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Metabolic and endocrine effects of metabolic acidosis in humans

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Summary

Metabolic acidosis is an important acid-base disturbance in humans. It is characterised by a primary decrease in body bicarbonate stores and is known to induce multiple endocrine and metabolic alterations. Metabolic acidosis induces nitrogen wasting and, in humans, depresses protein metabolism. The acidosis-induced alterations in various endocrine systems include decreases in IGF-1 levels due to peripheral growth hormone insensitivity, a mild form of primary hypothyroidism and hyperglucocorticoidism. Metabolic acidosis induces a negative calcium balance (resorption from bone) with hypercalciuria and a propensity to develop kidney stones. Metabolic acidosis also results in hypophosphataemia due to renal phosphate wasting. Negative calcium balance and phosphate depletion combine to induce a metabolic bone disease that exhibits features of both osteoporosis and osteomalacia. In humans at least, 1,25-$(OH)_2$ vitamin D levels increase, probably through phosphate depletion-induced stimulation of 1-alpha hydroxylase. The production rate of 1,25-$(OH)_2$ vitamin D is thus stimulated, and parathyroid hormone decreases secondarily. There is experimental evidence to support the notion that even mild degrees of acidosis, such as that occurring by ingestion of a high animal protein diet, induces some of these metabolic and endocrine effects. The possible role of diet-induced acid loads in nephrolithiasis, age-related loss of lean body mass and osteoporosis is discussed.

Keywords: acidosis; nitrogen balance; calcium, phosphate; PTH; glucocorticoid; growth hormone; IGF-1

Introduction

Metabolic acidosis is the frequent acid-base disturbance induced by a primary decrease in plasma bicarbonate levels. Decreases in plasma bicarbonate can be the result of addition of acid to body fluids (overproduction of organic acids such as lactic and keto acids or decreased elimination of acid by the kidney) or loss of base (i.e. in diarrhoea). A given acid load (or equivalently: base loss) will result in immediate changes in pH and $PaCO_2$ to the extent calculable by the Henderson-Hasselbalch equation. When acidosis (hypobicarbonataemia) persists for several minutes to hours, complex central signal pathways will elicit a hyperventilatory response which results in hypocapnia and thus tends to correct pH towards normal. In addition, over a period of hours to 3 days, renal acid excretory mechanisms are stimulated. Ammonium excretion is elevated due to enhanced ammoniagenesis in the proximal tubule and increased trapping of protons in distal parts of the nephron. Titratable acid excretion (for practical purposes equivalent to the excretion of titratable phosphate anions) is also increased. Both processes result in increased renal net acid excretion. In a new steady state, renal acid excretion is equal to the acid load resulting in stable but lower plasma bicarbonate concentrations, i.e. chronic metabolic acidosis.

In this review we concentrate on recent information concerning the clinical effects of metabolic acidosis in humans, summarise the effects of acidosis on protein metabolism, the calcium / phosphate / PTH / 1,25-$(OH)_2$ vitamin D axis, and the GH/IGF-1 endocrine axis, and, finally, discuss the effects of acidosis on thyroid hormones and glucocorticoid activity.

The effects on sodium and potassium metabolism are fairly well characterised and are summarised only briefly: metabolic acidosis results in natriuresis due to inhibition of tubular sodium reabsorption at both proximal and distal nephron sites. Natriuresis induces extracellular volume contraction, resulting in a secondary hyperaldosteronism [1]. In fact, before the emergence of the first diuretics over 50 years ago, administration of acid was the principal method of inducing negative sodium balance in volume-expanded patients. Acute metabolic acidosis is said to increase plasma potassium concentration due to a transcellular ex-

change of protons against potassium ions. However, the quantitative relationship between acidaemia and potassium is so poorly characterised that it precludes any diagnostic reliability. In addition, acidosis-induced hyperkalaemia is even less predictable in organic acidosis, inasmuch as organic anions can enter the cell with protons (obviating a stimulus for potassium exit) and some of them can stimulate insulin release, thus stimulating potassium uptake [1].

Effects of acidosis on nitrogen balance and protein metabolism

Metabolic acidosis in rats results in growth failure and increases in protein breakdown from skeletal muscle [2]. This proteolysis is strictly dependent on the presence of glucocorticoids [2]. Children with tubular acidosis also exhibit growth retardation (associated with increased urinary nitrogen excretion [3]) which is reversible upon treatment with alkali [4]. Metabolic acidosis has been shown to increase protein breakdown in humans and to stimulate branched chain amino acid oxidation in both humans and animals [5]. Protein (albumin) synthesis is also inhibited by metabolic acidosis in humans [6], but not skeletal muscle protein synthesis in rats [7].

Thus, metabolic acidosis affects protein metabolism both by decreasing synthesis (humans) and accelerating proteolysis and amino acid oxidation. Acidosis has a marked effect on nitrogen balance: normal subjects with experimentally induced metabolic acidosis (steady-state bicarbonate plasma levels around 15 mmol/l) lost about 360 mmol nitrogen or about 30 grams of protein per day (Figure 1). Based on these quantitative correlations, acidosis may well be the most important factor in the wasting syndromes associated with many illnesses, i.e. with uraemia [8], sepsis, trauma, HIV infection and chronic diarrhoea, and may thus adversely affect the prognosis of these conditions [9].

Whether part or all of the effects of metabolic acidosis on protein metabolism are glucocorticoid-dependent in humans as in the rat remains to be determined. However, Sicuro et al. have demonstrated that chronic metabolic acidosis increases glucocorticoid activity in normal human subjects [10]. Other endocrine mediators which may contribute to growth retardation and alterations in protein metabolism and nitrogen balance, in addition to glucocorticoids, include reported changes in the growth hormone/IGF-1 endocrine axis and in thyroid hormone metabolism (see below [11, 12]).

Mitch and coworkers have shown that among the many proteolytic pathways, an ATP-dependent ubiquitin-proteasome pathway is activated at the transcriptional level and mediates muscle proteolysis [13, 14]. Interestingly, mRNA expression of ubiquitin-proteasome genes in response to acidosis seems to depend on the presence of glucocorticoids [14, 15], providing further evidence that the glucocorticoid activity (stimulated in acidosis [10]) may be an important mediator in acidosis-induced protein catabolism.

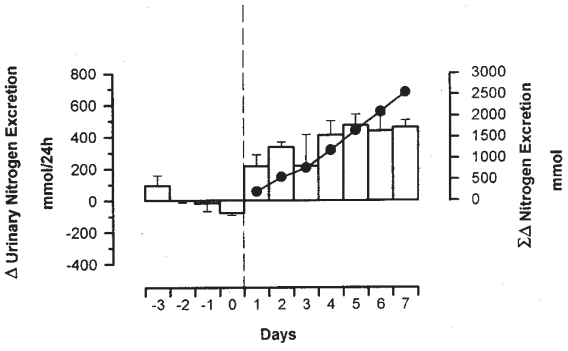

Figure 1

Effect of metabolic acidosis on nitrogen excretion. Subjects lost more than 2500 mmol of nitrogen over a period of one week. Induction of acidosis was performed by oral ingestion of NH_4Cl resulting in steady-state bicarbonate concentrations of around 15 mmol/l ([6], with permission, The Journal of Clinical Investigation).

Effect of metabolic acidosis on divalent ion, PTH and 1,25-$(OH)_2$ vitamin D metabolism

Metabolic acidosis profoundly affects calcium and phosphate metabolism, resulting in calcium loss from bone [16] in association with hypercalciuria [17, 18] (Figure 2). Hypercalciuria is the result of an increase in filtered load and decreased tubular reabsorption of calcium. The latter's cellular mechanisms are poorly understood, although calcium reabsorption is correlated with the luminal HCO_3 concentration in the distal tubule. The important clinical sequelae of the resultant negative calcium balance (combined with phosphate depletion, see below) are a metabolic bone disease with features of osteomalacia [20–22] and calcium nephrolithiasis [23].

In view of the citrate's role in calcium complexation, inhibition of stone formation and prevention of nephrocalcinosis, it is also important to consider the effects of metabolic acidosis on renal citrate metabolism. Citrate is derived from carbohydrate metabolism and contains three negatively charged carboxyl groups yielding – after complete oxidation – three bicarbonate ions. In response to acidosis, citrate reabsorption in the proximal tubule is increased and urinary citrate excretion

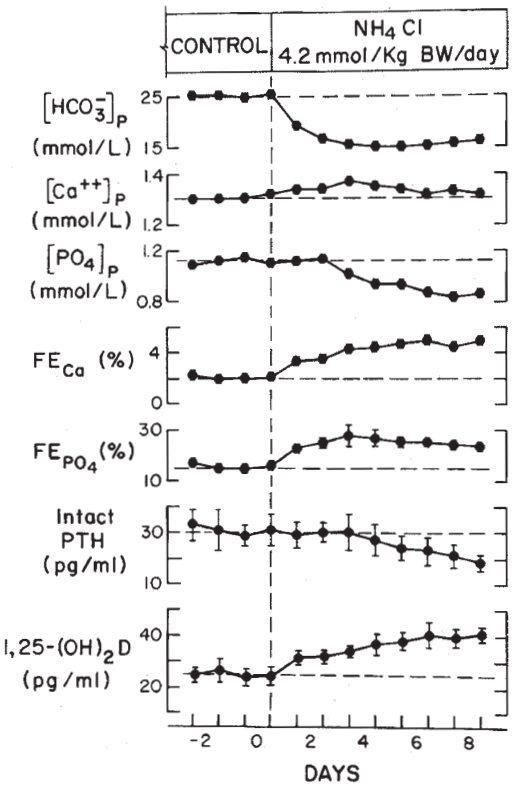

Figure 2

Effect of metabolic acidosis (induced by NH_4Cl ingestion) on bicarbonate, plasma ionised calcium and plasma phosphate concentrations, the fractional excretion rates of calcium and phosphate as well as intact PTH and 1,25-$(OH)_2$ vitamin D levels ([24], with permission, The Journal of Clinical Investigation).

decreased. Citrate retention thus serves a homoeostatic role by generating more bicarbonate in response to acidosis. The trade-off is hypocitraturia with increased risk of renal stone formation.

Metabolic acidosis also induces hypophosphataemia in association with increased renal phosphate clearance and decreased fractional excretion of phosphate, i.e. metabolic acidosis induces renal phosphate depletion [24]. Metabolic acidosis seems to affect renal regulation of phosphate reabsorption both directly (via effects on phosphate transport, notably the proximal tubule Na/PO_4 cotransporter [25, 26]) and indirectly via endocrine changes (increased glucocorticoid activity, decreased IGF-1 levels [10, 11]).

In animals, metabolic acidosis was found to decrease 1,25-$(OH)_2$ vitamin D levels [27], an effect generally attributed to decreased activity of renal 1-alpha-hydroxylase [28]. However, chronic metabolic acidosis was repeatedly shown to *increase* 1,25-$(OH)_2$ vitamin D (by stimulation of its production rate) and to concomitantly decrease PTH concentrations in humans [24, 29]. The effects of metabolic acidosis on ionised calcium concentration (no hypercalcaemia observed in humans, but prevalent in rats) and on the severity of phosphate depletion/hypophosphataemia seem to differ among species. Thus, it is likely that the changes in 1,25-$(OH)_2$ vitamin D levels and PTH concentrations observed are primarily determined by the occurrence or the severity of acidosis-induced hypercalcaemia which has been shown to override other potent stimuli of 1,25-$(OH)_2$ vitamin D production, including phosphate depletion [30, 31].

It is interesting to speculate that the elevated 1,25-$(OH)_2$ vitamin D levels in response to metabolic acidosis could serve a homoeostatic role, i.e. that elevated 1,25-$(OH)_2$ vitamin D could contribute to the normal acid excretory response to an acid load/acidosis. This question merits further experimental investigation inasmuch as vitamin D deficiency was shown to result in metabolic acidosis in chicks [32] and chronic 1,25-$(OH)_2$ vitamin D administration results in metabolic alkalosis (partly of renal origin) in thyroparathyroidectomised dogs [31].

In summary, metabolic acidosis in humans induces (1) hypercalciuria due to release of calcium from bone and decreased renal tubular calcium reabsorption, (2) renal phosphate depletion and hypophosphataemia, (3) an increase in 1,25-$(OH)_2$ vitamin D and a decrease in PTH, and (4) hypocitraturia.

Growth hormone (GH)/IGF-1 axis

Important effects of metabolic acidosis on the GH/IGF-1 endocrine axis were suggested by the observation of McSherry et al [4] that growth retardation in children with renal-tubular acidosis is reversible upon administration of alkali. In rats, Challa et al. have demonstrated decreased GH secretion and IGF-1 levels without significant effects on hepatic IGF-1 and GH receptor mRNA [33, 34]. In humans, serum IGF-1 concentrations are also decreased in response to metabolic acidosis. In sharp contrast to the findings in rats, the primary abnormality in humans is most likely due to peripheral insensitivity to GH action with GH secretion rates presumably elevated, on the basis of the demonstration of an exaggerated increase in GH in response to stimulation by GH releasing hormone [11]. In addition, acidosis was shown to exaggerate the GH response to exercise in humans [19]. These findings indicate that those in the rat may not be applicable to humans. The recent observations that administration of GH both partially corrects metabolic acidosis by a renal mechanism (primarily by an increase in ammonium excretion [10]), corrects acidosis-induced negative nitrogen balance, corrects renal phosphate depletion and hypophosphataemia and attenuates renal magnesium wasting [29], are evidence in favour of the notion that acidosis-induced changes in the GH/IGF-1 endocrine axis may be important in the mediation of several metabolic effects of metabolic acidosis. The novel finding that GH/IGF-1 administration at least partially corrects acidosis by a renal mechanism (Figure 3) raises interesting but as yet unexplored questions concerning the effects of GH/IGF-1 on renal acidification [10].

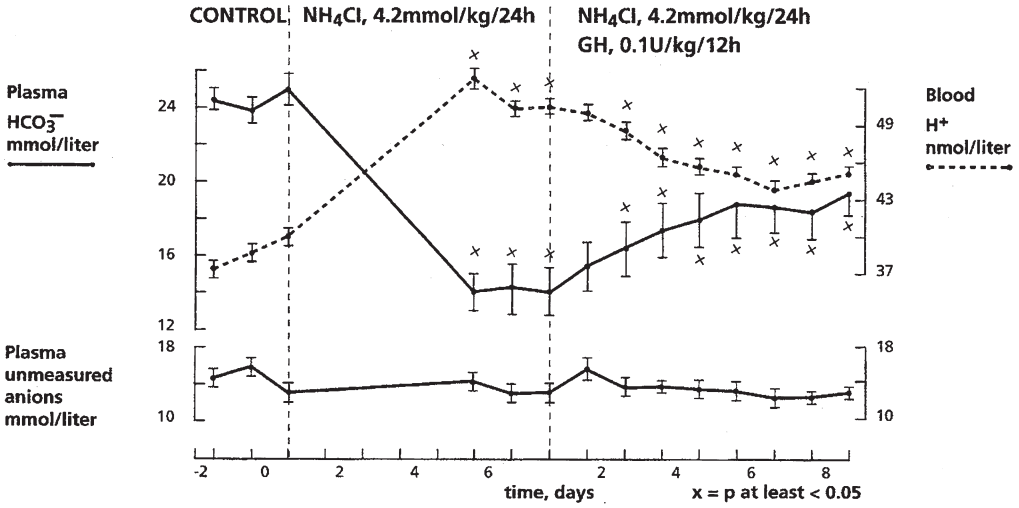

Figure 3

Effect of growth hormone administration on acid-base parameters in pre-exisiting chronic metabolic acidosis induced by NH_4Cl ingestion in normal humans Both proton and bicarbonate concentrations return towards normal in response to GH (01 U/kg bw/day, [10], with permission, American Society of Physiology).

Thyroid hormones

Chronic metabolic acidosis in humans slightly decreases freeT3 and freeT4 and significantly increases TSH serum concentrations with no change in reverse T3 [12], findings consistent with a primary decrease in thyroid hormone secretion, i.e. mild primary hypothyroidism. The quantitative importance of these changes in thyroid function with respect to acidosis-induced negative nitrogen balance is unknown. Hypothyroidism impairs urinary acidification in the rat [35], but only repletion experiments could clarify the role of the observed thyroid abnormalities in the overall renal response to acidosis in humans.

Glucocorticoids

Observations in rats suggest that increased glucocorticoid activity in response to metabolic acidosis is responsible for the acidosis-induced increase in protein degradation [13]. It is also possible that increased glucocorticoid activity could co-determine the systemic and renal response to an acid load, given the enhancing effects of glucocorticoids on renal acidification [36] and renal tubular acid-base transport mechanisms [37, 38]. As indicated, Sicuro et al. recently found that, based on determination of the daily excretion rates of tetrahydrocortisone and cortisol, chronic metabolic acidosis in humans significantly increases glucocorticoid activity [10].

Biological relevance of acidosis-induced metabolic and endocrine effects

Intuitively, correction of acidosis by removing its underlying cause or by supplementing base is the most important way to prevent these adverse effects. In a major example of chronic metabolic acidosis, uraemia, the effects of correcting acidosis are not clear since uraemia is a complex metabolic disorder which affects many of the metabolic and endocrine systems described. Wiederkehr et al. reported preliminary findings in acidotic haemodialysis patients [39]. Correction of renal acidosis by oral citrate administration to these patients partly corrected IGF-1 levels and reversed GH insensitivity. Nutritional parameters (among others: albumin, prealbumin, cholesterol and lymphocyte count) were also improved. However, there was no significant effect on cortisol levels and thyroid abnormalities. Thus, at least some of the uraemia-associated metabolic disturbances are amenable to improvement through correction of acidosis.

On a larger epidemiological scale, it is interesting to speculate on the effects of diet-induced acid loads. Western diet induces an endogenous acid load of about 50 to 100 mmol per day. Dietary animal protein content is positively correlated with calciuria [17], increased rates of renal calcium stones and hip fractures [40]. In addition, a large proportion of renal stone formers ingesting a high protein diet have decreased urinary citrate excretion, possibly due to the diet-induced acid load [41]. Based on these observations, it is also possible that the high animal protein content in western diet contributes to osteoporosis. It is also conceivable, although speculative, that the chronic acid load induces a state of chronic nitrogen wasting. This, together with the blunted acid excretion

associated with ageing, could contribute to the progressive decrease in muscle and bone mass in older people. Interestingly, Sebastian and coworkers have shown that neutralisation of endogenous acid production (by administering potassium bicarbonate) in postmenopausal women results in calcium retention and decreased bone resorption markers. In addition, renal nitrogen excretion decreased significantly [42, 43]. Maurer et al. tested the effect of bicarbonate supplements in young adults in their twenties. In this population there was rapid induction of a sustained positive calcium balance and a significant reduction in bone resorption markers (pyridinolines and n-telopeptide [44]). In view of these findings the quantitative role of diet-induced acid load on prevalent diseases such as nephrolithiasis, osteoporosis and age-associated reduction in lean body mass certainly merits its detailed investigation.

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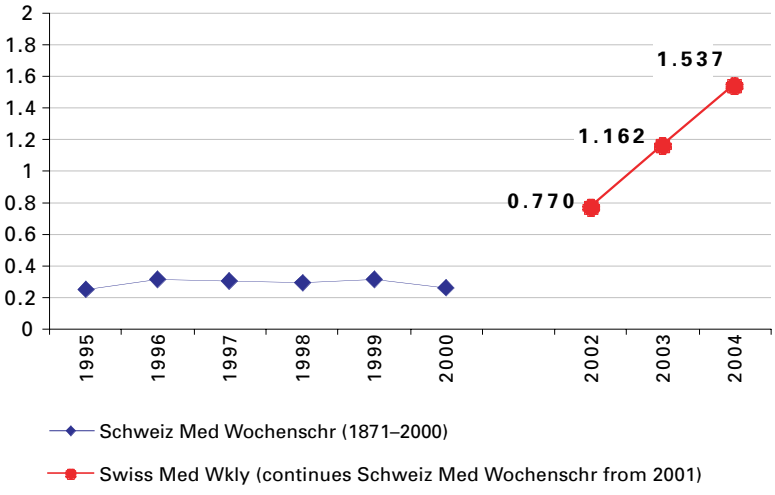

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