Metabolic Acidosis of Chronically Hemodialyzed Patients

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Key Words

Hemodialysis · Metabolic acidosis · Bicarbonate

Abstract

Metabolic acidosis is a condition that is commonly encountered in both chronic renal failure and in end-stage renal disease. Metabolic acidosis is associated with many adverse effects: negative nitrogen balance, increased protein decomposition, anorexia, fatigue, bone lesions, impaired function of the cardiovascular system, impaired function of the gastrointestinal system, hormonal disturbances, insulin resistance, hyperkalemia, altered gluconeogenesis and triglyceride metabolism, increased progression of chronic renal failure, and growth retardation in children. Even 'minor' degrees of metabolic acidosis are deleterious. Metabolic acidosis of end-stage renal patients could be successfully corrected with bicarbonate hemodialysis and with peroral bicarbonate-containing phosphate binders, i.e. calcium carbonate. Bicarbonate powder compared with bicarbonate solutions has some advantages and enables a stabile composition of electrolytes. 'High' dialysate bicarbonate (40–42 mmol/l) is a safe, well-tolerated and useful tool for better correction of the metabolic acidosis and must become a standard of hemodialysis treatment. Measured postdialysis blood bicarbonate concentration

should be obtained at least every month and correction of metabolic acidosis by maintaining serum bicarbonate ≥ 22 mmol/l should be a goal of the management of patients undergoing chronic hemodialysis.

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Renal Insufficiency and Metabolic Acidosis

Kidneys are among the main organs in the regulation of acid-base homeostasis [1]. Metabolic acidosis is a condition that is commonly encountered in both chronic renal failure and in end-stage renal disease. In mild chronic renal insufficiency, metabolic acidosis is due to reduced ability to resorb bicarbonate, to excrete ammonia, and to eliminate titratable acid excretion (hyperchloremic, normal anion gap acidosis). In a more severe renal insufficiency, organic and other conjugate anions of acids (nonvolatile acids) cannot be sufficiently excreted and elevated anion gap acidosis is seen [2].

Although the degree of acidosis could be quite variable among uremic patients, uremic acidosis is usually mild, but as it is sustained, this form of metabolic acidosis is associated with many adverse effects: negative nitrogen balance [3], increased protein decomposition [4], anorexia [5], fatigue, bone lesion (increased bone resorption and decreased bone formation [6], hypercalciuria [7], en-

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hancement of PTH secretion [8], hyperphosphatemia, reduced effect of 1 α -hydroxylase [9]), impaired function of the cardiovascular system (depression of myocardial contractility, sensitization to arrhythmias [10], arteriolar vasodilatation, peripheral vasoconstriction [11], increased pulmonary vascular resistance [12]), impaired function of the gastrointestinal system [13] (gastric atonia, nausea, vomiting), hormonal disturbances (increased catecholamines, aldosterone [14], renin, corticosteroids [15]), insulin resistance [16], hyperkalemia [17], gluconeogenesis cycle disorders [18], altered triglyceride metabolism [19], and increased progression of chronic renal failure [20]. Metabolic acidosis is associated with growth retardation in children. Conversely, the correction of acidosis in children with renal tubular acidosis or renal failure improves growth velocity [21]. Patients with diabetes and advanced renal failure may have a less severe metabolic acidosis because of a more efficient extrarenal generation of bicarbonate than end-stage renal failure patients without diabetes [22].

Uremic Acidosis and Malnutrition

One of the causes of malnutrition and chronic inflammation in dialysis patients is metabolic acidosis (due to amino acid and protein degradation). Malnutrition in chronic renal failure affects patient morbidity and mortality [23]. Serum albumin concentration and anion gap are two parameters that appear to be related to patient outcome [24]. Ballmer et al. [25] reported that chronic metabolic acidosis decreases the synthesis of serum albumin and induces a negative nitrogen balance in healthy subjects. Movilli et al. [26] found that correction of acidosis increases serum albumin concentration and concomitant decreases protein catabolic rate. Williams et al. [27] found that correction of acidosis in uremic patients can reduce muscle protein degradation and reduce urea generation rate. Metabolic acidosis in chronic renal failure induces loss of lean body mass while elimination of acidosis improved anthropometric indices. The mechanisms causing loss of lean body mass have been linked to: (1) acidosis-induced destruction of the essential, branched-chain amino acids (BCAA) – leucine, isoleucine and valine, which are important precursors for protein synthesis and constitute 18% of muscle protein, and (2) activation of the ATP-dependent ubiquitin – a proteasome system that degrades muscle protein [28]. Metabolic acidosis stimulates this ATP-ubiquitin-proteasome pathway [29]. In this pathway, protein destined for catabolism is joined to a

heat-shock protein known as ubiquitin, in an ATP-dependent reaction. The ubiquitin-labeled protein is then recognized by a multi-protein complex, the proteasome, which degrades the substrate protein and releases the ubiquitin. This process requires glucocorticoids. Price et al. [30] showed that metabolic acidosis increases gene activity as measured by higher levels of mRNA for ubiquitin. It is important to note that even modest degrees of metabolic acidosis stimulate activity of this pathway and can lead to progressive loss of lean body mass [31]. Metabolic acidosis also increases the oxidation of BCAA. England et al. [32] showed that in metabolic acidosis, a greater fraction of the branched-chain ketoacid dehydrogenase is present in the activated, dephosphorylated form. The enzyme activity to acidification requires glucocorticoids [33]. In uremic rats, acidosis-induced catabolism of BCAA is mostly due to stimulation of branched-chain ketoacid dehydrogenase [34].

Correction of acidosis decreases protein degradation and may improve the nutritional status of hemodialysis patients both by a reduction in protein catabolism and a reduced oxidation of BCAA. Kooman et al. [35] demonstrated increased levels of BCAA (valine, leucine and isoleucine) after bicarbonate supplementation (by dialysate and oral administration). Bergstrom et al. [36] observed correlation of intracellular valine and blood bicarbonate levels in chronic hemodialysis patients. Pickering et al. [37] demonstrated that correction of serum bicarbonate improves nutritional status due to down-regulation of BCAA degradation and muscle proteolysis via the ubiquitin-proteasome system. Lofberg et al. [38] observed an increase in intracellular levels of branched-chain amino acids in hemodialysis patients after correction of acidosis. Also, the insulin-like growth factor (IGF-1) response to growth hormone is decreased by metabolic acidosis [39].

Gao et al. [40] demonstrated that higher predialysis serum bicarbonate (predialysis total CO₂ concentration >19 mmol/l) significantly improves predialysis BUN, phosphorus, and uric acid concentrations. Graham et al. [41] demonstrated better leucine turnover with correction of acidosis. On the contrary, Uribarri et al. [42] could not demonstrate a correlation of serum total carbon dioxide level with nutritional parameters, such as serum creatinine and serum albumin levels. Kokot et al. [43] concluded that blood hydrogen ion concentration influences only moderately plasma leptin concentration in hemodialyzed patients.

Although available clinical data suggest that the catabolic effect of mild acidosis can be compensated by adequate nutrition and adequate dialysis, it would be desir-

able to aim at normalizing acid-base balance in combination with adequate nutritional intake and delivery of dialysis [44]. Further investigations are needed on the effect of modifying serum bicarbonate concentration on nutritional markers in hemodialysis patients. Lin et al. [45] suggest that metabolic acidosis, as a result of a higher protein intake, does not detrimentally affect nutritional status.

Insulin acts to modulate both glucose disposal and protein metabolism, and insulin resistance is a well-known feature of renal failure [46, 47]. Igarashi et al. [48] concluded that insulin binding in isolated rat adipocytes is reduced by up to 30% when exposed to an acid environment, and this also appeared to induce a postreceptor defect in insulin action. Furthermore, acidosis produces impairment of glucose metabolism due to reduced tissue sensitivity to insulin [49].

The treatment of metabolic acidosis decreases serum concentrations of triglycerides but has no effect on HDL and total cholesterol in patients with uremia on hemodialysis.

Uremic Acidosis and the Cardiovascular System

Acidosis may cause a depression in myocardial contractility and can predispose to the onset of arrhythmias. This negative inotropic effect seems to be related to a decrease in myocardial response to circulating catecholamines [10]. With metabolic acidosis, myocardial function declines and venoconstriction occurs [11]. Metabolic acidosis could also predispose to ventricular arrhythmias due to a decrease in sodium flux in ventricular myocytes [50].

Cardiopulmonary events can occur frequently during hemodialysis, and the frequency is dependent on the dialysate buffer used (acetate or bicarbonate) [51]. Cardiovascular instability is more frequent in patients undergoing acetate dialysis than bicarbonate dialysis. Noris et al. [52] demonstrated that nitric oxide (NO) and cytokines, released in excessive amounts during acetate dialysis, might contribute to hemodynamic instability. Low dialysate magnesium, potassium and bicarbonate may all favor intradialytic hypotension [53].

During bicarbonate hemodialysis, optimal correction of acid-base values resulted in symptom-free hemodialysis sessions with stable PaCO_2 in the normal range, cardiovascular stability, normal ventilation and higher oxygen consumption, decreased lactate production, absence

of EEG alterations and dialysis-induced symptoms. Additional bicarbonate administration (120–160 ml 8.4% NaHCO_3 solution over the venous line during hemodialysis) correcting the acid-base status guarantees normal PaCO_2 and facilitates a symptom-free hemodialysis in high-risk patients [54].

Ionized plasma calcium has the pivotal role for the regulation of blood pressure, and an increasing ionized plasma calcium level leads to an increased blood pressure [55]. The dialysate bicarbonate concentration has a significant influence on ionized plasma calcium. Leunissen et al. [55] demonstrated that shifting from the standard bicarbonate (35 mmol/l) to high bicarbonate (39.5 mmol/l) dialysate increased ionized plasma calcium and significantly decreased mean arterial pressure in hypertensive patients.

Uremic Acidosis and Renal Osteodystrophy

Metabolic acidosis adversely affects bone metabolism in patients with chronic renal failure. Lemann et al. [56] found that maintenance of homeostasis in acidosis relies upon mobilization of bone minerals and buffers, which results in a negative calcium balance. Metabolic acidosis also inhibits renal calcium reabsorption by the kidney, resulting in calciuria [57]. The net effect is loss of calcium from bone and results in bone demineralization, osteopenia and fractures. Metabolic acidosis contributes to renal osteodystrophy and together with hyperphosphatemia, hypocalcemia and altered vitamin D metabolism, may result in increased levels of intact parathyroid hormone (iPTH) and metastatic calcifications [58]. Some data provide evidence for reduced bone mineral content and osteomalacic lesions in uremic patients with severe acidosis [59]. Studies have shown that an acidic medium increases osteoclastic activity and inhibits osteoblastic activity [60, 61]. Correction of metabolic acidosis improves osteoblast function (measured as serum concentration of procollagen type I carboxyterminal propeptide) [62]. Movilli et al. [63] demonstrated that the correction of metabolic acidosis in chronic hemodialysis patients reduces iPTH concentrations and symptoms of secondary hyperparathyroidism, possibly by a direct effect on iPTH secretion. Correction of acidosis also increases sensitivity of the parathyroid glands to calcium [64] and may increase bone formation in patients with low bone turnover [6].

Papadoyannakis et al. [65] found that ingestion of sodium bicarbonate corrects metabolic acidosis and increases appetite and body mass of the end-stage renal failure patients. Oral administration of calcium carbonate at a dosage of 3–6 g/daily raises predialysis plasma bicarbonate concentration and substitutes sodium bicarbonate without sodium hypervolemic effect [66]. Calcium carbonate induces positive nitrogen balance due to correction of metabolic acidosis. Furthermore, calcium carbonate serves as a phosphate binder [67]. Instead of ingestion of the bicarbonate, calcium salts of organic acids could also be used as phosphate binders, i.e. acetate, citrate, gluconate or ketoglutarate, which all could be metabolized into bicarbonate [68]. Additionally, ketoglutarate serves as inhibitor of degradation of some essential amino acids [69].

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 [70]. 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 [71, 72]. In contrast to acetate dialysis, bicarbonate dialysis does not interfere with gluconeogenesis and lipid synthesis [73]. The buffer source in all modern versions of these therapies should be bicarbonate. The buffer must be administered during dialysis to stimulate the bicarbonate regeneration process by the normal kidney, as well as the bicarbonate lost through the dialysis session. Bicarbonate is a physiological buffer, therefore in bicarbonate dialysis, plasma bicarbonate concentration and blood pH progressively increase during the dialysis session [73]. The target for acid-base correction in dialysis is to maintain patients within or as close to the physiological plasma bicarbonate range as possible. Current dialysate base standards appear to be somewhat arbitrarily chosen. Standard concentrations of bicarbonate in dialysates (33–35 mmol/l) do not completely correct the acidosis [74]. Some observations confirmed that dialysate bicarbonate concentrations of 40 mmol/l appear safe and well tolerated [75, 76]. Oettinger and Oliver [77] demonstrated that high-bicarbonate dialysate (42 mmol/l) corrects predialysis acidosis in 75% of hemodialysis patients without causing progressive alkalemia, hypoxia, or hypercarbia and that predialysis BUN, calcium, ionized calcium and phosphorus are unaffected by high-bicarbonate dialysate. Williams et al. [78]

demonstrated that bicarbonate dialysate concentrations of 40 mmol/l were safe, well tolerated and produced better control of acidosis (significantly higher predialysis arterial plasma pH values as predialysis serum total CO₂), with an increase in triceps skinfold thickness, compared to a bicarbonate concentration of 30 mmol/l.

The amount of base transferred to the patient during dialysis depends on the patient's needs. Agroyannis et al. [79] showed a significant correlation between interdialytic weight gain and the values of prehemodialysis blood pH and bicarbonate, suggesting an important role of the interdialytic weight gain on acid-base equilibrium of uremic patients undergoing hemodialysis. Thus, patients with high interdialytic weight gains may require higher bicarbonate concentrations to achieve normal acid-base status whereas patients with low interdialytic weight gains may require lower bicarbonate concentrations to prevent alkalemia at the end of dialysis. In an observational study, hemodialysis patients using 35 mmol/l bicarbonate dialysate were studied over a 44-hour interdialytic interval and showed a slow linear decline in bicarbonate. The results from this study emphasize the importance of standardization of bicarbonate measurement in order to avoid spurious acidosis [80]. Nissenson et al. [81] found that in some of the dialysis patients a net loss of bicarbonate during dialysis occurred, in large part related to convective loss of bicarbonate in ultrafiltrated water. There is no doubt that individualized bicarbonate concentration is necessary for hemodialysis patients. Gotch et al. [82] suggested a single-pool mathematical model to forecast bicarbonate kinetics during dialysis. The model considered only bicarbonate diffusion from the dialysate to the blood, but did not take into account that the bicarbonate flux is influenced by the ultrafiltration rate. 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) [83]. This can be achieved by new dialysis machines and by bicarbonate profiling.

Furthermore, the base supply by dialysis does not seem to represent the main mechanism for acid-base correction by dialysis. Diet, intestine, bone and intermediate metabolism could play a pivotal role in the acid-base status of uremic patients [84]. 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 [85].

Bicarbonate solution is also an excellent growth medium for bacteria and an increased endotoxin level during the use of bicarbonate solution has also been reported [86]. These can be avoided by the use of online preparation of dialysis fluid from bicarbonate powder. Bicarbonate powder does not permit bacterial growth, and the dialysis fluid thus produced is a stable composition of electrolytes and buffer [87]. Severe acid-base disbalances during bicarbonate hemodialysis could also occur as the result of an error made in the selection of the dialysate concentrate [88]. Dialysis equipment should be fitted with online pH meters with alarm systems. Serum bicarbonate levels should be measured in chronically hemodialyzed patients once monthly [89].

Conclusion

The physician must monitor the patient's acid-base status and appreciate that even 'minor' degrees of metabolic acidosis are deleterious. Metabolic acidosis of end-stage renal patients could be successfully corrected with bicarbonate hemodialysis and with administration of bicarbonate-containing phosphate binders, i.e. calcium carbonate. Compared with bicarbonate solutions, bicarbonate powder has some advantages and enables a stable composition of electrolytes. High dialysate bicarbonate (40–42 mmol/l) is a safe, well-tolerated and useful tool for better correction of the metabolic acidosis. This 'high' dialysate concentration of bicarbonates must become a

standard in hemodialysis treatment, but an individualized bicarbonate concentration in dialysate is necessary for the hemodialysis patient to avoid postdialysis metabolic alkalosis. Net ultrafiltration, body mass, nutritional parameters, blood and dialysate flows, and blood pressure must be taken into consideration to set the dialysate concentration of bicarbonate. Profiled dialysis is a new conceptual approach to patient intradialytic vascular instability based on the continuous modulation of dialysis-operative parameters, such as dialysate sodium and ultrafiltration rate. Investigations have confirmed the clinical efficacy of profiled (sodium and ultrafiltration) dialysis in the prevention of dialysis intolerance episodes [90]. Despite the lack of any strong clinical evidence, the bicarbonate-profiling feature of the new dialysis machines could be useful to avoid abrupt correction of acidosis. The profile of the dialysate bicarbonate concentration should be a curve with an incremental and mild slope, to allow a slow increase of plasma bicarbonate concentration. In addition, dialysis machines should be fitted with online pH meters with alarm systems to avoid erroneous high bicarbonate concentration. Postdialysis blood bicarbonate concentration measurements should be obtained at least every month and correction of metabolic acidosis by maintaining serum bicarbonate ≥ 22 mmol/l should be a goal of the management of patients undergoing chronic hemodialysis [89]. More research is needed on the long-term effects of correcting acidemia on clinical outcomes of chronically hemodialyzed patients.

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