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Risks of chronic metabolic acidosis in patients with chronic kidney disease

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Risks of chronic metabolic acidosis in patients with chronic kidney disease. Metabolic acidosis is associated with chronic renal failure (CRF). Often, maintenance dialysis therapies are not able to reverse this condition. The major systemic consequences of chronic metabolic acidosis are increased protein catabolism, decreased protein synthesis, and a negative protein balance that improves after bicarbonate supplementation. Metabolic acidosis also induces insulin resistance and a decrease in the elevated serum leptin levels associated with CRF. These three factors may promote protein catabolism in maintenance dialysis patients. Available data suggest that metabolic acidosis is both catabolic and anti-anabolic. Several clinical studies have shown that correction of metabolic acidosis in maintenance dialysis patients is associated with modest improvements in nutritional status. Preliminary evidence indicates that metabolic acidosis may play a role in β2-microglobulin accumulation, as well as the hypertriglyceridemia seen in renal failure. Interventional studies for metabolic acidosis have yielded inconsistent results in CRF and maintenance hemodialysis patients. In chronic peritoneal dialysis patients, the mitigation of acidemia appears more consistently to improve nutritional status and reduce hospitalizations. Large-scale, prospective, randomized interventional studies are needed to ascertain the potential benefits of correcting acidemia in maintenance hemodialysis patients. To avoid adverse events, an aggressive management approach is necessary to correct metabolic acidosis. Clinicians should attempt to adhere to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines for maintenance dialysis patients. The guidelines recommend maintenance of serum bicarbonate levels at 22 mEq/L or greater.

METABOLIC ACIDOSIS

Severe chronic metabolic acidosis (i.e., the presence of excess hydrogen ions in blood) has two well-recognized major systemic consequences. First, metabolic acidosis, or acidemia, induces increased protein catabolism, decreased protein synthesis, and negative nitrogen and total body protein balance, which improve upon bicarbonate supplementation. Second, metabolic acidosis causes physicochemical dissolution of bone and cell-mediated bone resorption (inhibition of osteoblast and stimulation of osteoclast function).

To avoid a misdiagnosis of metabolic acidosis, it is important to handle blood specimens with utmost care. Underfilling of sample tubes may lead to evanescence of carbon dioxide, which results in falsely low values [1]. The transportation of blood specimens—particularly via air—to distant laboratories, could lead to loss of total CO2 and overestimation of the magnitude of acidosis. The mean CO2 level of shipped blood samples is 5 mEq/L lower than that of blood samples processed immediately [2]. Also, serum bicarbonate measurements may suggest an inaccurately increased bicarbonate level, because the total serum CO2 measurement usually overestimates the serum bicarbonate concentration. Thus, it is important to exercise caution when interpreting serum chemistry measurements that indicate metabolic acidosis in maintenance dialysis patients.

METABOLIC ACIDOSIS AND NUTRITION

In 1931, Lyon et al were the first investigators to suggest a potential link between metabolic acidosis and the nutritional status of patients with CRF (reviewed by
Mehrotra et al [3]). Additional literature has subsequently suggested that metabolic acidosis may play an important role in the pathogenesis of nutritional abnormalities associated with uremia. Increased protein catabolism, decreased protein synthesis, increased insulin resistance, inflammation, and reduced serum leptin levels are 5 potential mechanisms by which metabolic acidosis could contribute to these nutritional abnormalities.

**Catabolic effects: The ubiquitin-proteosome system**

Multiple studies suggest that metabolic acidosis could cause negative nitrogen balance in CRF patients, as well as in healthy individuals. Papadoyannakis et al measured nitrogen and potassium levels in 6 nondialyzed uremic individuals before and after supplementation with sodium chloride and sodium bicarbonate [4]. A significant decrease in blood urea nitrogen and a positive nitrogen and potassium balance were detected during bicarbonate supplementation (Fig. 1).

There are several studies that have investigated the effect of metabolic acidosis on protein metabolism [5–8], and all but one study [5] have shown that metabolic acidosis promotes proteolysis. In general, treatment to increase blood pH from acidemic levels to normal levels resulted in a decrease in protein degradation. Table 1 summarizes data from these studies, obtained from patients with varying stages of renal failure [5–8]. Researchers believe that metabolic acidosis promotes protein degradation by stimulation of the ubiquitin-proteosome system, through which proteins are generally targeted for digestion to peptides and amino acids. Acidemia causes an increase in gene transcription for the proteosome and increased ubiquitin synthesis. Increased activity of the proteolytic enzyme caspase-3 and the ATP-dependent ubiquitin-proteosome pathway has been implicated in mediating the catabolic effects of metabolic acidosis in CRF in both human and animal model systems [9]. For example, Bailey et al observed that in uremic rats metabolic acidemia is associated with increased protein degradation and amino acid oxidation. The mRNA for proteosome and ubiquitin in skeletal muscle cells was also found to be elevated. The addition of sodium bicarbonate to the diet of these animals resulted in a reversal of protein degradation [10].

Pickering et al made a similar observation in studies of muscle mRNA from patients with CRF. A significant decrease in ubiquitin mRNA abundance was seen after 4 weeks of bicarbonate treatment [11]. In addition, studies in isolated rat skeletal muscles exposed to an inhibitor of the proteosome, or depleted of ATP, in the presence of metabolic acidosis, have demonstrated that the increased protein degradation induced by metabolic acidemia was abolished. These observations indicate that the ubiquitin-proteosome pathway is an important mechanism for protein catabolism associated with metabolic acidemia.

**Catabolic effects: Branched-chain amino acids metabolism**

Branched-chain amino acids (BCAA) are often altered in pathologic conditions associated with metabolic acidosis. Studies in rats, as well as in isolated skeletal muscle cells, have shown that acidosis stimulates the breakdown of BCAA. Metabolic acidosis increases the gene transcription for an enzyme called branched chain keto-acid dehydrogenase (BCKAD). This enzyme degrades 3 essential branched chain amino acids: leucine, isoleucine, and valine [12].

Lower levels of plasma and muscle BCAA are reported in patients undergoing maintenance dialysis therapy, as well as in animal models of metabolic acidosis [13, 14]. Correction of metabolic acidosis in patients on maintenance hemodialysis results in an increase in the plasma BCAA levels, as seen in Figure 2 [14]. These observations suggest that patients suffering from CRF associated with metabolic acidosis experience increased activity of BCKAD, which causes increased catabolism of BCAA. Thus, increased activity of caspase-3, the ATP-dependent ubiquitin-proteosome and BCKAD appears to contribute significantly to the negative nitrogen balance observed in uremic patients with metabolic acidemia.

**Anti-anabolic effects of metabolic acidosis**

Metabolic acidosis possibly may decrease protein synthesis and produce anti-anabolic effects. Cell culture studies of myocytes in an acidic medium have shown reduced protein synthesis, and some studies of metabolic acidosis in humans demonstrate analogous results. Induction of metabolic acidosis in normal individuals with ammonium
**Table 1.** Improvement in metabolic acidosis and protein turnover: Summary of controlled studies in CRF patients

<table>
<thead>
<tr>
<th>First author</th>
<th>No. of subjects</th>
<th>Stage of renal failure</th>
<th>Baseline pH</th>
<th>Final pH</th>
<th>Protein synthesis</th>
<th>Protein degradation</th>
<th>Amino acid oxidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaich [6]</td>
<td>9</td>
<td>Nondialyzed</td>
<td>7.31</td>
<td>7.38</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Graham [7]</td>
<td>7</td>
<td>CPD</td>
<td>7.39</td>
<td>7.41</td>
<td>Decreased</td>
<td>Decreased</td>
<td>No change</td>
</tr>
<tr>
<td>Graham [8]</td>
<td>6</td>
<td>MHD</td>
<td>7.36</td>
<td>7.4</td>
<td>Decreased</td>
<td>Decreased</td>
<td>No change</td>
</tr>
<tr>
<td>Lim [5]</td>
<td>8</td>
<td>Nondialyzed</td>
<td>7.29</td>
<td>7.39</td>
<td>No change</td>
<td>No change</td>
<td>Increased</td>
</tr>
</tbody>
</table>

Abbreviations: CPD, chronic peritoneal dialysis; MHD, maintenance hemodialysis.

chloride caused a significant reduction in the fractional synthetic rate of muscle protein, while the fractional and absolute rate of albumin synthesis remained unchanged [15]. Conversely, in another study, chronic ammonium chloride-induced metabolic acidosis was reported to significantly reduce the fractional synthetic rate of albumin [16]. In light of these conflicting findings, the applicability of these observations to metabolic acidosis in CRF is uncertain, and additional data are needed to determine the effects of metabolic acidosis associated with CRF on protein synthesis. Figure 3 summarizes the mechanisms by which metabolic acidosis could induce protein energy malnutrition [3].

The anti-anabolic effects of ammonium chloride-induced metabolic acidosis could arise from possible alterations in 1 or more of 4 hormonal systems. First, metabolic acidosis could reduce the release of growth hormone. Experimental data suggest that peripheral resistance to growth hormone could result from metabolic acidosis. Second, metabolic acidemia may induce insulin resistance (see below). Third, in both human subjects and animal studies, plasma levels of insulin-like growth factor (IGF) and the hepatic content of IGF-1 mRNA, are significantly reduced in metabolic acidosis. Fourth, the anabolic effects of thyroid hormone and the reduced thyroid function induced by metabolic acidosis could contribute to decreased synthesis of muscle protein.

A modest, though significant, increase in the levels of thyroid-stimulating hormone has been reported in acute metabolic acidosis, without any change in the levels of free triiodothyronine (T3). Chronic acidosis in human subjects, however, is associated with significantly reduced T3 levels, with no change in the levels of thyroid-stimulating hormone. Additional studies are required to determine the relative contributions of these hormonal systems to the altered anabolic and catabolic pathways in CRF (reviewed by Mehrotra et al in [3]). In sum, these data suggest that metabolic acidosis has both catabolic and anti-anabolic effects on nutritional status of patients with CRF. Figure 3 summarizes the catabolic and anti-anabolic effects of metabolic acidosis.

**Hormonal triggers in metabolic acidosis**

Despite recent progress made in understanding the molecular mechanisms of proteolysis in the setting of metabolic acidosis, other triggers that activate these pathways are not fully understood.

**Cortisol**

Ammonium chloride-induced metabolic acidosis in adrenalectomized rats does not cause induction of protein degradation, or an increase in the gene expression of BCKAD or its activity, and does not lead to increases in mRNA for the ubiquitin-proteosome system in muscle. Additionally, in rats with acidic experimental renal failure, the urinary excretion of corticosterone was significantly elevated when compared with control animals. These observations implicate glucocorticoids as a major factor necessary for the induction of the catabolic pathways in metabolic acidosis. A direct, positive correlation of muscle protein degradation with plasma levels of cortisol, and a negative correlation with serum bicarbonate levels, suggests that a combination of acidosis and glucocorticoids may be needed to stimulate muscle protein degradation. However, other investigators have not been able to demonstrate increased concentrations of cortisol in the setting of chronic metabolic acidosis (reviewed by Mehrotra et al in [3]). Hence, the involvement of corticosteroids in stimulating skeletal muscle protein degradation needs further investigation.

**Insulin resistance**

It has been suggested that insulin resistance, a complication of CRF, plays a role in the activation of the
Metabolic acidemia

- ↑ Activity of branched chain ketoacid dehydrogenase
- ↑ Activity of caspase-3 and the ATP-dependent ubiquitin proteasome system

Increased muscle breakdown
Decreased muscle protein synthesis
Decreased albumin synthesis

Protein-energy malnutrition

Insulin resistance

Inflammation

Reduced serum leptin

? Protective effect

Fig. 3. Mechanisms by which metabolic acidosis may induce protein energy malnutrition. (From [3]).

Leptin

Leptin, a protein encoded by the obese (ob) gene, is involved with food intake, energy expenditure, and body weight. It has been studied as a potential mediator of protein energy malnutrition. Circulating leptin is partly cleared by the kidney, and is reported to increase 3-fold in individuals with CRF compared with healthy controls with similar body mass index [18]. Metabolic acidosis and hyperleptinemia are 2 common clinical findings in patients with CRF. In animal studies, decreased leptin secretion has been observed in adipocytes exposed to relatively acidic environments (pH 7.1). Sodium bicarbonate treatment of rats with renal failure showed significantly reduced leptin levels, compared with untreated rats. Plasma leptin concentrations were also lower in patients with diabetic ketoacidosis compared with healthy individuals. Initiation of insulin therapy resulted in increased leptin levels [19]. However, Kokot et al were unable to demonstrate a correlation between blood hydrogen concentrations and serum leptin levels in a cross-sectional study of 94 patients on maintenance hemodialysis [20]. The study did, however, reveal a trend toward progressively lower median leptin concentrations with progressively higher blood hydrogen concentrations. Because increased serum leptin levels are associated with weight loss, a decrease in serum leptin levels could adaptively ameliorate the catabolic effects of metabolic acidosis.

INFLAMMATION AND METABOLIC ACIDOSIS

Emerging evidence suggests that metabolic acidosis may induce chronic inflammation (reviewed by Mehrotra et al [3]). Increased production of a key inflammatory cytokine—tumor necrosis factor α (TNFα)—by peritoneal macrophages incubated in an acidic cell culture medium suggests a potential link between the inflammatory process and metabolic acidosis. Two recent studies have analyzed the link between metabolic acidosis and inflammation. In the first study, markers of inflammation, serum C-reactive protein (CRP) and interleukin-6 (IL-6), were evaluated in maintenance hemodialysis patients. No significant difference in serum levels of CRP or IL-6 was seen in 3 groups of patients subdivided on the basis of their serum CO2 levels [21]. In the second study, correction of metabolic acidosis in 8 chronic peritoneal dialysis patients was associated with significantly reduced levels of TNFα [11]. It is important to mention that the acidic pH in these studies is 7.39 and the alkaline pH is 7.42, and metabolic changes are seen within...
FIG. 4. The various mechanisms by which metabolic acidosis may contribute to bone disease. (From [3]).

this narrow pH range. These observations raise an important question as to whether there is an optimal pH for maintaining healthy nutritional status. In various studies, an increase in the pH from 7.23 to 7.7 of the cell culture medium results in a progressive increase in the rate of protein synthesis. Interestingly, at increased pH levels (pH >7.4), protein synthesis by skeletal muscles is enhanced, possibly suggesting an increased pH to be optimal for anabolism.

METABOLIC ACIDOSIS AND BONE DISEASE

Metabolic acidosis exerts multiple effects on bone. It causes the physicochemical dissolution of bone and cell-mediated bone resorption through the inhibition of osteoblast activity and stimulation of osteoclast function. These events are associated with a loss of calcium and phosphorus from the bone. Metabolic acidosis stimulates osteoblasts to release prostaglandins. This stimulates osteoclast function and inhibits osteoblast activity. Glucocorticoids can inhibit the production of prostaglandins by osteoblasts.

Metabolic acidosis is also associated with a decrease in the content of bone bicarbonate. Additionally, bicarbonate supplementation in postmenopausal women is associated with decreases in urinary calcium, phosphorus, and increased osteocalcin levels, indicating a beneficial effect. Figure 4 shows the mechanisms relating metabolic acidosis with bone disease [3]. These observations suggest that uncorrected metabolic acidosis has adverse consequences on bone anatomy and physiology.

METABOLIC ACIDOSIS AND SECONDARY HYPERPARATHYROIDISM

Metabolic acidosis is probably also associated with worsening of secondary hyperparathyroidism. Metabolic acidosis may decrease the sensitivity of PTH secretion to elevated ionized calcium [22]. The effect of metabolic acidemia on serum PTH level is rather variable [23]. On the other hand, Lefebvre et al studied the role of acidosis on hemodialysis osteodystrophy in a group of 21 patients dialyzed with varying amounts of HCO₃ over an 18-month interval [24]. These data show no increase in serum PTH levels in patients treated with higher dialysate bicarbonate. However, serum PTH levels increased significantly in patients with persistent metabolic acidosis who were treated with standard dialysate bicarbonate. Additionally, other investigators report a decrease in serum PTH levels after correcting metabolic acidosis in maintenance hemodialysis patients.

The combination of metabolic acidemia and elevated serum levels of parathyroid hormone, such as is found in patients with CRF, leads to a far greater efflux of Ca compared with either metabolic acidemia or hyperparathyroidism alone (reviewed in Bushinsky and Frick [25] and Bushinsky and Nilsson [26]). Correction of metabolic acidemia improves bone mineralization and histology in maintenance hemodialysis patients. Thus, the available data suggest that metabolic acidosis may lead to worsening of secondary hyperparathyroidism. Metabolic acidemia also reduces 1-α-hydroxylase activity in renal tubules of rats, but the effects on serum levels of 1,25-dihydroxycholecalciferol, the metabolic product of this enzyme, are more difficult to ascertain [3, 27].

OTHER CLINICAL AND METABOLIC ALTERATIONS OF METABOLIC ACIDOSIS

Preliminary evidence also suggests that metabolic acidosis, in addition to its effects on protein and bone metabolism, may play a role in the accumulation of β-2 microglobulin, hypertriglyceridemia, malaise,
hypotension, and in the resistance to catecholamines [28, 29]. The small subunit of the MHC class I molecule, β-2 microglobulin, is located on the cell membrane of many cells, including lymphocytes. Small amounts of β-2 microglobulin are found in serum, plasma, and urine of normal individuals, while elevated levels are often seen in the plasma and urine of patients with renal failure and kidney transplants. Studies using cell cultures as well as CRF patients have shown increased mRNA, as well as serum levels of β-2 microglobulin (reviewed by Mehrotra et al in [3]).

NATIONAL KIDNEY FOUNDATION KIDNEY DISEASE OUTCOME QUALITY INITIATIVE GUIDELINES FOR NUTRITION IN PATIENTS WITH CRF

The K/DQOI has developed guidelines for patients with CRF. One is the monthly measuring of serum bicarbonate levels in maintenance dialysis patients. It is recommended that the predialysis or stabilized serum bicarbonate should be maintained at ≥22 mEq/L in these individuals [30]. In patients with chronic kidney disease, stages 3, 4, and 5, the serum levels of total CO₂ also should be maintained at ≥22 mEq/L [31]. To achieve this goal, supplemental alkali should be given as required.

CONCLUSION

Uncorrected metabolic acidosis is detrimental to the nutritional status, may aggravate bone disease and, thus, may impact the overall health of maintenance hemodialysis patients. A small, persistent decrease in the rate of protein synthesis, or increase in protein degradation, could result in a substantial loss of muscle mass and development of more severe chronic bone disease, such as that seen in patients with CRF and end-stage kidney disease. The caspase-3, ubiquitin-proteasome system targets proteins for degradation and may contribute to protein catabolism and negative protein balance in CRF. However, additional catabolic signals may contribute to this process. New information that identifies mechanisms involved in the complex pathways of protein catabolism is crucial with regard to developing new therapies to prevent the loss of muscle mass in CRF. Based on currently available data, clinicians should adhere to the K/DQOI guidelines for maintenance dialysis patients and maintain predialysis bicarbonate concentrations ≥22 mEq/L. Large-scale, prospective, randomized interventional studies are needed to ascertain the potential benefits of correcting acidemia in both maintenance hemodialysis and chronic peritoneal dialysis patients. An aggressive approach to correcting metabolic acidosis seems indicated to help to prevent the multiple adverse consequences of this condition.

REFERENCES


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