Metabolic Acidosis and Protein Metabolism in Dialysis Patients

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INTRODUCTION

Severe metabolic acidosis in experimental animals and man has been shown to be a strong stimulus for protein catabolism[1]. Moderately low pre-dialysis serum bicarbonate concentrations are still common in hemodialysis patients despite the use of bicarbonate dialysate[2]. Since complete correction of cidosis may be associated with side effects of its own, an important clinical question that remains unresolved is whether mild metabolic acidosis in dialysis patients should be treated. During this presentation we will review the data on the effects of acidosis on protein metabolism in dialysis patients in an attempt to answer this question. This discussion will deal mostly with hemodialysis patients because significant acidosis is less commonly seen in CAPD patients[3].

1. Acidosis in the experimental animal

An extensive literature is available on the effect of metabolic acidosis in the experimental animal[4-7]. Both in vitro and in vivo experiments have shown that metabolic acidosis stimulates protein breakdown by activation of an ATP-ubiquitin-dependent proteolytic pathway and this effect seems to be mediated to a significant extent by cortisol[4, 7]. Experimental acidosis also stimulates the oxidation of amino acids by activating the branched-chain ketoacid dehydrogenase in rat muscle[6, 7].

2. Experimental acidosis in man

There have been well documented examples of the effects of experimental acidosis in man[8-10]. Ballmer, et al[9] showed a significant increase in the urinary excretion of nitrogen associated with metabolic acidosis (serum bicarbonate down to 19 mmol/l). Induction of acidosis with oral ammonium chloride for 7 days in 7 young healthy volunteers led to a drop of serum bicarbonate from 26±2 to 18±4 mmol/L and a simultaneous significant increase in leucine turnover rate and leucine oxidation[8]. Similar findings were observed by Straumann et al[10].

3. Acidosis in chronic renal failure patients

Table 1 summarizes the data on metabolic acidosis and protein metabolism in chronic renal failure patients. These studies[11-15] uniformly show that correction of severe acidosis (serum HCO_3 less than 20 mmol/L) in chronic renal failure patients is associated with improved nitrogen balance and decreased protein breakdown.

4. Acidosis in dialysis patients

1) Leucine kinetic studies

Studies using the radiolabeled amino acid leucine allow the determination of the following 3 parameters: protein synthesis, protein break-

Table 1. Data on Prptein Metabolism and Acid-Base Balance in CRF Patients

Ref	Patients	Method	Conclusions
11	21 CRF patients before and after supplementation with oral bicarbonate	BUN and urinary urea excretion rate	BUN and urea production decreased with bicarbonate supplements
12	6 CRF patients before and after correction of acidosis (HCO_3 from 15.8 to 23.4 mmol/L)	Nitrogen balance	Nitrogen balance improved significantly with correction of acidosis
13	9 CRF patients before and after correction of acidosis (HCO_3 from 15 to 21 mmol/L)	Leucine kinetics	Leucine turnover and oxidation rates decreased significantly with correction of acidosis
14	6 CRF patients before an after correction of acidosis (HCO_3 from 18 to 24 mmol/L)	Measurement of urinary 3-methyl histidine to creatinine ration	Correction of acidosis was associated with a decrease of protein breakdown and decreased urinary N excretion
15	9 CRF patients with HCO_3 of 20 and 4 CRF patienst with HCO_3 of 25 mmol/L	Phenylalanine kinetics	The protein turnover rate was increased in acidotics compared to normal bicarbonate and controls but the rate of net proteolysis was not significnatly different

down and amino acid oxidation. It is the oxidation of amino acids and not the overall protein breakdown what leads to urea production in the liver and determines the urea nitrogen appearance rate in a given patient.

Table 2 shows the data on leucine kinetic studies available in dialysis patients. In the first 3 studies[16-18] there is no mention of the acid-base status of the patients; the amino acid oxidation rates were high[17], normal[16] or low[18]. The fourth study examined dialysis patients with a normal serum bicarbonate and found a low amino acid oxidation rate[19]. The last 2 studies[20, 21] were performed by the same group of investigators and compared the same dialysis patients before and after correction of acidosis.

The findings were uniform : improvement of serum bicarbonate was associated with decreased overall protein turnover but no change in the rate of leucine oxidation. These findings, unlike the studies in experimental animals[4-7], during experimental acidosis in normal man[8-10] and in CRF patients[11-15], do not suggest that dialysis patients have an increase in net protein breakdown. It is unclear why dialysis patients behave differently but potential explanations include adequate dialysis and adequate food intake which may have an independent effect on protein metabolism as well as less severe acidosis.

2) Cross sectional studies

If metabolic acidosis were playing a significant negative role in the protein metabolism of dialysis patients one would predict a higher prevalence of inadequate nutrition among acidotic dialysis patients. However, no cross sectional study has shown any convincing evidence of increased prevalence of malnutrition in dialysis patients with mild metabolic acidosis[22-25, 2].

Acchiardo, et al[22] evaluated the effects of metabolic acidosis in a cross section analysis of 131 hemodialysis patients. When patients were divided in 3 groups according to their average serum total CO_2 (18.4, 20.1 and 23.3

Table 2. Data on Leucine Kinetic Studies in Dialysis Patients

Reference	Patients	Conclusions
16	2 HD patients	Increased leucine turnover rate but normal oxidation rate
17	7 HD patients	Normal leucine turnover rate but increased oxidation rate
18	10 CAPD patients	Normal leucine turnover rate but decreased oxidation
19	7 HD and 1 CAPD patients with a mean total CO_2 of 30.5 mmol/L	Normal leucine turnover but decreased oxidation rate
20	7 CAPD patients before and after correction of acidosis (HCO_3 from 19 to 26 mmol/L)	Decreased turnover rate but no effect on oxidation
21	6 HD patients before and after correction of acidosis (HCO_3 from 18.5 to 24.8 mmol/L)	Decreased turnover rate but no effect on oxidation rate

mmol/L) patients with the lowest pre-dialysis CO_2 had a significantly higher nPCR, dietary protein intake and serum phosphorus. Serum albumin, cholesterol and body weight were not significantly different in the 3 groups. Kang et al[23] performed a retrospective analysis of 106 CAPD patients divided into 3 groups according to their mean serum total CO_2 : mean total CO_2 less than 22 mmol/L; group II, mean CO_2 between 22 and 26; and group III, CO_2 greater than 26 mmol/L. Compared to group III, group I patients had significantly higher BUN, serum albumin, nPCR and ultrafiltration volume.

We[24] screened a group of HD patients and divided them in 2 groups according to their pre-dialysis serum total CO_2 : lower than 21 mmol/L and greater than 25 mmol/L. Several parameters were compared between both groups. A good correlation was found between pre-dialysis serum total CO_2 and nPCR and because patients with lower serum total CO_2 had a higher dietary protein intake the suggestion was made that low serum bicarbonate is the result rather than the cause of high nPCR.

A cross section analysis of the baseline laboratory data in the first 1,000 patients recruited to the HEMO study[2] looked for correlations between pre-dialysis serum total CO_2 and a variety of parameters. There was a significant correlation between CO_2 and nPCR, BUN, serum creatinine, serum albumin, serum potassium, serum phosphorus and age. Chaveau, et al[25] reported similar findings in the cross ectional analysis of 7,123 chronic hemodialysis patients; these preliminary data confirm a negative correlation between serum bicarbonate and nPCR and several nutritional parameters such as serum albumin, prealbumin, and lean body mass.

3) Prospective studies

Thus far, there have been 6 prospective studies in which patients are exposed to different levels of serum bicarbonate while a variety of biochemical and anthropometric parameters are followed over time. The results have been inconsistent as reviewed below[26-31].

a) Dumler, et al[26] prospectively examined the impact of acidosis on nutritional parameters in a group of 96 chronic dialysis patients divided between those with or without acidosis. Serum albumin remained unchanged in both groups. Body cell mass showed similar increases in both groups. Dietary protein intake was 23% greater in acidotic patients throughout the study period.

b) Lofberg, et al[27] studied 9 patients before and after 6 months of correction of metabolic

acidosis (serum HCO_3 concentration changed from 20.6 to 25.9 mmol/L after correction). No changes in body weight, body mass index, triceps skinfold, upper arm circumference and arm strength were observed during this period. No significant changes were recorded in the serum albumin, transferrin, IGF- 1, and nPCR after correction of acidosis.

c) Williams, et al[28] performed a study in 46 stable HD patients who were dialyzed using low bicarbonate (30 mmol/L) or high bicarbonate (40 mmol/L) dialysate in a single blind double crossover trial of two consecutive six month periods. Anthropometric indices, dialysis dose and biochemical parameters were monitored throughout the study. The only significant difference observed between the groups was an increase in triceps skinfold thickness during the high bicarbonate dialysis.

d) Stein, et al[29] randomized 200 consecutive new CAPD patients to receive either a high alkali or a low alkali dialysate and followed them for 1 year. At the end of that time, the average serum bicarbonate concentration was 23±0.3 mmol/L in the low alkali group and 27.2±0.3 mmol/L in the high alkali group. Body weight and midarm circumference increased significantly more in the high alkali group than in the low alkali group (6.1±0.66 kg vs 3.71±0.56 kg and 1.26±0.16 cm vs 0.61 ±0.16 cm). There were also fewer hospital admissions and fewer hospital days in the high alkali group when compared to the low alkali group (1.13+0.16 vs 1.71+0.22 admissions per patient per year and 16.4+1.4 vs 21.2+1.9 days/year respectively; the p value for both comparisons was <0.05). The main criticism to this very well designed study is that the nature of increased body weight was not characterized. Higher sodium intake in many patients of the high alkali group may have led to an increase in the body water content which is not always clinically apparent. Although there are no reliable, gold-standards to define an increase in lean body mass not related to fluid accumulation, the best information can be obtained from the creatinine appearance rate as an index of muscle mass. Serum creatinine in both groups was very similar at baseline and at 1 year of follow-up; since the creatinine clearance was lower at 1 year in the high alkali group (76.3 vs 80.1 L/week), one would assume that the creatinine appearance rate in this group must have been lower than in the low alkali group. Thus this information suggests that the increase in body weight in the high alkali group was the result, not of increasing muscle mass, but rather of fluid or fat accumulation. Even if we do not accept the increase in weight as reflecting "good weight", but rather an accumulation of fat and/or fluid, the study shows an undeniable better outcome in patients with a higher serum bicarbonate. A very relevant point of this study is that it shows a beneficial effect within the normal range of serum bicarbonate concentration.

e) Brady, et al (30) randomized 36 hemodialysis patients into 2 groups, one with persistent acidosis and another with partial correction of acidosis. No difference was observed between both groups in PCR and serum albumin after a follow-up period of 4 months.

f) Movilli, et al[31] studied 12 hemodialysis patients before and after 3 months of correction of acidosis. During the study, serum bicarbonate increased from 19.3±0.6 to 24.4± 1.2 mmol/L and serum albumin increased from 3.49±2 g/dL to 3.79±3 g/dL, while nPCR decreased from 1.11±0.17 to 1.03±0.17 g/kg/day.

CONCULSIONS

The data presented above emphasize the need for optimal correction of severe acidosis,

specially in the pre-ESRD patient not yet on dialysis. There is sufficient evidence that significant acidosis, ie, a pre-dialysis serum total CO_2 less than 20 mmol/L, should be treated aggressively. Moreover, the correction of severe metabolic acidosis is also important because of the association of acidosis with bone breakdown[32], insulin resistance[33] and a decreased sensitivity of the parathyroid glands to calcium[34].

However, it is not yet very clear if raising pre-dialysis serum bicarbonate to the high range of normal adds benefits to well-dialyzed. Are there any potential downsides to fully correcting mild metabolic acidosis in these patients? The answer is yes, and it has to do primarily with the risk of increased precipitation of calcium phosphate in soft tissues. An increase in blood pH from 7.3 to 7.4 can lead to a 20% increase in the concentration of HPO4=, the ionic form of phosphate which precipitates with calcium[35]. The pre-dialysis serum total CO_2 in HD patients is often increased by raising the concentration of bicarbonate in the dialysate; this in turn will increase the post-dialysis concentration of serum total CO_2. The problem with this approach is that to keep a pre-dialysis serum total CO_2 around 26 mmol/L one may need to raise the post-dialysis value to 30 mmol/L or more, a value that may potentially create problems during a period when the serum calcium also tends to be higher given the current practice of using a dialysate calcium concentration of about 2.5 mEq/L or more. Such vigorous control of acidosis with higher bicarbonate concentration in the dialysate may expose the patient to an environment favorable for precipitation of calcium phosphate in the period immediately after hemodialysis.

From the above discussion one may conclude that if a decision is made to fully normalize the serum bicarbonate concentration in hemodialysis patients the best approach might be to achieve a serum total CO_2 value of about 25 mmol/L at the end of a hemodialysis session and avoid further drop of this value by the daily addition of a small amount of oral bicarbonate supplements. We have previously found that interdialytic net acid production in a group of hemodialysis patients is about 30 mmol/day, a value far less than normal and lower than predicted from protein intake[36]. One could potentially maintain a stable serum bicarbonate at about 25 mmol/L by the daily administration of only 30 mmol/day of oral $NaHCO_3$, an amount unlikely to produce many problems related to sodium gain. Acidosis is less commonly seen in CAPD patients nowadays; we have demonstrated an average serum total CO_2 of 27.6 ± 3 mmol/L in a group of 40 CAPD patients dialyzed with a lactate concentration of 40 mmol/L in the dialysate[3].

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