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Metabolic Acidosis and Malnutrition-Inflammation Complex Syndrome in Chronic Renal Failure

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ABSTRACT

Metabolic acidosis, a common condition in patients with renal failure, may be linked to protein-energy malnutrition (PEM) and inflammation, together also known as malnutrition-inflammation complex syndrome (MICS). Methods of serum bicarbonate measurement may misrepresent the true bicarbonate level, since the total serum carbon dioxide measurement usually overestimates the serum bicarbonate concentration. Moreover, the air transportation of blood samples to distant laboratories may lead to erroneous readings. In patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD), a significant number of endocrine, musculoskeletal, and metabolic abnormalities are believed to result from acidemia. Metabolic acidosis may be related to PEM and MICS due to an increased protein catabolism, decreased protein synthesis, endocrine abnormalities including insulin resistance, decreased serum leptin level, and inflammation among individuals with renal failure. Evidence suggests that the catabolic effects of metabolic acidosis may result from an increased activity of the adenosine triphosphate (ATP)-dependent

ubiquitin-proteasome and branched-chain keto acid dehydrogenase. In contrast to the metabolic studies, many epidemiologic studies in maintenance dialysis patients have indicated a paradoxically inverse association between mildly decreased serum bicarbonate and improved markers of protein-energy nutritional state. Hence metabolic acidosis may be considered as yet another element of the reverse epidemiology in ESRD patients. Interventional studies have yielded inconsistent results in CKD and ESRD patients, although in peritoneal dialysis patients, mitigating acidemia appears to more consistently improve nutritional status and reduce hospitalizations. Large-scale, prospective randomized interventional studies are needed to ascertain the potential benefits of correcting acidemia in malnourished and/or inflamed CKD and maintenance hemodialysis patients. Until then, all attempts should be made to adhere to the National Kidney Foundation Kidney Disease and Dialysis Outcome Quality Initiative guidelines to maintain a serum bicarbonate level in ESRD patients of at least 22 mEq/L.

Metabolic acidosis is quite common in patients with chronic renal insufficiency (CRI), including those with chronic kidney disease (CKD), classes 3–5, and end-stage renal disease (ESRD). Acidemia is believed to be an important cause of morbidity and many adverse consequences in CRI and ESRD patients (1). Protein-energy malnutrition (PEM), another common condition and a risk factor for poor outcome in renal failure, may be related to acidemia (2,3). Recent data indicate that a chronic state of inflammation is frequently observed in renal failure and may be a cause of both PEM and an increased rate of cardiovascular and atherosclerotic disease in this population. Some investigators believe that the malnutrition-inflammation complex is the strongest predictor of mortality and poor outcome in maintenance dialysis patients, even stronger than the conventional risk

factors (4). Hence a better understanding of factors that engender PEM and inflammation would be of great importance for improving outcomes in CKD and ESRD patients. Whether metabolic acidosis is an important cause of PEM and inflammation, together also known as malnutrition-inflammation complex syndrome (MICS) (4), in CKD and ESRD patients is not completely clear. This article reviews the literature that explores this matter. In order to better understand such associations, a basic knowledge of acid-base homeostasis in health and disease is required. This is reviewed briefly at the beginning of this article.

Hydrogen Ion Homeostasis

Normal hydrogen ion (proton) concentration in body fluid is maintained at a concentration of 40 nEq/L (or nmol/L). The negative value of the logarithm of 0.000,000,040 is 7.398, which is the pH of the blood. Arterial blood is usually used for standard pH measurements. The use of pH in lieu of hydrogen ion concentration, although a convenient way to handle a very small

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TABLE 1. Hydrogen ion concentrations in different pH values

pH	H ⁺ concentration (nEq/L)	Acid-base status
7.50	32	Alkalemia
7.40	40	Normal
7.30	50	Acidemia
7.20	63	Acidemia
7.10	80	Acidemia
7.00	100	Acidemia
6.90	125	Acidemia

number, may be misleading, since it does not clearly describe the extent to which H⁺ concentration changes under different pH values. For instance, even though a pH of 7.10 is unequivocally recognized as severe acidemia, many clinicians may not be aware that H⁺ concentration is twice normal, that is, it has increased from 40 nEq/L to 80 nEq/L at this pH level (see Table 1).

Daily acid production varies under different conditions and usually ranges between 50 and 70 mEq/day in healthy individuals (5,6). As a rule of thumb, 1 mEq of H⁺ is produced per kilogram of body weight per day, and each gram of dietary protein intake leads to 1 mEq of H⁺ generation (5,6). Each milliequivalent is one million nanoequivalents. Hence the amount of daily acid production is enormous compared to the minuscule amount of H⁺ concentration in the extracellular fluids (40 nEq/L). The sources of acid production include loss of bicarbonate from the lower gastrointestinal tract (20–30 mEq/day); breakdown of proteins, amino acids, and nucleic acids from dietary sources (20–30 mEq/day); and oxidation of carbohydrates and fats primarily in muscle cells, leading to the production of lactic acid and keto acids, respectively (10–20 mEq/day). The former mechanism can increase greatly in hypercatabolic states, whereas the latter increases under anaerobic conditions or insulin deficiency (5).

The calculated gap between the measured cations and anions, also known as the anion gap (the concentration of sodium minus the sum of concentrations of chloride and bicarbonate), normally is a reflection of negatively charged plasma proteins such as albumin. However, the anion gap can be substantially increased if the concentration of inorganic anions, such as lactate or phosphate, is increased. The magnitude of the increase in the anion gap has been used as a surrogate measure of the severity of nonhyperchloremic metabolic acidosis. Moreover, a relative increase in serum anion gap in malnourished or inflamed patients subsequent to nutritional support may be due to an increased serum albumin, and hence a favorable sign (see below).

Serum bicarbonate constitutes the main buffering system for an acute increase in H⁺ concentration. Intracellular proteins such as hemoglobin also play a major role in buffering up to 50% of the acid load. However, in chronic acidosis, bone plays a major role (see below) (7). The serum bicarbonate concentration in the body fluid is approximately 24 mEq/L. The generated H⁺ can thus be buffered by body fluid bicarbonate according to the following equation, facilitated by the ubiquitous enzyme carbonic anhydrase:



In the steady state, the product of the concentrations of one side equals the product of concentrations of the other side: $[\text{H}^+] \times [\text{HCO}_3^-] = [\text{H}_2\text{CO}_3]$. Since H₂CO₃ is difficult to measure, this equation is transformed into $[\text{H}^+] \times [\text{HCO}_3^-] = 24 \times \text{P}_{\text{CO}_2}$. The number 24 is a constant factor when the partial pressure of CO₂ (P_{CO₂}) is measured. The above equation can be converted into the Henderson equation (5):

$$[\text{H}^+] = 24 \times \text{P}_{\text{CO}_2} / [\text{HCO}_3^-].$$

The P_{CO₂} in the blood is essentially a function of respiration. Therefore the numerator of the Henderson equation represents the lung function. On the other hand, the denominator is a function of the kidney, which controls serum bicarbonate handling. While blood gas analyzers use the above equations to calculate serum bicarbonate based on measured hydrogen ion concentration and P_{CO₂} in the blood, the chemistry analyzers convert bicarbonate into CO₂ and measure the “total” CO₂, which is 1–2 mEq/L (= 0.03 × P_{CO₂}) higher than the real serum bicarbonate level. Unless expressed otherwise, in this manuscript serum bicarbonate is used for measured total CO₂.

Two factors may distort the measurement of total CO₂ levels: underfilling of sample tubes, since evanescence of CO₂ may result in falsely low measurements (8); and shipping of blood samples by air to laboratories several hundred miles away, a standard practice of major dialysis care providers. The latter may be associated with a spurious metabolic acidosis, since the mean total CO₂ content of such blood samples is up to 5 mEq/L lower than samples that undergo more immediate processing (9,10). It is also possible that changes in atmospheric pressure in the pressurized airliner cabin or in the cargo hold lead to the escape of CO₂ from the tube (11). Indeed, if the sample is stored either at room temperature or refrigerated for 24 hours, without air transport, the change in total CO₂ is only 1 mEq/L (9,12).

The buffering system is an efficient, but self-limited mechanism for controlling acid accumulation, and the daily generated H⁺ must eventually be excreted from the body. The kidney is the main organ of excretion of this huge amount of acid load (i.e., 50–70 mEq/day). Moreover, the bicarbonate used for the buffering process is also regenerated in the kidneys. The renal mechanisms responsible for acid excretion and bicarbonate generation include 1) reclamation of filtered bicarbonate to overcome the loss of bicarbonate during glomerular filtration by means of H⁺ reabsorption in the proximal tubules; 2) excretion of net acid in the medullary collecting ducts via proton pumps in the apical membrane (aldosterone responsive); 3) excretion of acid buffers such as phosphate, creatinine, and many other compounds; and 4) ammoniogenesis, which is by far the most efficient acid elimination and excretion system. The kidneys make approximately 40 mEq of ammonia (NH₃) per day, which can be increased several-fold, if needed. The NH₃ is generated by deamidization of glutamine in the proximal tubule and is titrated to ammonium (NH₄⁺) in

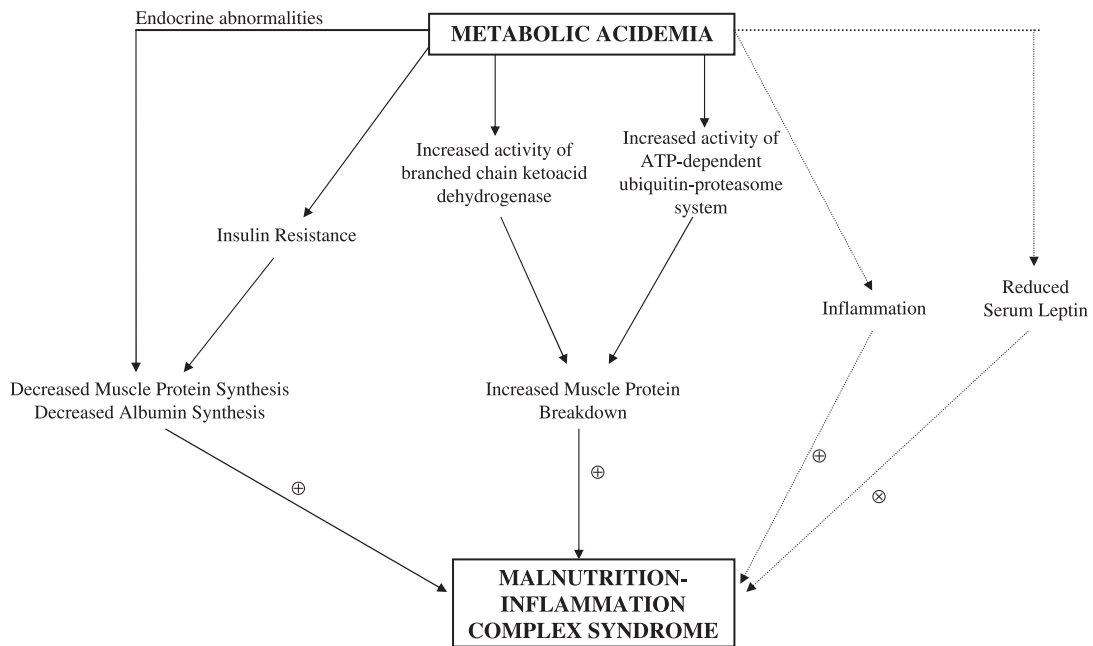


FIG. 1. The mechanisms by which metabolic acidemia is related to the malnutrition-inflammation complex syndrome. Dotted lines indicate that the data supporting the role of these pathways are less well documented at this time. (Adapted with permission from Mehrotra M, Kopple JD, Wolfson M. Metabolic acidosis in maintenance dialysis patients: clinical considerations. *Kidney Int Suppl* 88:S13–S26, 2003.)

the collecting ducts (5,6). The NH_4^+ generation mitigates the otherwise acidic pH of the urine by buffering H^+ (acid) into NH_4^+ (base).

Metabolic Acidosis in Renal Failure

Based on the above comments, it is clear that hydrogen ion homeostasis is significantly deranged in CKD patients and that metabolic acidosis almost invariably occurs in these individuals. Although compensatory mechanisms to mitigate the acute metabolic acidosis are normally fairly effective, the body has less tolerance for chronic metabolic acidosis in CRI and ESRD. The severity of metabolic acidosis varies widely in patients with renal failure (12,13). For instance, diabetic patients with CKD or ESRD may have less severe metabolic acidosis than their nondiabetic counterparts (14,15). Metabolic acidemia interferes with a number of important functions in renal failure patients and intensifies endocrine and musculoskeletal disorders (16). Several mechanisms have been suggested that link metabolic acidosis and PEM in renal failure (see Fig. 1 and below).

Endocrine abnormalities are common in CKD-associated metabolic acidosis. Both acidemia and renal failure are associated with an increase in circulating adrenocorticotropic hormone (ACTH) (17), leading to increased production of glucocorticoids and mineralocorticoids. Both of these hormones increase renal acid excretion in the distal nephron (18,19). Acidemia may also have a direct effect on the adrenal gland to stimulate the release of aldosterone. The uremia and acidosis-associated stimulation of glucocorticoid production is an important factor in abnormalities of protein metabolism (20). Aldosterone release, however, may be detrimental, since spironolac-

tone, an aldosterone receptor blocker, improves survival in patients with congestive heart failure and fluid overload, a condition that occurs frequently in renal failure (21). Similarly the favorable effect of spironolactone in slowing the rate of progression of CKD suggests that the acid-induced increase in aldosterone may be detrimental in these patients (22). Acidosis also interferes with the effect of insulin and insulin-like growth factor (IGF)-I on cellular signaling and may induce insulin resistance in peripheral tissues (23). The density of IGF-I receptors in muscle cells may be reduced in acidemia (24–26). Acidosis stimulates the release of parathyroid hormone (PTH) in patients with CKD or ESRD due to its direct effect on the parathyroid gland, independent of phosphate excretion or vitamin D production abnormalities (27–29). Finally, acidosis lowers serum levels of free T3 and T4, but unlike uremia, it may raise reverse T3 slightly (30–32).

Musculoskeletal abnormalities of uremia are accentuated with chronic metabolic acidosis. The chronic buffering of acid by bone leads to a loss of bone mineral and may worsen renal osteodystrophy (7,27). Bone buffers acid directly because of hydrogen ion exchange with sodium and potassium and degradation of carbonate in bone minerals (33). Moreover, the chronic state of metabolic acidosis stimulates osteoclasts and suppresses osteoblasts (34). Thus acidosis contributes directly to negative calcium balance. Indeed, correction of acidosis has been shown to improve bone mineralization and histology in maintenance hemodialysis (MHD) patients (35). Other consequences of metabolic acidosis, especially more severe acidemia, include malaise, weakness, hypotension, resistance to catecholamines, increased generation and release of β_2 -microglobulin, and hypertriglyceridemia (see Table 2).

TABLE 2. Clinical and metabolic alterations related to metabolic acidosis in CKD and ESRD patients

Endocrine alterations:
Increased ACTH and adrenal gland stimulation
Increased glucocorticoids
Increased mineralocorticoids
Insulin resistance
Decreased release of growth hormone
Reduced IGF-I receptors in muscle cells
Increased PTH release
Decreased free T3 and T4 and increased reverse T3
Musculoskeletal abnormalities
Bone buffering: H ⁺ exchange with Na ⁺ and K ⁺
Stimulation of osteoblasts
Suppression of osteoclasts
Increased PTH release
Protein-energy malnutrition
Hypercatabolism (increased proteolysis)
Negative nitrogen balance
Increased activity of the ATP-dependent ubiquitin-proteasome
Increased activity of branched-chain keto acid dehydrogenase
Antianabolism
Reduction in protein synthesis
Decreased release of growth hormone
Insulin resistance
Decreased serum leptin
Inflammation
Increased intake of acidosis inducing phosphate binders
Other clinical and metabolic alterations
Malaise
Hypotension
Resistance to catecholamines
Increased generation and release of β_2 -microglobulin
Hypertriglyceridemia

Metabolic Acidosis and Malnutrition-Inflammation Complex in Dialysis Patients

End-stage renal disease patients lack the kidney function required for hydrogen ion homeostasis. Hence, without dialysis treatment, severe metabolic acidemia incompatible with life will eventually occur. One of the goals of dialysis treatment is to correct metabolic acidosis. However, conventional dialysis treatments cannot optimally correct metabolic acidosis in many ESRD patients. Variation in serum bicarbonate concentration occurs during the interdialytic and intradialytic periods in MHD patients, with the highest bicarbonate level occurring immediately after the dialysis session and the lowest immediately before the next dialysis session (a sawtooth pattern). In contrast, patients undergoing chronic peritoneal dialysis (CPD) tend to have less fluctuation of their serum bicarbonate levels, although the anion gap is increased in the majority of these patients (36). Moreover, CPD patients tend to retain their residual renal function for longer periods of time. This may cause metabolic acidosis due to loss of bicarbonate in the urine in case an acquired renal tubular acidosis should coexist. The widened anion gap in MHD and CPD patients may be due to higher serum concentrations of sulfate and phosphate and other inorganic and organic compounds.

Metabolic acidosis may play an important role in the pathogenesis of PEM and inflammation associated with uremia (1). Several mechanisms may contribute to the development of PEM from metabolic acidosis in mainte-

nance dialysis patients, including increased protein catabolism, decreased protein synthesis, endocrine abnormalities including insulin resistance, a reduction in serum leptin levels, and inflammation per se (see Fig. 1).

Increased Protein Catabolism

Rodriguez et al. (37) showed that metabolic acidosis in dogs led to increased total-body leucine oxidation. Leucine oxidation diminished in response to metabolic alkalosis (37). Studies in rats with normal renal function showed that ammonium chloride-induced metabolic acidosis led to an increase in skeletal muscle protein degradation and amino acid oxidation (17,38–41). Increased muscle protein degradation was also reported in rats who underwent partial nephrectomy to produce renal insufficiency, while adding sodium bicarbonate to the diet slowed the rate of protein breakdown in these rats (42).

In human subjects with CKD or ESRD, metabolic acidosis has been shown to produce a negative nitrogen balance (43–45). The first study showing a link between metabolic acidosis and worsening nutritional status in human patients with CKD was presented by Lyon et al. (46) more than half a century ago. Since then, a number of studies in human subjects with various stages of renal insufficiency have demonstrated that metabolic acidosis promotes protein degradation (28,45,47–52). Papadoyannakis et al. (45) found that correction of metabolic acidosis led to improvement of both nitrogen and potassium balance in six nondialyzed CKD patients. Williams et al. (47) examined six CKD patients on a low-protein diet and found that the ratio of the urinary excretion of 3-methylhistidine to creatinine, an indicator of skeletal muscle protein catabolism, was increased in the presence of metabolic acidosis and reduced with bicarbonate supplementation. Garibotto et al. (49) studied nine nondialyzed CKD patients and showed that net ³H-phenylalanine release from the forearm was inversely correlated with the degree of acidemia. Several other investigators studied L-[1-¹³C]leucine kinetics in nondialyzed CKD patients and reported a reduced rate of protein synthesis and a higher rate of leucine oxidation (48,50) and higher rates of net protein breakdown (51). Metabolic studies in ESRD patients have shown similar results. Graham et al. (53) showed reduced whole-body protein degradation and synthesis due to metabolic acidosis in six MHD patients using L-[1-¹³C]leucine kinetics. However, no effect on leucine oxidation was found in another study (28). In contrast, Löfberg et al. (52) found an increased intracellular concentration of branched-chain amino acids in nine MHD patients who underwent correction of their metabolic acidosis.

The pathophysiologic mechanisms leading to increased protein degradation in metabolic acidosis are not completely clear. Evidence indicates that increased activity of the ATP-dependent ubiquitin-proteasome may play a role in mediating the catabolic effects of metabolic acidosis in CKD (Fig. 2). In rats with renal insufficiency, metabolic acidosis was associated with an increase in the muscle content of the messenger ribonucleic acid (mRNA) encoding the ATP-dependent ubiquitin and the subunits of the proteasome, a process that was reversed

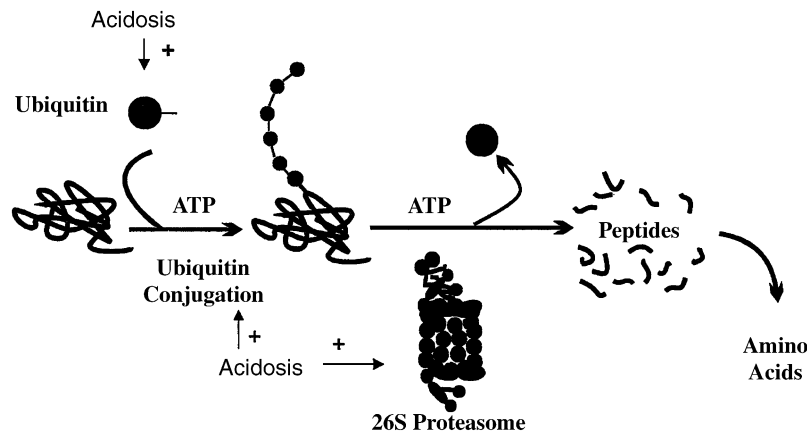


FIG. 2. Acidosis stimulates the ubiquitin-proteasome system by affecting multiple steps. Proteins targeted for destruction are conjugated with ubiquitin and the ubiquitin targets them to the proteasome, where they are destroyed. Acidosis increases the amount of ubiquitin and proteasomes and also increases the conjugation of protein with ubiquitin. (Adapted with permission from Franch H, Mitch W: Metabolic and nutritional responses to acidemia. In: Kopple J, Massry S (eds). *Nutritional Management of Renal Disease*, 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 2003:151–158)

by feeding bicarbonate-containing chow (54,55). Other investigators have shown that when isolated rat muscles are either depleted of ATP or exposed to an inhibitor of the proteasome, the increase in protein degradation seen otherwise in metabolic acidosis no longer occurred (17,41,55). Bailey et al. (55) showed that in rats with renal failure and metabolic acidosis, incubating skeletal muscle with an inhibitor of the proteasome suppressed protein degradation. In a recent, longitudinal study involving CPD patients, Pickering et al. (56) showed that an increase in serum bicarbonate, as reflected by total CO_2 , was associated with a significant reduction in the muscle content of ubiquitin mRNA. In contrast, in a cross-sectional study of eight MHD patients with only mild metabolic acidosis, there was no demonstrable increase in the muscle ubiquitin mRNA levels as compared to healthy controls (57).

Increased activity of the rate-limiting enzyme branched-chain keto acid dehydrogenase (BCKAD) may also play a role in acidemia-associated proteolysis. In CKD and ESRD patients, metabolic acidosis causes increased activity of BCKAD, which in turn leads to increased catabolism of branched-chain amino acids (BCAAs), such as leucine, isoleucine, and valine (1). Metabolic acidosis stimulates the breakdown of BCAAs in intact rats and in isolated muscles (58), a process that is associated with increased activity of BCKAD (17,59). Plasma and muscle levels of at least some BCAAs are significantly lower in animals with metabolic acidosis, as well as in humans undergoing maintenance dialysis treatment (38,60,61). In MHD patients, the free valine concentration in the muscle correlates with both the pre- and postdialysis plasma bicarbonate level (61). Correction of metabolic acidosis in MHD patients may lead to an increase in plasma BCAA levels (62).

It is unclear how metabolic acidosis triggers the catabolic pathways described above. Ammonium chloride-induced metabolic acidosis in adrenalectomized rats does not induce protein degradation, an increase in gene expression or activity of BCKAD, or an elevation in some of the mRNAs of the ubiquitin-proteasome system in muscle (17,54,63). However, the urinary excretion of

corticosterone in acidemic rats with experimental renal failure is significantly higher than that of pair-fed control rats (38). These data suggest that glucocorticoids may play a permissive role in engendering the catabolic pathways in metabolic acidosis. A glucocorticoid-responsive element in the promoter region of BCKAD has recently been discovered (64). Hence corticosteroids may need to be present for acidemia to stimulate skeletal muscle protein degradation (49).

Decreased Protein Synthesis

Metabolic acidosis may have an antianabolic effect in muscle cells. A significant reduction in protein synthesis in skeletal muscle cells cultured in acidic medium is observed (65,66). Moreover, acidic culture medium significantly reduced the albumin and transferrin concentrations in the supernatant of HepG2 cell culture (67). Kleger et al. (68) showed that acute ammonium chloride-induced metabolic acidosis in normal individuals was associated with a significant reduction in the fractional synthetic rate of muscle protein, whereas the rate of albumin synthesis remained unchanged. In contrast, chronic ammonium chloride-induced metabolic acidosis has been reported to significantly reduce the fractional synthetic rate of albumin (43). Whether these findings also hold in the uremic milieu is uncertain. Paradoxically, several studies of L-[1- ^{13}C]leucine kinetics in MHD patients have shown an increased, rather than a decreased, total body protein synthesis with metabolic acidosis, which was reversed upon correction of acidosis (28,48,69). However, even in these studies, metabolic acidemia was still associated with a significantly greater increase in the rate of proteolysis, resulting in a net negative protein balance (28,48,69).

Endocrine Abnormalities and Insulin Resistance

Endocrine alterations may contribute to the antianabolic effects of ammonium chloride-induced metabolic acidemia. For instance, the release of growth hormone may be reduced in metabolic acidosis, which may also

lead to peripheral resistance to growth hormone (67,70). Metabolic acidemia may significantly reduce the plasma levels of IGF-I by suppressing the release of this hormone (30,43,70,71). Moreover, decreased thyroid function induced by metabolic acidosis might reduce the synthesis of skeletal muscle protein (68). Acidemia may promote insulin resistance, and reduced tissue levels of or increased resistance to other anabolic hormones may stimulate the catabolic processes in metabolic acidosis (see below).

Renal failure-associated insulin resistance may be a direct consequence of metabolic acidosis (72,73). Insulin resistance may play a role in the activation of the ubiquitin-proteasome system (see above). The high rate of protein degradation in rats with acute onset of diabetes mellitus is not reduced by correction of diabetic ketoacidosis, but administration of insulin for 12 hours eliminated the excess proteolysis and higher ubiquitin mRNAs (74). Moreover, insulin-stimulated phosphorylation of the insulin-receptor substrate-1 phosphatidylinositol-3 kinase is significantly reduced in the muscle of rats with renal failure (75). Suppressed phosphatidylinositol-3 kinase activity may activate the ubiquitin-proteasome pathway and muscle protein degradation (75). Hyperglycemic and euglycemic clamp studies in the presence of ammonium chloride-induced metabolic acidosis have revealed impaired glucose metabolism due to reduced tissue sensitivity to insulin (72).

Leptin and Metabolic Acidosis

Although in the general population leptin is considered an "appetite inhibitor," its role in CKD and ESRD patients is unclear. Serum leptin is generally elevated in CKD and ESRD patients, but this has not been shown to be a cause of uremia-related anorexia (76,77). Three longitudinal/observational studies in MHD patients indicate that individuals with high serum leptin levels are more likely to lose weight (78–80). However, more recent studies in maintenance dialysis patients suggest a paradoxically inverse association between higher serum leptin and improved markers of nutritional status (76,77), a finding that is consistent with the theory of reverse epidemiology (81). Indeed, leptin, similar to serum albumin, has been reported to be a negative acute phase reactant in ESRD patients (77).

Administration of growth hormone to maintenance dialysis patients increases plasma leptin levels (82,83). Fouque et al. (83) measured serum leptin in eight well-nourished MHD patients receiving anabolic factors for 3 days as either recombinant IGF-I or a combination of recombinant growth hormone plus recombinant IGF-I, in a random cross-over trial. Serum leptin was strongly correlated with the patient's dry body weight ($p = 0.01$) and body fat ($p = 0.0001$). Both treatments affected serum leptin in a rapid and opposite manner. IGF-I decreased serum leptin from 11.2 to 4.3 $\mu\text{g/L}$ ($p = 0.01$), whereas the combination of growth hormone and IGF-I increased serum leptin from 7.4 to 21.0 $\mu\text{g/L}$ ($p = 0.01$). They concluded that both IGF-I and growth hormone acutely regulate serum leptin in dialysis patients (83). Iglesias et al. (82) and Aguilera et al. (84) studied 38 CPD patients and

found a strong direct correlation between serum leptin and both body mass index (BMI) ($r = 0.70$) and triceps skinfold thickness ($r = 0.77$). Higher leptin levels were also associated with higher serum triglycerides and total cholesterol levels. Healthier patients with a lower clinical atherosclerosis score ($n = 19$) had higher plasma leptin levels than those with higher scores (82.4 ng/ml versus 35.8 ng/ml, respectively). CPD patients with anorexia ($n = 12$) had lower leptin levels than those with a normal appetite (19.2 ng/ml versus 91.3 ng/ml, respectively). In nonobese patients (BMI < 25 kg/m², $n = 14$), there were statistically significant, direct linear correlations between serum leptin and markers of nutritional status, including serum albumin ($r = 0.63$), transferrin ($r = 0.40$), and cholesterol ($r = 0.65$) (82,84).

To our knowledge, there are no published data regarding a direct interaction of metabolic acidemia with serum leptin levels and the relative contribution of each of these to the nutritional status of maintenance dialysis patients. Teta et al. (85) showed that leptin secretion was decreased in adipocytes exposed to an acidic environment (pH = 7.1). In rats with renal failure treated with sodium bicarbonate, serum leptin was significantly lower than in those not treated with bicarbonate (85). In general, plasma leptin concentrations are lower in patients with diabetic ketoacidosis than in healthy subjects, and the plasma leptin level increases after initiation of insulin therapy (86,87). Diabetic ketoacidosis is associated with insulinopenia, ketonemia, and increased sympathetic nervous activity, and these factors might independently affect serum leptin levels (1). In CKD patients, correction of metabolic acidemia is associated with an increase in serum leptin levels (88). On the other hand, Kokot et al. (89) conducted a cross-sectional study in 94 MHD patients and found a trend, although not statistically significant, toward progressively lower median leptin concentrations with increasingly higher blood hydrogen ion concentrations.

Inflammation

Inflammation has been shown to be associated with anorexia and decreased protein intake in MHD patients (90,91). Bellocq et al. (92) showed that incubation of peritoneal macrophages in an acidic culture medium results in increased production of tumor necrosis factor (TNF)- α , suggesting a possible link between metabolic acidosis and the inflammatory cascade. They showed that the exposure of macrophages to an acidic microenvironment in inflammatory lesions led to the up-regulation of nitric oxide activity through the activation of nuclear factor (NF)- κB (92). Two recent studies have investigated the link between metabolic acidosis and inflammation. In a cross-sectional study of MHD patients, no significant difference was observed in the serum levels of C-reactive protein (CRP) and interleukin (IL)-6 in three groups of patients divided on the basis of their serum bicarbonate levels (mean total CO₂ in the three groups: 19.2, 24.4, and 27.5 mmol/L) (93). In contrast, the correction of metabolic acidosis in eight CPD patients was associated with a significant decrease in TNF- α levels (56). Moreover, Kaysen et al. (94) recently found that the

serum concentration of albumin, a negative acute phase reactant, correlated with both the normalized protein equivalent of nitrogen appearance (nPNA) and serum CRP levels, but not serum bicarbonate, in both cross-sectional and longitudinal analyses of HEMO study data. Similarly the Nutritional and Inflammatory Evaluation in Dialysis (NIED) study, a prospective longitudinal study with more than 600 MHD patients thus far, has not found any association between nutritional and inflammatory markers, including CRP, TNF- α , and IL-6, and serum bicarbonate (90). However, such secondary analyses of data cannot exclude the proinflammatory effect of metabolic acidosis in dialysis patients. Further studies will be needed to resolve the relationship between CRI-associated metabolic acidosis and inflammation.

Acidosis-Inducing Phosphate Binders

Until recently, most CKD and ESRD patients were treated with calcium-based phosphate binders including calcium acetate and calcium carbonate, which are alkalis. These medications have had a correcting effect on metabolic acidosis. In the past several years, non-calcium-containing phosphorus binders such as sevelamer hydrochloride have increasingly become the primary medicinal treatment of hyperphosphatemia in maintenance dialysis patients, because of concerns that calcium-containing binders are associated with a higher rate of coronary artery calcification and poor cardiovascular outcome in CKD and ESRD patients (95,96). Sevelamer hydrochloride acts as an ion exchange resin in the gastrointestinal tract (i.e., it releases 1 mole of chloride for every mole of phosphorus that it binds). Since 17% of sevelamer hydrochloride is chloride (by weight), treatment with four 800 mg tablets of sevelamer hydrochloride three times a day with meals provides about 46 mEq of chloride load per day (1). The chloride thus released is buffered by bicarbonate, leading to a hyperchloremic metabolic acidosis. These considerations suggest that a change from widespread use of alkalis for phosphate binding to the use of an agent that fosters chloride loading may lead to a greater prevalence of persistent metabolic acidosis among MHD and CPD patients (97–99).

Reverse Epidemiology and Metabolic Acidosis in ESRD

Despite the fact that much research has indicated an adverse catabolic response to metabolic acidosis, the vast majority of recent epidemiologic studies in maintenance dialysis patients have shown a paradoxically inverse relationship between metabolic acidosis and nutritional status in ESRD patients (93,100–106). Previous studies are not inconsistent with the theory of reverse epidemiology in maintenance dialysis patients. This theory advances the concept that many traditional risk factors including hypercholesterolemia, hyperhomocysteinemia, obesity, and high blood pressure values are paradoxically associated with a greater survival, whereas low values of serum cholesterol, plasma homocysteine, BMI,

and blood pressure are associated with poor dialysis outcome (81,107). Evidence suggests that malnutrition-inflammation complex is the main cause of the reverse epidemiology in ESRD patients (108). In this regard, the explanation for the reverse association between metabolic acidosis and better nutritional status may also lie in the likelihood that healthier MHD and CPD patients tend to have a greater appetite and thus ingest more protein. A higher intake of dietary protein is associated with a higher dietary acid load and thus a lower serum bicarbonate. It has recently been shown that subjective reported appetite is a strong predictor of survival in MHD patients (91). A higher protein intake, as indicated by an increased nPNA, is associated with decreased mortality and hospitalization, even in those MHD patients who receive a higher than average dose of dialysis (i.e., *Kt/V* single-pool greater than 1.20) (109). This relationship appears to confound the association of low serum bicarbonate levels with increased protein catabolism. Hence it is quite possible, but not unequivocally shown, that lower serum bicarbonate levels are associated with better dialysis survival (see below).

Several studies in MHD patients show a paradoxical association between metabolic acidosis and improved markers of nutritional state. Uribarri (101) reported a significant inverse relationship between serum bicarbonate and nPNA and found that MHD patients with a serum bicarbonate ≤ 21 mEq/L (versus those with a bicarbonate ≥ 25 mEq/L) had a higher serum creatinine and urea concentration. In a study of 995 MHD patients, Uribarri (101) also found that serum bicarbonate correlated inversely with dietary protein intake and nPNA. Dumler et al. (102) reported higher serum albumin, creatinine, and nPNA levels in acidotic MHD patients. Gao et al. (103) found an inverse association between serum bicarbonate and serum urea, phosphorus, and uric acid in 50 MHD patients. Lin et al. (93) reported a higher BMI, triceps skinfold thickness, dietary protein intake, nPNA, and serum potassium in acidemic MHD patients. Finally two epidemiologic studies with large sample sizes by Leavey et al. (104) ($n = 3891$) and Chauveau et al. (105) ($n = 7123$) found a significant inverse relationship between serum bicarbonate and serum albumin, as well as serum prealbumin, nPNA, and BMI, respectively.

Similar studies have been reported in CPD patients. Kang et al. (100) studied 106 CPD patients and found that those with a serum bicarbonate less than 22 mEq/L, compared to ≥ 26 mEq/L, had higher relative body weight, serum urea, albumin, nPNA, and ultrafiltration volume. Dumler et al. (110) showed that BMI was higher in acidemic CPD patients. Kung et al. (106) studied 43 CPD patients and found that malnourished patients, as determined by subjective global assessment, had higher serum total CO₂ than well-nourished subjects.

It is important to appreciate that many of the above-mentioned studies rely upon improved nutritional status as a surrogate and do not examine objective clinical outcome measures such as mortality. However, one epidemiologic analysis of a large sample size showed that bicarbonate level in the range of 17.5–25 mEq/L was associated with the lowest dialysis mortality (111) (see below). While such findings contribute to our better

understanding of the field, the cause-and-effect associations and the direction of the causal pathway remain undetermined (112). However, very few studies have reported the opposite direction of associations. In a cross-sectional study of 81 MHD patients, Movilli et al. (113) showed a direct association between higher serum bicarbonate and increased serum albumin. Similarly Ge et al. (114) demonstrated that MHD patients with severe metabolic acidosis had significantly lower relative body weight, triceps skinfold thickness, midarm muscle circumference, serum albumin, transferrin, and fibronectin levels when compared to those with higher serum bicarbonate levels. However, it is important to note that the protein catabolic effects associated with metabolic acidosis may be a transient process, since most individuals were studied after establishing the metabolic acidemia or receiving bicarbonate supplementation for relatively short periods of time. Finally, it is important to appreciate that making therapeutic decisions based on inferences from epidemiologic studies may be a risky approach. To argue that a patient who has metabolic acidosis lives longer is not inconsistent with the hypothesis that the same patient would live even longer if metabolic acidosis were corrected.

Metabolic Acidosis and Clinical Outcome

Metabolic acidosis may play a role in the poor clinical outcome in dialysis patients. An epidemiologic analysis of a large cohort of MHD patients by Lowrie and Lew (111) showed that the association between the baseline serum bicarbonate and prospective mortality was J-shaped, in that the risk of death was higher when serum bicarbonate was either less than 17.5 mEq/L or greater than 25 mEq/L. In another analysis by the same investigators, a higher anion gap was paradoxically found to be associated with a lower odds ratio of death in MHD patients (115). However, when the data were also adjusted for serum albumin and creatinine levels, an increase in anion gap was associated with a progressive increase in the risk of death (115). It is possible that, as indicated above, since the anion gap may covary with serum albumin and possibly serum creatinine, adjusting anion gap models for serum albumin may be flawed (overadjustment bias) (112). It is not clear, however, whether an increase in dialysis dose can normalize the anion gap or whether such a decline in anion gap will reduce mortality in MHD patients.

Interventional Studies to Improve Acidosis

Several prospective clinical trials in ESRD patients have examined the beneficial effect of bicarbonate-increasing interventions (62,93,116–121). Seyffart et al. (116) showed a significant increase in dry body weight in 11 of 21 MHD patients after 12–19 months of intervention. Kooman et al. (62) increased plasma BCAA levels in 12 MHD patients by correcting their metabolic acidosis, but there was no change in body composition, serum proteins, or dietary intake. Movilli et al. (117) showed

that increasing plasma pH from 7.34 to 7.40 in 12 MHD patients increased serum albumin, but decreased nPNA. Similarly Verove et al. (118) also showed a significant increase in serum albumin and prealbumin levels, but a decrease in nPNA, and no change in dietary protein intake. Williams et al. (119) conducted a double-blind cross-over trial in 46 MHD patients; using different bicarbonate concentrations in the dialysate bath for 6 months, they showed an increased triceps skinfold thickness only in the high-bicarbonate group (pH 7.43) versus the rest of the patients (pH 7.38). There was no change in serum albumin, nPNA, or midarm muscle circumference (119).

Among interventional studies in CPD patients, Stein et al. (121) randomized 200 consecutive new CPD patients in a single-blind fashion to receive either a high- or low-alkali dialysate for 1 year. They found a greater gain in body weight and midarm muscle circumference in the higher pH group (7.44) versus the other group (7.40). Moreover, a reduction in hospitalization frequency and total days of hospitalization was reported by the same investigators (121). Recently Szeto et al. (122) studied the effect of oral bicarbonate in 60 CPD patients with $Kt/V < 2.1$. Patients were randomly assigned to oral sodium bicarbonate (0.9 g three times a day) or placebo and were followed for 12 months. Treatment with oral bicarbonate resulted in a higher plasma bicarbonate level at 4 weeks (27.8 ± 2.6 mmol/L versus 24.7 ± 3.9 mmol/L; $p = 0.002$), and the difference persisted for a year. Bicarbonate treatment had a significant effect on the change in overall subjective global nutritional assessment (SGA) score. The nPNA rose in the treatment group (1.17 ± 0.32 g/kg/day to 1.28 ± 0.26 g/kg/day; $p = 0.03$), but declined in the placebo group. The treatment group had shorter hospitalizations than the placebo group, but mortality was not significantly different (122).

In contrast, Lin et al. (93) and Roberts et al. (120) did not show any benefit based on diverse interventions that increased serum pH in MHD patients. There are several major limitations in the above-mentioned studies. In many of these studies there were small sample sizes, failure to restrict study subjects to those with PEM, no controls for concurrent food intake, and no or inadequate adjustment for comorbid conditions. Nutritional interventions were employed for only fairly short periods of time, and patients were often followed for only short intervals. Until large-scale, prospective randomized interventional studies are conducted, it will be difficult to ascertain the benefits of correcting metabolic acidosis in malnourished maintenance dialysis patients. However, as described above, recent data in CPD patients are more encouraging.

Conclusions and Therapeutic Implications

While the traditional literature suggests that metabolic acidosis is detrimental to overall health and specifically to nutritional status and bone metabolism in CKD and ESRD patients, some recent epidemiologic studies in maintenance dialysis patients show a paradoxically inverse association between low serum bicarbonate and improved

nutritional markers. This reverse association is consistent with the recently described reverse epidemiology phenomenon, especially if future studies confirm a better outcome in slightly acidemic patients (81). Hence the relative contribution of metabolic acidosis to the development and persistence of PEM and inflammation in maintenance dialysis patients remains unclear, even though, as the basis of short-term metabolic studies, the correction of metabolic acidosis in CKD patients appears to be an appropriate goal. PEM, inflammation, and MICS are common conditions in ESRD patients and strongly associated with high morbidity and mortality (4). The mechanisms by which PEM is related to poor clinical outcome are not completely clear. In order to define the relative contribution of metabolic acidosis to PEM and inflammation and to morbidity and mortality in CKD and ESRD patients, large-scale, randomized prospective interventional trials are needed.

There are at least two unresolved issues to be considered while seeking to minimize the protein wasting that could possibly ensue from uncorrected metabolic acidosis among maintenance dialysis patients. First, there are limitations to the use of various methods that are used in clinical practice to assess the degree of metabolic acidosis (i.e., arterial pH, serum anion gap, or bicarbonate). The measurement of arterial pH, while precise, is impractical and often unavailable in most dialysis units. The relationship between anion gap and bicarbonate appears to be altered, probably as a result of the bicarbonate or lactate loads received during hemodialysis or peritoneal dialysis. With regard to anion gap in the presence of ESRD, the relationship between serum anion gap and bicarbonate is shifted to the right when compared to individuals with normal renal function (i.e., a mixed acid-base disorder wherein a metabolic alkalosis is superimposed on the metabolic acidosis) (36). This makes the anion gap an inappropriate surrogate for assessing the degree of acidosis. Thus, notwithstanding the technical problems in the measurement of serum bicarbonate associated with the shipping of blood samples (as described earlier), serum bicarbonate is the parameter that is most readily available and easy to interpret (9–12).

A second unresolved issue is a limitation of our understanding of the pathophysiologic mechanisms by which metabolic acidosis triggers protein wasting. Thus it is unclear whether the adverse consequences of metabolic acidosis are triggered by a high arterial concentration of hydrogen ions or low serum bicarbonate levels or retained inorganic acids (viz. sulfates) or simply the process of buffering of the acid loads by protein. Indeed, there are some data that suggest that in ESRD patients with apparently normal arterial pH or serum bicarbonate, alkali supplementation may result in an improvement in protein balance and nutritional status, and a reduction in morbidity (69,119,121,122). Consistent with these findings, in a preliminary analysis of data from an ongoing metabolic balance study in ESRD patients undergoing automated peritoneal dialysis, an increase in arterial pH from 7.37 to 7.47–7.49 was associated with a 30–59% improvement in nitrogen balance (123). Thus the threshold for the use of alkali supplementation remains to be

defined and may be a higher serum bicarbonate level or arterial pH than has been previously considered. Until more data become available to resolve the limitations of our understanding, it appears to be appropriate to use the threshold defined by the Nutrition and Bone Disease subcommittees of the National Kidney Foundation Kidney Disease and Dialysis Outcome Quality Initiative (K/DOQI) (124,125). It follows then that all attempts should be made to maintain serum total CO₂ levels at ≥ 22 mEq/L, and in a patient with persistently low serum total CO₂ levels, alkali supplementation should be considered.

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