chloride concentration is unchanged), but effective SID decreases (as a result of a decrease in bicarbonate concentration) and SIG therefore becomes positive [15]. One major departure from the traditional approach is classification of acid-base disorders as a result of alteration in ATOT. ATOT, representing all nonbicarbonate buffers pairs (HA + A⁻), is made up of charges contributed primarily by serum proteins (mainly albumin) with phosphate and other buffers playing a minor role. On the basis of this classification, an increase in serum protein would result in metabolic acidosis and a decrease, metabolic alkalosis [15,16].

Parameter	Acidosis	Alkalosis
Respiratory	↑PCO2	↓PCO2
Nonrespiratory (metabolic)		
Abnormal SID		
Water excess/deficit	↓SID, ↓ [Na]	↑SID, ↑[Na]
Imbalance of Strong anions		
Chloride excess/deficit	↓SID, ↑[Cl]	↑SID, ↓[Cl]
Unidentified anion excess	↓SID, SID "/> 0	
Nonvolatile weak acids		
Serum albumin	↑[Alb]	↓[Alb]
Inorganic phosphate	↑[Pi]	↓[Pi]

Table 1. Classification of acid-base disturbances according to Stewart´s approach [4]

5. Pathophysiology of acidosis in CKD

Classical uremic acidosis is characterized by a reduced rate of NH^{4+} production and excretion because of cumulative and significant loss of renal mass [17]. Usually, acidosis does not occur until a major portion of the total functional nephron population (>75%) has been destroyed, because of the ability of surviving nephrons to increase ammonia genesis. However, there is a decrease in total renal ammonia excretion as renal mass is reduced to a level at which the GFR is 20 mL/min or less. PO_4^{3-} balance is maintained as a result of both hyperparathyroidism, which decreases proximal PO_4^{3-}absorption, and an increase in plasma PO_4^{3-} as GFR declines. In advanced renal insufficiency, including hemodialysis patients, the hyperchloremic acidosis discussed earlier converts to a typical high AG acidosis. Poor filtration plus continued reabsorption of poorly identified uremic organic anions resulting from diet and body metabolism contributes to the pathogenesis of this metabolic disturbance [17].

Libórioet al. [1] showed when using Stewart´s approach to acid–base disorders in maintenance hemodialysis that unmeasured anions are an important cause of acidosis in this population, contributing to more than 40% of reduction in serum bicarbonate. A surprising finding was the role of hyperchloremia in acidosis etiology, which had a similar quantitative effect in acidosis. Recently, a study carried out in nondialysis chronic renal failure patients disclosed the main role of hyperchloremia in acidosis [18]; however, the acidosis composition in the dialysis population is still largely unknown.

The lack of quantitative analysis has led major textbooks to the assumption that the acidosis in these patients is due to the accumulation of unmeasured anions only, leading to high anion gap acidosis. Rocktaeschelet al. [19] showed in acute renal failure, acidosis also has complex and multiple etiologies in maintenance hemodialysis.

Sevelamer hydrochloride is a known cause of acidosis in hemodialysis due to the load of hydrochloric acid (each 800 mg tablet of sevelamer hydrochloride leads to an acid load equivalent to 4 mEq hydrochloric acid) [20].Another potential culprit in the cause of hyperchloremia is the chloride levels in the dialysate bath. In a literature review,15 considerable variations were found in dialysate chloride levels: from 90 to 125 mEq/l. The elevation in chloride is accompanied by a reduction in dialysate SID. Considering this fact, the maximum level of dialysate chloride must be 105 mEq/l, allowing the dialysate SID to increase up to 40 mEq/l, a value similar to that of plasma [7].

Acidosis in maintenance hemodialysis has multiple etiologies. Unmeasured anions and hyperchloremia are the main components, and hyperphosphatemia has a minor effect. Hyperchloremia cannot be attributed to sevelamer hydrochloride therapy alone, and we speculate that high levels of chloride in dialysate constitute a potential culprit. Additional studies assessing the relationship between the nature of acidosis and its detrimental effects on bone, inflammation, and nutrition are warranted [1].

6. Consequences of metabolic acidosis

6.1. Exacerbation of bone disease and impaired growth in children

Studies indicate that metabolic acidosis can be a contributory factor to the development or exacerbation of bone disease in both adults and children and that it can impair growth in children with or without CKD. Direct effects of an acidic milieu on bone and indirect effects mediated by changes in PTH levels and/or its actions or vitamin D levels appear to contribute to these pathological effects [21].

Bone disease in CKD is mainly due to alterations in parathyroid hormone (PTH) and vitamin D levels. Certain toxins, such as aluminum may play a role [22]. However there is a substantial amount of data relating chronic metabolic acidosis as an additional important factor [23,24]. In vitro and in vivo studies have demonstrated that prolonged metabolic acidosis

can directly stimulate osteoclast-mediated bone resorption and inhibit osteoblast mediated bone formation [24-27]. Some animal and human studies have shown that metabolic acidosis can reduce vitamin D levels and stimulate PTH secretion. Metabolic acidosis also attenuates the cellular response to PTH, as measured by cAMP accumulation in rat tissues. The actions of the calcium sensing receptor might also be attenuated by a decrease in extracellular pH, perhaps contributing to an increase in PTH levels [21]. Chloride might also be related to higher PTH levels and worsening bone disease. Using Stewart´s physicochemical approach Liborio et al. [28] found a higher PTH levels in hemodialysis patients with higher chloride serum concentration and a significant relationship between chloride, PTH levels and serum markers of mineral bone disease.

In adult patients on chronic maintenance hemodialysis, amelioration of the acidosis by raising the dialysate base concentration was found to attenuate the rise in PTH, reduce bone resorption, and improve bone formation. In another study in dialysis patients, correction of the acidosis restored the normal suppression of PTH secretion in response to infused calcium [21]. Although controlled studies of the impact of correction of metabolic acidosis alone on the growth in children with CKD are not available, metabolic acidosis is considered to be a contributory factor to short stature in children with CKD prior to or after initiation of chronic maintenance dialysis. It´s recommended that it be corrected prior to the initiation of growth hormone therapy [29].

Data about chloride and SID changing in dialysis bath and bone disease outcomes are still lacking. New studies in dialysis population assessing the long term effect this measure might influence in the amelioration of bone disease must emerge.

6.2. Increased muscle wasting

Muscle wasting is increased in CKD. This is not only due nutritional deprivation or exposure to a uremic milieu. Metabolic acidosis in CKD stimulates muscle wasting and may impair growth in children [30].

The increased protein degradation was due to the increased transcription of genes encoding proteins of the ATP-dependent ubiquitin–proteasome pathway, resulting in increased activity of the ATP-dependent ubiquitin–proteasome system (UPS) [30]. Of interest, activation of muscle protein degradation requires endogenous glucorticoids [21]. Recent studies have identified the dependency on glucocorticoids to increase muscle protein wasting as a nongenomic mechanism by which the glucocorticoid receptor sequesters phosphatidylinositol-3-kinase to interrupt insulin–IGF-1 signaling [31]. Several conditions including CKD and metabolic acidosis appear to be related to the activation of the UPS. In several studies, amelioration of metabolic acidosis by the provision of base to patients with CKD before or after initiation of maintenance dialysis decreased the rate of protein degradation and urea generation, resulting in improved protein balance and increased muscle mass [30].

Similar to bone disease, some evidence suggests that a detectable fall in serum [HCO_3^-] may not be necessary to stimulate muscle degradation. [21]

6.3. Reduced albumin synthesis

Hypoalbuminemia is the most common marker of protein-energy wasting in dialysis patients and has strong association with increased morbidity and mortality. Hypoalbuminemia is associated with development and recurrent cardiac failure in hemodialysis patients [32].

Experimental induction of metabolic acidosis in normal humans for at least 7 days has in some studies caused a reduction in albumin synthesis, thereby predisposing the individual to the development of hypoalbuminemia [33,34]. Indeed, analysis of more than 1500 patients > 20 years of age who participated in the NHANES III study revealed that the age-adjusted odds ratio of serum $[HCO_3^-]$ for hypoalbuminemia rose from 1.0 for serum $[HCO_3^-]$ > 28 mEq/l to 1.54 for serum $[HCO_3^-]$ ≤22 mEq/l [35]. Furthermore, in two studies of adult patients with CKD either prior to or after initiation of chronic maintenance dialysis, improvement of the metabolic acidosis by the provision of base caused the serum albumin concentration to rise and protein catabolic rate to fall [36,37].

Reduced protein synthesis, increased protein breakdown, and enhanced amino acid oxidation have all been suggested as factors contributing to a reduced serum albumin concentration with metabolic acidosis. A decrease in protein intake might also play a role, although in one study in which dietary intake was examined, no difference in protein intake was found in patients with CKD before or after correction of the acidosis [21].

6.4. Accelerating the progression of CKD

Studies in humans have supported the potential role of metabolic acidosis in the progression of CKD. In a large cohort of patients with CKD followed at a single medical center, a serum $[HCO_3^-]$ of <22 mEq/l was associated with a 54% increased hazard of progression of CKD when compared with a serum $[HCO_3^-]$ of 25–26 mEq/L [38]. In two separate studies, one in patients with hypertensive renal disease [39]and another in patients with CKD of diverse etiology [40], the administration of base slowed the progression of CKD. In the latter study, the rate of decline in GFR in those given bicarbonate was less than half that in the control group. Moreover, the bicarbonate group was less likely to experience a rapid decline in GFR or develop end-stage renal disease [21].

Three mechanisms have been postulated to explain the acceleration of progression of CKD in response to metabolic acidosis. First, it has been suggested that the increase in renal medullary ammonia concentration resulting from the stimulation of ammonia production by metabolic acidosis activates the alternative complement pathway and causes progressive tubulointerstitial injury [41]. Second, it has been suggested that new bicarbonate synthesized by the kidney in response to acidosis alkalinizes the interstitium and encourages precipitation of calcium in the kidney [42]. Finally, evidence in both animals and humans has been accrued to suggest that increased endothelin production may mediate the tubulointerstitial injury and decline in GFR noted with the metabolic acidosis of CKD [43].

6.5. Impaired glucose homeostasis

Studies in patients with CKD demonstrated impaired glucose tolerance and insulin resistance, both prior to and after the initiation of chronic maintenance dialysis. The effect of uremia on insulin resistance appeared to be related, in part, to metabolic acidosis, because the administration of base to stable hemodialysis patients improved, although it did not normalize, insulin sensitivity. The insulin resistance and glucose intolerance of uremia per se are generally not severe, but it is possible that they contribute to the development of other clinical abnormalities [21].

6.6. Accumulation of β2-microglobulin

The accumulation of β2-microglobulin in individuals with CKD contributes to the development of amyloidosis. Amyloid infiltration can cause the carpal tunnel syndrome, bone cysts and, possibly, cardiomyopathy [44]. This accumulation of β2-microglobulin is primarily related to the number of years on dialysis, which has been interpreted as suggesting that the predilection to amyloidosis is due to reduced excretion of β2-microglobulin and, in the case of hemodialysis, also to chronic exposure of blood to the dialysis membrane [44].

Metabolic acidosis has been suggested as a possible additional factor in promoting β2-microglobulin accumulation. First, there is an inverse correlation between serum $[HCO_3^-]$ and β2-microglobulin levels in patients with CKD. Furthermore, β2-microglobulin concentrations have been found to be higher in patients dialyzed with acetate who have a lower serum $[HCO_3^-]$ than those dialyzed with bicarbonate [44].

6.7. Abnormal thyroid function

Individuals with uremia have low basal metabolic rates. This could be related in part to the associated metabolic acidosis affecting thyroid hormone levels, since ammonium chloride-induced metabolic acidosis has been found to be associated with reduced triiodothyronine (T3) and thyroxine (T4) and elevated thyroid-stimulating hormone levels [21]. Correction of metabolic acidosis in patients with CKD causes T3 levels to rise towards normal [45].

6.8. Stimulation of inflammation

Exposure of macrophages to an acidic environment leads to the increased production of tumor necrosis factor α (TNFα) [46]. In one study, the correction of metabolic acidosis in a small number of patients maintained on chronic ambulatory peritoneal dialysis was associated with a reduction in TNFα levels [21]. Thus, it has been suggested that metabolic acidosis is associated with the stimulation of inflammation and, therefore, that it represents a chronic inflammatory state. However, no significant difference was observed in the serum levels of C-reactive protein and interleukin-6 (two biomarkers of inflammation) among three separate groups of dialysis patients with a mean serum $[HCO_3^-]$ of 19.2, 24.4, and 27.5 mEq/L, respectively [47].

6.9. Development or exacerbation of cardiac disease and increase in mortality

Low serum bicarbonate level is related to higher mortality in CKD patients both prior [48] to and after initiation of chronic maintenance dialysis [21]. A retrospective analysis of laboratory data obtained from more than 12,000 hemodialysis patients showed an increased risk of death in patients with a serum $[HCO_3^-]$ <15–17 mEq/L [49]. Also, patients with CKD not on dialysis had a greater risk of death when their serum $[HCO_3^-]$ was <22 mEq/L [50]. Navaneethanet al. [48]found a higher mortality rate in the group of patients with lower serum bicarbonate ($[HCO_3^-]$ < 23 mEq/L) level in a trial of 41.445 stage 3 and 4 CKD patients. An interesting finding of this trial was that higher level ($[HCO_3^-]$ > 32 mEq/L) was also associated with poor outcome and higher mortality rate. The DOPPS study [51] showed better outcomes in maintenance hemodialysis patients with midweek bicarbonate serum level of 21,1 to 22 mEq/L. In this study both low ($[HCO_3^-]$ < 17 mEq/L) and higher (>24 mEq/L) were related to higher hospitalization and mortality rate. These data point to the importance of a strict control of metabolic acid base disturbances in CKD patients and the harmful effect of overcorrection of acidosis.

Cardiovascular disease is the most common cause of death in patients with CKD. There are strong evidence that inflammation plays an important role in the genesis and progression of atherosclerotic heart disease. As discussed earlier in this text acidosis is a chronic inflammatory state and it is reasonable to speculate that metabolic acidosis could be related to increased prevalence or severity of cardiovascular disease [21].

6.10. Renal replacement therapy and liver failure

Anticoagulation with heparin might be a problem in patients with increased bleeding risk specially critically ill patients and cirrhotic patients requiring continuous renal replacement therapy (CRRT). There is increasing evidence questioning the safety of heparin in such patients and there are accumulating data on a potential better alternative, regional anticoagulation with citrate. Sodium citrate administered before the filter inhibits the generation of thrombin. For anticoagulation the citrate dose is adjusted to blood flow to attain low ionized calcium (< 0,4 mmol/l) concentration in the filter, the lower the calcium concentration the higher the degree of anticoagulation. Citrate is partially removed by the filter and the remaining amount is metabolized in citric acid cycle predominantly in the liver. The chelated calcium is than released and the lost calcium is replaced after filter. The systemic coagulation is unaffected [52].

Buffer strength of citrate depends on the proportion of strong cations in the fluid counterbalancing citrate concentration. Assuming the citrate is completely metabolized, one micromole of trisodium citrate provides the buffer as 3 mmol sodium bicarbonate. The Stewart Concept provides an easier way to understand the buffering effect of citrate: after metabolized in the liver the remaining sodium increases serum SID. Increased SID produces alkalosis. Sodium citrate has a SID of zero until citrate is metabolized, so in conditions where citrate metabolism is grossly impaired, such as severe liver dysfunction the citrate alkalinizing effect might be compromised. Citrate accumulation decreases the SID leading to a metabolic acidosis [52]. For this reason anticoagulation free or low heparin regimens have been

used for patients with severe liver dysfunction requiring continuous renal replacement therapy. This strategy reduces bleeding risk however lowers the procedure efficiency and thefilter patency.

Recent studies have emerged showing protocol using sodium citrate as a safe alternative for anticoagulation even in patients with liver dysfunction. In a prospective randomized open label crossover trial of regional citrate anticoagulation vs. anticoagulation free liver dialysis by the Molecular Adsorbents Recirculating System (MARS) Meijers et al. [53] demonstrated that citrate anticoagulation significantly increased the likelihood of completed MARS treatment (P = 0,04), higher bilirubin reduction ratio when citrate was applied and improvement in systemic ph levels. In this study, systemic ionized calcium concentrations were significantly reduced during citrate anticoagulation but remained within a safe range even using standard protocol for extracorporeal calcium levels. There were no major adverse events in the citrate group. Other study in early post liver transplantation patients requiring CRRT showed efficacy and safety of regional citrate anticoagulation without severe decrease in calcium concentration and acidosis [54]. Another study applied anticoagulation with sodium citrate in patients with severely impaired liver dysfunction (mean Child-Pugh score: 10,5) under renal replacement therapy with sustained low efficiency dialysis (SLED) after repeated filter clotting (filter lifetime < 2h) under heparin free or low dose heparin therapy. The dialysis time with citrate anticoagulation was 17,3 h, filter lifetime increased to 23,3 h. No major bleeding episodes related to dialysis therapy were observed, total calcium, ionized calcium, calcium gap, electrolytes and base excess were maintained at stable levels during therapy and thereafter. There were no significant hypotensive episodes and norepinephrine dose was reduced during therapy. This protocol used lower citrate infusion rate with higher post-filter ionized calcium levels and absence of routine calcium supplementation at venous line and the use of high-flux dialyser for reducing the risk of accumulating calcium citrate complexes [55].

These data show increasing evidence that citrate might be used for anticoagulation even in patients with impaired liver function. However clinicians should be alert when using this strategy, measuring the citrate levels and use of high-flux dialyser must be applied for warranting safety of maintaining low citrate concentrations. Data showing safety of citrate regional anticoagulation and recommendation of its use in patients with liver impairment under CRRT are scarce and don´t warranty recommendation of its application for this modality of treatment.

7. Treatment of metabolic acidosis in hemodialysis patients

The standard recommendation for correction of metabolic acidosis in CKD patients is for reaching a bicarbonate level at least 22 mEq/L in dialytic and conservative management patients [5]. Reaching this level may be a challenging schedule [1,6,7]. Current dialysate base standards appear to be somewhat arbitrarily chosen. Standard concentrations of bicarbonate in dialysates (33–35 mEq/L) do not completely correct the acidosis [56].

Alkali therapy has been shown to retard the progression of CKD in patients with reduced GFR not in dialysis therapy [57]. Benefits of correcting this disturbance in hemodialysis patients have already been reported in this chapter.

Routine measuring bicarbonate serum levels and the application of one of the following strategies might be of utility for maintaining bicarbonate target concentration and improving outcomes.

7.1. Oral supplementation

In CKD patients in conservative management acidosis should be treated by administering base in the form of oral bicarbonate or organic anions that are metabolized to bicarbonate such as citrate. Once serum bicarbonate reaches the desired level, the amount of base administered can be reduced to the minimal necessary to maintain this level [21]. A Systematic review on treatment of metabolic acidosis in non-dialysis patients showed improvement in kidney function, which may afford a long term benefit in slowing the progression of CKD [57]. Papadoyannakis et al. [58]found that ingestion of sodium bicarbonate corrects metabolic acidosis and increases appetite and body mass of the end-stage renal failure patients.

In dialysis patients oral administration of calcium carbonate at a dosage of 3–6 g/daily raises pre-dialysis plasma bicarbonate [59]. Calcium carbonate induces positive nitrogen balance due to correction of metabolic acidosis. Furthermore, calcium carbonate serves as a phosphate binder [60]. Instead of ingestion of the bicarbonate, calcium salts of organic acids could also be used as phosphate binders, i.e. acetate, citrate, gluconate or ketogluterate, which all could be metabolized into bicarbonate [61].

7.2. Bicarbonate based dialysis solution

Whichever dialysis therapy is used, there is a similar need for correcting the acid-base balance. The most important tool for this aim is the buffer in the dialysis fluid. Bicarbonate dialysis achieves much better hemodialysis stability [62]. Based on clinical and experimental studies, different side effects of hemodialysis treatment have been attributed to acetate, such as nausea, vomiting, headache, muscle cramps, hypotension, hemodynamic instability and increased cytokine release [63,64]. In contrast to acetate dialysis, bicarbonate dialysis does not interfere with gluconeogenesis and lipid synthesis [65]. The buffer source in all modern versions of these therapies should be bicarbonate. Bicarbonate is a physiological buffer, therefore in bicarbonate dialysis, plasma bicarbonate concentration and blood pH progressively increase during the dialysis session[65].

7.3. Higher bicarbonate in dialysate

Rising bicarbonate level in dialysate is effective in correcting metabolic acidosis. This correction is associated with improvement in CKD related anorexia and influencing the nutritional status [6]. Choosing dialysate bicarbonate level might be challenging. Some observations confirmed that dialysate bicarbonate concentrations of 40 mEq/L appear safe and well tolerated [66,67]. Oettinger and Oliver [68] demonstrated that high-bicarbonate dialysate (42

mEq/L) corrects pre-dialysis acidosis in 75% of hemodialysis patients without causing progressive alkalemia, hypoxia, or hypercarbia and that pre-dialysis BUN, calcium, ionized calcium and phosphorus are unaffected by high-bicarbonate dialysate. Williams et al. [69] demonstrated that bicarbonate dialysate concentrations of 40 mEq/L were safe, well tolerated and produced better control of acidosis (significantly higher pre-dialysis arterial plasma pH values as pre-dialysis serum total CO_2), with an increase in triceps skinfold thickness, compared to a bicarbonate concentration of 30 mEq/L. The amount of base transferred to the patient during dialysis depends on the patient's needs. Agroyannis et al. [70] showed a significant correlation between interdialytic weight gain and the values of pre-hemodialysis blood pH and bicarbonate, suggesting an important role of the interdialytic weight gain on acid-base equilibrium of uremic patients undergoing hemodialysis.

There is no doubt that individualized bicarbonate concentration is necessary for hemodialysis patients. Therefore, the choice of dialysate bicarbonate concentration should also be predicted on the basis of the patient's determinants (hydrogen generation, bicarbonate distribution space) and technique-related factors (membrane permeability, ultrafiltration rate, blood and dialysate flow) [71]. This can be achieved by new dialysis machines and by bicarbonate profiling.

7.4. Changing SID – The physicochemical approach

The base supply by dialysis does not seem to represent the main mechanism for acid-base correction by dialysis. Using Stewart's physicochemical approach Liborio et al. [1], showed in that chloride might play a pivotal role in pathogenesis of metabolic acidosis in hemodialysis patients. Other study found a better correction in bicarbonate levels after dialysis with a chloride level of 107 mEq/L rather than 111 mEq/L [7]. Such correction in serum bicarbonate might be possible due to elevation in plasma SID by exposing plasma to higher SID in dialysis solution. However although not expected, correction of metabolic acidosis in this study was mainly due to reduction of unmeasured anions, represented in Stewart's model by SIG.

This unexpected reduction in unmeasured anions can be explained by Gibbs Donnan equilibrium. The reduction in serum chloride during the post-dialysis period can facilitate redistribution from the intracellular or interstitial compartment, this decrease in intracellular chloride can improve the intracellular capacity of buffering other negative charges, reducing plasma unmeasured anions. Another possible explanation may be found in the dialysate compartment. It has been suggested that a higher dialysate chloride concentration, through Gibbs-Donnan equilibrium across the dialyzer membrane, partially prevents an adequate clearance of unmeasured anions due to a charge effect, i.e., electric repulsion of a negative charge. Moreover, based on this principle, it is not possible to exclude that an improvement in bicarbonate diffusion might have been the result of using a lower dialysate chloride concentration [7].

Diet, intestine, bone and intermediate metabolism could play a pivotal role in the acid-base status of uremic patients. Probably, more attention needs to be paid to the possible noxious effect of overcorrection of acidosis. Rapid correction of acidosis by bicarbonate dialysis may cause drowsiness, unconsciousness, hypokalemia and cardiac arrhythmia [72].

8. Conclusion

Metabolic acidosis is a detrimental condition both for CKD patients on hemodialysis thera‐py or conservative management. Several adverse effects of maintenance of an acidic state come with the falling in GFR and developing and worsing of acidosis. Several strategies have been employed for correction of that disturbance as listed before, some need more re‐searches for finding consistent results of the benefits of such strategies. Stewart´s approach brought new perspectives for understanding and treating this disturbance. Studies validat‐ing changing SID, chloride or other components of the dialysate bath are still need.

Attention must be paid for the metabolic alkalosis in this population as a result of overcor‐rection or overtreatment of acidosis. This one brings deleterious effects like metabolic acido‐sis. How metabolic alkalosis impairs survival in CKD is still unknow, new researches are need in this field.

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