Evidence for an independent role of metabolic acidosis on nutritional status in haemodialysis patients

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Abstract

Background. Malnutrition in haemodialysis (HD) patients has been referred to underdialysis with low protein intake, and to acidosis. However, the separate effects of underdialysis and acidosis on nutrition have not been clearly demonstrated. To evaluate the role of the dialysis dose and of metabolic acidosis on nutrition, we measured the predialysis serum HCO₃⁻, pH, serum albumin, PCRn, Kt/V, and BMI in 81 uraemic patients on maintenance bicarbonate HD for 93±80 months. Patients with chronic liver diseases, malignancies, and cachexia were excluded.

Results. Mean age was 59±17 years, Kt/V was 1.29±0.21, PCRn 1.06±0.22 g/kg/day, serum albumin 4.07±0.28 g/dl, BMI 23±4 kg/m², HCO₃⁻ 21.1±1.9 mmol/l, pH 7.36±0.04. Serum albumin showed a significant direct correlation with: PCRn (P=0.001), HCO₃⁻ (P=0.001), pH (P=0.002), but no correlation with Kt/V and BMI. Serum HCO₃⁻ correlated inversely with PCRn (P=0.027). Multiple regression analysis confirmed the significant role of serum bicarbonate and age, but not of Kt/V, on serum albumin concentrations. The role of PCRn appeared to be marginal compared to serum bicarbonate in determining serum albumin levels. Dividing patients into two groups, serum albumin was 3.96±0.22 g/dl with HCO₃⁻ <20 mmol/l and 4.18±0.31 g/dl in those with serum HCO₃⁻ ≥23 mmol/l (P=0.002). PCRn in the same groups was respectively 1.14±0.24 g/kg/day and 1.01±0.23 g/kg/day (P=0.03). Most importantly, serum albumin levels did not appear to be affected by the dialysis dose, with Kt/V ranging from 0.90 to 1.88.

Conclusions. In HD patients with adequate Kt/V, metabolic acidosis exerts a detrimental effect on serum albumin concentrations partially independently of the protein intake, as evaluated by PCRn. In the presence of moderate to severe metabolic acidosis, PCRn does not reflect the real dietary protein intake of the patients, probably as a result of increased catabolism of endogenous proteins. For this reason PCRn should be considered with caution as an estimate of the dietary protein intake in HD patients in the presence of metabolic acidosis.

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

Introduction

Protein-energy malnutrition is present in a large proportion of maintenance haemodialysis (HD) patients [1]. Low levels of serum albumin concentrations have been associated with increased morbidity and mortality [2,3]. Many causes predispose to malnutrition in HD patients but recently the role of reduced values of protein catabolic rate (PCRn) and Kt/V, as expression of low nutritional intake and anorexia associated with suboptimal dialysis prescription [4,5], and metabolic acidosis [6] have been stressed. Studies aimed to measure protein degradation in humans have shown that the induction of acidosis increases the whole-body protein degradation [7]. The correction of acidosis in chronic renal failure patients [8,9] and in haemodialysis patients [10], has been shown to reduce protein degradation and amino-acid oxidation. However, the respective effects of both underdialysis and acidosis on nutritional status have not yet been clearly demonstrated in the clinical setting. Aim of this study was to elucidate the respective roles of the dialysis dose and metabolic acidosis on serum albumin concentrations and PCRn in a large in-centre HD population.

Subjects and methods

Eighty-one uraemic patients (52 men, 29 women) on regular chronic haemodialysis for 6–315 months (median 67 months) were studied. Patients with neoplasia, systemic diseases, chronic liver diseases, and cachexia were excluded. All of them were treated by bicarbonate HD thrice weekly, with 1.3–1.8 m² cellulosic membranes (Gambro Lun-Dia A700; Belloco NT 1808). The duration of the dialysis procedure ranged from 180 to 270 min (median 228 min). Blood flow...
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Dialysate flow rate was 500 ml/min. Dialysate fluid composition was: sodium 140 mmol/l, potassium 2–3 mmol/l, calcium 1.5–1.75 mmol/l, bicarbonate 35 mmol/l, acetate 4 mmol/l, and glucose 5.55 mmol/l. The underlying renal diseases were chronic glomerulonephritis in 24 patients, polycystic kidney disease in 14 patients, nephroangiiosclerosis in 12 patients, tubulointerstitial nephropathy in 10 patients, diabetes in 2 patients, and undiagnosed nephropathy in 19 patients. Urea kinetic modelling (UKM) was performed midweek every 3 months. Dialysis schedule was managed to maintain a Kt/Vurea > 0.9. 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 autoanayser. The values for Kt/V, PCRn, and TACurea were the means of three separate tests. The deviation from the mean for each test was within ±6%.

The duration of each dialysis session, duration of elapsed times between dialysis, and weight gains between dialysis were recorded. All patients were anuric or very oliguric (daily urine volume <100 ml/24 h). All patients were instructed to eat a diet containing 35 kcal/kg BW/day and 1–1.2 g protein/kg BW/day [11] and had been free of acute illness for at least 3 months before the study.

In order to evaluate the role of the dose of dialysis and of metabolic acidosis on nutritional status, the following parameters were assessed: Kt/V urea, arterial pH, serum bicarbonate concentration, serum albumin concentration, PCRn, and body mass index (BMI). Acid–base and laboratory parameters were drawn from the arterial side of the AV fistula at the start of the dialysis session in the long dialysis interval. pH and serum bicarbonate were measured on a whole-blood sample taken anaerobically. During withdrawal of blood there was no hand motion. The samples were analysed as quickly as possible, as a rule within 30 min, by ABL 510 (Radiometer, Copenhagen). The other biochemical parameters were assayed by standard laboratory methods.

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 and Watson [12];

Kt/V was calculated according to Daugirdas [13];

TACurea: \( (C_1 + C_2)T_d + (C_2 + C_3)T_i/d \)

G: \( C_3V_2 - C_2V_1 \)/Tid;

PCRn: \( (9.35G + 0.294V_1) / (V_1/0.58) \).

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; Td is the dialysis time; Tid is the interdialysis time. V1 is the volume of distribution of urea at the end of dialysis, V2 is the volume of distribution of urea at the beginning of the next dialysis session.

All the data are expressed as mean ± SD. Linear regression analysis, the Student’s t test for unpaired data and multiple regression analysis were adopted for statistical evaluation. Significant differences were defined by \( P < 0.05 \).

Results

Kt/V for the whole group of patients was 1.28 ± 0.20, TACurea was 16 ± 3 mmol/l, PCRn 1.06 ± 0.22 g/kg BW/day, serum pH 7.36 ± 0.03, serum bicarbonate 21 ± 2 mmol/l, serum albumin 4.07 ± 0.28 g/l, BMI 23 ± 4 kg/m², body weight 63 ± 14 kg.

Figure 1 shows that serum albumin concentrations did not correlate with Kt/V. Figure 2 shows the significant correlation between serum albumin and PCRn. Figure 3 shows the correlation between serum albumin and serum bicarbonate. A significant direct correlation was evident. Figure 4 shows the correlation between PCRn and serum bicarbonate. A significant inverse correlation between the two parameters was found.

The multiple regression analysis of the data (Table 1) confirmed the significant role of serum bicarbonate levels and age, but not of Kt/V, PCRn, and BMI on serum albumin concentrations.

The presence of the direct correlation between serum albumin concentrations and both PCRn and serum bicarbonate, and the inverse correlation between PCRn and serum bicarbonate levels.
and serum bicarbonate, prompted us to divide the patients into two groups: group A patients with serum bicarbonate levels ≤ 20 mmol/l; group B patients with serum bicarbonate levels ≥ 23 mmol/l.

Table 2 shows serum albumin concentrations, PCRn, and Kt/V levels in the two groups of patients. Patients of group A showed significantly lower serum albumin concentrations compared to patients of group B. At the same time PCRn levels in patients of group A were significantly higher than in patient of group B. Kt/V did not differ between the two groups.

Discussion

Low serum albumin concentrations are considered one of the most sensitive and early markers of malnutrition in HD patients [14]. The association between low serum albumin levels, as expression of malnutrition, and mortality has been reported by several investigators both in HD [15,16] and peritoneal dialysis patients [3]. There are many causes of malnutrition in patients treated with HD, some being related to the endocrine and metabolic derangements of uraemia, and some being related to the dialytic procedure. Based on nitrogen balance studies on nutritional intakes and nutritional status in dialysed patients, it is assumed that protein requirements in HD patients are considerably higher than in normal individuals [17]. At steady state protein catabolic rate (PCRn) is assumed to be approximately equal to dietary protein intake [18] 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 dietary sources and that from catabolism of endogenous proteins. A controversial issue is the extent to which the adequacy of HD might influence protein intake and nutritional status. A direct correlation between PCRn and the dose of dialysis, as evaluated by Kt/V, has been reported by several authors [19,20]. However, the positive effect of Kt/V on PCRn is lost when adequate levels of Kt/V are attained [21,22].

Metabolic acidosis has been recognized as an important stimulus for net protein catabolism [23]. However, the clinical importance of uraemic acidosis as an independent factor for the development of malnutrition in HD patients is far from clear. In this study we have analysed the separate effects of the dose of dialysis (Kt/V), and of metabolic acidosis (serum bicarbonate levels) on PCRn and serum albumin concentrations. Patients were managed to maintain a Kt/V > 0.9 so that the level for this parameter ranged from 0.9 to 1.88, with a mean of 1.28 ± 0.20, which is considered to indicate a fully adequate dialysis prescription [24]. In such a situation we did not find any correlation between Kt/V and serum albumin concentrations, as shown in Figure 1, and between Kt/V and PCRn (data not shown). This confirms the findings from previous work [21] indicating that at optimal dialysis prescription, nutrition does not depend on the dose of dialysis delivered but is dependent on other factors not yet fully established.

The direct correlation between serum albumin concentrations and PCRn, and between serum albumin concentrations and serum bicarbonate levels (Figures 2 and 3), is consistent with the concept that the ingestion of an adequate amount of proteins, and a lesser degree of acidosis are associated with a better nutritional status [25]. However, in these patients we also found a significant inverse correlation between PCRn and serum bicarbonate levels. This finding is in agreement with the data reported by Bastani et al. [26] of a greater degree of acidosis associated with higher levels of PCRn, but the concomitant direct correlation between serum albumin and bicarbonate levels, and serum albumin and PCRn, suggests that protein intake, evaluated by kinetic criteria, could be overestimated in the presence of important metabolic acidosis. In fact, as shown in Table 2, dividing the patients into two groups, serum albumin concentrations and PCRn were

Table 1. Multivariate analysis of the data

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Serum albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Coefficient</td>
</tr>
<tr>
<td>S. bicarbonate</td>
<td>0.062</td>
</tr>
<tr>
<td>Age</td>
<td>−0.006</td>
</tr>
<tr>
<td>PCRn</td>
<td>0.299</td>
</tr>
<tr>
<td>Kt/V</td>
<td>0.031</td>
</tr>
<tr>
<td>BMI</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Table 2. Serum albumin concentrations, PCRn, and Kt/V in patients with different serum bicarbonate levels

<table>
<thead>
<tr>
<th>Group A (n = 36)</th>
<th>Group B (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bicarbonate</td>
<td>Serum bicarbonate</td>
</tr>
<tr>
<td>≤20 mmo/l</td>
<td>≥23 mmo/l</td>
</tr>
<tr>
<td>S. albumin (g/dl)</td>
<td>3.96 ± 0.22</td>
</tr>
<tr>
<td>PCRn (g/kg/day)</td>
<td>1.14 ± 0.24</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.34 ± 0.23</td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
</tr>
</tbody>
</table>

respectively 3.96 ± 0.22 g/dl and 1.14 ± 0.24 g/kg/day in the group of patients with serum bicarbonate levels ≤20 mmo/l, while serum albumin concentrations were significantly higher and PCRn lower in the group of patients with serum bicarbonate levels ≥23 mmo/l compared to the more acidic group. Multiple regression analysis of the data (Table 1) confirmed the significant role of acidosis and age, but not of Kt/V, on serum albumin concentrations. The role of PCRn appeared to be marginal compared to serum bicarbonate and age in determining serum albumin levels. This is in agreement with previous data [21], showing a significant effect of age on serum albumin levels and PCRn in patients with adequate dialysis prescription.

Metabolic acidosis has been reported as an important stimulus for net protein catabolism [7,23]. This effect seems to be mediated, in experimental animals, by the activation of muscle proteolysis by augmenting the transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway [27]. Moreover, Ballmer et al. [28] have recently reported that chronic metabolic acidosis decreases the synthesis of serum albumin and induces a negative nitrogen balance in healthy subjects, while Roberts et al. [29] have shown that the correction of metabolic acidosis has no effect on appetite in uremic patients.

Our data are in agreement with these observations, and suggest that in the presence of a moderate to severe metabolic acidosis, PCRn may not adequately reflect the real dietary protein intake in adequately dialysed patients, probably as a result of increased catabolism of endogenous proteins induced by the metabolic acidosis itself.

In conclusion, our data demonstrate that serum albumin levels are not affected by the dose of dialysis, at least with a Kt/V ranging from 0.9 to 1.88. Metabolic acidosis exerts a detrimental effect on serum albumin concentrations partially independent of the protein intake, as evaluated by PCRn. In the presence of moderate to severe metabolic acidosis, PCRn does not reflect the real dietary protein intake of the patients, probably as a result of increased catabolism of endogenous proteins. For this reason PCRn should be considered with caution as an estimate of the dietary protein intake in HD patients in the presence of metabolic acidosis.

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