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Hypercalciuria during Acidosis in Hypoparathyroidism* (32607)

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Acidosis has been shown to cause an increase in urinary calcium excretion(1–3). The following studies were done to determine if the parathyroid glands had a role in the hypercalciuria occurring during acidosis.

Methods. Animal study. Female Sprague-Dawley rats initially weighing 100–125 gm were used for the animal experiments. The control diet was tap water and Wayne Lab Blox Chow (calcium 1.2%, phosphorus 0.99%, vitamin D 4.4 units/gm). The acidotic diet

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was tap water and the chow supplemented with 0.2% NH_4Cl and 0.15% acetazolamide. The animals ate and drank *ad libitum* for all experiments. Operated animals underwent surgical thyroparathyroidectomy 3 days before the start of the calcium experiment. Rat blood samples were taken from the abdominal aorta with the animals under pentobarbital anesthesia. All acidosis experiments were done with simultaneous controls.

The rats were divided into 4 groups of 8 each; unoperated rats were fed the control diet, unoperated rats were fed the acidotic diet, thyroparathyroidectomized rats were fed the control diet, and thyroparathyroidectomized rats were fed the acidotic diet.

The rats were kept in metabolism cages, 2 rats per cage, and 24-hour urine collections were made every other day starting on day 5. An earlier experiment had shown that the unoperated rats on the acidotic diet do not develop hypercalciuria in less than 6 days. Blood was obtained on day 10 from the abdominal aorta and the samples from both rats in each cage were pooled for calcium determination. Blood and urine calcium determinations were done by atomic absorption spectrophotometry.

Clinical study. One 74-year-old postthyroidectomy hypoparathyroid woman was studied on a metabolic ward. The general methods of study have been previously reported(3). She was stabilized in the hospital on a balanced diet including 725 mg phosphorus, 830 mg calcium, 1200 mg of medicinal calcium, and 100,000 units of vitamin D. This intake was kept constant for 3 weeks prior to NH_4Cl administration. The NH_4Cl was given for 8 days and then a 10-day recovery period followed. The $NaHCO_3$ was given during the first day of the recovery period. Informed consent was obtained from both the patient and her daughter prior to the experiment.

Blood and serum values are for single samples taken at the end of each period. Urine values are median daily excretion of the last 4 days of each period.

All statistical analyses are by the Mann-Whitney U test comparing 2 groups(4).

Results. Animal experiments. The effect of the acidotic diet on arterial pH and pCO_2 was determined in 4 separate experiments on a total of 49 rats. Measurements were made 3 days to 2 weeks after initiating the diet and compared with simultaneous controls in each experiment. The overall median pH fall was 0.15 unit and the median pCO_2 rise was 5 mm Hg. The results of experiments measuring pH and pCO_2 after 4 days and 7 days of eating the diet are presented in Table I.

TABLE I. Effects of Feeding Rats Acidotic Diet on Arterial pH[a] and pCO_2.

Animal number	pH	Animal number	pH	pCO_2
After 4 days on diet		After 7 days on diet		
Control Diet		Control Diet		
1	7.48	1	7.48	37
2	7.56	2	7.56	32
3	7.47	3	7.54	37
4	7.48	4	7.47	42
Median	7.48	Median	7.51	37
Acidotic Diet		Acidotic Diet		
1	7.35	1	7.20	44
2	7.14	2	7.26	41
3	7.43	3	7.34	42
4	7.33	4	7.35	37
5	7.30	Median	7.30	41
6	7.30			
7	7.33			
Median	7.33			

[a] Difference between groups significant at $p<.02$.

The acidotic diet produced hypercalciuria in both operated and unoperated rats (Table II). The serum calcium was significantly lower in the operated rats.

Human experiment. The NH_4Cl-induced acidosis in the hypoparathyroid patient caused an increase in her urinary calcium excretion and a fall in her serum calcium concentration. She developed tetany and the acidosis period was terminated 2 days earlier than planned. Table III presents the blood and serum values at the end of each period and the median daily urinary calcium of the last 4 days of each period.

Discussion. The animal experiments demonstrate that the increase in urinary calcium excretion in response to acidosis can occur in the absence of thyroid and parathyroid glands. A similar response occurred in a hypoparathyroid human. Aub *et al.*(5) also demonstrated an increase in urinary calcium ex-

TABLE II. Effects of Acidotic Diet on Urine (mg/2 rats/24 hours) and Serum (mg per 100 ml) Calcium of Rats.

Cage number	UC[a]	UA[b]	TC[c]	TA[d]
	Urine Ca, day 5			
1	0.53	0.73	0.51	1.19
2	0.23	0.70	0.47	0.92
3	0.47	0.21	0.42	1.56
4	0.24	0.07	0.20	1.13
Median	0.36	0.45	0.45	1.16[e]
	Urine Ca, day 7			
1	0.30	0.89	0.28	1.35
2	0.22	1.04	0.36	0.80
3	0.18	1.04	0.39	1.51
4	0.18	0.72	0.25	0.91
Median	0.20	0.97[e]	0.32	1.13[e]
	Urine Ca, day 9			
1	0.62	1.30	0.59	0.85
2	0.68	1.19	0.31	1.19
3	0.62	1.03	0.52	1.34
4	0.61	1.35	0.39	1.21
Median	0.62	1.25[e]	0.46	1.21[e]
	Serum Ca, day 10			
1	11.8	11.5	8.0	9.2
2	11.4	11.5	6.0	8.4
3	11.4	11.9	7.2	9.5
4	11.0	11.4	7.2	8.4
Median	11.4	11.5	7.2	8.8[e]

[a] Unoperated control diet.

[b] Unoperated acidotic diet.

[c] Thyroparathyroidectomized control diet.

[d] Thyroparathyroidectomized acidotic diet.

[e] $p<.02$ (Mann-Whitney Test) between acidotic and similar nonacidotic controls. Serum Ca of TC and TA significantly lower than UC and UA $p<.02$.

cretion during experimental acidosis in one hypoparathyroid patient whom they maintained on 15 units of parathyroid hormone daily. From this, we conclude that the thyroid and parathyroid gland are unnecessary for the hypercalciuria that occurs during acidosis.

Summary. Both normal intact and hypocalcemic thyroparathyroidectomized rats developed hypercalciuria when made acidotic by NH_4Cl plus acetazolamide administration. One hypoparathyroid patient developed hypercalciuria and hypocalcemia when given NH_4Cl. This demonstrates that the hypercalciuria of acidosis can occur in the absence of parathyroid hormone and thyrocalcitonin.

TABLE III. Response of Hypoparathyroid Human to NH_4Cl Acidosis.

	Before acidosis	Acidosis	Recovery
Serum calcium (mg per 100 ml)	8.8	6.4	9.6
Serum phosphorus (mg per 100 ml)	5.8	5.3	5.2
Urine calcium (mg per 24 hours)	73	233[a]	108[a]
Arterial pH	7.42	7.21	
Total serum CO_2 (meq/liter)	29	12	25

[a] $p<.05$ (Mann-Whitney Test) comparing this period with previous period. All values other than urine calcium are single measurements and not subject to statistical analysis.

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Since preparation of this paper, J. Lemann, J. R. Litzow, and E. J. Lennon reported [J. Clin. Invest. 46, 1318 (1967)] hypercalciuria occurring in four hypoparathyroid patients during NH_4Cl-induced acidosis.

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