Acetate and hypercalciuria during total parenteral nutrition[1-3]

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ABSTRACT Hypercalciuria and negative calcium balance are complications of total parenteral nutrition (TPN). Because metabolism of the TPN formula generates an acid load that can induce hypercalciuria, we evaluated the effect of supplementing the formula with acetate. In a randomized crossover study six patients on continuous and six on cyclic TPN received no added acetate or 160 mmol acetate/d replacing 160 mmol chloride/d for 3 d each. Blood and urine measurements were obtained on day 3 of each formula. Acetate, which is metabolized to bicarbonate, increased blood pH and decreased renal acid excretion. Urinary Ca decreased in every patient from 422 ± 63 to 240 ± 46 mg/d (10.5 ± 1.6 to 6.0 ± 1.4 mmol/d) and from 468 ± 68 to 285 ± 54 mg/d (11.7 ± 1.7 to 7.1 ± 1.3 mmol/d) during continuous and cyclic TPN, respectively. Filtered Ca load decreased slightly whereas renal tubular Ca reabsorption increased significantly with acetate. Serum parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and urinary cyclic AMP were not different. *Am J Clin Nutr* 1988;48: 1482–9.

KEY WORDS Total parenteral nutrition, hypercalciuria, acetate, calcium, parathyroid hormone, vitamin D

Introduction

Hypercalciuria is a complication of both short-term (1–3) and long-term (4–7) total parenteral nutrition (TPN) and contributes to the risk of negative calcium balance and metabolic bone disease (4–8). One factor influencing hypercalciuria during TPN may be the acid load generated from constituents of the TPN formula, such as acid-generating amino acids, because acid loads are known to result in hypercalciuria (9–15) and negative Ca balance (9, 10, 13). In contrast, alkaline loads are known to reduce urinary Ca losses (13–21) and improve Ca balance (13, 16–20).

In this study we determine whether supplementing the TPN formula with acetate, which is metabolized in the liver to bicarbonate, reduces urinary Ca losses in patients receiving TPN. We studied both continuous and cyclic TPN because we (2) previously showed that the latter technique accentuates calciuria. We also ascertain which determinants of urinary Ca excretion, specifically, filtered Ca load, renal-tubular Ca reabsorption, or the parathyroid hormone–1,25-dihydroxyvitamin D axis [PTH–1,25-$(OH)_2D$], contribute to changes in calciuria with supplemental acetate.

Methods

Subjects

The subjects were hospitalized but ambulatory patients with gastrointestinal diseases who received TPN as part of their medical management. Only patients without cardiopulmonary, hepatic, or renal compromise and without disorders affecting Ca metabolism were eligible.

Two groups of six subjects were studied while they received short-term TPN and ate nothing by mouth. One group received TPN continuously for 24 h/d (continuous TPN). The other group received TPN for 12 h/day (cyclic TPN) as is common for patients on home TPN. Two subjects participated in both the continuous- and the cyclic-TPN protocols. The age, sex, disease, and nutritional characteristics of these patients are listed in **Table 1.**

All patients had received TPN for at least 2 d (range, 2–28 d) before entering the study. Medications, including corticosteroids, were kept constant for each individual throughout the study. Five of six subjects in each group were receiving corticosteroids at a mean dose of 24 ± 5 mg prednisolone/d.

Subjects were studied under a protocol approved by the University of Chicago Clinical Investigation Committee.

Study design

In a randomized crossover design all subjects were given two TPN formulas, each formula for 3 d, as follows: one TPN formula contained no added acetate; the other contained 160

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TABLE 1
Characteristics of patients

	Continuous TPN	Cyclic TPN
Number	6	6
Sex (M,F)	3,3	4,2
Disease*	5 IBD, 1 PP	5 IBD, 1 PP
Age (y)	35 ± 4 yrs.	36 ± 9 yrs.
Serum albumin (g/L)	33 ± 3	33 ± 2
Percent IBW†	98 ± 9	95 ± 9

* IBD, inflammatory bowel disease; PP, pancreatic pseudocyst.
† Percent ideal body weight from reference 22.

mmol acetate/d replacing 160 mmol chloride/d. After 3 d on one TPN formula, each subject was crossed over to receive the other formula for an additional 3 d, thus serving as his or her own control. Each subject received a constant TPN formula except for the change in acetate and chloride content throughout the 6 d. On day 3 of administration of each formula, 24-h urine and venous blood samples were obtained. Blood was drawn between 0700 and 0800 during the TPN infusion.

TPN formulas

The carbohydrate, amino acid, and lipid content of the TPN formulas was held constant for each individual throughout the study. Five of the six subjects in both the continuous and the cyclic TPN groups received 2 L of a solution containing 20 or 25% dextrose and 4.25% amino acids (Travasol®, Travenol Laboratories, Deerfield, IL) as well as 500 mL of 10 or 20% lipid emulsion (Travemulsion®, Travenol Laboratories) daily. One large male patient with a pancreatic pseudocyst who participated in both the continuous- and cyclic-TPN groups received 3 L of a 15% dextrose and a 4.25% amino acid solution daily but no lipid emulsion. The TPN solutions provided 38 ± 2 kcal/kg ideal body weight (IBW) and 42 ± 2 kcal/kg IBW in the continuous- and cyclic-TPN groups, respectively, and 1.4 ± 0.1 g of amino acids/kg IBW in both groups.

The 4.25% amino acid solution itself contained 17 mmol acetate/L and 27 mmol chloride/L. The following total amounts of electrolytes and minerals were then added daily: Ca, 240 mg (5.99 mmol) (as Ca gluconate); magnesium, 244 mg (10.04 mmol) (as Mg sulfate); phosphate, 465 mg (15.01 mmol) (as neutral potassium phosphate); sodium, 110 mmol; and K, 110 mmol. Acetate was given as the Na or K salt to replace equimolar amounts of NaCl or KCl. Thus, one of the TPN formulas contained 220 mmol/d of added chloride and no added acetate whereas the other formula contained 160 mmol/d of added acetate and 60 mmol/d of added chloride.

The formulas also contained a multiple-vitamin preparation MVI® (LyphoMed Inc, Melrose Park, IL), 5 mL/d; selenium, 80 μg/d (1.01 μmol/d); trace-element mix (International Medical Systems Ltd, S el Monte, CA), 4 mL/d; vitamin K, 10 mg/wk (22.2 μmol/wk); iron, 10 mg/wk (179 μmol/wk); and vitamin B-12, 50 μg/wk (36.9 pmol/wk). Two subjects in the continuous-TPN group and four subjects in the cyclic-TPN group received additional zinc, 4 mg/d (61 μmol/d).

Analytical methods

Venous blood samples were collected on ice and promptly centrifuged and the sera were frozen at −25 °C for later measurement of parathyroid hormone by radioimmunoassays that recognize the middle and amino-terminal portions of the hormone molecule (Immuno Nuclear Corp, Stillwater, MN), and measurement of 1,25-dihydroxyvitamin D by a receptor-binding radioimmunoassay (23) (Immuno Nuclear Corp). Serum 25-hydroxyvitamin D [25-(OH)D] was measured with a competitive binding assay (24). Venous blood for pH and bicarbonate was collected in a heparinized syringe, capped, placed on ice, and immediately analyzed by an automated ABL 3 blood gas analyzer (Radiometer, Copenhagen, Denmark).

Serum and urinary Ca, creatinine, albumin, and total protein were analyzed by colorimetric methods (Ektachem 700 analyzer, Eastman Kodak Co, Rochester, NY). Urinary creatinine was measured colorimetrically (Astra 8, Beckman Instruments, Fullerton CA). Serum ionized Ca was measured with a Ca ion-selective electrode (Model 7, Nova, Newton, MA).

An aliquot of each 24-h urine sample was acidified to a pH of 2–3 with hydrochloric acid and analyzed for Ca and creatinine within 24 h. Additional aliquots were frozen at −60 °C for later measurement of urine tritratable acidity by tritration (PHM61 laboratory pH meter, Radiometer America Inc, Westlake, OH), ammonia by spectrophotometry (25), cyclic AMP by radioimmunoassay (Immuno Nuclear Corp), and total hydroxyproline by colorimetric analysis (Autoanalyzer, Technicon Instruments, Tarrytown, NY). Urinary pH was measured using a pH meter (pH1 40, Beckman Instruments, Palo Alto, CA).

Calculations

Serum ultrafilterable Ca was calculated from the published equation of Moore (26) based on blood pH and serum total Ca, albumin, and globulin. Filtered Ca load was determined as the product of ultrafilterable Ca and creatinine clearance.

Statistical analysis

A two-tailed, paired Student's t test was used to analyze changes with acetate. The changes in the continuous-TPN group were compared with those in the cyclic-TPN group with a two-tailed, unpaired Student's t test. A stepwise, multiple linear regression analysis of paired data was used for identification of factors influencing the change in calciuria with supplemental acetate (27). Data are expressed as mean ± SEM. Statistical significance was defined as $p < 0.05$.

Results

Effect of acetate on urine and blood acidity

The effects of 160 mmol/d of added acetate on blood and urinary acidity are presented in **Table 2.** Supplementing the TPN formula with acetate resulted in significant increases in venous blood pH and bicarbonate during both continuous and cyclic TPN. This was accompanied by a significant decrease in renal acid excretion as measured both by titratable acidity and ammonium excretion.

Urinary calcium excretion

Continuous TPN. The effect of acetate on 24-h urinary Ca excretion during continuous TPN is illustrated in **Figure 1.** The addition of acetate resulted in a marked decrease in urinary Ca excretion for every subject. The reduction was 44 ± 6% (range 31–57%) from 422 ± 63 mg/d (10.5 ± 1.6 mmol/d) without acetate to 240 ± 46 mg/d (6.0 ± 1.4 mmol/d) with acetate. Without acetate all subjects lost more Ca in their urine than they received intravenously and hence they were in negative Ca bal-

TABLE 2
Effect of acetate on blood and urine acidity during continuous and cyclic TPN

	Continuous TPN			Cyclic TPN		
	− Acetate*	+ Acetate†	*p*	− Acetate*	+ Acetate†	*p*
Blood						
pH	7.37 ± 0.02	7.46 ± 0.02	<0.001	7.33 ± 0.02	7.44 ± 0.01	<0.0025
Bicarbonate (mmol/L)	26 ± 2	31 ± 1	<0.001	23 ± 1	30 ± 1	<0.001
Urine						
pH	5.5 ± 0.1	7.4 ± 0.3	<0.0001	5.0 ± 0.2	6.8 ± 0.4	<0.001
Titratable acidity (mmol/d)	21 ± 4	4 ± 3	<0.001	32 ± 2	7 ± 5	<0.001
Ammonium (mmol/d)	33 ± 3	8 ± 2	<0.001	35 ± 5	10 ± 4	<0.005
Total acid excretion (mmol/d)	53 ± 5	12 ± 5	<0.0001	66 ± 6	17 ± 9	<0.001

* Without supplemental acetate.
† With supplemental acetate.

ance. When the TPN formula was supplemented with acetate, Ca intake minus urinary Ca loss improved significantly. This value changed from negative to positive in three subjects, from negative to essentially neutral in one, and became less negative in two.

Cyclic TPN. The effect of acetate on urinary Ca excretion during cyclic TPN is illustrated in Figure 1. Each subject demonstrated a marked reduction in urinary Ca with supplemental acetate. The reduction in urinary Ca excretion was 38 ± 7% (range 20–62%) from 468 ± 68 mg/d (11.7 ± 1.7 mmol/d) to 285 ± 54 mg/d (7.1 ± 1.3 mmol/d). When given TPN formulas not supplemented with acetate, five of the six subjects excreted more Ca in their urine than they received intravenously. Ca intake

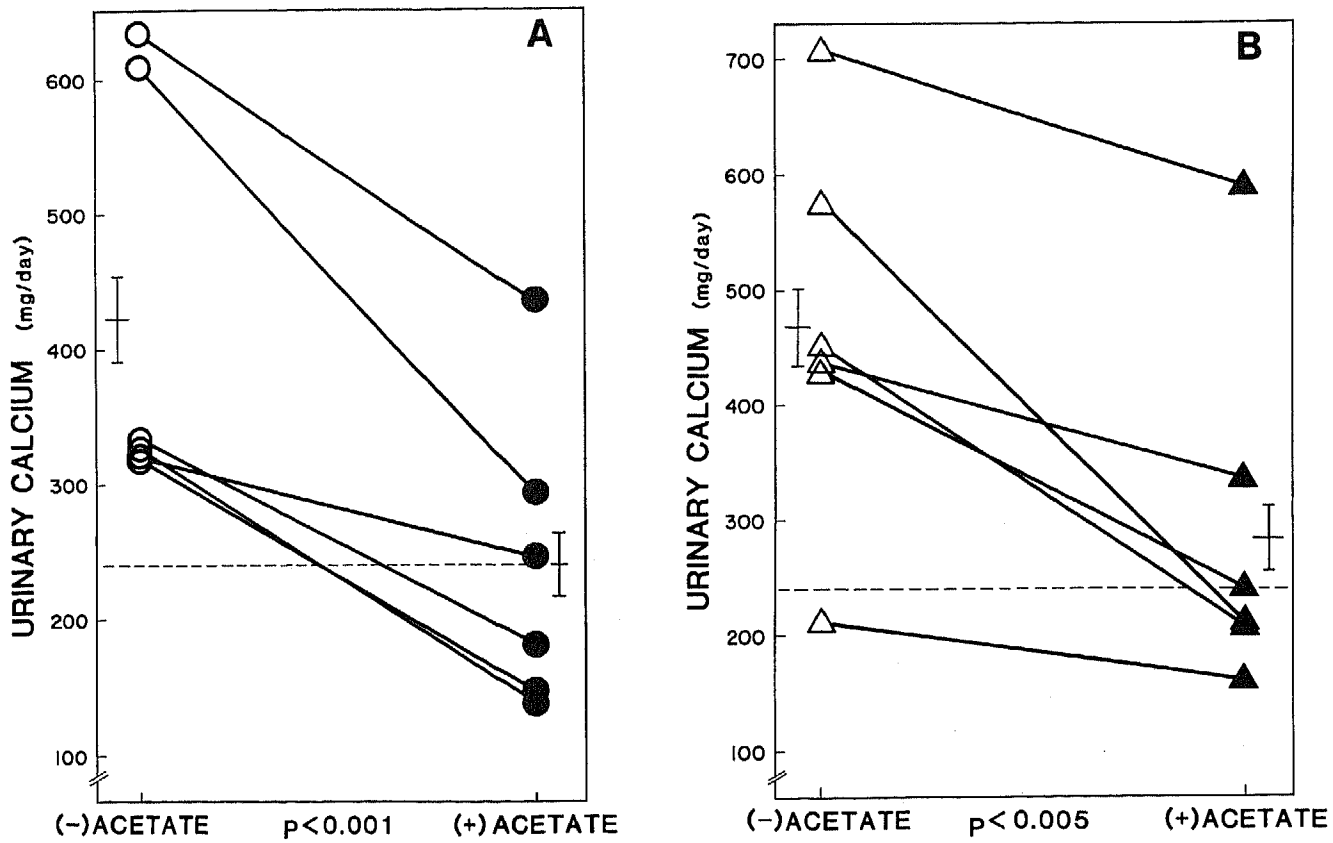

FIG 1. Urinary calcium excretion during continuous (A) and cyclic (B) TPN. Values obtained without acetate, (−) Acetate, are represented by the O during continuous TPN and Δ during cyclic TPN. Values obtained with supplemental acetate, (+) Acetate, are represented by the ● during continuous TPN and ▲ during cyclic TPN. – – – indicates calcium infused intravenously. $\bar{x}$ ± SEM is shown for each set of values. (To convert from mg Ca/d to mmol/d, multiply by 0.02495.)

TABLE 3
Effect of Acetate on filtered calcium load and renal tubular calcium excretion

	− Acetate*	+ Acetate†	p
Continuous TPN			
Creatinine clearance (ml/min)	89 ± 8	87 ± 3	NS
Serum ultrafilterable Ca			NS
mg/dL	6.3 ± 0.2	6.1 ± 0.2	
mmol/L	1.57 ± .05	1.52 ± 0.5	
Filtered Ca load			NS
mg/min	5.7 ± 0.7	5.3 ± 0.3	
mmol/min	0.14 ± 0.2	0.13 ± .01	
Fractional Ca excretion (%)	5.2 ± 0.3	3.1 ± 0.5	<0.0025
Renal tubular Ca reabsorption (%)	94.8 ± 0.3	96.9 ± 0.5	<0.0025
Cyclic TPN			<0.05
Creatinine clearance (mL/min)	101 ± 10	93 ± 9	
Serum ultrafilterable Ca			<0.05
mg/dL	6.3 ± 0.1	6.1 ± 0.1	
mmol/L	1.57 ± .02	1.52 ± .02	
Filtered Ca load			<0.01
mg/min	6.4 ± 0.7	5.7 ± 0.5	
mmol/min	0.16 ± .02	0.14 ± .01	
Fractional Ca excretion (%)	5.3 ± 0.7	3.7 ± 0.6	<0.025
Renal tubular Ca reabsorption (%)	94.7 ± 0.7	96.3 ± 0.6	<0.025

* Without supplemental acetate.
† With supplemental acetate.

minus urinary Ca loss improved with the addition of acetate from −228 ± 68 mg/d (−5.7 ± 1.7 mmol/d) to −45 ± 54 mg/d (−1.1 ± 1.3 mmol/d).

Mechanisms contributing to reduction in calciuria with acetate

To assess the mechanisms contributing to the reduction in calciuria with acetate, we evaluated the determinants of urinary Ca excretion, specifically, filtered Ca load, renal-tubular Ca reabsorption, and the PTH–1,25-$(OH)_2D$ axis.

Filtered calcium load. Giving supplemental acetate resulted in a small decrease in serum ionized Ca in four of five subjects in which it was measured, from 4.81 ± 1.3 mg/dL (1.20 ± 0.32 mmol/L) to 4.66 ± 0.8 mg/dL (1.16 ± 0.20 mmol/L). We, therefore, determined serum ultrafilterable Ca levels and creatinine clearances to assess filtered Ca loads (**Table 3**). During continuous TPN creatinine clearance was unchanged with acetate. However, there was a trend toward a reduction in serum ultrafilterable Ca with acetate that tended to cause a reduction in filtered Ca load. During cyclic TPN acetate resulted in significant decreases in serum ultrafilterable Ca and filtered Ca load.

Comparison of responses during continuous and cyclic TPN. The continuous-TPN group was compared with the cyclic-TPN group with respect to the changes in blood and urinary acidity, urinary Ca excretion, filtered Ca load, and fractional Ca excretion induced by acetate. The responses in the continuous-TPN group were not significantly different from those in the cyclic TPN group. Therefore, both groups were pooled for further analysis of the mechanisms contributing to the reduction in calciuria with acetate.

Relationship of filtered calcium load to urinary calcium excretion. **Figure 2** illustrates the relationship of urinary Ca excretion to filtered Ca load for the TPN formulas with and without added acetate. Filtered Ca load correlates positively with urinary Ca excretion both with ($r = 0.75$, $p < 0.01$) and without ($r = 0.74$, $p < 0.05$) added acetate. The regression lines are parallel but their intercepts differ. Thus, at a given filtered Ca load, urinary Ca excretion is less with supplemental acetate, indicating enhanced tubular Ca reabsorption.

We further evaluated the relationship of the change in filtered Ca load induced by acetate treatment to the change in urinary Ca excretion. The change in urinary Ca excretion (y) correlates positively with the change in filtered calcium load (x) ($y = [-140 \pm 24] + [45 \pm 19]$ x, $p < 0.05$). The y intercept of this regression line is 140 ± 24, which is significantly different from 0 ($p < 0.001$). Thus, even without a change in filtered Ca load, acetate reduces urinary Ca by 140 ± 24 mg/d (3.5 ± 0.6 mmol/d). The mean reduction in urinary Ca (based on 10 independent pairs of data) was 166 ± 82 mg/d (4.1 ± 2.0 mmol/d). Therefore, the lower filtered Ca load contributes only slightly to the total reduction in calciuria with acetate.

In addition, we performed a stepwise, multiple linear regression analysis of paired data to identify the factors contributing to the reduction in calciuria with acetate. Variability was defined as the sum of squares of deviations of urinary Ca values from the mean urinary Ca excretion. Because each subject was studied twice, with and without acetate, we were able to determine that subject-to-subject variability accounted for 58% of total variance. Entering filtered Ca load and total acid excretion successively demonstrated that both significantly reduced the variance.

Relationship of urinary calcium excretion and acid excretion. **Figure 3** illustrates the relationship of urinary Ca excretion to urinary total acid excretion. The urinary Ca excretion significantly parallels the total urinary acid excretion.

Parathyroid hormone–1,25-dihydroxyvitamin D axis. The effect of acetate on the PTH–1,25-$(OH)_2D$ axis is listed in **Table 4.** Serum PTH levels were normal or suppressed overall and serum 25-(OH)D, and 1,25-$(OH)_2D$, levels, as well as urinary cyclic AMP levels, were normal. No significant differences in the PTH–1,25-$(OH)_2D$ axis could be detected with acetate supplementation.

Discussion

Our results demonstrate that supplementing the TPN formula with acetate provides an alkaline load that

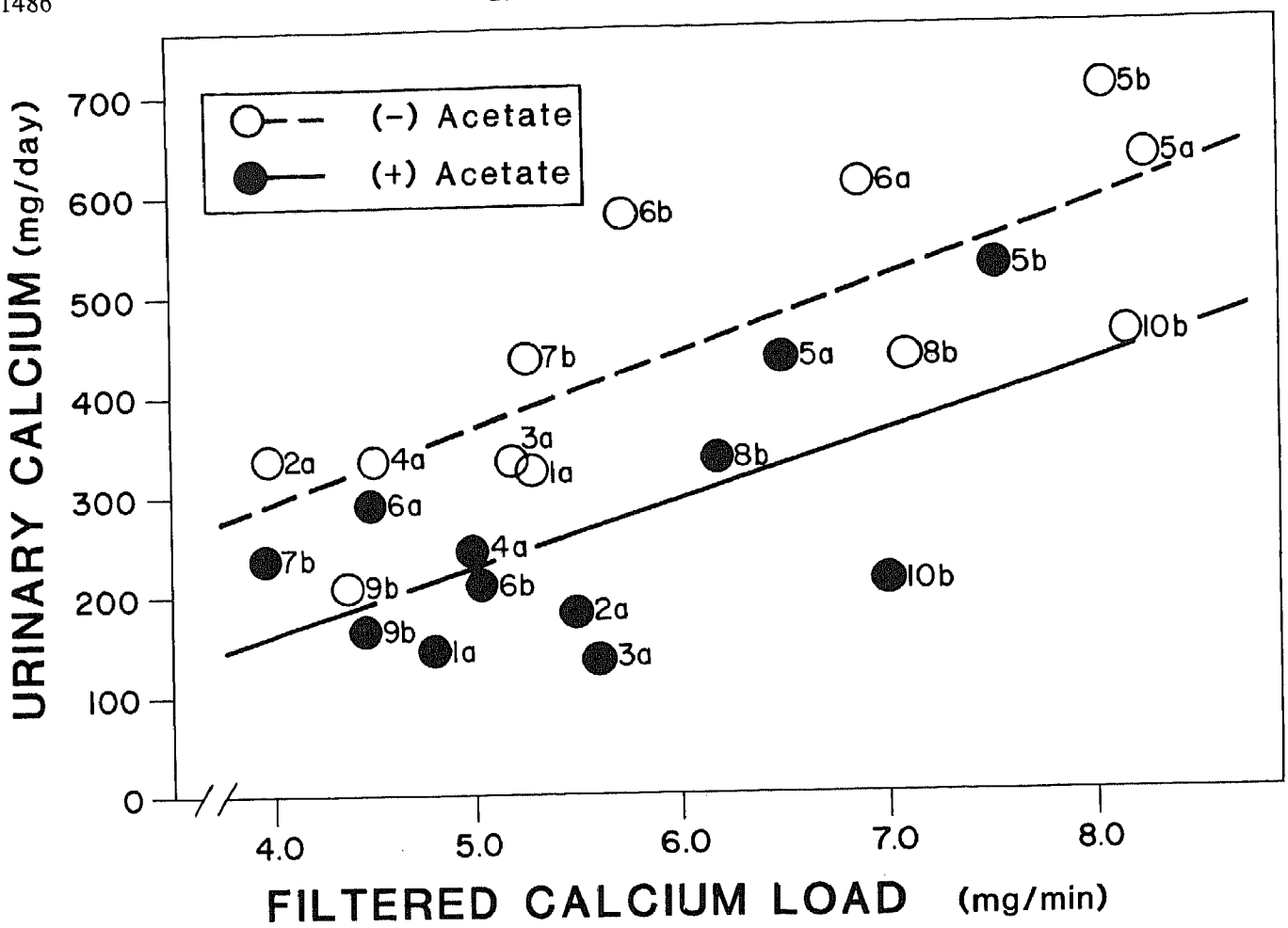

FIG 2. Relationship of filtered calcium load and urinary calcium excretion. Numbers refer to individual subjects. a refers to continuous TPN and b refers to cyclic TPN. (To convert mg Ca/d to mmol/d and to convert mg Ca/min to mmol/min, multiply by 0.02495.)

markedly reduces TPN-induced hypercalciuria. This is consistent with the known effects of orally administered acid and alkaline loads on urinary Ca excretion. Acid loads, whether induced by ammonium chloride (9–13, 15) or by high-protein diets (1, 9, 16, 28) result in hypercalciuria and negative Ca balance. Alkali therapy, on the other hand, is known to reduce urinary Ca excretion and improve Ca balance (13–21). This was shown in patients with chronic metabolic acidosis (17, 18), renal tubular acidosis (20), and idiopathic calciuria (21) as well as in normal subjects (19) and in volunteers ingesting high-protein diets (16). Lemann et al (19) observed a reduction in urinary Ca of 60% in a normal subject when 150 mmol/d of dietary sodium bicarbonate replaced 150 mmol/d of sodium chloride. Reidenberg et al (17) noted a 50% reduction in urinary Ca excretion when 88 mmol/d of sodium bicarbonate replaced an equimolar amount of sodium chloride during metabolic acidosis associated with fasting. When 70 mmol/d of sodium bicarbonate, replacing 70 mmol/d of sodium chloride, was administered for 10 d to postmenopausal women consuming high-protein diets, the protein-induced hypercalciuria was reduced by 33% overall and by 43% on the 10th day of treatment (16). The reduced urinary Ca loss with alkali therapy resulted in an improved Ca balance because gastrointestinal Ca absorption was improved or unchanged (16, 18).

Urinary Ca excretion is ultimately determined by the filtered Ca load and subsequent renal-tubular Ca reabsorption. In this study supplemental acetate caused the blood pH to rise and, consistent with the known effects of an increase in blood pH (29), serum ionized and ultrafilterable Ca levels fell. As a consequence supplemental acetate slightly decreased filtered Ca load. The reduction in filtered Ca load with acetate accounted for only a small fraction of the reduction in urinary Ca. This indicates that acetate treatment predominantly enhances renal-tubular Ca reabsorption. This is consistent with previous studies in animals (14, 15, 30) and man (11, 12). Lemann et al (11) demonstrated that during ammonium chloride-induced acidosis glomerular filtration rate and filtered Ca load decreased but urinary Ca excretion increased. Nephron micropuncture (14) and renal clearance (15, 30) studies in dogs also demonstrated the important influence of luminal acid and alkali on renal-tubular Ca reabsorption. These studies (14, 15) showed

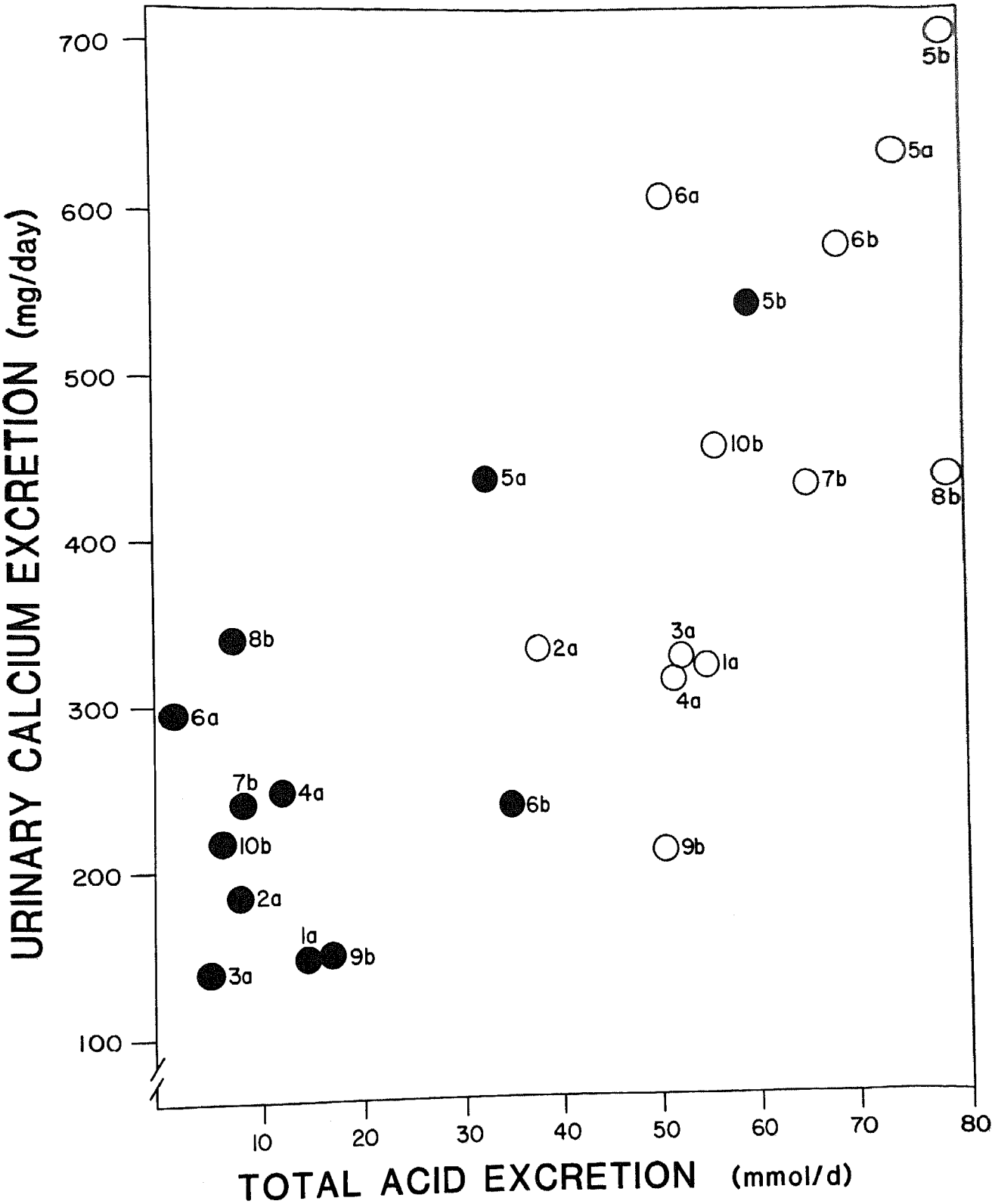

FIG 3. Relationship of urinary total acid excretion and calcium excretion. Numbers refer to individual subjects. a refers to continuous TPN and b refers to cyclic TPN. (To convert mg Ca/d to mmol/d, multiply by 0.02495.)

TABLE 4
Effect of acetate on the parathyroid hormone—1,25-dihydroxyvitamin D axis

	− Acetate*	+ Acetate†	p
Serum PTH			
Midmolecule			
Continuous TPN (ng/mL)	0.2 ± 0.1	0.3 ± 0.1	NS
Cyclic TPN (ng/mL)	0.5 ± 0.1	0.5 ± 0.1	NS
Amino terminal			
Continuous TPN (ng/mL)	4 ± 4	3 ± 1	NS
Cyclic TPN (ng/mL)	undetectable	undetectable	
Urinary cyclic AMP			
Continuous TPN (nmol/dL GF)‡	6 ± 3	4 ± 1	NS
Cyclic TPN (nmol/dL GF)	4 ± 1	3 ± 1	NS
Serum 25-(OH)D			
Continuous TPN (ng/mL)	22 ± 2	21 ± 2	NS
Cyclic TPN (ng/mL)	25 ± 4	26 ± 5	NS
Serum 1,25-$(OH)_2$D			
Continuous TPN (pg/mL)	30 ± 5	31 ± 7	NS
Cyclic TPN (pg/mL)	36 ± 5	35 ± 5	NS

* Without supplemental acetate.
† With supplemental acetate.
‡ GF, glomerular filtrate.

that acidosis inhibits Ca reabsorption in the distal renal tubule whereas bicarbonate infusion enhances Ca reabsorption in the distal renal tubule. Similarly, chronic metabolic alkalosis was shown to enhance distal-renal-tubular Ca reabsorption and decrease urinary Ca compared with controls (15). Urinary bicarbonate was shown to augment renal-tubular Ca reabsorption independent of systemic acid-base change (30).

We investigated whether the mild change in acid-base status induced by supplemental acetate results in changes in the PTH–1,25-$(OH)_2$D axis because this axis may influence filtered Ca load, renal-tubular Ca reabsorption, and, therefore, urinary Ca. We showed that although supplemental acetate is associated with a slight decrease in ionized Ca levels, no detectable changes in serum levels of 25-(OH)D, 1,25-$(OH)_2$D, or PTH occur. Urinary cyclic AMP excretion also did not change, indicating that the renal response to the prevailing PTH levels was likewise unaltered. We, therefore, conclude that the reduction in calciuria with acetate is not mediated by measurable alterations in the PTH–1,25$(OH)_2$D axis. This finding is consistent with the results of previous studies that demonstrated that the changes in calciuria with acid and alkaline loads are independent of PTH (9, 12–15). Acid loads induce hypercalciuria in hypoparathyroid patients (11) and augment urinary Ca excretion in normal subjects without causing alterations in levels of serum PTH (9, 12). In addition, because urinary cyclic AMP levels were also unchanged in these studies, the end-organ effect of PTH on the kidney was unaltered (31).

Changes in calciuria induced by alterations in acid-base status were also shown to occur independently of changes in serum 1,25-$(OH)_2$D levels (9, 12) as in our study. In man hypercalciuria induced by oral acid loads is accompanied by unchanged serum 1,25-$(OH)_2$D levels (9, 12). Although conversion of 25-(OH)D to 1,25-$(OH)_2$D was shown to be impaired during metabolic acidosis in animals (32), this was not consistently demonstrated in man (9, 12, 33).

Although a potential adverse effect of administering alkaline loads is nephrolithiasis, the alkaline load is accompanied by both a reduced filtered Ca load and a reduced urinary Ca concentration. In addition, alkaline loads are known to increase urine concentration of citrate (34), which is a potent inhibitor of Ca-salt nucleation and crystallization (35). Thus, any increase in urinary saturation for Ca salts brought about by a mild increase in urinary pH would be mitigated by the marked reduction in urinary Ca concentration and by the increase in urinary citrate concentration.

Although fecal Ca losses were not measured in this study, the role of the gastrointestinal tract in Ca homeostasis was minimized because all of the subjects were consuming nothing by mouth. Previous studies of orally administered acid or alkaline loads showed that fecal Ca losses remained unchanged (9, 12, 16, 18). Thus, change in Ca balance with acid and alkaline loads is determined largely by urinary Ca loss.

Administration of the TPN formula without added acetate did not cause significant acidemia and resulted in urinary titratable acidity and ammonium excretion within the ranges seen with normal diets. Administration of 160 mmol/d of acetate caused a mild alkalemia and a marked decrease in urinary acid excretion. Even with this degree of acetate supplementation, urinary Ca losses equalled or exceeded infused Ca in some patients. The acid load generated from metabolism of the nutrients in the TPN, therefore, contributes to urinary Ca losses but other factors must also be playing significant roles (1, 36, 37).

In conclusion, this study demonstrates that supplementing the TPN formula with 160 mmol/d of acetate markedly reduces TPN-induced hypercalciuria. This effect is independent of changes in the PTH–1,25-$(OH)_2$D axis and results from both a small decrease in filtered Ca load and, predominantly, from an enhanced renal-tubular Ca reabsorption. Further studies are required to determine whether the improved Ca conservation with acetate observed during short-term TPN also improves Ca balance and bone-mineral mass in patients receiving long-term TPN.

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