What Unique Acid-Base Considerations Exist in Dialysis Patients?

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Because a typical modern diet results in net production of acid, and the kidney is normally the main organ responsible for generating alkali to maintain acid-base homeostasis, chronic metabolic acidosis is commonly observed in patients with chronic renal insufficiency. In this article we will deal with the clinical characteristics, pathophysiology, and therapeutic approach to this condition.

Clinical Characteristics

In most patients with chronic renal insufficiency, mild metabolic acidosis is a common occurrence, with serum bicarbonate levels moderately reduced but remaining stable for prolonged periods. This acidosis results from decreased net acid excretion secondary mainly to decreased urinary ammonia excretion. Since renal acid excretion is a function of the renal tubules, any defect in renal acid excretion represents tubular dysfunction. In practice, however, the term renal tubular acidosis is reserved only for disorders caused by a specific tubular defect with either normal or slightly impaired glomerular filtration rate (GFR), while acidosis resulting from advanced renal insufficiency is called uremic acidosis. Thus the hallmark of uremic acidosis is diminished GFR.

The level of GFR at which uremic acidosis develops varies depending on a multiplicity of factors including 1) endogenous acid production, which in turn depends on the diet, 2) diuretic therapy and hypokalemia, which tend to stimulate ammonia production and may delay the development of acidosis, and 3) the etiology of the renal disease. In predominantly tubulointerstitial renal diseases, acidosis tends to develop earlier in the course of renal insufficiency than in predominantly glomerular diseases. In general, metabolic acidosis is rare when the GFR is greater than 25–20 ml/min.

Diet has the most significant effect on acid production. Because protein is the source of sulfuric acid, the quantity of sulfuric acid production varies with the quantity of protein intake. Furthermore, the sulfate content varies with the types of protein that are ingested. In general, proteins of animal sources (meat, fish, and egg) contain greater amounts of sulfate for a given amount of protein than proteins of plant origin (cereal and nuts) (1). On the other hand, ingestion of vegetables and fruits results in net production of alkali, and therefore increased ingestion of these foods will tend to delay the appearance of metabolic acidosis in chronic renal failure (Fig. 1).

Acidosis of advanced renal failure characteristically presents with a high anion gap (normochloremic acidosis) caused by accumulation of sulfate, phosphate, and organic anions. However, the accumulation of these anions per se is not the cause of the acidosis. Metabolic acidosis would not disappear if these anions were removed, for example, by dialysis. Reduction in renal acid excretion and accumulation of uremic anions are both the result of reduced renal function, but not causally related to each other. When metabolic acidosis develops with milder renal impairment, the anion gap is typically normal (hyperchloremic acidosis) because at this stage of renal impairment, net acid excretion is sufficiency reduced to cause metabolic acidosis, but accumulation of uremic anions is insufficient to cause an abnormally high anion gap.

There are no specific manifestations of metabolic acidosis that can be detected by history and physical examination, except for hyperventilation in cases of severe acidosis. Thus the diagnosis of metabolic acidosis is based on the results of laboratory tests. A decreased serum total carbon dioxide (CO_2) on a routine chemistry profile might suggest the condition, but confirmation of the diagnosis requires the knowledge of the CO_2 partial pressure (pCO_2) and/or pH from blood gases.

Pathophysiology

Most of our current understanding about the mechanisms of renal acidosis comes from the seminal studies of Goodman et al. (2) and Litzow et al. (3). These authors studied acid-base balance in a small number of patients with chronic renal insufficiency who presented with low, but stable serum bicarbonate concentration. In one study (2), acid-base balance was determined from the difference between acid production (urinary excretion of sulfate and organic anions) and urinary net acid excretion (urinary ammonia + titratable acidity − bicarbonate)

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Seminars in Dialysis—Vol 17, No 5 (September–October) 2004 pp. 351–354

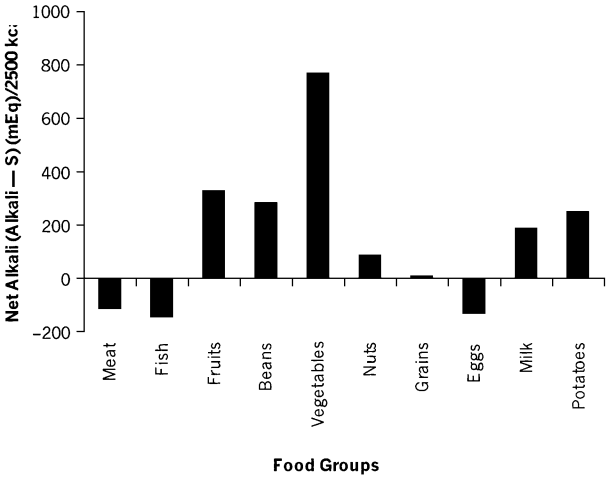

FIG. 1. Net alkali content of food, including the content of sulfur. In general, foods of animal origin have a net acid content, whereas foods of plant origin have a net alkali content.

while patients were ingesting a specially formulated neutral liquid diet. In this study the authors assumed that net gastrointestinal (GI) alkali absorption was zero because the net acid content of the diet was neutral. In the other study (3), acid-base balance was determined as the difference between acid production and urinary net acid excretion while the subjects were ingesting a regular diet. The estimation of acid production in this study included the amount of alkali from dietary sources absorbed from the GI tract (3). The alkali absorbed from the diet was termed net GI alkali, which was calculated from the difference between potential alkali in the diet and the potential alkali in the stools (3). Potential alkali in the diet and stools in turn was estimated by the difference between noncombustible cations (Na + K + Ca + Mg) and noncombustible anions (Cl + P) in the diet and stools, respectively. In both of these studies (2,3), daily acid production was not significantly different from normal, but exceeded daily renal acid excretion by 19 mmol/day in patients consuming the liquid diet and by 10 mmol/day in patients consuming the regular diet. If the subjects were in acid-base balance, it is expected that net acid production that includes net GI absorption of alkali would equal net acid excretion (Fig. 2).

The implication from both studies was that chronic renal insufficiency represents a state of continuous positive hydrogen ion balance. To reconcile this finding with the observation that serum bicarbonate remains remarkably constant over time despite a substantial positive acid balance, the authors speculated that the retained hydrogen ion was being buffered by bone, which was thought to be the only potential source of alkali that contained sufficient alkali to buffer acids for many years. This line of thinking seemed to be strengthened by the well-known observation that experimentally induced metabolic acidosis is followed by severe hypercalciuria and negative calcium balance (4,5).

A subsequent quantitative analysis of the potential buffers available in bone led to the conclusion that the magnitude of the cumulative acid load predicted from the above data exceeds the total buffer capacity of bone (6). There is simply not enough bone alkali to account for the postulated positive acid balance over prolonged periods of time. Further evidence against bone as the source of alkali in chronic renal failure is the absence of hypercalciuria in this condition. In fact, hypocalciuria is a characteristic manifestation of impaired renal function. Even if the bone were to provide alkali to the extracellular space by dissolution of calcium salts, precipitation of

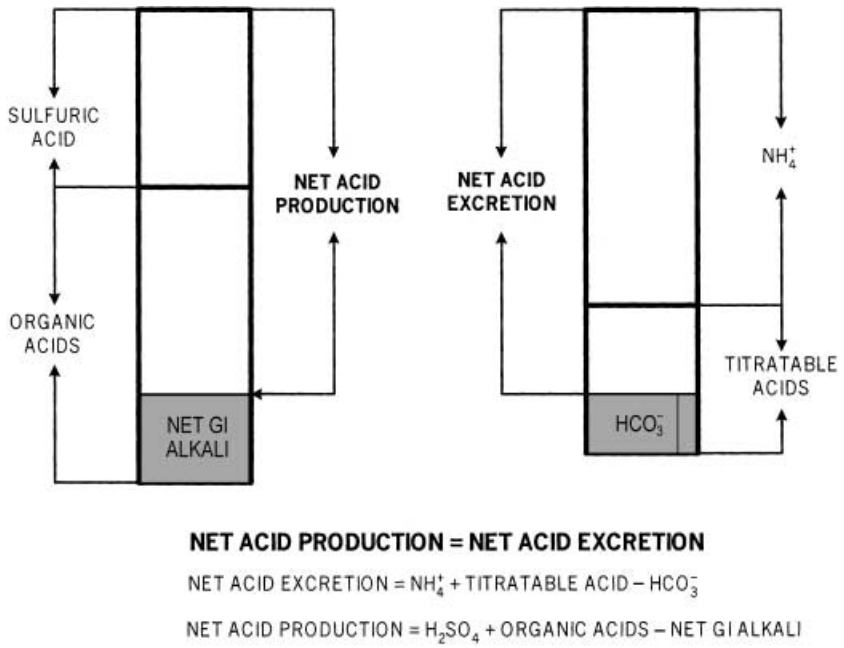

FIG. 2. In states of acid-base balance, net acid production equals net acid excretion. Net acid production is measured as the sum of sulfuric acid and organic acid production (which are measured as urinary sulfate and organic anions) minus the net GI alkali absorption. Net acid excretion is measured as the sum of ammonium and titratable acid minus bicarbonate.

calcium in soft tissues or its loss in the stools, accompanied by organic anions or carbonate, would reclaim all or most of the alkali that was added to the extracellular fluid during initial dissolution of bone. In other words, release of calcium from bone will result in the net addition of alkali to the extracellular fluid only if calcium is excreted in the urine.

If release of bone alkali is not the explanation for a stable serum bicarbonate concentration in the presence of an apparent positive acid balance in chronic renal insufficiency, alternative explanations are required. The most plausible explanation is that the observed discrepancy between acid production and acid excretion is only apparent, and is the result of errors in measurement of net acid production and/or net acid excretion.

To further clarify this issue we determined acid-base balance, using a new technique to estimate net GI alkali absorption, in a group of stable ambulatory patients with chronic renal insufficiency eating their usual diet (7). In this new technique, electrolytes are measured in a 24-hour collection with the assumption that, in the steady state, the difference between noncombustible cations (Na + K + Ca + Mg) and noncombustible anions (Cl + 1.8P) in the urine would equal net GI alkali absorption (8). The traditional method of measuring net GI alkali absorption consists of measuring the noncombustible electrolytes in food and stools (2,3). The main advantage of the new technique is avoidance of stool collection. Moreover, the urinary method of measuring net GI alkali absorption includes addition of alkali from non-GI sources such as bone (8). Ordinarily the non-GI contribution to the net GI alkali absorption is negligible, but if chronic renal acidosis caused substantial release of alkali from bone, this non-GI component of the net GI alkali absorption should become significant in patients with this condition.

One would have predicted that including the contribution of bone to the alkali balance with the urinary method to calculate net GI alkali absorption should have eliminated the positive acid balance observed in this condition if the serum bicarbonate was maintained constant by addition of bone alkali. Our study showed that acid balance was essentially zero in patients with renal failure and normal serum bicarbonate, but patients with renal failure and subnormal serum bicarbonate still had a positive acid balance of 16 mmol/day (7).

When we compared the sum of all urinary cations to that of all urinary anions, we found a cation gap of the same magnitude as the positive hydrogen ion balance in patients with low serum bicarbonate (7). Since a real cation gap is impossible, the positive hydrogen ion balance must have been only apparent, not real. The most likely explanation for the cation gap is systematic technical errors in the methods used to measure the different parameters of acid-base balance, either an underestimation of net acid excretion or an overestimation of acid production. If the positive hydrogen ion balance, as Goodman et al. (2) and Litzow et al. suggested (3), had resulted from bone buffering in chronic renal acidosis, it would have disappeared in our study, since our estimation of acid-base balance included the contribution of bone buffering (7).

A likely error in the estimation of acid excretion is in the measurement of titratable acidity. The current method to measure titratable acidity includes only those substances titrated between actual urinary pH and 7.4, and it assumes that ammonium is the only urinary buffer that escapes measurement by this titration. However, this assumption appears to be incorrect, since urine of normal subjects contains about 7.6 mEq/g creatinine/day of organic compounds other than ammonium that are not measured as titratable acidity (9). Urinary excretion of these compounds represents urinary acid excretion just as urinary ammonium does, but it is not included in the measurement of titratable acid and ammonia. Therefore it appears that the current method of measuring net acid excretion results in systematic underestimation of urinary acid excretion.

Measurement of urinary organic anions has traditionally utilized the Van Slyke and Palmer (10) titration method, which includes the contribution of all potential organic anions. The limitations of this technique were recognized by Relman et al. (11) when they used the method for acid-base balance studies. The main source of error in this method derives from the initial phase of precipitation of phosphorus by adding calcium hydroxide to the solution, since this precipitation also leads to the loss of organic anions. Measuring each one of the urinary organic anions to determine total urinary organic anions would be almost impossible because a large number of organic anions are present in normal urine and the nature of these organic anions are not entirely known. A newly described modification of the Van Slyke and Palmer technique eliminates the precipitation phase and avoids some of the pitfalls of the original method (12).

All the above data suggest that the traditional method for estimating urinary acid excretion, that is, NH_4 + titratable acid − bicarbonate, consistently underestimates this parameter, and the van Slyke and Palmer technique also consistently underestimates urinary organic anion excretion. By coincidence, the underestimation of urinary organic anions seems to be similar in magnitude to the underestimation of the postulated unmeasured urinary cations (12). Coexistence of these two errors may have resulted in the observed neutral acid balance in studies by Relman et al. (11) and Lennon et al. (13). However, in acidotic uremic subjects, the two errors do not seem to cancel out. It is possible, for example, that patients with uremic acidosis excrete greater amounts of unmeasured organic cations in urine than normal subjects.

The normal daily acid production of 1 mmol/kg/day, or 70 mmol/day in a 70 kg man, is mostly the result of urinary excretion of organic anions (40 mmol/day) and sulfate (30 mmol/day). As renal dysfunction progresses, this pattern of acid production seems to remain unchanged (7). However, by the time patients progress to end-stage renal disease (ESRD) requiring maintenance dialysis, their net acid production is much lower than that in normal subjects with a similar amount of protein intake (14,15). This reduced net acid production in dialysis patients was found to result from reduced production of both sulfuric acid and organic acids (14,15).

The mechanism of decreased sulfuric acid production is unknown, but postulated explanations include increased loss of sulfate in stool and/or loss of sulfur in other forms, such as taurine and sulfate-conjugated compounds.

Metabolism of sulfur-containing amino acids results in acid production only if the final metabolite is excreted as sulfate. Reduced organic acid production can be explained partly by the reduced renal excretion of metabolizable organic anions. In anuric patients, only the nonmetabolizable organic acids contribute to acid production in the interdialytic period because, in the absence of renal excretion, metabolizable organic anions are eventually metabolized to regenerate alkali that was consumed by organic acids.

Therapeutic Approach

Severe metabolic acidosis in experimental animals and man has been shown to be a strong stimulus for protein breakdown (16). Acidosis has other negative effects, such as bone disease (17), insulin resistance (18), and a decreased sensitivity of the parathyroid glands to calcium (19). Thus aggressive therapy of even mildly subnormal serum bicarbonate should be attempted in chronic renal insufficiency unless there are specific contraindications such as congestive heart failure, marked edema, or hypertension. Therapy should aim to obtain a serum bicarbonate level as close to normal as possible (i.e., 23–25 mmol/L).

The best way to initiate therapy is with oral sodium bicarbonate (1 tablet by mouth three times a day) and to increase the dosage as necessary. The usual tablet of 650 mg of sodium bicarbonate contains 7.5 mmol of alkali. Occasionally patients experience gastric discomfort with sodium bicarbonate because of the gas production resulting from the reaction between sodium bicarbonate and hydrochloric acid. In these cases, one may use Shohl's solution (a mixture of sodium citrate and citric acid). An important consideration in these patients is that the use of sevelamer (Renagel), a new non-calcium-containing phosphorus binder increases daily acid load because some of chloride ions in the resin are exchanged for organic anions. Exchange of chloride for an organic anion is tantamount to production of hydrochloric acid. In dialysis patients, treatment of acidosis relies on the gain of alkali from the dialysate either as bicarbonate in hemodialysis or as lactate in peritoneal dialysis.

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Metabolic acidosis is a common metabolic disturbance in patients with chronic kidney disease (CKD). While acidosis is not overtly symptomatic, there is evidence that it is associated with a number of physiologic changes that contribute to common complications of CKD. The impact of acidosis on protein metabolism and nutrition has been widely studied. Metabolic acidosis is a catabolic stimulus both in experimental animals and in humans. An important clinical question that remains unresolved is whether mild metabolic acidosis should be treated in CKD patients. While there are fairly convincing animal data to support the link between metabolic acidosis in uremia and protein catabolism, strong evidence to support the importance of correcting mild metabolic acidosis

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Seminars in Dialysis—Vol 17, No 5 (September–October) 2004 pp. 354–358

in humans is lacking. Furthermore, the administration of sodium bicarbonate ($NaHCO_3$) may aggravate hypertension and cause volume overload.

In this article we will examine the evidence that metabolic acidosis in uremia induces protein catabolism and will critically appraise the studies in humans with CKD that examine the effect of correcting metabolic acidosis on protein metabolism. A discussion of how acid-base balance is maintained will follow to help determine the dose of $NaHCO_3$ needed to maintain a normal plasma bicarbonate (HCO_3) concentration in these patients.

Animal Studies

There is a large body of evidence from studies in animals suggesting that acidosis is a catabolic signal. In normal rats, administration of ammonium chloride (NH_4Cl) leads to increased protein oxidation as measured by leucine kinetics (1). While glucocorticoids seem to be involved in mediating this catabolic effect, correction of metabolic acidosis has a favorable effect on protein metabolism, nitrogen balance, and growth (2). Acidosis causes protein degradation and loss of lean body mass in uremic animals. May et al. (3) found that uremic rats with metabolic acidosis (HCO_3 concentration 16 mmol/L) had stunted growth and significantly increased rates of urea appearance and urinary nitrogen excretion as compared to pair-fed control rats. Isolated perfused hindquarters from uremic rats with acidosis demonstrated twice the rate of protein degradation, measured by the release of tyrosine, as compared to control rats. Correcting metabolic acidosis with $NaHCO_3$ supplementation eliminated these changes, invoking a primary role for acidosis in the abnormal protein metabolism of uremia. There was, however, an additional defect in insulin-stimulated protein synthesis that was independent of metabolic acidosis.

Acidosis causes not only protein degradation, but also targets amino acids for oxidation and thereby leads to negative nitrogen balance. Decarboxylation of the branched-chain amino acid (BCAA) valine was significantly increased in incubated epitrochlearis muscles from uremic acidotic rats as compared to those from pair-fed control rats (4). Supplementation with $NaHCO_3$ to correct the acidosis significantly decreased the rate of valine decarboxylation. This is important because BCAAs are essential amino acids that are not only rate limiting for protein synthesis, but also have a regulatory effect on muscle protein metabolism.

Cellular mechanisms that mediate the catabolic effect of acidosis include up-regulation of the ubiquitin-proteasome pathway and activity of the muscle enzyme branched-chain keto acid dehydrogenase (BCKAD). Mitch et al. (5) and Mitch and Goldberg (6) were the first to discover activation of the adenosine triphosphate (ATP)-dependent ubiquitin-proteasome pathway by metabolic acidosis. Proteins degraded by this pathway are first covalently tagged with a chain of ubiquitin monomers. The protein is recognized by the large 26s proteasome complex, which releases ubiquitin for recycling. The protein is then unfolded and cleaved into small peptides that are rapidly degraded to amino acids by cytoplasmic peptidases. Price et al. (7) showed that incubating muscles from uremic acidotic rats with an inhibitor of the proteasome blocked muscle proteolysis. Activation of this ATP-dependent pathway in muscles of uremic rats with acidosis is associated with an increase in messenger RNA (mRNA) encoding for ubiquitin and for subunits of the proteasome. This increase in mRNA was abolished if metabolic acidosis was corrected in these uremic rats (7). While these findings are intriguing, it remains to be determined how acidosis targets proteins for degradation. Insulin deficiency (8) and inflammatory cytokines (9) are other signals that cause activation of the ATP-dependent ubiquitin-proteasome pathway and may contribute to protein catabolism in uremia.

Decarboxylation of BCAA is the first committed step in their oxidation. This reaction is catalyzed by the enzyme BCKD, which is the rate-limiting step in BCAA oxidation. May et al. (10) found an increase of BCKD activity in muscles from acidotic rats likely related to an increase in the amount of the enzyme found in the dephosphorylated active form. An increase in mRNA encoding for subunits of the enzyme was also shown (11). The level of BCKD subunit proteins in muscles of acidotic rats was not changed, however, perhaps reflecting an increase not only in enzyme synthesis, but also in its degradation.

In summary, there is strong evidence from animal studies that mild metabolic acidosis induces protein catabolism in uremic animals, a process that is reversed with correction of the acidosis.

Human Studies

Before examining the evidence from human studies concerning the impact of correcting metabolic acidosis on protein metabolism in patients with CKD, it may be helpful to briefly comment on the methods used to study protein metabolism.

Protein kinetics can be studied on various levels. The simplest method of evaluating protein metabolism is nitrogen balance. This technique simply computes the difference between nitrogen ingested and nitrogen excreted. Negative nitrogen balance implies a catabolic state, while positive nitrogen balance is compatible with an anabolic state. However, measurement of dietary nitrogen intake and urinary nitrogen output does not reflect the ongoing dynamic state of protein turnover. The daily turnover of protein in an adult consuming 60 g of protein per day is about 300 g. In other words, 300 g of protein is both broken down and synthesized daily. It is not the absolute amount of either protein synthesis or degradation that results in net anabolism or catabolism, but rather the imbalance between these two processes. Whole body protein turnover can be studied using isotopic tracers. Studies using radiolabeled leucine allow the following three parameters to be measured: protein synthesis, protein breakdown, and amino acid oxidation.

A summary of human studies that examined the effect of correction of acidosis on protein metabolism in patients with CKD is provided in Table 1. One should note that the endpoint in these studies was parameters related to protein metabolism rather than clinical outcomes.

TABLE 1. Summary of studies examining the impact of correction of metabolic acidosis on protein metabolism in CKD patients

Reference	Design	Methods	Outcome
12	Six patients with CKD (creatinine clearance 9.5 ml/min) and metabolic acidosis (plasma HCO_3 15.8 mmol/L), treatment with $NaHCO_3$ or NaCl	Nitrogen and potassium balance	$NaHCO_3$ raised plasma HCO_3 to 23.4 mmol/L and resulted in positive nitrogen and potassium balance.
13	Eleven patients with CKD (mean serum creatinine 570 μmol/L) and metabolic acidosis (mean serum HCO_3 19 mmol/L), maintained on protein-restricted diet, studied before and after 8 weeks supplementation with $NaHCO_3$	Urinary urea excretion, measurement of midarm circumference.	Treatment with $NaHCO_3$ increased plasma HCO_3 to 24 mmol/L. There was a nonsignificant decrease in urinary urea excretion and no change in midarm circumference.
14	Six patients with CKD (mean GFR ~13 ml/min) and mean serum HCO_3 ~17 mmol/L, studied on unrestricted protein intake and before and after $NaHCO_3$ while on a low-protein diet.	Urinary nitrogen excretion, urine 3-methyl histidine: creatinine ratio	$NaHCO_3$ raised plasma HCO_3 to 24.3 mmol/L and resulted in decreased urinary nitrogen losses and urine 3-methyl histidine:creatinine ratio.
15	Nine patients with CKD (mean creatinine clearance 24 ml/min) and metabolic acidosis (mean serum HCO_3 20 mmol/L), four patients with CKD and normal serum HCO_3, eight healthy control subjects.	Forearm perfusion and ^{3}H-phenylalanine kinetics	Patients with acidosis had higher protein turnover, but net proteolysis was not significantly increased.
16	Nine patients with CKD (serum creatinine 565–810 μmol/L) and metabolic acidosis (mean serum HCO_3 15 mmol/L), studied before and after 2- to 4-week treatment periods with $NaHCO_3$ and then equimolar NaCl.	Leucine kinetics	$NaHCO_3$ treatment increased plasma HCO_3 to 21 mmol/L and caused a decrease in leucine appearance, disappearance, and oxidation.
17	Nine patients with CKD (mean serum creatinine 1087 μmol/L) and metabolic acidosis (mean total CO_2 19 mmol/L) and five normal control subjects, before and after treatment with $NaHCO_3$.	Leucine kinetics	Treatment with $NaHCO_3$ increased total CO_2 to 25.5 mmol/L. With correction of metabolic acidosis, patients adapted to their lower protein intake by decreasing amino acid oxidation and protein degradation.

In a widely quoted study by Papadoyannakis et al. (12), six patients with CKD and metabolic acidosis underwent nitrogen and potassium balance studies before and after treatment with either $NaHCO_3$ or sodium chloride (NaCl). There were a total of 200 balance studies performed. While the experimental design was not exactly one of a "balance" study, it was noted that calorie, protein, and potassium intake were calculated by the same dietitian from standard tables and did not differ significantly between control and supplementation periods. Compared to treatment with NaCl, in all six patients, correcting metabolic acidosis resulted in positive nitrogen balance and net potassium gain. However, if the balance data were taken as representative daily averages, some patients would have accumulated about 4 g of nitrogen per day. This translates into the synthesis of 25 g of protein and a daily gain of 125 g of muscle. This is rather unlikely and raises concerns about the balance data.

Jenkins et al. (13) studied 11 patients with CKD and metabolic acidosis. Again, the experimental design was not a "balance" study, although it was mentioned that patients were stabilized on a 40 g protein diet for 2 months prior to the study. With the correction of metabolic acidosis, there was a significant decrease in blood urea nitrogen (BUN). There was, however, no significant decrease in 24-hour urea excretion and no change in body weight or measurements of midarm circumference.

Williams et al. (14) examined six CKD patients with metabolic acidosis. Of note is that acidotic patients on an unrestricted protein intake (~80 g/day) were in positive nitrogen balance. However, the presence of metabolic acidosis seemed to limit the normal adaptive decrease in protein oxidation in response to dietary protein restriction. With correction of metabolic acidosis, the nitrogen balance became positive in patients on restricted protein intake. Correcting metabolic acidosis also resulted in decreased muscle myofibrillar protein degradation, as assessed by measurement of the urinary 3-methyl histidine:creatinine ratio. Similar comments about the magnitude of the change in nitrogen balance, as in the study by Papadoyannakis et al. (12), apply here. Patients on unrestricted protein intake were in positive balance of about 4 g of nitrogen per day. The difference in nitrogen excretion before and after correction of acidosis would account for the loss of approximately 1 kg of muscle per month in acidotic subjects. There was, however, no change in body weight during the study. Furthermore, a large proportion of the nitrogen excretion in these patients was nonurea nitrogen (NH_4^+). Indeed, the rate of excretion of NH_4^+ was measured to be in excess of 150 mmol/day in patients on unrestricted protein intake. These measured high rates of excretion of NH_4^+ are surprising considering that these patients had very low glomerular filtration rates (GFRs).

Garibotto et al. (15) measured muscle protein turnover across the forearm in nine patients with CKD and metabolic acidosis and in eight control subjects using ^{3}H-phenylalanine kinetics. Since this amino acid is not metabolized in muscle, its rate of appearance in blood should reflect protein catabolism, whereas its rate of disappearance should reflect protein synthesis. Patients with acidosis had a higher rate of protein turnover, as

indicated by a higher rate of uptake and release of phenylalanine compared to control subjects. The high rate of protein degradation, however, was balanced by a high rate of protein synthesis, and net proteolysis was only slightly increased. Phenylalanine net release (net proteolysis) was inversely correlated to plasma HCO_3 concentration. However, this study had a small number of patients; seven of nine patients had plasma HCO_3 values of 20–22 mmol/L. The strength of this inverse correlation seems to be largely due to two patients at opposite ends of the spectrum of plasma HCO_3 concentrations.

Reaich et al. (16) studied the effects of correcting metabolic acidosis on protein metabolism in CKD patients using leucine kinetics. Treatment with $NaHCO_3$ but not NaCl led to a reduction in leucine appearance, disappearance, and oxidation, suggesting that correction of acidosis removed a catabolic stimulus. Body weight was not affected by any of the study conditions. Of note is that the study was not a double-blind crossover trial and the sequence of interventions was not randomized. Protein intake was not controlled or formally evaluated. It is possible, although not likely, that changes in leucine oxidation may have been caused by a decrease in protein intake during the $NaHCO_3$ period.

Lim et al. (17) studied protein metabolism using leucine kinetics in nine acidotic patients with advanced renal dysfunction and five normal control subjects before and after correction of metabolic acidosis. Since these investigators attempted to control dietary factors by prescribing a diet during the study that matched each subject's previous food record, protein intake was held constant in each individual but was not standardized across individuals. Protein intake was significantly lower in CKD patients (0.9 g/kg/day). Correction of metabolic acidosis allowed these patients with advanced renal failure to appropriately down-regulate protein degradation and amino acid oxidation in response to their lower protein intake, while maintaining a normal rate of protein synthesis.

In summary, while the findings of human studies are consistent with those from animal experiments, the evidence is not robust. Nevertheless, taken together, there appears to be a benefit to treating mild metabolic acidosis in CKD patients in terms of reducing protein catabolism. The issue is to try to balance the possible benefit and harm of treating metabolic acidosis in these patients when irrefutable evidence might not be forthcoming. Concerns about the administration of $NaHCO_3$ to these patients relate mainly to the sodium load causing extracellular volume expansion and aggravating hypertension in these patients with a high prevalence of cardiac disease. To address these issues, and to decide on an appropriate dose of $NaHCO_3$, one needs to consider how acid-base balance is maintained.

Acid-Base Balance

For this analysis, the mechanism of renal disposal of each of the three components of nonvolatile net acid production needs to be examined.

Sulfuric Acid

Sulfuric acid (H_2SO_4) is produced from the metabolism of sulfur-containing amino acids (18). The affinity of SO_4^{2-} for H^+ is so low that SO_4^{2-} in the urine cannot bind a significant number of H^+ ions even at the lowest possible urine pH. Acid balance is achieved when SO_4^{2-} is excreted in the urine with an equivalent amount of NH_4^+. The usual rate of excretion of NH_4^+ in an adult consuming a typical North American diet is close to 30–40 mmol/day.

Phosphoric Acid

The metabolism of dietary nucleic acids (DNA, RNA) as well as phospholipids yields phosphoric acid ($H_2PO_4^-$) (equation 1). These $H_2PO_4^-$ ions dissociate immediately at body fluid pH to yield H^+ and HPO_4^{2-} ions. Because the pK of HPO_4^{2-} is approximately 6.8, when the urine pH is in the usual range (approximately 6), virtually all the H^+ formed from $H_2PO_4^-$ is eliminated as $H_2PO_4^-$. Hence there is no net acid-base impact of this metabolic process of phosphate turnover:

$$H_2PO_4^- \text{ (from diet)} \rightarrow H^+ + HPO_4^{2-} \text{ (body)} \rightarrow H_2PO_4^- \text{ (urine)}. \quad (1)$$

Endogenous Acid Production

Organic anion excretion represents the production of endogenous acids (19), yet accounting for the elimination of H^+ produced with these organic acids has not been included in the net acid excretion (NAE) formula (equation 2). To address this issue one needs to consider how base balance is maintained, because the diet also provides an alkali load that is derived mainly from ingested fruits and vegetables. In the NAE formula, dietary alkali is supposedly accounted for by being eliminated as excreted HCO_3^-. There is not, however, an appreciable quantity of HCO_3^- in the 24-hour urine (urine pH is close to 6.0). Thus base balance needs to be examined in a different way (20,21). The first step in the process of base balance is that the alkali load stimulates production of endogenous acids (e.g., citric acid). The second step is that the H^+ produced titrates dietary alkali. The third step is that the alkali load decreases the reabsorption of citrate anions by the proximal tubule cells and therefore augments their excretion in the urine. Excretion of these organic anions makes them end products of metabolism and hence completes the process of eliminating the dietary alkali load. Therefore excretion of organic anions does not represent a net H^+ gain because it is the response to ingested dietary alkali:

$$NAE = NH_4^+ + TA - HCO_3^-. \quad (2)$$

In summary, acid balance is maintained by excreting NH_4^+ at a rate that is equal to the rate of excretion of SO_4^{2-} in milliequivalent (mEq) terms. The usual rate of excretion of NH_4^+ in an adult consuming a typical North American diet is close to 30–40 mmol/day. Therefore, in patients with CKD, once metabolic acidosis is corrected, the daily dose of $NaHCO_3$ needed to maintain acid

balance would appear to be at most 30–40 mmol/day. This assumes no renal HCO_3 generation (no NH_4^+ excretion) and a "usual" dietary protein intake. This sodium load is relatively small and not likely to cause significant adverse effects.

Conclusion

Evidence from animal and human studies indicates that acidosis is a catabolic signal, particularly when protein intake is limited. Well-designed animal studies document an improvement in protein metabolism in response to correction of metabolic acidosis with $NaHCO_3$. Data from human studies have a number of limitations so that one cannot draw definitive conclusions based on the available evidence about the merit of correcting mild metabolic acidosis in CKD patients. On the other hand, it appears that the dose of $NaHCO_3$ required to maintain acid balance is small and the sodium load is small and unlikely to pose a significant risk.

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The majority of patients with severe renal failure necessitating chronic dialysis have metabolic acidosis (1). Although it seems reasonable to assume that normalization of plasma bicarbonate concentration would be beneficial, this assumption might not be correct. Here we address several questions pertaining to the acid-base status of patients requiring chronic dialysis.

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Seminars in Dialysis—Vol 17, No 5 (September–October) 2004 pp. 358–360

What is the Impact of Metabolic Acidosis on Organ Function?

Several adverse effects have been attributed to the metabolic acidosis associated with chronic renal failure.

Risk of Cardiovascular Death

A retrospective analysis of laboratory data obtained from more than 12,000 patients with end-stage renal disease (ESRD) receiving chronic hemodialysis yielded an increased risk of death when predialysis plasma bicarbonate concentration was low (less than 17 mEq/L) (2).

Because cardiovascular disease is the most common cause of death in dialysis patients, it has been inferred that the prevailing metabolic acidosis somehow increases the risk of cardiovascular death. Obviously these observational studies cannot establish causality between metabolic acidosis and cardiovascular death. Acute severe metabolic acidosis (blood pH less than 7.1) is associated with depression of cardiovascular output and increased prevalence of arrhythmias (3). However, lesser degrees of acidemia have not been implicated in such pernicious effects (3). Whether the mild chronic acidemia usually observed in dialysis patients can increase the risk of cardiovascular death remains to be determined.

Bone Disease

Bone disease in chronic renal failure is primarily due to abnormalities of calcium, phosphorus, parathyroid hormone, and vitamin D, as well as exposure to toxins such as aluminum, but metabolic acidosis has also emerged as a potentially important factor. Metabolic acidosis can induce bone resorption, inhibit bone formation, and increase the levels of parathyroid hormone (PTH) or enhance end-organ sensitivity to PTH, thereby accentuating the hormone's deleterious effects on bone (4). In animals, prolonged metabolic acidosis is associated with the development of osteoporosis or exacerbation of PTH-induced bone disease (4). In some reported cases of humans with renal failure, the severity of osteomalacia and osteitis fibrosa cystica has been related to the severity of the accompanying metabolic acidosis (4).

In controlled studies performed in stable hemodialysis patients with various forms of bone disease, amelioration of metabolic acidosis attenuated the increase in PTH and reduced bone resorption in those with osteitis fibrosa, whereas it improved bone formation in patients with adynamic bone disease (5). Also, normalization of plasma bicarbonate concentration in patients with elevated PTH levels was associated with increased sensitivity of PTH secretion to ionized calcium and, theoretically, an enhanced therapeutic response to vitamin D. Further, the direct beneficial effects of vitamin D on bone were augmented (6). Although metabolic acidosis is not likely to be a dominant factor, these studies indicate that it can contribute to the development of bone disease in dialysis patients.

Muscle Wasting

In rats with chronic renal failure, the presence of metabolic acidosis increases degradation of muscle without affecting protein synthesis (7). Also, metabolic acidosis reduces expression of insulin-like growth factor and growth hormone receptor (8). Some, but not all, studies in patients on chronic dialysis confirmed the negative impact of metabolic acidosis on muscle metabolism. Thus correction of even mild degrees of metabolic acidosis by administering oral bicarbonate or raising the dialysate base concentration decreased protein degradation and urea generation, improved protein balance, and increased muscle mass (9).

Albumin Synthesis

Metabolic acidosis decreases albumin synthesis in subjects with normal renal function, and full correction of acidosis increases plasma albumin concentration in stable hemodialysis patients (10). This effect was not observed, however, in other studies of dialysis patients when only partial correction of the acidosis was achieved (11).

Insulin Sensitivity

Exposure to an acidic milieu in vitro impairs insulin sensitivity (12). Normalization of plasma bicarbonate improves insulin sensitivity of diabetic patients with renal failure prior to and after initiation of chronic dialysis (12). Beyond its impact on glucose homeostasis, altered insulin sensitivity might have an impact on other metabolic abnormalities and blood pressure regulation in dialysis patients.

β_2-Microglobulin Levels

There is an inverse correlation between the concentration of plasma bicarbonate and β_2-microglobulin levels in patients with chronic renal failure (13). Moreover, patients dialyzed against bicarbonate-based dialysate, who had a higher plasma bicarbonate concentration than those dialyzed against acetate-based dialysate, also had a lower serum level of β_2-microglobulin (13). These observational studies suggest that metabolic acidosis could contribute to the abnormal accumulation of β_2-microglobulin in dialysis patients, but a role for acetate itself rather than the graded degrees of metabolic acidosis cannot be excluded.

What is the Optimal Plasma Bicarbonate Concentration in Dialysis Patients?

Although predialysis plasma bicarbonate concentrations less than 20 mEq/L were frequent when acetate was the sole source of base in the dialysate (14), such low values are less common with the use of bicarbonate-based dialysate at a concentration of 35 mEq/L (14). Nonetheless, in the first 1000 patients randomized in the HEMO study, who were dialyzed against a bicarbonate-based dialysate at 35 mEq/L, mean predialysis plasma bicarbonate concentration was 21.6 mEq/L, whereas 25% of the patients had values less than 19 mEq/L (15). Typically plasma bicarbonate concentration rises by 4–5 mEq/L during dialysis, but returns gradually to predialysis levels over the ensuing 48 hours. The decrease in plasma bicarbonate concentration depends, in part, on endogenous acid production (a reflection of protein intake), the "acid space" (approximately 50% of body weight), and the duration of the interdialytic period. Therefore plasma bicarbonate concentration can be lower following a longer interdialytic period.

Elevation in dialysate bicarbonate concentration to 39–40 mEq/L raises predialysis plasma bicarbonate concentrations to 24–25 mEq/L (16). On completion of

dialysis, blood pH and plasma bicarbonate increase to approximately 7.5 and 28–32 mEq/L, respectively (17). This mild alkalemia is short lived, with values returning to normal over the ensuing 48 hours.

In patients maintained on continuous ambulatory peritoneal dialysis (CAPD), plasma bicarbonate concentration can be slightly below normal (mean 22 mEq/L), particularly if the base concentration in the dialysate is 35 mEq/L (14). Increasing the dialysate base to 40 mEq/L results in complete normalization of plasma bicarbonate concentration in the majority of patients. In all patients, plasma bicarbonate concentration remains stable throughout the day, in contrast to the temporal variability of hemodialysis patients.

Given the adverse effects associated with metabolic acidosis in dialysis patients, it would seem reasonable to raise plasma bicarbonate concentration toward normal. However, what the optimal plasma bicarbonate concentration is in subjects with either normal renal function or renal failure remains unclear. In one large series, mean arterial blood pH and plasma bicarbonate concentration were 7.40 ± 0.02 and 25.4 ± 0.09 mEq/L in normal males, and 7.41 ± 0.02 and 24.4 ± 1.3 mEq/L in normal females (18). However, Sebastian et al. (19) and Frasetto et al. (20) have argued that normal acid-base parameters might not be sufficient to prevent the abnormalities in bone and muscle associated with the contemporary net acid-producing diet. Administration of sufficient bicarbonate to neutralize the endogenous acid load in postmenopausal women, while raising plasma bicarbonate concentration by only 1.8 ± 1.1 mEq/L improved bone metabolism and nitrogen balance (19,20). They inferred from these studies that even normal acid-base parameters are not optimal for muscle and bone metabolism.

Similar studies have not been performed in dialysis patients, therefore it is not possible to determine if results achieved in normal subjects can be extrapolated to patients with renal failure on dialysis. The optimal plasma bicarbonate concentration in dialysis patients remains to be determined.

What are the Adverse Effects of Correcting Metabolic Acidosis?

Utilization of a high-bicarbonate dialysate (40 mEq/L) can produce a transient alkalemia (17). Because alkalemia can facilitate vascular calcifications, patients dialyzed against a bicarbonate-based dialysate at 40 mEq/L, who had a mild postdialysis alkalemia, were compared with those treated against a bicarbonate-based dialysate at 36 mEq/L, who had normal postdialysis plasma bicarbonate concentrations but mild predialysis metabolic acidosis. No differences in total plasma calcium, ionized calcium, calcium-phosphorus product, or the risk of metastatic calcifications assessed by biochemical means were found (17). Since sophisticated techniques for identifying calcifications were not used, the presence of some calcifications cannot be excluded. Also, patients with poor calcium and phosphorus control were excluded. Finally, similar studies have not been performed in CAPD patients. Therefore further studies are required to determine the potential effect of the high-bicarbonate dialysate on development of vascular calcifications in hemodialysis and peritoneal dialysis patients.

In summary, although considerable progress has been made in delineating the adverse effects associated with metabolic acidosis and achieving normalization of the acid-base parameters in dialysis patients, much work remains to be done to determine what the optimal level of plasma bicarbonate might be in these patients and how best to achieve it.

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The most significant acid-base disorder faced by end-stage renal disease (ESRD) patients is metabolic acidosis. Exceptions to this rule are rare and are generally limited to patients with ESRD due to Bartter's syndrome or patients with mild to moderate renal disease dialyzed primarily for control of volume overload in severe congestive heart failure. Such unusual individuals may exhibit metabolic alkalosis as a primary condition. However, the vast majority of ESRD patients suffer acidosis and acidemia due to their inability to excrete acid and generate new bicarbonate. This must always be kept in mind when analyzing any acid-base abnormality in the dialysis patient. These facts notwithstanding, respiratory acid-base abnormalities can and do complicate the lives of dialysis patients and the physicians who care for them. Because nephrologists are, rightly, primarily concerned about the metabolic acidosis afflicting their patients, the occurrence of respiratory acid-base abnormalities is underappreciated. Increased awareness of these issues and their effects should improve the care given to patients in whom they develop.

General Acid-Base Definitions and Issues of Interpretation

One cannot reliably diagnose an acid-base disorder from a solitary serum bicarbonate value. A low serum bicarbonate concentration suggests either metabolic acidosis or respiratory alkalosis; an elevated serum bicarbonate concentration is equally compatible with respiratory acidosis or metabolic acidosis. The medical history of the patient should always be used when generating an hypothesis to explain a given abnormality of serum bicarbonate concentration (Table 1). Thus, in the presence of renal failure, a low serum bicarbonate concentration most often indicates insufficiently treated metabolic acidosis due to impaired renal function, but the presence of an additional disorder, or even misleading laboratory data, cannot be excluded (1). Similarly a normal serum bicarbonate concentration does not necessarily indicate that success has been achieved by dialysis therapy. Rather, the patient may have a second disorder that also affects the bicarbonate concentration; in this instance, metabolic alkalosis, perhaps due to emesis or bicarbonate ingestion, or respiratory acidosis, although the impact of respiratory acidosis on the serum bicarbonate is limited in renal failure (2). For the ESRD patient, as for any other individual, accuracy of interpretation demands further data in terms of a set of blood gas measurements. Because hemodialysis patients are regularly exposed to treatments that have a major impact on serum bicarbonate, carbon dioxide (CO_2) tension, and pH, knowing the timing of a blood gas determination relative to the time of a hemodialysis treatment is crucial when one interprets the results.

TABLE 1. Special acid-base considerations in dialysis patients

The universality of metabolic acidosis
The importance of blood gas sample timing relative to dialysis treatment
The likelihood of post dialysis metabolic alkalosis
The normality of respiratory compensation
The absence of metabolic compensation
The severity of pH shifts in respiratory acid-base disorders

Respiratory acidosis is a primary pathophysiologic event characterized by a primary decrease in alveolar ventilation relative to CO_2 production. Respiratory alkalosis is a primary pathophysiologic event characterized by an increase in alveolar ventilation relative to CO_2 production. The term compensation describes a secondary physiologic response to a primary abnormality. Compensation always crosses systems and serves to correct the blood pH toward normal. Metabolic, that is, renal, compensation occurs in response to respiratory acid-base disorders; respiratory compensation occurs in metabolic acid-base disorders. The increase in minute ventilation seen in response to metabolic acidosis that reduces the arterial CO_2 tension and raises the arterial pH is termed respiratory compensation. Though rarely seen, a decrease in minute ventilation in response to severe metabolic alkalosis that raises the blood CO_2 tension and lowers the arterial blood pH is also a form of respiratory compensation. Both types of respiratory compensation result from the detection of abnormal pH by central chemosensors and subsequent alteration of ventilatory rate within bounds set by the effects of ventilatory change on oxygen tension and the maximum minute ventilation. Because of the absence of renal function, no metabolic compensation for respiratory disorders is possible in the dialysis patient. In ESRD, respiratory compensation occurs normally, but metabolic compensation is constrained by the absence of kidney function. Serum bicarbonate will change in response to a respiratory acid-base disorder only to that degree driven by physicochemical buffering.

Dialysis patients generally exhibit some degree of chronic mild to moderate metabolic acidosis with appropriate respiratory compensation. The respiratory compensation to metabolic acidosis is necessarily incomplete, that is, it will never fully correct the serum pH to normal. Most dialysis patients exhibit normal respiratory adaptation to acidosis (3–6). In the absence of perfect replacement of bicarbonate lost to buffering and the failure of the diseased kidney to generate sufficient new bicarbonate, the expected average interdialytic acid-base balance of the hemodialysis patient includes some

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Seminars in Dialysis—Vol 17, No 5 (September–October) 2004 pp. 361–364

degree of depression of bicarbonate (typically a bicarbonate value of 23 mEq/L or higher before dialysis), mild depression of the arterial pCO_2, and an arterial pH less than 7.4. The predialysis bicarbonate, it should be noted, is also significantly affected by excessive weight gain; an increase in gain of 1 kg may lower the measured bicarbonate concentration by as much as 1 mEq/L.

To treat the acidosis of ESRD, most dialysis units in the United States now dialyze with an alkaline, bicarbonate-based dialysate, generally dialyzing against a final bicarbonate concentration near 35 mEq/L. Immediately after a hemodialysis session, the serum bicarbonate will tend to exceed normal, the pCO_2 will rise to normal, and the serum pH may exceed 7.4. Over the course of the next 2–3 days this will change as bicarbonate is consumed to buffer generated and ingested fixed acids. Respiratory responses being normal in ESRD, ventilation should vary in concert.

Serum bicarbonate will increase slightly as carbonic acid dissociates in respiratory acidosis, but there can be no renal response in terms of generating new bicarbonate in the ESRD patient. Adaptation is limited; respiratory acidosis results in more significant decreases in pH for any given degree of respiratory failure. The lack of adaptive response also renders diagnosis more direct. As Gennari (3) points out, "a P_{CO_2} 5 mmHg greater than that expected for the current bicarbonate establishes the presence of respiratory acidosis." The "expected" pCO_2 can be calculated from the following two equations:

$$pCO_2\ (mmHg) = 40 - 1.3 \times (24 - HCO_3^-),$$

when the $[HCO_3^-]_p < 24$ mEq/L, and

$$pCO_2\ (mmHg) = 40 + 0.7 \times (HCO_3^- - 24),$$

when the $[HCO_3^-]_p > 24$ mEq/L (3).

Unique Respiratory Conditions Related to Hemodialysis Treatment (Table 2)

Hypoxemia and Respiratory Alkalosis

Hypoxemia and respiratory alkalosis were recognized as complications of hemodialysis in the 1970s (7–13). Past hypotheses of the origin of dialysis hypoxemia include generation of pulmonary microemboli, intravascular leukostasis, acetate-driven increases in oxygen consumption, and diffusive CO_2 loss across the dialysis membrane. The last of these is the most widely accepted. Acetate-buffered dialysis solution contains little CO_2, thus when acetate dialysis is used, there is a large gradient that favors the movement of CO_2 across the membrane from the blood to the bath. Blood entering the kidney has a pCO_2 of about 40 mmHg; the bath contains little or no CO_2. The transfer of CO_2 driven by this gradient results in considerable CO_2 clearance by the artificial kidney. The value of CO_2 clearance by the artificial kidney approached 2–3 mmol/min with the relatively small surface area artificial kidneys used at the time of past studies (14). The addition of CO_2 clearance by the dialyzer thus takes the total minute clearance (ventilation plus dialyzer) beyond the metabolic needs of the patient, who generally is quietly seated in a recliner. By definition, this condition, CO_2 excretion in excess of metabolic generation, is respiratory alkalosis.

TABLE 2. Respiratory issues unique to dialysis

In the presence of acetate dialysate
Dialysis hypoxemia
Dialysis respiratory alkalosis
With the use of "cartridge" dialysis machines
Acute respiratory acidosis due to CO_2 dumping
Respiratory acidosis while on a ventilator
Sleep apnea in peritoneal dialysis
Transient respiratory alkalosis
Pleural effusion due to transdiaphragmatic leak
Dialyzer "ventilation"

Carbon dioxide clearance is less an issue when bicarbonate bath is used, because bicarbonate bath generates its own substantial CO_2 tension when a high bicarbonate concentration alkali bath is mixed with an acid bath to generate dialysate. Thus no important gradient exists. Studies comparing the effects of bicarbonate and acetate baths in individual patients using the same dialysis membranes have shown that CO_2 tension actually rises during dialysis when bicarbonate dialysate is utilized, whereas there is a sharp decrease in CO_2 tension when acetate baths are used (12,13).

As respiratory alkalosis develops due to CO_2 clearance during acetate dialysis, the respiratory center decreases minute ventilation to correct the mismatch between ventilation and CO_2 generation. In the absence of serious hypoxia, the effect of lower ventilatory rate on oxygen tension will not be significant enough to override the effect of pH. Because ventilation is down-regulated, mild hypoxia develops. Intradialytic hypoxemia is well known during hemodialysis treatments using acetate-buffered dialysate. Characteristically hypoxemia occurs within the first hour of treatments when acetate is used as a buffer, and results in a decrease in oxygen tension of about 10 mmHg. Hypoxemia is less severe and somewhat delayed in onset if bicarbonate dialysate is utilized. The pH returns to predialysis levels rapidly when acetate is used, and somewhat more slowly when bicarbonate is used.

CO_2 Generation Related to Cartridge Dialysis Systems

Cartridge-based dialyzers (such as the Redy-Sorb system) are not commonly used now due to the lower efficiency of these machines and the greater availability of other portable dialysis systems capable of generating dialysate from concentrate on site. Cartridge-based systems use a urease reaction to generate bicarbonate and ammonium (later exchanged for protons) from urea to replace bicarbonate that has been transferred to the patient by diffusion (15). Because of sharp drops in dialysate pH within the cartridge system, high pCO_2 tension is generated in the bath, exceeding 200 mmHg

after 2 hours. Whenever a patient was disconnected from the machine for a time but circulation of dialysis solution within the cartridge is continued, even more extreme levels of CO_2 are generated within the device. This is known to result in a syndrome of acute respiratory acidosis on reconnection of the patient, who may suffer headaches, flushing, "oppression," and immediate hyperventilation (16,17). In addition, if the patient being dialyzed depends on mechanical ventilation, the rate of CO_2 addition to the blood may exceed the fixed rate of removal, resulting in an "artificial" respiratory acidosis (18).

Peritoneal Dialysis

Once a patient is accommodated to peritoneal dialysis, the effect of dialysis on respiratory function is small. Because therapy is both slow and frequent, acid-base shifts are not prominent. In some studies hypoxemia and respiratory alkalosis were noted upon the onset of treatment. The presence of the typical 2 L exchange volume was noted to initially depress most lung volumes, resembling a mild restrictive defect (19). Repeated measurements over time show adaptation to the additional volume and a decrease in hypoxemia (20–22). Typically the pO_2 decreases 5 mmHg in the sitting position and 8 mmHg with the patient supine, with a detectable decrease in functional residual capacity when the individual is new to dialysis; later these changes in pO_2 diminish. Still, significant pulmonary disease remains a contraindication to peritoneal dialysis.

There is one other peritoneal dialysis-specific complication to consider. Hydrothorax is known to occur in approximately 1.6% of continuous ambulatory peritoneal dialysis (CAPD) patients (23). The presence of a high glucose concentration and low protein content in the pleural fluid is strongly suggestive of a "leak" across the diaphragm. Radionuclide studies may confirm direct transfer of fluid across the diaphragm and discontinuation of peritoneal dialysis may be required.

Sleep Apnea

Sleep apnea has emerged as a significant issue for ESRD patients (24). Its prevalence ranges from 27% to 41% in both hemodialysis and peritoneal dialysis patients (25). Chronic hypocarbia, metabolic acidosis, uremic toxins, hemodialysis, peripheral neuropathies, and underlying diseases have all been suggested as causes. Its occurrence in peritoneal dialysis as well as hemodialysis patients would seem to exclude hemodialysis as a cause, and the disorder seems to be less associated with obesity here than in the nonrenal population (26). Zocalli et al. (27) have recently linked sleep apnea with the occurrence of autonomic neuropathy in dialysis patients.

Sleep apnea may be diagnosed by observation of snoring or disordered breathing while patients sleep at the hemodialysis unit, or more prospectively, by the administration of appropriate symptom surveys (28). Polysomnography should be used to confirm the diagnosis. Whereas the diagnosis is sometimes suggested by elevation of serum bicarbonate in non-ESRD patients, it is less likely that an elevated serum bicarbonate concentration would be detected in the dialysis population. The obese patient with ESRD due to focal glomerulosclerosis may be at greater risk (29). Metabolic alkalosis secondary to bicarbonate abuse has also been noted as a cause of sleep apnea.

The major effects of sleep apnea in the dialysis patient population are increased cardiovascular mortality, elevation of blood pressure, and signs of pulmonary hypertension. Nocturnal hypoxemia appears to directly increase the risk for adverse cardiovascular outcomes (30). The usual treatment is the same as in the non-ESRD population, and includes changing sleep posture, positive airway pressure, oxygen, and weight loss when indicated (31). However, nocturnal dialysis has been shown to correct the abnormalities (32). The effect of nocturnal dialysis may have been due to the increased schedule of dialysis, but a role of the kidney in oxygenating blood in the extracorporeal circuit seems possible (33).

Other Considerations

Finally, it is uniquely dangerous for a patient with ESRD to develop respiratory alkalosis due to either acute or chronic lung disease. The ability of the normal kidney to lose bicarbonate and retain acid when CO_2 tension falls protects the normal patient from the effects of severe alkalemia. Even though the normal renal response to respiratory alkalosis can completely correct the serum pH, it does so at the cost of buffer capacity. The patient with fully compensated respiratory alkalosis is at increased risk for dangerous acidemia if a metabolic acidosis of any sort is superimposed on the compensated respiratory alkalosis.

Consider then the problem of the hemodialysis patient with chronic respiratory alkalosis due to asthma, ongoing pneumonia, pleural effusions, heart failure, emphysema, or chronic obstructive pulmonary disease. This patient starts with a predialysis serum bicarbonate concentration that is depressed due to metabolic acidosis and a CO_2 tension lowered by respiratory compensation. When respiratory alkalosis is superimposed on this state, the pH will rise and the bicarbonate will fall slightly as buffers shift, but no metabolic adaptation follows. The patient will not suffer the loss of buffer capacity seen in the patient with normal renal function, but the increase in pH will, as a consequence, be greater. When the patient is then dialyzed, a mass of bicarbonate is rapidly added to the system. This corrects the metabolic acidosis, but is clearly a "maladaptive" response to respiratory alkalosis. If enough bicarbonate is given, a state of metabolic alkalosis is added to respiratory alkalosis, and the serum pH will rise acutely, with all the risks inherent to severe alkalemia. Thus, in the immediate postdialysis period, the patient would be anticipated to have an increased risk for cardiac arrhythmia, confusion, decreased cerebral perfusion, decreased dissociation of calcium from serum proteins, seizure, and coma. Once past the postdialytic

peak, the serum bicarbonate will again progressively decline and pH will again be depressed before dialysis.

The principle dangers for hemodialysis patients who develop chronic respiratory alkalosis are the risk of excessive alkalemia immediately after hemodialysis treatment, and the risk that the depressed predialysis serum bicarbonate concentration will be misinterpreted as undertreated metabolic acidosis. There is strong emphasis on the correction of metabolic acidosis at present because of the perceived benefits for bone and muscle metabolism. A depressed predialysis bicarbonate concentration may indicate either metabolic acidosis or respiratory alkalosis, a combination of the two, other complex disorders, or, as has been described in the literature, laboratory error. If the practicing nephrologist reflexively responds to low bicarbonate concentration by increasing the dialysis bicarbonate or by the addition of interdialytic alkali therapy, significant harm may be done to the uncommon patient with respiratory alkalosis.

The lesson is that one should first confirm that the bicarbonate is low by repeating the measurement of bicarbonate in a local laboratory if the usual monthly samples are sent to a distant site for analysis, and then, if an erroneous value is thus excluded, that one should then proceed to measure a set of arterial blood gas values and carefully interpret the results. A predialysis sample should show a mildly low pH and CO_2 in the well-treated patient, marked depression of pH and low pCO_2 in the acidemic patient, and markedly depressed pCO_2 but relatively high pH in combined respiratory alkalosis and chronic metabolic acidosis.

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