MECHANISM OF HYPERCALCIURIA IN EXPERIMENTAL METABOLIC ACIDOSIS

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Summary : To study the mechanism of hypercalciuria in metabolic acidosis, ammonium chloride loading (long) test was performed in 68 stone formers and 50 controls. Administration of ammonium chloride in both stone formers and controls produced a significant increase in urinary volume, ammonium and calcium excretions, no change in plasma calcium and creatinine clearance and significant decrease in plasma bicarbonate. However, on the third day of ammonium chloride loading test, urinary ammonium excretion and plasma bicarbonate levels were significantly lower while urinary calcium excretion was significantly greater in stone formers than in controls. Thus calciuresis could be correlated with the degree of metabolic acidosis but not with the rate of urinary ammonium excretion.

Key words: metabolic acidosis hypercalciuria urinary ammonium

INTRODUCTION

Experimental metabolic acidosis is since long known to produce hypercalciuria. The mechanism of increased urinary calcium excretion however, remains controversial. Williamson and Freeman (22) attributed it to increased glomerular filtration of calcium. Other workers have ascribed it to reduced tubular reabsorption of calcium because of natriuresis (20) or increased urinary ammonium excretion (13). The effect could not be due to reduced secretion of parathermone because it is also observed in patients with hypoparathyroidism (17). While investigating renal excretion of hydrogen ions in stone formers (14), we too observed hypercalciuria after ammonium chloride administration. We have tried to explore the mechanism of hypercalciuria.

MATERIALS AND METHODS

68 adult patients (52 males and 16 females) with upper urinary tract calcium oxalate stones and 50 sex and age matched controls were investigated. Other details of the clinical material are described elsewhere (14).

The subjects were investigated before and after administration of ammonium chloride load for 3 days (8). Urine samples were investigated for urinary volume, pH, titratable

acid (16), ammonium (11), creatinine (19) and calcium (19). Plasma samples were investigated for calcium (19), bicarbonate (16) and creatinine (19). Plasma calcium values were corrected to the specific gravity of 1.027 (6). To eliminate the effect of different glomerular filtration rates, urinary calcium excretion was also calculated as *mg*/100 *ml* G.F. (15).

RESULTS

Administration of ammonium chloride in both controls and stone formers produced a significant increase in urinary volume, ammonium and calcium excretion, no change in plasma calcium and creatinine clearance and a significant decrease in plasma bicarbonate (Table I). Mean increment of urinary calcium was 48 *mg* per day in controls and 85 *mg* per day in stone formers. In Table II, some of the effects of ammonium chloride administtion in stone formers and controls have been compared. Whereas urinary calcium excretion and metabolic acidosis were significantly greater, urinary ammonium excretion was significantly lower in the stone formers.

TABLE I : Effect of ammonium chloride administration in controls and stone formers (mean±S.D.).

	Controls n = 50			*Stone formers n = 68*		
	Before	After	P value	Before	After	P Value
Plasma calcium, *mg*%	10.08±0.51	10.02±0.79	>0.05	10.35±0.75	10.13±0.62	>0.05
Plasma bicarbonate, *mEq/l*	26.93±1.84	24.16±1.78	<0.001	26.75±2.18	23.25±2.32	<0.001
24-hour urinary volume, *ml*	1361±650	1686± 621	<0.05	1425± 662	1796±712	<0.05
24-hour urinary ammonium, *mEq*	33.59±28.3	58.34±16.18	<0.001	28.19±10.35	42.83±15.37	<0.001
Creatinine clearance, *ml/min*	87.25±21.80	92.31±22.37	>0.05	75.76±28.06	81.22±28.88	>0.05
24-hour urinary calcium, *mg*	120.40±28.3	168.47±59.86	<0.001	134.00±72.16	219.56±101.34	<0.001
Urinary calcium, *mg*/100 *ml* G.F.	0.093±0.032	0.133±0.055	<0.001	0.144±0.083	0.221±0.126	<0.001

TABLE II : Comparison of plasma bicarbonate levels and urinary calcium and urinary ammonium excretion in controls and stone formers on the 3rd day of ammonium chloride administration (mean±S.D.)

	Controls	*Stone formers*	*P Value*
Plasma bicarbonate, *mEq/l*	24.16±1.78	23.25±2.32	<0.025
Urinary calcium *mg*/100 *ml*, G.F.	0.133±0.055	0.221±0.126	<0.001
24-hour urinary ammonium, *mEq*	58.34±16.18	42.83±15.37	<0.001

DISCUSSION

On administration of acid load, increased urinary excretion of water, ammonium and calcium observed in this study (Table I) has been reported earlier by numerous workers (1, 4, 10, 12, 13, 18). However, the mechanism of increased urinary calcium excretion in experimental acidosis remains controversial. Increased glomerular filtration of calcium seems unlikely because administration of ammonium chloride did not produce any significant increase in creatinine clearance nor any rise in plasma calcium levels. Lemann *et al.* (13) calculated the filtered load of calcium and observed a significant fall during ammonium chloride acidosis. Some workers (22) however, have demonstrated increased filtered calcium load after administration of massive amount of ammonium chloride in dogs.

Diuresis, a common feature of ammonium chloride acidosis (10) has also been incriminated in the production of hypercalciuria. Calciuresis is said to be a consequence of natriuresis since renal clearance of sodium and calcium have been found to be coupled and natriuresis can be recorded during osmotic diuresis produced by diverse agents (20) However, significant natriuresis and calciuresis have been observed only in acute experiments and at high rates of urine flow i.e. 2.5 *ml* per min in the dog. (20). During chronic administration of many diuretics, calcium and sodium clearances can be seperated (7). Chlorothiazide administration enhances urinary sodium excretion without producing calciuresis (2). Moreover, aldosterone selectively alters sodium but not calcium excretion (13). In view of these facts different transport mechanisms are believed to exist for the two ions in the distal tubule (2).

Lemann *et al.* (13) have attributed the hypercalciuria of metabolic acidosis to increased excretion of urinary ammonium and have shown a linear relationship between the increments in urinary ammonium and calcium excretions. But as Fraquharson *et al.* (9) have suggested long ago, it is possible that the increased ammonium excretion and the increased urinary calcium excretion may be separate responses to a common cause and may not be directly related. Systemic acidosis could be the common factor. We have observed significant metabolic acidosis and increased ammonium excretion in our cases and it may seem difficult to decide which of these is the primary factor producing hypercalciuria. However, comparison of the biochemical data of controls and stone formers after ammonium chloride administration (Table II) helps to clarify the issue. Due to reasons discussed elsewhere (14) majority of our stone formers had defective power of urinary acidification, as shown by statistically significant lower urinary titratable acid, urinary ammonium and plasma bicarbonate levels than in controls. In such a situation urinary calcium excretion was 0.221 *mg*$\pm$0.126 per 100 *ml* G.F. in stone formers compared to 0.133 *mg*$\pm$0.055 per 100

ml G.F. in controls ($P<0.001$). Thus stone formers with lesser urinary ammonium excretion but greater metabolic acidosis than controls have shown greater calciuresis. These observations are supported by the fact that hypercalciuria is a usual feature in patients of renal tubular acidosis in whom urinary ammonium excretion is characteristically reduced (3,21). Obviously urinary calcium excretion can be correlated with the degree of metabolic acidosis but not always with the rate of urinary ammonium excretion.

Borle has recently studied the effect of acid-base changes on calcium transport in isolated kidney cells. Intracellular acidosis was found to decrease cellular calcium influx, total cell calcium and both the cytosol and mitochondrial calcium pools (5). Thus metabolic acidosis seems to produce calciuresis by a direct action on the reabsorptive mechanism in the renal tubules.

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