Effect of chronic metabolic acidosis on vitamin D metabolism in humans

JEFFREY A. KRAUT, EARL M. GORDON, JOHN C. RANSOM, RONALD HORST, EDUARDO SLATOPOLSKY, JACK W. COBURN, and KIYOSHI KUROKAWA

Bone disease may occur in disorders associated with chronic metabolic acidosis. This has been attributed, in part, to reduced production of 1,25(OH)2D3. Although metabolic acidosis in the vitamin D deficient animal has been associated with a reduction in the conversion of radio-labeled 25(OH)D3 to 1,25(OH)2D3, studies in D-replete humans have revealed no effect of acidosis on 1,25(OH)2D3 metabolism. To examine this issue further, we measured serum 25(OH)D3, 1,25(OH)2D3, and 24,25(OH)2D3 levels in six healthy subjects before and after 9 days of metabolic acidosis induced by the ingestion of ammonium chloride. In four subjects, we measured the increment in serum levels of 1,25(OH)2D3 in response to the infusion of parathyroid extract both during control and acidosis. Serum levels of 1,25(OH)2D3, 13.6 ± 1.3 and 14.3 ± 0.9 pg/ml, in control and acidosis, respectively, were not different. The serum 1,25(OH)2D3 levels in control and acidosis rose to a similar degree with the infusion of PTE. These data provide strong evidence that metabolic acidosis does not have a substantial impact on the synthesis of 1,25(OH)2D3 in vitamin D-replete humans.

Bone disease occurs in disorders associated with chronic metabolic acidosis [1, 2]. The presence of bone disease in these disorders has been attributed, in part, to reduced production of 1,25(OH)2D3 by the kidney. Indeed, studies in vitamin D deficient rats and chicks have shown that the conversion of 3H-25-(OH)D3 to 3H-1,25(OH)2D3 is reduced by metabolic acidosis [3—5]. Studies in vitamin D-repleted humans and animals have revealed conflicting results: Basal plasma 1,25(OH)D levels [6] and the conversion of radio-labeled 25(OH)D3 [7] to 1,25(OH)2D3 were not reduced by metabolic acidosis of 10 to 14 days in humans. Also, the increments in plasma levels of 1,25(OH)2D noted in response to a low calcium and moderately low phosphate diet were normal in rats [8], while another study showed that metabolic acidosis in the rat suppressed the rise in plasma 1,25(OH)2D noted in response to a low calcium diet [9]. In the latter study, acidosis did not affect the serum levels of 1,25(OH)2D in rats fed a normal calcium diet.

The increased synthesis of 1,25(OH)2D3 in response to a low calcium diet is related, in part, to increased circulating levels of PTH [10], whereas the increased synthesis of 1,25(OH)2D3 in response to a low phosphate diet is not [11]. Moreover, studies in vitamin D-deficient rats have demonstrated that metabolic acidosis alters vitamin D metabolism by interfering with the activation of 1α-hydroxylase by parathyroid hormone [12]. These data suggest that, if metabolic acidosis alters vitamin D metabolism, it should primarily affect the increased synthesis of 1,25(OH)2D3 induced by parathyroid hormone. To test this hypothesis, we measured both basal serum levels of 1,25(OH)2D3 and the changes in serum 1,25(OH)2D3 in response to an infusion of parathyroid extract in vitamin D-replete humans during a control period and after metabolic acidosis of 9 days duration.

The results of the present studies indicate that metabolic acidosis for 9 days does not attenuate the increment in the serum levels of 1,25(OH)2D3 observed in response to a parathyroid extract infusion nor does acidosis affect basal levels of 1,25(OH)2D3 in normal individuals fed a regular calcium diet. These data cast doubt on the importance of metabolic acidosis as a factor in reducing 1,25(OH)2D3 production in humans. Moreover, they suggest that the bone disease observed in chronic acidic states may not be mediated primarily by reduced vitamin D production.

Methods

Studies were conducted in six healthy adult volunteers, ages 33 to 53 years (mean, 45 ± 3). None of the subjects had renal
Effect of metabolic acidosis on vitamin D metabolism

were determined using the student’s t test for paired data. The sample recovery was 50 to 70%; 50% displacement occurred at 40 pg per assay tube. Further details of these methods have been described previously [18]. All results are expressed as the mean ± SEM.

Table 1. Blood composition in the control and acidic periods

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metabolic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.42 ± 0.01</td>
<td>7.32 ± 0.01b</td>
</tr>
<tr>
<td>(HCO3)p, mEq/liter</td>
<td>28.0 ± 0.7</td>
<td>18.0 ± 0.4b</td>
</tr>
<tr>
<td>iPTH, nl, 2 to 10 μEq/ml</td>
<td>3.0 ± 0.07</td>
<td>2.9 ± 0.07</td>
</tr>
<tr>
<td>Total Ca, mg/dl</td>
<td>9.5 ± 0.2</td>
<td>9.2 ± 0.1a</td>
</tr>
<tr>
<td>Phosphorus, mg/dl</td>
<td>4.5 ± 0.1</td>
<td>5.1 ± 0.1a</td>
</tr>
<tr>
<td>Mg, mg/dl</td>
<td>3.2 ± 0.2</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>2.1 ± 0.1</td>
<td>2.0 ± 0.1</td>
</tr>
</tbody>
</table>

a Data are mean ± SEM.

b P < 0.01 compared to control.
c Three of the six measurements of iPTH were arbitrarily assigned a value of 2 μEq/ml.
d P < 0.05 compared to control.

Results

Serum values for the control and acidic periods are shown in Table 1. The ingestion of ammonium chloride led to a significant fall in plasma pH from 7.42 ± 0.01 to 7.32 ± 0.01 and in plasma bicarbonate concentration from 28 ± 0.7 to 18.0 ± 0.4 mEq/liter (P < 0.01). Serum calcium fell slightly but significantly from 9.5 ± 0.2 to 9.2 ± 0.1 mg/dl (P < 0.05), whereas ionized calcium rose from 4.5 ± 0.1 to 5.1 ± 0.1 mg/dl (P < 0.05). Serum inorganic phosphate and magnesium in control and acidosis were not significantly different. Immunoreactive parathyroid hormone (iPTH) levels were below 3 μEq/ml, the level of detection, in three patients during both the control and acidic periods and a value of 2 μEq/ml was arbitrarily assigned in these cases to enable us to calculate an arithmetic mean for iPTH. As seen in Table 1, iPTH levels were not significantly different in control and acidosis. Creatinine clearances in control and acidosis, 111 ± 10 and 113 ± 12 ml/min, respectively, were not significantly different.

Average daily urinary calcium and phosphorus excretion rose from 158 ± 18 and 966 ± 72 mg in control to 456 ± 48 and 1125 ± 75 mg, respectively (P < 0.01) during the acidotic period. Similarly, average daily urinary magnesium excretion increased from 151 ± 14 to 179 ± 19 mg (P < 0.05).

Figure 1 depicts the serum 1,25(OH)2D and 24,25(OH)2D levels during control and metabolic acidosis. As can be seen, the serum 1,25(OH)2D in control and acidosis, 13.6 ± 1.3 and 14.3 ± 0.9 pg/ml, respectively, and the serum 24,25(OH)2D in control and acidosis 2.7 ± 1.2 and 2.4 ± 1.1 ng/ml were not significantly different. Previous studies have demonstrated that the serum 24,25(OH)2D levels are critically dependent on the prevailing levels of 25(OH)D [19]. As depicted in Figure 2, this close relationship between serum 24,25(OH)2D and serum 25(OH)D was maintained in metabolic acidosis. Furthermore, serum 25(OH)D levels in control and acidosis, 29 ± 7 and 28 ± 7 ng/ml, respectively, were similar.

Figure 3 depicts the effect of infusion of PTE on serum 25(OH)2D in the four individual subjects. As can be seen, the response in each subject was not less in the acidic period than the control period, although the changes in serum 1,25(OH)2D during PTE infusion varied among the individual subjects. Indeed, in three subjects the increment in serum levels of 1,25(OH)2D in control and acidosis were virtually identical, whereas in one subject the rise in serum 1,25(OH)2D was higher in the acidic than in the control period. The maximal increment in ionized calcium, as determined by
the difference between the preinfusion value and the value at
the completion of PTE infusion, averaged 0.4 ± 0.1 mg/dl in
both the control and acidotic periods.

Discussion

The present studies indicate that prolonged metabolic acido-
sis does not impair 1,25(OH)2D3 production in humans receiv-
ing a normal dietary intake of calcium. This conclusion is based
on the demonstration that basal serum 1,25(OH)2D levels were
not reduced by metabolic acidosis and that the increase of
serum 1,25(OH)2D in response to a prolonged infusion of PTE
was not attenuated.

The basal levels of 1,25(OH)2D were relatively low, presum-
ably due to an intake of calcium that was normal but slightly
higher than average. Thus, it might be argued that a fall in
serum 1,25(OH)2D levels during acidosis might be difficult to
detect since the values of 1,25(OH)2D in control were already
low. However, were metabolic acidosis to have a significant
impact on 1,25(OH)2D production in humans, one would
anticipate that the increment in serum 1,25(OH)2D levels in
response to PTE infusion would be blunted. Indeed, studies
examining the changes in serum 1,25(OH)2D levels in response
to the administration of parathyroid hormone to patients with
osteoporosis or pseudohyoparathyroidism, disorders in which
defective production of 1,25(OH)2D has been postulated, have
shown a blunted increment in serum 1,25(OH)2D levels [20, 21].
However, the rise in serum 1,25(OH)2D levels in the present
study were virtually identical in control and acidosis. More-
over, the more than twofold rise in serum 1,25(OH)2D in
response to infusion of PTE was similar to the rise observed by
others who gave parathyroid hormone to normal subjects [20–
22]. Therefore, the normal PTE induced rise in serum
1,25(OH)2D levels in the present study provides strong evi-
dence against a significant effect of metabolic acidosis on the
production of 1,25(OH)2D in humans.

The metabolic acidosis in the present study was mild in
nature; thus, it might be argued that a more severe degree of
acidosis is required to impair 1α hydroxylase activity. Whether
the severity of metabolic acidosis is a critical factor regulating
1α hydroxylase activity in the rat or in the human is unknown.

However, in the present study, other effects on the kidney
attributable to metabolic acidosis, such as an increase in urinary
calcium and phosphorus excretion, were observed.

The results of these studies agree with previous studies in D-
replete humans showing that metabolic acidosis had no effect
on either plasma 1,25(OH)2D levels [6] or the conversion of
radiolabeled 25(OH)D3 [7] to 1,25(OH)2D3. Moreover, they are
consistent with our earlier studies in vitamin D-replete rats that
have shown that metabolic acidosis does not blunt the incre-
ment in plasma 1,25(OH)2D levels in response to a low calcium
and moderately low phosphate diet [8]. Indeed, in this latter
study serum levels actively rose in the acidotic rats, probably
occurring in response to a fall in serum phosphorus. Studies by
Bushinsky et al [9], however, demonstrated that the rise in
plasma 1,25(OH)2D levels noted in rats fed a low calcium diet
was inhibited by metabolic acidosis if supplemental dietary
phosphate was given to prevent a fall in serum phosphorous
concentration. Thus, it appears that severe metabolic acidosis
can reduce the 1,25(OH)2D generation in the rat when vitamin
D production is stimulated by either a low calcium diet [9] or by
Effect of metabolic acidosis on vitamin D metabolism

647

Fig. 3. Serum 1,25(OH)2D levels after infusion of parathyroid extract, 1 U/kg/hr in four subjects. Data denoted by solid line were obtained during the control period and those with interrupted lines were obtained during metabolic acidosis.

vitamin D deficiency [3, 4, 12]. However, data obtained in vitamin D-replete humans consuming a normal calcium diet would appear to be more relevant in assessing a possible contributory role of impaired vitamin D production to the pathogenesis of bone disease in states with chronic acidosis.

On the basis of the improvement in bone disease in individuals with distal RTA during treatment with alkali and the demonstration of reduced production of 1,25(OH)2D3 in the acidic vitamin D deficient animal, it has been postulated that altered vitamin D levels might contribute to the pathogenesis of the bone disease noted with metabolic acidosis [2]. However, when considering the present and previous observation in humans concerning vitamin D metabolism with metabolic acidosis, this thesis is questioned. Whether or not alterations in the sensitivity of bone to vitamin D may contribute to the pathogenesis of bone disease, however, remains open to question.

Acknowledgments

A portion of this work was presented at the Fifth Workshop on Vitamin D in Williamsburg, Virginia, February 14–19, 1982. This study was supported by National Institutes of Health (NIH) grants AM21351, AM14750, NIH training grant AM07270, and research funds from the Veterans Administration. The authors thank Dr. K. Gerszki for technical skill, the nurses of the Special Diagnostic and Treatment Unit, and Mrs. B. Bales and Ms. L. Reed for secretarial assistance.

Reprint requests to Dr. J. W. Coburn, Nephrology Training Program, Veterans Administration Medical Center (691/11111), Wilshire and Sawtelle Boulevards, Los Angeles, California 90073, USA

References

6. ADAMS ND, GRAY RW, LEMANN J Jr: The calciuria of increased fixed acid production in humans: evidence against a role for
parathyroid hormone and 1,25(OH)₂-vitamin D. *Calcif Tissue Int* 28:233–238, 1979