Growth Hormone Corrects Acidosis-Induced Renal Nitrogen Wasting and Renal Phosphate Depletion and Attenuates Renal Magnesium Wasting in Humans

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We have shown previously that chronic hyperchloremic metabolic acidosis (CMA) induces severe negative nitrogen balance and renal phosphate depletion and decreases serum insulin-like growth factor-1 (IGF-1) in association with growth hormone (GH) insensitivity in humans. The present study investigated whether acidosis-induced renal nitrogen wasting and renal phosphate depletion are mediated by GH insensitivity/low IGF-1 and thereby responsive to GH treatment. The effects of GH on acidosis-induced changes in divalent cation metabolism and acidosis-induced hypothyroidism were also investigated. CMA ($\Delta[HCO_3]$, −10.5 mmol/L) was induced in six healthy male subjects ingesting 4.2 mmol NH_4Cl/kg body weight [BW]/d for 7 days. Recombinant human GH (0.1 U/kg BW/12 h subcutaneously) was administered for 7 days while acid feeding was continued. GH increased serum IGF-1 from 22.1 ± 1.4 to 87 ± 8.4 nmol/L (control level, 36.4 ± 2.2). GH decreased urinary nitrogen excretion, resulting in a cumulative nitrogen retention of 2,404 mmol, thereby correcting the acidosis-induced cumulative increase in nitrogen excretion (2,506 mmol) despite continued acid feeding. GH attenuated the acidosis-induced hyperphosphaturia (cumulative phosphate retention, 91 mmol) and corrected the hypophosphatemia. GH did not affect acidosis-induced ionized hypercalcemia, but further exacerbated acidosis-induced hypercalciuria (cumulative loss, 27.3 mmol). GH significantly further increased serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and further decreased intact PTH (from 10 ± 1 to 6 ± 1 pg/mL). Acidosis also induced hypomagnesemia and hypermagnesuria (cumulative loss, 9.4 mmol, ie, renal magnesium wasting), a novel finding, which was significantly attenuated by GH (cumulative retention, 5.0 mmol). In conclusion, GH corrected acidosis-induced renal nitrogen wasting, which may be caused, at least in part, by decreased IGF-1 levels. GH further increased serum $1,25(OH)_2D$ and the systemic calcium load, which account for the suppression of parathyroid hormone (PTH) despite renal PO_4 retention and correction of hypophosphatemia. GH attenuated acidosis-induced renal magnesium wasting.

CHRONIC HYPERCHLOREMIC metabolic acidosis (CMA) has potent effects on nitrogen metabolism and thyroid, glucocorticoid, mineralocorticoid, and 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) hormone homeostasis, as well as divalent ion metabolism, in humans.[1,2] We have recently reported that sustained administration of growth hormone (GH) to subjects with CMA results in a significant stimulation of renal net acid excretion of sufficient magnitude to effect partial correction of acidosis despite significant reductions in glucocorticoid and mineralocorticoid activity.[3] Thus, GH has joined mineralocorticoid, glucocorticoid, parathyroid hormone (PTH), and $1,25(OH)_2D$ as a new class of hormone capable of generating and maintaining a sustained increase in the plasma bicarbonate concentration by a renal mechanism.[3]

In addition to its well-known sustained hypobicarbonatemia and hypokalemia, CMA results in profound nitrogen catabolism, renal phosphate wasting, hypercalciuria, hypermineralocorticoidism, hyperglucocorticoidism, and hypophosphatemia-induced increases in serum $1,25(OH)_2D$, as well as multiple derangements in thyroid homeostasis suggestive of mild hypothyroidism.[1-4] Since GH administration to humans is known to result in significant nitrogen anabolism in eucaloric nonacidotic subjects but no anabolism in starved subjects with chronic ketoacidosis, the effects of sustained GH administration in subjects with the common clinical condition of CMA are difficult to predict.[5] Long-term GH administration is also reported to increase serum free triiodothyronine (fT_3) in humans to levels sufficient to suppress the serum thyrotropin (TSH) concentration.[5-8] Whether GH administration, by virtue of its effect to increase serum fT_3, may mitigate or even abrogate GH-induced nitrogen anabolism in acidotic subjects with preexisting reductions in serum fT_3 is unknown. The potential role of GH treatment to mitigate CMA-induced alterations in divalent ion and vitamin D metabolism in humans remains unexplored in any species. Based on the reported insensitivity of GH to induce normal insulin-like growth factor-1 (IGF-1) production in subjects with CMA, it is possible that many effects of GH, in addition to those reported for nitrogen anabolism in ketoacidosis, may be minimized or absent.[9]

Accordingly, the present studies were conducted in normal human subjects under conditions of metabolic balance in which the endocrine, metabolic, and divalent-ion effects of sequential induction of NH_4Cl-induced CMA and then CMA with superimposed sustained GH administration were determined. The acid-base and electrolyte effects of GH administration in these same subjects have been reported previously.[3]

SUBJECTS AND METHODS

Subjects

To assess the effects of recombinant human GH on nitrogen balance and the renal and systemic regulation of divalent ion metabolism and thyroid hormones in preexisting NH_4Cl-induced metabolic acidosis, six normal male subjects were examined under metabolic ward conditions. None were smokers or were taking any medications before or during the study. Each subject ingested a constant metabolic, whole-food diet throughout 3 study periods (control, acidosis, and acidosis with GH administration). The diet was calculated to provide 1.8 mmol sodium,

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Foundation (3200-050940.97/1 to R.K.)

Submitted July 24, 1998; accepted December 10, 1998.

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0026-0495/99/4806-0015$10.00/0

1.1 mmol potassium, 44.4 mL water, and 36 kcal per kilogram body weight (BW) per day.

All subjects volunteered for the study, received payment for participation, and provided written informed consent. The study protocol was approved by the ethics committee of the Kantonsspital St. Gallen.

Experimental Design

After establishment of the control period steady state (variation of plasma bicarbonate, ≤1.5 mmol/L; in press), CMA was induced by oral administration of NH_4Cl (4.2 mmol/kg BW/d) in gelatin capsules in six divided doses. On day 8 of acidosis, recombinant human GH (Genotropin; Kabi Pharmacia, Uppsala, Sweden) 0.1 U/kg BW every 12 hours was administered as two daily subcutaneous injections (using an automated-dosage device provided by the manufacturer) with continued acid feeding and observation for 7 additional days.

Analytical Procedures

All determinations were performed in duplicate. Divalent ions were determined as described previously.[10,11] The ionized calcium level was measured with an ion-selective electrode (model 634; Ciba-Corning, Corning, NY). Twenty-four-hour nitrogen excretion was determined photometrically after wet incineration followed by formation of indophenol with salicylate and hypochlorite.[1] Serum intact PTH and $1,25(OH)_2D$ levels were measured with specific radioimmunoassays and radioreceptor kits, respectively (Nichols Institute, San Juan Capistrano, CA).[2] fT_3 and free thyroxine (fT_4) were determined using the IMX microparticle immunoassay method as previously validated versus equilibrium dialysis.[4,12] TSH levels were measured by a third-generation microparticle enzyme immunoassay.[13] All samples were analyzed within a single assay. All hormones were determined on the last 2 days of each period. The values reported represent the mean of these determinations.

All steady-state values represent the mean of the last 3 days of the corresponding study periods. Results are reported as the mean ± SE. Statistical analysis was performed by ANOVA for repeated measures and Student's *t* test for paired data using SYSTAT software. Significant differences are indicated by a *P* value less than .05. The acid-base, electrolyte, and steroid metabolism data from this protocol have been reported previously.[3]

RESULTS

As reported previously, NH_4Cl feeding resulted in chronic stable metabolic acidosis (decrease of plasma bicarbonate, 10.1 ± 0.9 mmol/L, $P < .001$). GH with continued acid feeding increased plasma bicarbonate by 4.5 ± 0.4 mmol/L from 14.0 ± 0.6 (acidosis) to 18.6 ± 0.5 mmol/L (acidosis + GH, $P < .001$[3]). Tables 1 and 2 depict steady-state plasma values for urea and divalent ions and the steady-state urinary excretion of nitrogen (corrected for nitrogen in administered NH_4Cl) and divalent ions and the creatinine clearance rate, respectively.

Figure 1 illustrates that GH administration completely corrected the acidosis-induced urinary nitrogen loss. In accordance with our previous observations, NH_4Cl-induced acidosis resulted in a cumulative increase in nitrogen excretion of 2,506 mmol for the 7-day acidosis period.[1] Despite continued acid feeding, GH induced a large retention of urinary nitrogen (cumulative retention, 2,404 mmol over 7 days) of sufficient magnitude for complete correction of the previous acidosis-induced nitrogen losses. Since dietary intake was identical throughout, the method of presentation in Figure 1 is equivalent to nitrogen balance assuming that stool nitrogen excretion remained small and constant.[1] Thus, GH is able to correct or prevent acidosis-induced renal nitrogen wasting.

Table 1. Effects of Acidosis and GH Administration on Steady-State Urea and Divalent Ion Plasma Concentrations (mmol/L)

Condition	Urea	PO_4	Ion Ca	Mg
Control	5.4 ± 0.3	1.19 ± 0.04	1.21 ± 0.02	0.87 ± 0.02
Acidosis	3.5 ± 0.4*	0.97 ± 0.04*	1.29 ± 0.02*	0.77 ± 0.02*
Acidosis + GH	4.0 ± 0.4†	1.26 ± 0.08*	1.28 ± 0.01†	0.79 ± 0.02†

NOTE. Results are the mean ± SE.

*P at least <.05 *v* previous steady state.

†P at least <.05 for acidosis + GH *v* control.

Figure 2 demonstrates that GH administration corrected acidosis-induced hypophosphatemia and was accounted for, at least in part, by a significant attenuation of the hyperphosphaturia characteristic of metabolic acidosis. GH induced a cumulative renal phosphate retention of 91 mmol (*v* acidosis without GH), thereby partially correcting the acidosis-induced phosphate depletion. The fractional excretion of phosphate (FE_{PO4}) was 18.0% ± 1.4% during the control period and increased significantly to 30.5% ± 1.7% during acidosis. GH decreased FE_{PO4} significantly to 15.1% ± 1.1% during continued acidosis.

The effects of GH on calcium and phosphate metabolism are shown in Figs 3, 4, and 5. The blood ionized calcium concentration increased from 1.21 ± 0.02 mmol/L during the control period to 1.29 ± 0.02 mmol/L during acidosis ($P < .005$; Figs 3 and 4). GH had no significant additional effect on the acidosis-induced increase in ionized calcium (1.28 ± 0.01). Figure 4 shows that NH_4Cl-induced metabolic acidosis resulted in a significant increase in $1,25(OH)_2D$ and a significant decrease in intact PTH serum concentrations. In accordance with our previous observations, $1,25(OH)_2D$ increased significantly in response to acidosis, from 126 ± 5 to 152 ± 9 pmol/L ($P < .025$), while intact PTH decreased significantly from 16 ± 1 to 10 ± 1 pg/mL ($P < .05$[2]). GH administration further significantly increased $1,25(OH)_2D$ to 182 ± 9 pmol/L ($P < .025$) and significantly decreased intact PTH to 6 ± 1 pg/mL ($P < .05$). Figure 4 also illustrates that these GH-induced changes in both $1,25(OH)_2D$ and intact PTH occurred despite the reversal of previous acidosis-induced hypophosphatemia and no significant change in the blood ionized calcium concentration.

Figure 3 shows that GH administration resulted in sustained exacerbation of acidosis-induced hypercalciuria. Acidosis induced a large cumulative (7-day) increment in urinary calcium of 56.8 mmol ($P < .001$[2]). GH administration for 7 days induced a significant further increment of 27.3 mmol ($P < .001$). The increase in renal calcium excretion is likely accounted for by increased intestinal calcium absorption via GH-induced elevation of $1,25(OH)_2D$ levels (Figure 4). In this regard, Figure 6 shows that GH induced a significant increase in the glomerular filtration rate as evidenced by the creatinine clearance rate (increase from 2.15 ± 0.16 mL/s during acidosis to 2.45 ± 0.22 mL/s during acidosis + GH), whereas the fractional excretion of calcium was not affected significantly (Figure 6).

The effects of acidosis and GH administration during acidosis on magnesium metabolism are shown in Figures 5 and 6. Acidosis significantly increased renal magnesium excretion (cumulative loss, 9.4 mmol over 7 days, $P < .001$). Acidosis-induced hypermagnesuria accounted, at least in part, for the

Table 2. Effects of Acidosis and GH Administration During Acidosis on Steady-State Urinary Excretion (mmol/24 h) of Nitrogen (corrected for administerd NH_4Cl) and Divalent Ions and Creatinine Clearance Rate (mL/s)

Condition	Nitrogen	PO_4	Ca	Mg	Creatinine Clearance
Control	995 ± 47	18.0 ± 0.9	3.9 ± 0.4	4.3 ± 0.3	2.30 ± 0.13
Acidosis	1,410 ± 106*	49.6 ± 1.4*	14.2 ± 0.4*	4.9 ± 0.2*	2.11 ± 0.17
Acidosis + GH	945 ± 53*	38.1 ± 1.8*†	20.2 ± 0.5*†	4.2 ± 0.2*	2.46 ± 0.20*

NOTE. The mean weight gain of 1.8 kg during GH administration[3] multiplied by the mean value for plasma urea of 4.0 mmol/L (Table 1) represents a maximal value of 7.2 mmol nitrogen accumulation within total body water as a result of extracellular fluid expansion with an unchanged plasma urea concentration. This value represents only 0.3% of the 2,506 mmol nitrogen retained as assessed by urinary nitrogen excretion.

*P at least <.05 *v* the previous steady state.

†P at least <.05 for acidosis + GH *v* control.

significant decrease in plasma magnesium (from 0.87 ± 0.02 to 0.77 ± 0.02 mmol/L, $P < .005$). During continued acidosis, GH did not affect the plasma magnesium concentration significantly (0.79 ± 0.02 mmol/L). However, renal magnesium wasting was significantly attenuated, since GH induced a renal magnesium retention of 5.0 mmol ($P < .025$). GH increased the tubular reabsorption of magnesium as evidenced by the significant decrease in the magnesium fractional excretion rate (acidosis, 3.51% ± 0.21%; acidosis + GH, 2.91% ± 0.16%, $P < .05$; Fig 6). In view of the nonsignificant tendency for GH to increase plasma magnesium (Figure 5, days 6 and 7 of acidosis + GH) and significantly decrease renal magnesium excretion, it is possible that more prolonged GH administration might have completely corrected the acidosis-induced hypomagnesemia.

Figure 7 depicts the effects of GH on acidosis-induced alterations in thyroid hormone and TSH levels. GH significantly increased fT_3 from 369 ± 27 to 506 ± 39 pg/dL ($P < .005$), while fT_4 levels further decreased significantly from 1.35 ± 0.14 to 1.21 ± 0.11 ng/dL during GH administration. Concurrently, TSH decreased significantly from 0.91 ± 0.07 to 0.47 ± 0.09 mU/L ($P < .0025$).

DISCUSSION

Administration of GH in acidotic subjects in the present studies, while resulting in only partial correction of metabolic acidosis, resulted in complete reversal of the catabolic nitrogen wasting caused by experimentally induced CMA. Moreover, in addition to correcting the ongoing daily nitrogen losses of CMA, the magnitude of GH-induced anabolism was such that 7 days of GH administration were sufficient to repair fully the nitrogen deficit accumulated during the previous 7 days of CMA. Thus, the present studies confirm our previous report[1] of CMA-induced renal nitrogen wasting in human subjects and provide the first evidence of the reversibility of this condition. The relative contribution of the effects of partial correction of acidosis and acidosis-independent effects of GH on protein anabolism, per se was not determined with precision. However, our previous studies showed that subjects exposed to a lesser acid load and degree of acidosis (mean plasma bicarbonate,

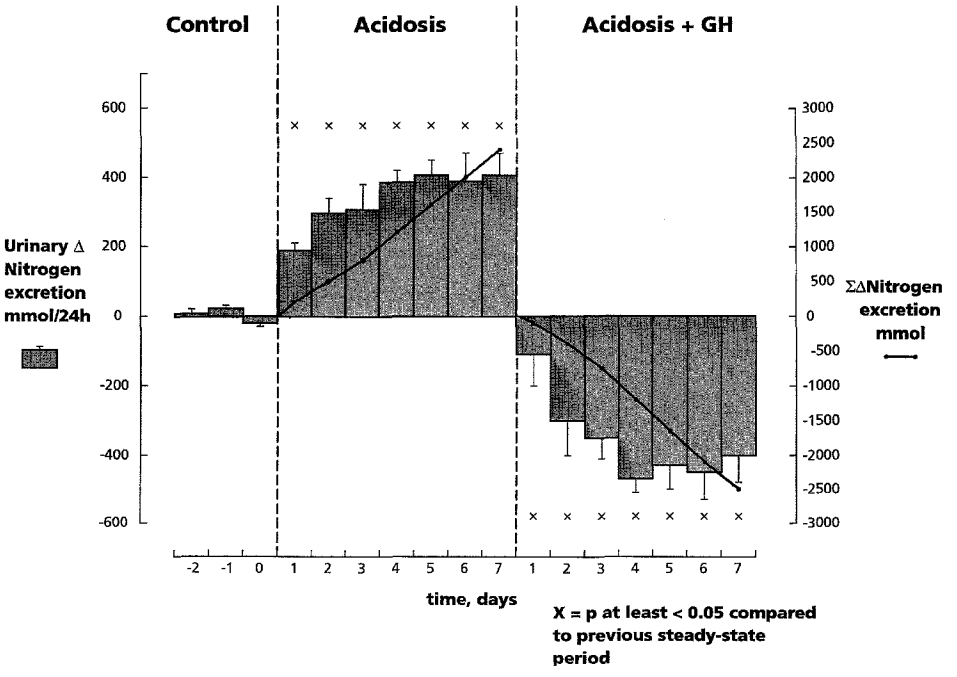

Fig 1. Effect of acidosis and GH during continued acidosis on urinary nitrogen excretion. Bars indicate the magnitude of daily changes in urinary nitrogen excretion *v* the previous steady-state period. ΣΔ denotes the accumulated sum of daily changes *v* the previous steady-state period. ×*P* at least < .05 *v* the previous steady-state period.

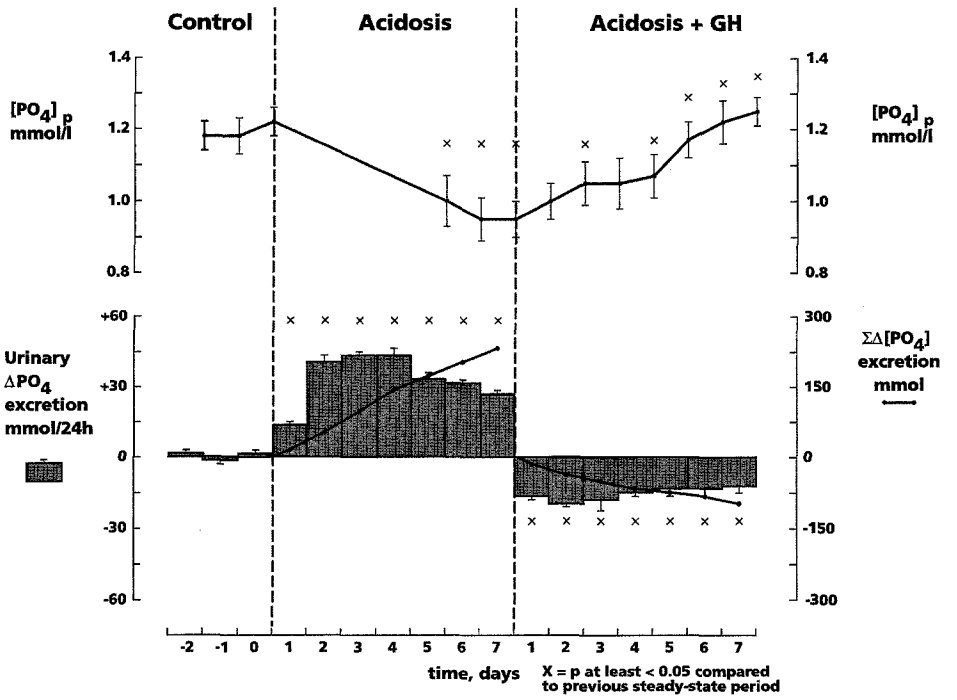

Fig 2. Effect of acidosis and GH during continued acidosis on plasma phosphate (PO_4) concentration and urinary phosphate excretion. Bars indicate the magnitude of daily changes *v* the previous steady-state period. ΣΔ denotes the accumulated sum of daily changes *v* the previous steady-state period. ^{x}P at least < .05 *v* the previous steady-state period.

19.1 mmol/L), with a bicarbonate level similar to that found during GH administration in the present studies, exhibited an attenuated magnitude of nitrogen wasting relative to subjects receiving the presently used high acid load. Nevertheless, the persistence of urinary nitrogen wasting during mild acidosis in the previous study is evidence for an acidosis-independent effect of GH administration to fully correct nitrogen wasting in the present studies. A determination of the precise physiologic role of GH in modulating both acid-base equilibrium and protein metabolism will require protocols designed for independent restoration of normal levels of GH and IGF-1, versus the supernormal levels achieved in the present studies.

The magnitude of daily nitrogen anabolism induced by GH in the present studies of acidotic subjects (6.5 g/24 h) is surprisingly large in comparison to values reported previously for both nonacidotic subjects (0.004 to 2.8 g/24 h[5,14-17]) and ketoacidotic starved subjects (no effect[5]) administered similar doses of GH. The failure of GH to improve nitrogen balance in starvation ketoacidosis has been attributed to the effect of GH to cause a severe lipolysis-induced exacerbation of ketoacid production and consequent worsening of systemic acidosis with associated increases in ammonium excretion despite a decrease in urea excretion.[5] Whereas the mechanism of the GH-induced greatly augmented anabolism in subjects with hyperchloremic mineral

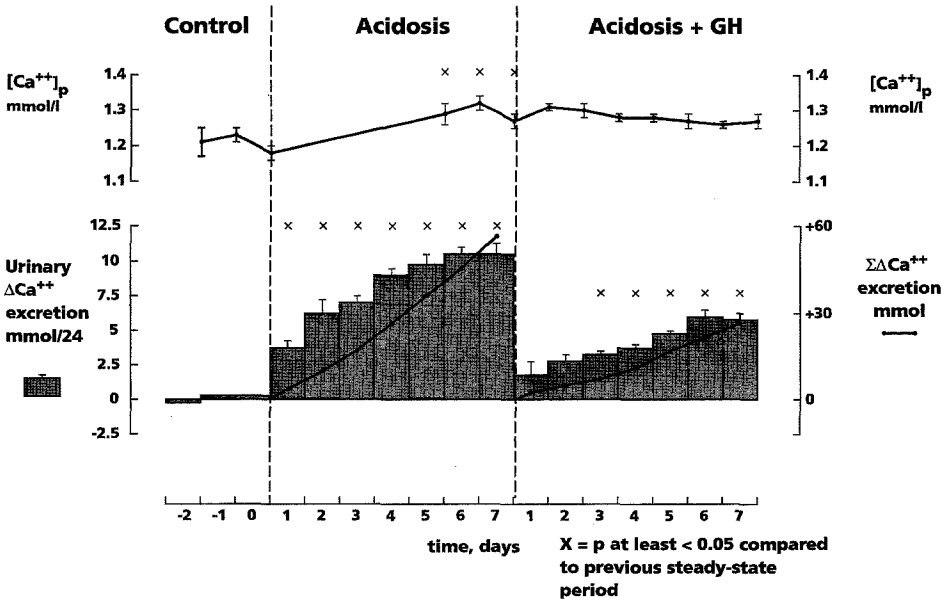

Fig 3. Effect of acidosis and GH during continued acidosis on plasma ionized calcium (Ca^{++}) concentrations and urinary calcium excretion. Bars indicate the magnitude of daily changes *v* the previous steady-state period. ΣΔ denotes the accumulated sum of daily changes *v* the previous steady-state period. ^{x}P at least < .05 *v* the previous steady-state period.

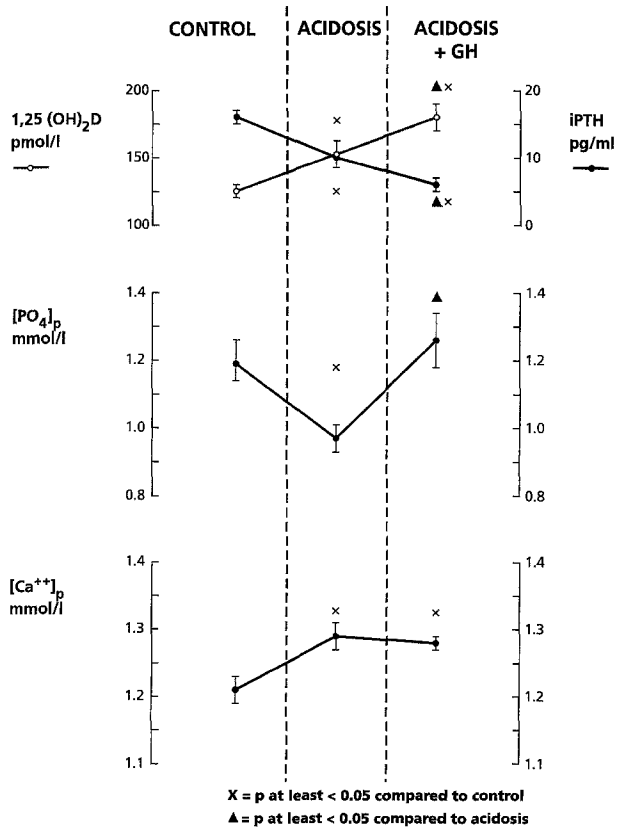

Fig 4. Effect of acidosis and GH during continued acidosis on steady-state 1,25(OH)$_2$D and intact PTH serum concentrations and steady-state plasma concentrations of phosphate and ionized calcium. ^{x}P at least < .05 *v* control; $^{▲}P$ at least < .05 *v* acidosis without GH.

acidosis versus nonacidotic subjects is unknown, a mechanism for the GH-induced reduction in the magnitude of acidosis, if present, cannot operate by reducing the need for ammonium excretion, since the mechanism of correction of acidosis in the present studies occurs via augmented renal net acid excretion that is accounted for by a large and significant accumulated increment in urinary ammonium excretion (+194 mmol over 8 days). Moreover, in the steady-state GH treatment in the present studies, urinary ammonium and net acid excretion had returned to values essentially identical to those present before GH administration, when acidosis was more severe.[3] This observation suggests that GH-induced anabolism is accounted for exclusively by diminished urea production and excretion. An additional factor likely to be contributory to GH-induced nitrogen anabolism is the finding that GH administration results in a complete correction, or even overcorrection, of CMA-induced hyperglucocorticoidism.[3] Thus, GH might have both direct and indirect effects (suppression of hyperglucocorticoidism) on nitrogen balance. The GH-induced complete correction of nitrogen wasting and full reversal of accumulated catabolism in hyperchloremic acidosis are expected to improve lean body mass. The potential therapeutic benefits of this effect warrant thorough investigation in diverse acidotic clinical conditions.

The present studies provide substantial insight into the action of GH to modulate divalent ion metabolism. GH administration in the present studies resulted in significant attenuation of the hyperphosphaturia of CMA and complete correction of CMA-induced hypophosphatemia. Since IGF-1 is known to increase tubular reabsorption of phosphate,[18] the overcorrection of CMA-induced elevations in the fractional urinary excretion of phosphate to frankly subnormal levels during GH administration suggests that the tubular effect of GH-stimulated IGF-1 levels may have greater potency than the offsetting effect of persisting mild acidosis.[2] A GH-induced reduction in glucocorticoid activity may also participate in augmented tubular reabsorption of phosphate.[3] The persistence of supernormal values for daily phosphate excretion during GH administration is likely accounted for by the stimulatory effects of increased serum 1,25(OH)$_2$D (vide infra) on intestinal phosphate absorption,[18] since GH-induced bone and muscle anabolism would tend to reduce the systemic load of phosphate requiring daily excretion.[19] Thus, both renal and extrarenal processes may have

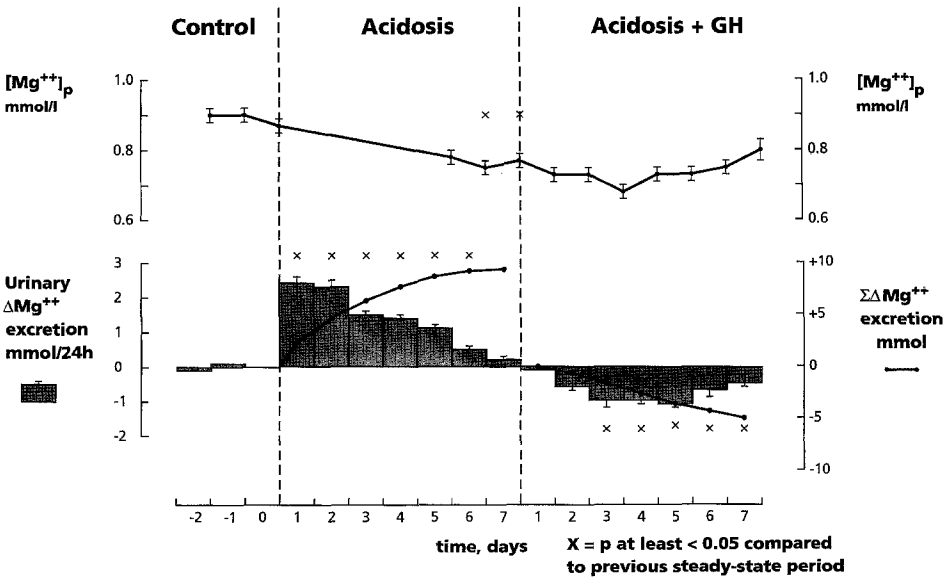

Fig 5. Effect of acidosis and GH during continued acidosis on plasma magnesium (Mg^{++}) concentration and urinary magnesium excretion. Bars indicate the magnitude of daily changes *v* the previous steady-state period. ΣΔ denotes the accumulated sum of daily changes *v* the previous steady-state period. ^{x}P at least < .05 *v* the previous steady-state period.

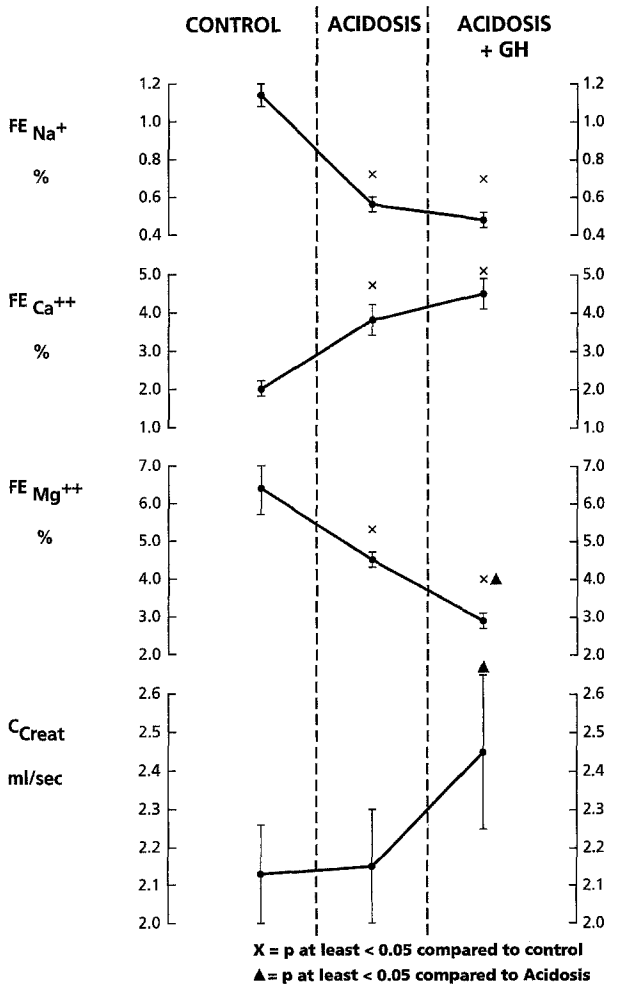

Fig 6. Effect of acidosis and GH during continued acidosis on the fractional urinary excretion (FE) of sodium, calcium, and magnesium and on creatinine clearance. For calculation, the plasma magnesium concentration was not corrected for protein binding. ˣ*P* at least < .05 *v* control; ▲*P* at least < .05 *v* acidosis without GH.

contributed to the normalization of plasma phosphate concentrations.

The acidosis-induced increment in serum $1,25(OH)_2D$ confirms our previous report that CMA-induced renal phosphate wasting is associated with hypophosphatemia-induced increments in $1,25(OH)_2D$ production.[2] The present finding of a further increase in serum $1,25(OH)_2D$ during superimposed long-term GH administration in association with a large GH-induced increase in plasma phosphate cannot be explained by factors known to modulate the $1,25(OH)_2D$ concentration. Although chronic hypocalcemia, hypophosphatemia, and elevated PTH are known to result in sustained increments in serum $1,25(OH)_2D$,[20,21] the GH-induced increase in $1,25(OH)_2D$ in the present studies was of sufficient potency to override an opposing stimulus from two of these factors, serum PTH and plasma phosphate, with no change in the serum ionized calcium concentration. Although GH has been reported to increase serum $1,25(OH)_2D$ in nonacidotic subjects,[14,22,23] the present studies provide the first data for acidotic subjects. In the report by Marcus et al[14] in nonacidotic subjects, GH administration resulted in a significant increase in serum PTH as assessed by an assay using a single antibody. In the present study and in the recent report by Wright et al,[22] sustained GH administration resulted in decreased serum PTH as discerned using the modern dual-antibody assay for intact PTH. Evidence has been adduced that IGF-1 infusion in mice results in increased $1,25(OH)_2D$ production by increasing the activity of 25-hydroxyvitamin D-1-α-hydroxylase in renal homogenates.[24] Whether IGF-1 is the proximate effector of the GH effect to increase the circulating $1,25(OH)_2D$ concentration independently of the known factors controlling this concentration, has not been determined in any species.

Regardless of the mechanism for the elevation of serum $1,25(OH)_2D$, it is likely that this effect of GH administration accounts, at least in part, for the sustained exacerbation of hypercalciuria observed in the present studies. This finding is consistent with the reported GH-induced 50% increase in serum $1,25(OH)_2D$ that correlated with intestinal hyperabsorption of

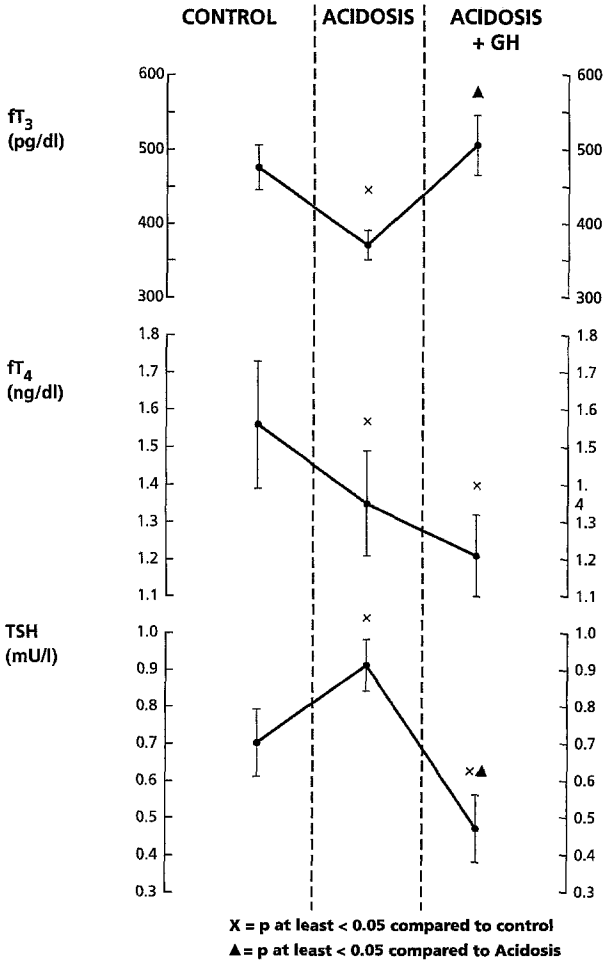

Fig 7. Effect of acidosis and GH during continued acidosis on steady-state fT_3, fT_4, and TSH serum concentrations. ˣ*P* at least < .05 *v* control; ▲*P* at least < .05 *v* acidosis without GH.

calcium and increased intestinal calbindin-D9K expression in rats.[25] However, the magnitude of the GH-induced increment in net intestinal calcium absorption was greater than could be accounted for by changes in the $1,25(OH)_2D$ concentration alone, suggesting GH effects independent of altered vitamin D metabolism. Although sustained hypercalciuria could also result from sustained losses of bone mineral, this possibility is not likely in view of the substantial evidence supporting the effect of GH administration to cause net bone accretion in humans and experimental animals.[19,26] Sustained hypercalciuria has also been reported in response to long-term GH administration in nonacidotic subjects.[14,16] The significant GH-induced increase in fractional urinary calcium excretion in the present studies is consistent with the presence of extracellular fluid volume (ECFV) expansion due to GH-induced antinatriuresis,[3] and is sufficient to override the known effect of an augmented filtered bicarbonate load to increase tubular calcium reabsorption.[27]

Whereas GH administration resulted in exacerbation of the hypercalciuria of CMA, it had an opposite effect on the hypermagnesuria of CMA. Urinary magnesium excretion was reportedly unchanged in nonacidotic normal subjects during sustained GH administration,[28] and studies in rats and humans have demonstrated no effect of long-term GH administration on net intestinal magnesium absorption.[25,28] Thus, the effect of GH administration to reduce urinary magnesium excretion in the present studies, while unanticipated based on prior reports in nonacidotic subjects, is likely to reflect the effect of net bone mineral accretion[26] in conjunction with no change in net intestinal magnesium absorption. This finding suggests the possibility that such putative GH-induced magnesium retention in acidotic subjects might reflect hyperresponsive bone mineral accretion in acidotic subjects with preexisting bone loss relative to nonacidotic subjects. The GH-induced increment in plasma magnesium from the decreased values for CMA is consistent with the effect of increments in plasma bicarbonate to increase the tubular reabsorption of magnesium,[29] as demonstrated in the present studies by a significant decrease in the fractional urinary excretion of magnesium, which occurred despite demonstrable ECFV expansion caused by GH-induced antinatriuresis.[3] Whether GH-induced phosphate and potassium retention played independent roles in the augmented tubular reabsorption of magnesium remains to be determined.[30] The finding in the present studies that sustained CMA per se results in consistent and significant hypermagnesuria of sufficient magnitude to cause sustained hypomagnesemia (renal magnesium wasting) is the first in any species. Whereas small and inconsistent changes in urinary magnesium have been noted in humans with CMA,[31-35] only one study has reported a significant reduction in the serum magnesium concentration, and it did not detect significant alterations in urinary magnesium.[31] Although frank hypermagnesuria was not demonstrated in acidotic dogs[29] or acidotic rats,[36] the study in acidotic rats reported that the fractional urinary excretion of magnesium was significantly increased while the filtered load of magnesium was similar to that in the control state. The reasons that previous studies did not detect significant renal magnesium wasting are not known with certainty in each case, but may include the lesser severity of reported CMA and the lack of 24-hour urinary excretion data in certain reports. Since extracellular acidity inhibits magnesium uptake into cultured mouse distal convoluted tubule cells, and since this segment is thought to provide the final regulation of urinary magnesium excretion,[37] it is possible that diminished transport at this site is responsible, at least in part, for the renal magnesium wasting of CMA.

The present studies have confirmed the presence of a significant CMA-induced decrease in serum fT_3 and fT_4 concentrations in association with a significant elevation in TSH, suggestive of a mild hypothyroid state.[4] As reported in nonacidotic normal subjects,[6-8] GH administration in acidotic subjects resulted in a significant increase in serum fT_3 in association with significant decreases in serum fT_4 and TSH. Although GH-induced increments in the T_4 degradation rate have not been documented in humans when assessed,[38,39] the reciprocal GH-induced changes in free and total T_3 and T_4 concentrations have been attributed to augmented peripheral monodeiodination of T_4.[6-8] Whether the observed GH-induced sustained suppression of TSH to values significantly less than those found before CMA induction reflects a degree of hyperthyroidism sufficient to counterregulate any of the anabolic actions of GH (bone and muscle protein) remains to be determined. However, since long-term administration of T_3 to nonacidotic subjects resulted in nitrogen wasting that was reversible during superimposed GH administration,[40] any catabolic effect of GH-induced hyperthyroidism in the present studies is likely without appreciable consequence.

The present data may be relevant for a number of clinical conditions. By increasing lean body mass, GH is of potential benefit in chronic acidotic conditions such as renal failure, chronic diarrhea, and renal tubular acidosis. Acidosis-induced magnesium and phosphate wasting may lead—among other effects—to decreased muscle contractility, impaired oxygen transfer to tissue, increased neuromuscular irritability, and impaired cellular immune response. It needs to be determined to what extent these various functions are affected by acidosis and whether they are reversible upon GH treatment.

In conclusion, GH administration completely corrected the accumulated and ongoing renal nitrogen wasting caused by CMA in humans. GH administration also resulted in a variety of effects on divalent ion metabolism in chronic acidosis, including correction of renal phosphate wasting, exacerbation of hypercalciuria, and attenuation of renal magnesium wasting. The finding that CMA per se results in renal magnesium wasting is novel inasmuch as it has not been reported previously in any species. The effect of GH to increase serum $1,25(OH)_2D$ despite its effect to increase serum phosphate and to decrease PTH provides evidence for its potency in the control of $1,25(OH)_2D$ metabolism, and is consistent with its ability to produce substantial hypercalciuria.

ACKNOWLEDGMENT

The authors gratefully acknowledge the generous supply of GH by Kabi Pharmacia (Switzerland/Sweden).

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