

*Original Article***Correction of metabolic acidosis increases serum albumin concentrations and decreases kinetically evaluated protein intake in haemodialysis patients: a prospective study**

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Abstract

Background. Metabolic acidosis in haemodialysis (HD) patients increases whole body protein degradation while the correction of acidosis reduces it. However, the effects of the correction of acidosis on nutrition have not been clearly demonstrated.

Study design. In this study we have evaluated the effects of 3 months of correction of metabolic acidosis by oral sodium bicarbonate supplementation on protein catabolic rate (PCRn) and serum albumin concentrations in 12 uraemic patients on maintenance HD for at least 6 months (median 49 months; range 6–243 months). Pre-dialysis serum bicarbonate, arterial pH, serum albumin, total serum proteins, serum creatinine, plasma sodium, haemoglobin, PCRn, Kt/V, and TACurea, were evaluated before and after correction.

Results. Serum bicarbonate levels and arterial pH increased respectively from 19.3 ± 0.6 mmol/l to 24.4 ± 1.2 mmol/l ($P < 0.0001$) and 7.34 ± 0.03 to 7.40 ± 0.02 ($P < 0.0001$). Serum albumin increased from 34.9 ± 2.1 g/l to 37.9 ± 2.9 g/l ($P < 0.01$), while PCRn decreased from 1.11 ± 0.17 g/kg/day to 1.03 ± 0.17 g/kg/day ($P < 0.001$). No changes in Kt/V, total serum proteins, serum creatinine, plasma sodium, haemoglobin, body weight, pre dialysis systolic and diastolic blood pressure, and intradialytic weight loss were observed.

Conclusions. Our data demonstrate that correction of metabolic acidosis improves serum albumin concentrations in HD patients. The correction of acidosis induces a decrease in PCRn values, as evaluated by kinetic criteria, suggesting that in the presence of moderate to severe acidosis this parameter does not reflect the real dietary protein intake of the patients probably as a result of increased catabolism of endogenous proteins. The correction of metabolic acidosis should be considered of paramount importance in HD patients.

Key words: uraemia; acidosis; dialysis; nutrition; PCRn; Kt/V; serum albumin

Introduction

Malnutrition occurs in a large proportion of maintenance haemodialysis (HD) patients [1], and low levels of serum albumin concentrations have been associated with increased morbidity and mortality [2,3]. There are several causes that predispose to malnutrition in HD patients, but recently the role of metabolic acidosis has been stressed [4,5]. We have recently reported [6], in a large cross-sectional study, that in HD patients with adequate Kt/V, metabolic acidosis may exert a detrimental effect on serum albumin concentrations partially independent of the protein intake, as evaluated by PCRn, suggesting that in the presence of moderate to severe metabolic acidosis PCRn might not reflect the real dietary protein intake of the patients probably as a result of increased catabolism of endogenous proteins. Moreover, it has been recently reported that the correction of acidosis decreases whole body protein degradation [7] and may improve nutritional status in HD patients.

We have undertaken a prospective study to verify which effect the correction of metabolic acidosis exerts on serum albumin concentrations and PCRn in HD patients.

Subjects and methods*Subjects*

Twelve uraemic patients (10 men, 2 women), mean age 56 ± 15 years (range 30–72 years), who had been on regular chronic bicarbonate haemodialysis (BD) for at least 6 months (median 49 months; range 6–243 months) were studied. All had evidence of metabolic acidosis at the time they were recruited with serum bicarbonate levels ≤ 20 mmol/l for at least 3 months before the study. No patient had diabetes,

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neoplasia, liver disease, or cachexia. The underlying renal diseases were chronic glomerulonephritis in seven patients, polycystic kidney disease in one, nephroangiosclerosis in one, undiagnosed nephropathy in three patients. All had been free of acute illness for at least 3 months before the beginning of the study.

Study protocol

Patients were studied before (Pre) and after 3 months of correction (Post) of the metabolic acidosis by oral supplementations of sodium bicarbonate (mean dose 2.7 ± 0.94 g/day; range 1–4 g/day). Serum bicarbonate levels during correction were maintained between 23 and 26 mmol/l by weekly pre-dialysis monitoring of the parameter evaluated in the long-dialysis interval.

All patients were treated by BD thrice weekly, with 1.3–1.8 m² cellulosic membranes (Gambro Lun-Dia A700; Bellco NT 1808). The duration of the dialysis procedure ranged from 210 to 240 min (median 240 min), blood flow rate was 300 ml/min, dialysate flow rate was 500 ml/min and did not change during the period of study. Dialysate fluid composition was sodium 140 mmol/l, potassium: 2 or 3 mmol/l, calcium 1.75 mmol/l, bicarbonate 35 mmol/l, acetate 4 mmol/l, glucose 5.55 mmol/l.

To evaluate the role of metabolic acidosis on nutritional status, the following parameters were assessed either before and after correction of acidosis: Kt/V, TAC urea, arterial pH, serum bicarbonate concentration, serum albumin concentration, total serum proteins, plasma sodium, haemoglobin, PCRn, serum creatinine. Acid–base and laboratory parameters were drawn from the arterial side of the AV fistula at the start of the dialysis session after the long-dialysis interval. pH and serum bicarbonate were measured on a whole blood sample taken anaerobically. During blood sampling the patient was at rest and there was no hand motion. The samples were analysed as quickly as possible, as a rule within 30 min, by ABL 510 (Radiometer, Copenhagen). Serum albumin concentrations were assessed by nephelometric assay, the other biochemical parameters were assayed by standard laboratory methods.

Urea kinetic modelling (UKM) was performed midweek. Samples for BUN were drawn from the arterial side of the AV fistula at the start, 15 min after the end and at the beginning of the next dialysis session and processed by Autoanalyser. The duration of each dialysis session, duration of elapsed times between dialysis, intradialytic weight loss and interdialytic weight gains were recorded.

All patients were anuric or very oliguric (daily urine volume <100 ml/24 h). All patients were advised to eat a diet containing 35 kcal/kg BW/day and 1–1.2 g protein/kg BW/day [8] and were specifically requested not to change their usual dietary habits during the period of the study.

Calculations

The following equations were used to calculate the volume of distribution of urea (V), Kt/V, time-averaged urea concentration (TACurea), urea generation rate (G), and protein catabolic rate PCRn):

V was calculated according to the formula of Watson *et al.* [9];

Kt/V was calculated according to Daugirdas [10];

TACurea: $((C1 + C2)T_d + (C2 + C3)T_{id}) / [2(T_d + T_{id})]$;

G: $(C3 * V2 - C2 * V1) / T_{id}$;

PCRn: $(9.35G + 0.294V1) / (V1/0.58)$.

C1 and C2 are BUN concentrations at the start and 15 min after the end of dialysis; C3 is the BUN concentration at the beginning of the next dialysis; T_d is the dialysis time; T_{id} is the interdialysis time. V1 is calculated from the dry weight at the end of dialysis according to the formula of Watson *et al.* [9], V2 is equal to V1 plus the interdialytic weight gain.

All the data are expressed as mean \pm SD. The Student *t* test for paired data was adopted for statistical evaluation. Significant differences were defined by $P < 0.05$.

Results

Figure 1 shows the changes in serum bicarbonate levels, and arterial pH before and after the correction of acidosis. With sodium bicarbonate therapy all patients showed a significant increase in serum bicarbonate concentrations and pH that increased respectively from 19.3 ± 0.6 mmol/l to 24.4 ± 1.2 mmol/l ($P < 0.0001$), and from 7.34 ± 0.03 to 7.40 ± 0.02 ($P < 0.0001$).

Table 1 shows the behaviour of plasma sodium, haemoglobin, body weight, pre-dialytic systolic and diastolic blood pressure and intradialytic weight loss before and after the correction of acidosis. No significant changes in the parameters were observed.

Table 2 shows the changes in serum albumin, PCRn, Kt/V, TACurea, total serum proteins and serum creatinine before and after the correction of acidosis. Serum albumin concentrations showed a significant increase after the correction of acidosis. PCRn decreased significantly; Kt/V, total serum proteins and serum creatinine did not change. TACurea tended to decrease, but the change was not statistically significant.

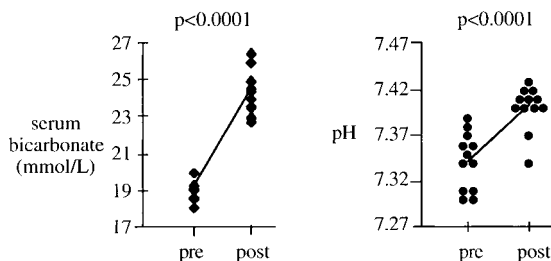


Fig. 1. Changes in serum bicarbonate levels and arterial pH before and after the correction of acidosis.

Table 1. Changes in plasma sodium, haemoglobin, body weight, pre-HD systolic and diastolic blood pressure and intradialytic weight loss before and after the correction of acidosis

Parameter	Pre	P	Post
Plasma sodium (mmol/l)	139 ± 2.8	NS	140 ± 2.6
Haemoglobin (g/dl)	11.5 ± 1.4	NS	11.5 ± 0.9
Body weight (kg)	66 ± 11	NS	67 ± 11
Pre-HD systolic BP (mmHg)	147 ± 8	NS	150 ± 15
Pre-HD diastolic BP (mmHg)	82 ± 4	NS	82 ± 7
Intra-HD weight loss (kg)	2.1 ± 0.4	NS	2.0 ± 0.6

Table 2. Changes in serum albumin, PCRn, Kt/V, TACurea, total serum proteins, and serum creatinine levels before and after the correction of acidosis

Parameter	Pre	P	Post
Serum Albumin (g/l)	34.9±2.1	0.01	37.9±2.9
PCRn (g/kg/day)	1.11±0.17	0.001	1.03±0.17
Kt/V	1.26±0.14	NS	1.26±0.12
TACurea (mmol/l)	7.5±1.7	NS	7.3±1.3
Total serum proteins (g/dl)	6.4±0.6	NS	6.5±0.3
Serum creatinine (mmol/l)	937±283	NS	1017±212

Discussion

Metabolic acidosis has been recognized as an important stimulus for net protein catabolism [4]. However, the clinical importance of uraemic acidosis as an independent factor for the development of malnutrition in HD patients is far from clear. The correction of metabolic acidosis in chronic renal failure [11] as well as in HD patients [7] has been shown to decrease protein degradation and amino acid oxidation. Moreover, Ballmer *et al.* [12] have recently reported that chronic metabolic acidosis decreases the synthesis of serum albumin and induces a negative nitrogen balance in healthy subjects. In a recent study [6] we have observed that moderate to severe metabolic acidosis, in HD patients, may exert a detrimental effect on serum albumin concentrations partially independent of the protein intake as evaluated by PCRn, suggesting that this parameter might not adequately reflect the real protein intake of the patients in this setting. To further investigate this hypothesis we have prospectively studied 12 HD patients before and after 3 months of correction of their metabolic acidosis by oral bicarbonate supplementations.

As shown in Figure 1, all patients attained the expected control of their metabolic acidosis, while intradialytic weight loss, pre-dialysis systolic and diastolic blood pressure, plasma sodium, and haemoglobin did not change (Table 1), thus excluding any expansion of the extracellular fluid volume while on oral bicarbonate supplementation. However, as shown in Table 2, a significant increase in serum albumin concentrations and a concomitant significant decrease in PCRn were evident. These variations occurred without any change in Kt/V, total serum proteins and serum creatinine levels between the two periods, thus excluding that variations in dialysis efficiency might have played a role on the observed changes in serum albumin concentrations and PCRn. TACurea tended to decrease, but the change was not statistically significant. Moreover, as the variations in PCRn and serum albumin concentrations are in opposite directions, it seems extremely unlikely that a change in the dietary intake could be an explanation for the observed changes. This is in agreement with the observation reported by Roberts *et al.* [13] that the correction of acidosis has no effect on dietary protein intake in uraemic patients. For these reasons the observed vari-

ations in serum albumin and PCRn support the hypothesis of a significant role for the correction of metabolic acidosis in reducing the rate of endogenous catabolism induced by the acidosis itself. At steady state PCRn is assumed to be approximately equal to dietary protein intake [14] and it is used as an objective tool to quantify protein intake and patients' compliance with the dietary prescription in HD patients.

However, while PCRn may provide an index of protein catabolism, it does not differentiate between protein derived from the dietary sources or catabolism of endogenous proteins [15]. Metabolic acidosis, in experimental animals, has been reported to stimulate net protein catabolism in muscle by augmenting the transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway [16] and directly stimulating oxidative catabolism through activation of branched-chain α -keto acid dehydrogenase [17]. The correction of acidosis results in an improvement in plasma branched-chain amino-acid levels due to a decreased activity of branched-chain α -keto acid dehydrogenase [18,19]. Thus a reduction of PCRn, as expression of decreased catabolism of endogenous proteins, after the correction of acidosis might be an expected event. Indeed, recent work has shown an increase in triceps skinfold thickness and body weight after the correction of metabolic acidosis in both HD [20] and CAPD patients [21], suggesting an improvement in nutritional status in these patients. A trend toward higher values of serum albumin and lower values of PCRn after the correction of acidosis was present, but did not reach statistical significance.

The present study is in agreement with these observations, and confirms, on a prospective basis, the results of previous work [6] showing a detrimental effect of metabolic acidosis on serum albumin synthesis. Low serum albumin concentrations are considered one of the most sensitive and early markers of malnutrition in HD patients [22,23]. The association between low serum albumin concentrations and mortality has been reported by several Investigators both in HD [24,25] and peritoneal dialysis patients [2]. For this reason the observed increase in serum albumin levels after the correction of metabolic acidosis could be important in reducing the risk of malnutrition and the attained increased morbidity and mortality in HD patients.

In conclusion our data demonstrate that the correction of metabolic acidosis improves serum albumin concentrations in HD patients. Correction of acidosis induces a decrease in PCRn values, as evaluated by kinetic criteria. This suggests that in the presence of moderate to severe acidosis PCRn does not reflect the real dietary protein intake of the patients probably as a result of increased catabolism of endogenous proteins. The correction of metabolic acidosis should be considered of paramount importance in HD patients.

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