Correction of metabolic acidosis improves thyroid and growth hormone axes in haemodialysis patients

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Abstract
Background. Chronic metabolic acidosis (CMA) in normal adults results in complex endocrine and metabolic alterations including growth hormone (GH) insensitivity, hypothyroidism, hyperglucocorticoidism, hypoalbuminaemia and loss of protein stores. Similar alterations occur in chronic renal failure, a prototypical state of CMA. We evaluated whether metabolic acidosis contributes to the endocrine and metabolic alterations characteristic of end-stage renal disease.

Methods. We treated 14 chronic haemodialysis patients with daily oral Na-citrate for 4 weeks, yielding a steady-state pre-dialytic plasma bicarbonate concentration of 26.7 mmol/l, followed by 4 weeks of equimolar Na-chloride, yielding a steady-state pre-dialytic plasma bicarbonate of 20.2 mmol/l.

Results. Blood pressure, body weight and dialysis adequacy were equivalent in the two protocols. Na-citrate treatment corrected CMA, improved GH insensitivity, increased and normalized plasma free T3 concentration, and improved plasma albumin. Correction of CMA had no significant effect on measured cytokines (interleukin-1β and -6, tumour necrosis factor-α) or acute phase reactants (C-reactive protein, serum amyloid A, α2-macroglobulin).

Conclusion. CMA contributes to the derangements of the growth and thyroid hormone axes and to hypoalbuminaemia, but is not a modulator of systemic inflammation in dialysis patients. Correcting CMA may improve nutritional and metabolic parameters and thus lower morbidity and mortality.

Keywords: albumin; dialysis; growth hormone; metabolic acidosis; thyroid

Introduction

Chronic metabolic acidosis (CMA) in rats induces protein catabolism through the ubiquitin–proteasome pathway and glucocorticoids [1]. In humans, whole-body leucine flux studies have confirmed increased protein turnover during CMA [2]. Other hormones besides glucocorticoids may be involved, because CMA in rats induces lower serum insulin-like growth factor (IGF) 1 and 2 levels, and a tendency for lower mRNA levels of hepatic IGF and growth hormone (GH) receptor [3]. In healthy adults, CMA suppresses albumin synthesis, increases glucocorticoids levels and urinary nitrogen excretion, and induces GH insensitivity [4,5]. Furthermore, it lowers levels of free thyroxin (fT4) and tri-iodothyronine (fT3) in the presence of an increased thyroid-stimulating hormone (TSH) and an exaggerated response to thyrotropin (TRH) [6]. Thus, CMA induces complex hormonal derangements that may mediate the acidosis-induced loss of protein stores including a negative nitrogen balance and a low serum albumin.

Patients on haemodialysis commonly exhibit some degree of metabolic acidosis and multiple hormonal and metabolic derangements. In patients with chronic renal insufficiency as well as dialysis patients, GH/IGF-1 insensitivity is present, with higher GH levels due to increased GH bursts and a prolonged half-life of GH [7]. Conversely, IGF-1 serum levels are lower and its half-life reduced in association with impaired metabolic effects in dialysis patients [8]. The thyroid hormone axis is also abnormal, with low plasma T3 and T4 levels, a normal TSH and a blunted response to TRH [9].

Hypoalbuminaemia due to diminished synthetic rate is common in uraemia, but the mechanism for this finding is unknown. There appears to be an influence of inflammation [10] and possibly acidosis since CMA can suppress albumin synthesis [4], but the latter remains controversial in haemodialysis patients [11–14]. Identifying a mechanism could be important because hypoalbuminaemia is a major predictor of mortality in these patients [15,16].
We investigated whether and to what extent correction of metabolic acidosis in haemodialysis patients would affect derangements in the GH/IGF-1 and thyroid hormone axes, glucocorticoid activity and serum albumin.

Subjects and methods

The study was performed at the Cantonal Hospital St Gallen, Switzerland. The dialysis unit comprises a total of 59 haemodialysis patients. Eight patients were not available or had central venous catheters; in the remaining 51 patients, we assessed the degree of metabolic acidosis by arterial blood gas (ABG) analyses, showing a mean pre-dialysis plasma bicarbonate concentration of 19.9±0.7 mmol/l. Of these patients, 16 were found not suitable for enrolment due to special transportation needs, five were recovering from or scheduled for a surgical procedure, and four patients were excluded due to serious co-morbid conditions. Of the remaining 26 patients, 14 (nine men, five women) agreed to be enrolled in the study and received compensation. ABGs revealed a pre-dialysis plasma bicarbonate of 19.1±1.9 mmol/l in the 14 study participants, and 20.2±2.5 mmol/l in the 37 non-participants.

Patients were instructed to maintain their usual diet and daily activities throughout the study; concomitant medications were not changed. All patients were dialysed three times weekly at a dialysate bicarbonate concentration of 32 mmol/l. Equilibrated dual-pool dialysis dose (eKt/V) and normalized protein catabolic rate (nPCR) were calculated using well established formulae.

The study lasted 56 days and was divided into two sequential experimental periods lasting 29 and 27 days (Figure 1). First, a prescribed amount of Na-citrate was adjusted to achieve a pre-dialytic plasma bicarbonate of 24–26 mmol/l as guided by thrice weekly fistula-derived pre-dialytic ABG values (accepted if pO2 was >65 mmHg; mean±SD 81.3±9.6 mmHg, n=138). In the second period, the subjects received an equimolar amount of Na-chloride. The final daily doses were 1.13±0.10 mmol/kg for Na-citrate and 1.10±0.08 mmol/kg for Na-chloride. Both were taken as gelatin capsules and were well tolerated. We investigated the GH/IGF-1 axis by administration of GH and growth hormone-releasing hormone (GHRH) as shown in Figures 3–7.

Except for ABGs, all serum samples were immediately placed on ice and stored at −70°C until analysis. GH measurements were assayed by immunoreassay (CLIA; Immulite, Diagnostic Products Corporation). IGF-1, free IGF-1 and IGF-binding protein 3 (BP3) samples were assayed by immuno-radiometry (DSL-2800, DSL-9400, DSL-6600; Diagnostic Systems Laboratory), measured on a gamma-counter (1261 Multigamma, Wallac) and calculated using a well established formulae.

The estimation of endogenous IGF-1 by GH injected at 0, 12 and 24 h provoked a rapid rise of plasma total and free IGF-1, and, after a brief delay, of IGF-BP3. Although the total IGF-1 response to GH administration was not different for the two time periods, free IGF-1 was higher and IGF-BP3 lower with Na-citrate compared with the period with CMA (Figures 2–4). In parallel to the rise in IGF-1 after stimulation by GH, we observed a rapid rise in c-peptide levels. The area under the curve (AUC) for c-peptide was higher.
during Na-citrate compared with Na-chloride (Figure 6); glucose levels did not rise in either period. There was no difference between fasting insulin (AUC 21.6 ± 2.6 vs 24.2 ± 4.1 U/2 h/l, P = 0.50) or fasting plasma glucose levels (AUC 8.3 ± 0.3 vs 8.0 ± 0.5 mmol/2 h/l).

The GH response to GHRH between 0 and 45 min (before octreotide) was not different during Na-citrate vs Na-chloride administration. However, the endogenous MCR for GH was reduced and, correspondingly, its half-life prolonged during CMA, as measured after octreotide administration to inhibit endogenous GH production (Figure 7).

### Effect of correction of CMA on cytokines and acute phase reactants

Plasma levels of IL-1β, IL-6 and TNF-α and the acute phase reactants CRP and serum amyloid A (SAA) were all increased (Table 2). In contrast, acute phase reactants Lp(a) and α-MG were normal. Correction of acidosis by supplementing with Na-citrate did not alter the cytokine and acute phase reactant profile, with the exception of a decrease in plasma Lp(a) concentration (P = 0.04).

### Discussion

Our data indicate that some metabolic abnormalities associated with chronic renal failure and dialysis are at least partially associated with metabolic acidosis. More importantly, these defects can be partially corrected by giving Na-citrate. We found that CMA in dialysis patients contributes to low fT3 and to GH insensitivity. CMA is also associated with lower levels of serum albumin. In contrast, the cytokine and acute phase reactant expression profile so typical of uraemia was not affected by CMA, suggesting that CMA suppresses albumin as well as the thyroid and GH axes independently of inflammation.

### Protein metabolism and nutritional parameters

We found a significantly higher serum albumin during Na-citrate therapy compared with Na-chloride, determined both by routine chemistry assay and by nephelometry (Table 1). Other investigators have not found significant effects of acidosis correction on albumin levels [12], but their studies were either cross-sectional or did not add a comparable amount of neutral anions to the control group to correct for possible volume effects of base supplementation. An association of CMA with hypoalbuminaemia is...
Fig. 2. Comparison of blood bicarbonate levels at different time points in relation to dialysis. HCO$_3^-$ immediately after dialysis ('post') was 27.5±0.5 during Na-citrate and 26.6±0.5 mmol/l during Na-chloride (black bars); 2 h later, 26.5±0.5 and 24.2±0.7 mmol/l ($P=0.02$; grey bars), and pre-dialysis ('48 h post') 26.1±0.4 and 20.4±2.2 mmol/l ($P<0.001$, light bars), respectively. *$P=0.02$ for pH, pO$_2$, HCO$_3^-$ comparison Na-citrate vs Na-chloride. #P<0.001 for pH, pO$_2$, HCO$_3^-$ comparison Na-citrate vs Na-chloride. Paired $t$-test ($n=14$). Means±SE.

Fig. 3. Time course of total IGF-1 after administration of GH. The AUC is 568±63 µg x h/l for Na-citrate (open circles, dashed lines) and 560±68µg x h/l for Na-chloride (solid lines and circles). $P=0.64$, paired $t$-test ($n=13$). Means±SE.
Fig. 4. Time course of IGF-BP3 after administration of GH. The AUC is 7.26 ± 0.30 mg × h/l for Na-citrate (open circles, dashed lines) and 7.58 ± 0.34 mg × h/l for Na-chloride (solid lines and circles). \( P = 0.03 \), paired \( t \)-test (\( n = 13 \)). Means ± SE.

Fig. 5. Time course of free IGF-1 after administration of GH. The AUC is 3.08 ± 0.42 µg × h/l for Na-citrate (open circles, dashed lines) and 2.57 ± 0.37 µg × h/l for Na-chloride (solid lines and circles). \( P = 0.001 \), paired \( t \)-test (\( n = 13 \)). Means ± SE. *\( P < 0.05 \) for mean values.
Fig. 7. Time course of GH after administration of GHRH and octreotide. The AUC between 0 and 45 min (before octreotide) is $13.7 \pm 2.4 \, \mu g \times \text{min/l}$ for Na-citrate (open circles) and $16.0 \pm 4.6 \, \mu g \times \text{min/l}$ for Na-chloride (solid circles) time periods ($P = 0.57$). The half-life is longer ($30.2 \pm 0.8$ vs $28.1 \pm 0.6 \, \text{min}$, $P = 0.02$) and metabolic clearance rate lower ($72.7 \pm 2.0 \, \text{ml/min} \times \text{m}^2$ vs $78.3 \pm 1.6 \, \text{ml/min} \times \text{m}^2$, $P = 0.01$) during Na-chloride, measured during octreotide. Paired $t$-test ($n = 14$). Means $\pm$ SE.

Fig. 6. Time course of free c-peptide after administration of GH. The AUC is $7.90 \pm 0.83 \, \text{nmol} \times \text{h/l}$ for Na-citrate (open circles, dashed lines) and $6.86 \pm 0.77 \, \text{nmol} \times \text{h/l}$ for Na-chloride (solid lines and circles). $P = 0.046$, paired $t$-test ($n = 13$). Means $\pm$ SE. *$P < 0.01$ for mean values.
consistent with an earlier prospective study of haemodialysis patients, in which plasma albumin increased with correction of CMA [14]. Our study extends this report by adding a control period using equimolar Na-chloride supplementation during CMA. The choice of equimolar oral Na-chloride control to mimic the chronic extracellular fluid volume (ECV) expansion of Na-citrate was based on both human and animal data, showing a similar increase of ECV and plasma volume on either salt. We did not measure ECV in this study. However, pre-dialysis weights and interdialytic weight gain, as well as blood pressure values remained very stable during both time periods, as illustrated in Table 1. Therefore, it is unlikely that there is any significant confounding influence of ECV expansion. Finally, to ensure steady-state conditions and adequate exposure to each sodium salt, at least 21 (Na-citrate) or 23 (Na-chloride) days were required before assessing laboratory parameters. A carry-over effect from the Na-citrate period to the Na-chloride period is possible, but, if present, would only minimize the difference between Na-chloride and Na-citrate administration.

Serum albumin is a complex parameter influenced by both protein intake (nutrition), and albumin synthesis and degradation, the latter reflecting its role as an acute phase protein. Since the cytokine and acute phase reactant profile was not altered by acidosis [except for Lp(a)], we believe that the lower albumin concentration observed during Na-chloride supplementation is not a direct consequence of an enhanced inflammatory state. While the difference observed is quite small (4.0 vs 3.8 g/dl), there is a direct and linear correlation between serum albumin levels and mortality in haemodialysis patients; a level of 3.7 vs 4.0 g/dl constitutes a difference, as just recently shown [16]. Na-citrate supplementation beyond the 4 weeks used in our study would possibly have an even greater impact.

**Endocrine analysis**

Uraemic patients demonstrate complex thyroid dysfunction characterized by markedly depressed levels of T₃ and lower (but still normal) T₄ with a normal TSH, a decreased thyroid response to exogenous TSH, a blunted TSH release to TRH, as well as decreased peripheral conversion of T₄ to T₃ [9]. In normal adults, we found that induction of CMA caused reduced serum levels of fT₄ and fT₃ and a physiological rise in TSH, suggesting a primary intrathyroidal hormonal secretory defect [6]. In ESRD patients, our findings confirm thyroid dysfunction in uraemia, but furthermore show that plasma fT₃ can be fully corrected by eliminating CMA.

Low levels of plasma free IGF-1 are present in both (non-uraemic) CMA and renal failure patients, and are believed to signal the presence of malnutrition in haemodialysis patients (4,17). CMA plays an important role because the free IGF-1 response improved by supplementing with Na-citrate and because similar results occur in normal adults with CMA [5]. Post-dialysis plasma levels of IGF-1 and GH are similar in both experimental time periods. However, progressive acidosis within each interdialytic cycle occurs only during administration of Na-citrate. Free IGF-1 levels are therefore expected to be lowest during maximum acidosis, i.e. pre-dialysis, when GH is expected to be highest due to loss of negative feedback inhibition by IGF-1. The difference in acid–base status among the two groups became greater during the experiment, and, correspondingly, there is progressive acidosis-related attenuation of plasma free IGF-1 after GH infusion, as illustrated in Figure 5. We could not find a significant difference in the plasma GH response after GHRH infusion, but demonstrated a diminished metabolic clearance rate and prolonged half-life of GH during acidosis.

While insulin levels after GH stimulation were no different for both time periods, we found an attenuated increase in c-peptide during acidosis despite comparable plasma glucose levels. C-peptide is a better marker of insulin secretion because of its greater stability and less variable clearance. Correction of metabolic acidosis in uraemia leads to both increased insulin sensitivity and insulin secretion, as measured by euglycaemic and hyperglycaemic clamp studies [18].

Metabolic acidosis has proteolytic effects and leads to increased cortisol secretion in normal subjects [4]. Glucocorticoids also appear to be necessary mediators of protein catabolism [1]. We did not find a difference in the plasma cortisol levels between the Na-chloride and Na-citrate treatments (data not shown), and we cannot comment on the role of glucocorticoids in proteolysis in haemodialysis patients. Notably, others have found that correction of metabolic acidosis suppresses whole-body protein degradation in these patients [13].

**Inflammatory response**

Acute phase reactants such as CRP, 2-MG, SAA, and the cytokines IL-1β, IL-6 and TNF-α are reported to be elevated in patients on long-term haemodialysis. These markers of inflammation have been correlated with hypoalbuminaemia, but it is not known whether the inflammatory response is related to acidosis. Except for normal serum levels for 2-MG and Lp(a), our results

### Table 2. Cytokines and acute phase reactants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal mean ± SD</th>
<th>Na-citrate mean ± SD</th>
<th>Paired t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β (pg/ml) (7)</td>
<td>&lt;0.1</td>
<td>9.3 ± 10.7</td>
<td>7.8 ± 8.8</td>
<td>0.16</td>
</tr>
<tr>
<td>IL-6 (pg/ml) (13)</td>
<td>&lt;3.1</td>
<td>3.6 ± 2.2</td>
<td>4.4 ± 5.6</td>
<td>0.58</td>
</tr>
<tr>
<td>TNF-α (pg/ml) (5)</td>
<td>&lt;6.3</td>
<td>7.4 ± 6.4</td>
<td>6.4 ± 4.5</td>
<td>0.57</td>
</tr>
</tbody>
</table>

**Acute phase reactants**

- **CRP (mg/l) (11)**
  - Normal: <5
  - Mean: 8.0 ± 4.8
  - Paired t-test: 12.2 ± 17.5
  - P-value: 0.45

- **SAA (mg/l) (13)**
  - Normal: <6.4
  - Mean: 17 ± 23
  - Paired t-test: 32 ± 94
  - P-value: 0.51

- **2-MG (g/l) (12)**
  - Normal: 1.3–3.0
  - Mean: 1.8 ± 0.7
  - Paired t-test: 1.7 ± 0.7
  - P-value: 0.18

- **Lp(a) (mg/l) (11)**
  - Normal: <300
  - Mean: 116 ± 113
  - Paired t-test: 131 ± 130
  - P-value: 0.04

Values in parentheses are number of measurements available.
Endocrine effects of metabolic acidosis in haemodialysis patients

confirm a cytokine expression profile typical of dialysis patients. While correcting acidosis did not change these markers of inflammation, it was associated with a higher serum albumin level. This suggests an independent effect of acidosis on albumin levels, and, hence, provides additional information that the mechanisms for hypoalbuminaemia in kidney failure patients are more complex than a reflection of an inadequate diet.

Lp(a) is an acute phase reactant that is structurally similar to LDL and represents a cardiovascular risk factor in haemodialysis patients. We found that the Lp(a) concentration was greater during CMA, possibly reflecting GH insensitivity, since IGF-1 administration decreases plasma Lp(a) in normal adults [19]. Correction of acidosis may therefore lower Lp(a) levels and improve cardiovascular risk.

In summary, we find that acidosis is responsible for some of the endocrine derangements found in chronic haemodialysis patients. Dialysate bicarbonate concentration can be safely increased from 36 to 42 meq/l and will correct metabolic acidosis in 75% of patients without progressive alkalalaemia, hypoxia or hypercarbia [20], and Na-alkali therapy can be given between dialysis sessions with minimal or no complications. It is conceivable that this strategy will improve abnormalities in protein metabolism, endocrine status and possibly long-term outcome of haemodialysis therapy.

Conflict of interest statement. None declared.

References


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