Urol. Res. 9, 263-269 (1981)

Urological Research

Effects of a Cation Exchange Resin on Intestinal Calcium Absorption and Urinary Calcium in Calcium Stone Formers

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Accepted: December 30, 1980

Summary. The effect on the urinary excretion of calcium of an oral cation exchange resin without phosphorus was studied in healthy control subjects and patients with recurrent calcium lithiasis under out-patient conditions. An immediate reduction of intestinal calcium absorption and urinary calcium excretion was found in five control subjects and in one patient after ingestion of resin, whereas calcium excretion remained unchanged in all other patients during long-term treatment. In addition, signs of mild transitory hyperparathyroidism together with an increase in intestinal calcium transport were observed during treatment. It is suggested that intraluminal binding of calcium ions to the resin leads to substantial changes in calcium metabolism with the result that urinary calcium excretion returns to pre-treatment values.

Key words: Calcium urolithiasis, Cation exchange resin, Intestinal calcium absorption, Calcium excretion.

INTRODUCTION

Raised urinary calcium excretion, either alone or in addition to other factors promoting stone formation (e. g. deficiency of inhibitors) is considered to be one of the aetiological factors in calcium urolithiasis. A reduction in urinary calcium excretion is, therefore, the main aim of treatment in this group of patients. The simplest form of therapy would be a restriction of dietary calcium intake. In practice, however, patients adhere only incompletely to a low calcium diet and for this reason cation exchange resins, partly coupled with inorganic phosphate, were developed. In the lumen of the gut calcium is bound to this resin and excreted in the faeces. With this treatment both urinary calcium excretion and the frequency of stone recurrence are reduced (1, 6). Similar results were reported for a cation exchange resin without phosphorus (11). In rats the administration of this resin caused signs of secondary hyperparathyroidism (3), but similar observations had not been reported in man up until now. We report our results of long-term administration of this resin in patients with recurrent urolithiasis.

MATERIALS AND METHODS

Abbreviations: Intestinal calcium absorption - CaA; absorptive hypercalciuria - AHC; normocalciuria - NC; renal threshold phosphate concentration - TmP; cyclic 3'-5'-adenosinemonophosphate - cAMP; calcium oxalate - CaOx; brushite - CaP; relative supersaturation - RSP; serum parathyroid hormone - PTH; bone mineral content - BMC.

1. The Cation Exchange Resin[1] Consisted of:

100 g granulate containing 50 g exchange material (sulphonated styrene-divinylbenzene-copolymerisate, with 8% divinylbenzene) and potassium (3.1 mmol/g). Filling materials were sorbit, sodium carboxymethylcellulose and aromatic substances. The in vitro exchange capacity of the resin was 2 mmol calcium/g resin. The recommended dose is 7.5 g twice a day.

[1] Trade name Campanyl®; kindly donated by Temmler Werke, Marburg, Federal Republic of Germany

0300-5623/81/0009/0263/$ 01.40

2. Three Studies were Performed:

a. Changes of Intestinal Calcium Absorption (CaA) in Healthy Control Subjects After Acute Administration of the Exchange Resin. Five metabolically healthy male volunteers (ages 22-28 years, mean 25) received, with their informed consent, on separate days in a random order after an overnight fast (12-15 h) either 100 ml distilled water alone (control study) or 3.75 g or 7.5 g of the drug dissolved in 100 ml distilled water. 15 min after drinking, 2.5 mmol calcium ions (as calcium chloride, Merck) in 100 ml distilled water were given for the determination of the CaA. In addition urine was collected over this time period.

b. Influence of the Exchange Resin on Mineral Metabolism of Patients with Recurrent Calcium Lithiasis During Long-Term Treatment. Twelve male patients with recurrent calcium lithiasis (17) (ages 30-57 years, mean 44) were treated orally with two different doses of the drug for 48 weeks. Six patients received 7.5 g twice a day (group A) and 6 patients received 7.5 g four times a day (group B). In each group 2 patients had absorptive hypercalciuria (AHC; 7). The other patients had normal urinary calcium excretion (= normocalciuria, NC; 7). None of the patients had signs of primary or secondary hyperparathyroidism. During the treatment period no other medication was given.

Clinical Investigations: On the day before the study all patients collected a 24 h urine without dietary restrictions. After an overnight fast (12-15 h) blood was taken at 8 a.m.; immediately afterwards patients received distilled water in a dose of 5 ml/kg body weight and after 45 min a further dose of 0.5 ml/kg body weight was given. Urine was collected for 90 min and thereafter the CaA was determined. Using this schedule patients were studied before treatment and after 6, 12, 24 and 48 weeks. In five patients the resin was withdrawn after 36 weeks of treatment. In group B the daily dose was reduced to 7.5 g twice a day after 24 weeks of treatment.

c. Influence of Long-Term Administration of the Resin on CaA During a Test Meal and the Mineral Metabolism of Patients with Calcium Lithiasis. Four male patients with recurrent calcium lithiasis (ages 30-53 years, 2 with AHC and 2 with NC) were treated orally with 7.5 g of the resin twice a day for 52 weeks. Before, and 3 and 12 months after the beginning of treatment the following protocol was performed: after collection of a 24 h urine without dietary restriction, blood was taken on the next day at 8 a.m. after an overnight fast of 12-15 h. Then patients received 7.5 g of the resin dissolved in 100 ml distilled water and after 15 min a standard test meal (Vivasorb®, Pfrimmer, Erlangen, FRG) containing 30 KJ/kg body weight and 0.08 mmol calcium/kg body weight dissolved in 5 ml distilled water/kg body weight. The CaA during this meal was measured.

Analyses: Urinary and serum calcium (total, ultrafiltrable, ionized) were determined by complexometry, ultrafiltration and spectrophotometry; magnesium by AAS, inorganic phosphate by colorimetry; creatinine, bicarbonate, chloride, alkaline phosphatase, sodium, potassium by autoanalyzer (Technicon); urinary pH by glass electrode (Metrohm; Herisau). Renal threshold phosphate concentration (TmP) was calculated from the nomogram of Bijvoet (18). The following were determined by enzymatic methods: uric acid, urinary oxalate (14) and citrate (15). Urinary cyclic 3'-5'-adenosinemonophosphate (cAMP) was measured by protein binding assay (commercial kit of Amersham Buchler, Braunschweig, FRG) and values were calculated in nmol/min in the fasting urine, and in μmol/l endogenous creatinine clearance in the 24 h urine. CaA was measured by a double isotope method (8). Haemoglobin, erythrocyte, leucocyte, thrombocyte and differential blood cell counts were determined by routine methods; blood sugar, blood fat (triglycerides) and liver function values (bilirubin, transminases) by autoanalyser (Technicon). The activity products of calcium oxalate (CaOx) and brushite (CaP) in the urine were calculated using the computer programme of Robertson (10), and values are indicated as relative supersaturation (RSP). Serum parathyroid hormone (PTH) was determined by radioimmunoas-

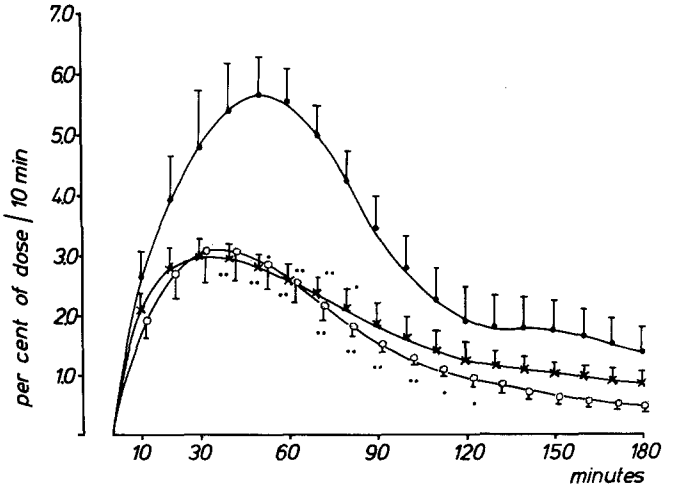

Fig. 1. Intestinal calcium absorption in five healthy control subjects without (•) and with 3.75 g (x) resp. 7.5 g (o) of the cationic exchange resin. Means ±1 SEM are shown. $^{\cdot}p<0.05$; $^{\cdot\cdot}p<0.01$ vs trial without resin

say using an antibody which predominantly recognizes the whole human molecule (AS 211/32, Wellcome, Beckenham) and bovine reference material (13). Bone mineral content (BMC) was measured by photon-absorptiometry (Americium 241, Gambro, Sweden) in the distal radius of the patients' non-dominant forearm. Normal values were based on the investigation of members of the hospital and students (n = 42; ♂/♀ = 22/20; age 20-68 years, mean 40).

All 24 h urinary excretion rates were calculated for 1.73 m^2 body surface.

Statistics: Results are indicated as mean ± 1 standard error (SEM). To compare normal values to pre-treatment values and values before and during medication, the t-test for paired and unpaired data was used in cases of normal distribution, otherwise the test of Mann and Whitney (12) was used. Correlations were calculated according to Spearman (12).

RESULTS

1. CaA and Urinary Excretion of Stone Forming Substances After Acute Administration of the Resin in Healthy Subjects (Fig. 1)

After the oral calcium test dose (2.5 mmol) the volunteers absorbed 58.0 ± 4.2% of the dose within three hours. When taking 3.75 g and 7.5 g of the resin 15 min before, the CaA was significantly reduced to 33.1 ± 3.8 ($p < 0.05$) and 28.9 ± 2.7 ($p < 0.01$) % of the dose respectively. During the three hours significant differences were found in CaA between 40 to 80 min after a dose of 3.75 g resin and between 50 to 120 min after a dose of 7.5 g resin in comparison to the control group. Thus from the calcium test load 43% and 50% were bound to the resin after a dose of 3.75 g and 7.5 g respectively. This resulted in an in vivo exchange capacity of 0.17 mmol and 0.1 mmol calcium per g of resin when taking 2.5 mmol of calcium in the two treatment groups. The urinary excretion rates (μmol/min) during the three hours of the study after the ingestion of 3.75 g and 7.5 g of the resin were: calcium fell from 3.85 ±1.23 to 2.00 ± 0.55 after 3.75 g of resin and 2.68 ± 1.35 after 7.5 g of resin, oxalate rose from 0.053 ± 0.015 to 0.094 ± 0.030 after 3.75 g of the resin and to 0.115 ± 0.047 after 7.5 g of the resin. Phosphate fell from 20.9 ±4.3 to 15.3 ± 3.0 after 3.75 g of resin and to 13.2 ±2.6 after 7.5 g of resin, magnesium from 2.46 ± 0.62 to 1.03 ± 0.53 after 3.75 g of resin and to 0.78 ± 0.33 after 7.5 g of resin, uric acid from 2.81 ± 0.33 to 2.40 ± 0.65 after 3.75 g of resin and to 2.02 ± 0.91 after 7.5 g of resin. These differences were not significant and no correlation was found between CaA and the different urinary excretion values.

2. Influence of the Resin on the Mineral Metabolism of Patients During Long-Term Treatment (Table 1)

a. Fasting Serum Values. TmP was low before treatment in group A ($p < 0.01$) and in group B ($p < 0.05$) in comparison with healthy subjects. In group A, not in group B, the mean TmP decreased during treatment; these differences were not significant. In group A the mean PTH concentration increased after 6 and 12 weeks ($p < 0.05$). The values of all other substances measured (magnesium, uric acid, sodium, potassium, bicarbonate, chloride, alkaline phosphatase) remained unchanged (not shown).

b. Values in the Fasting Urine. The clearance of potassium increased in both groups during treatment, but differences were only significant in group B after 6 and 24 weeks ($p < 0.05$). cAMP was slightly elevated in both groups after 6 and 12 weeks, and after 48 weeks elevated values were only found in those patients who continued medication (not significant). The excretion of the other measured substances (calcium, uric acid, sodium, magnesium, pH) remained unchanged.

c. CaA. The CaA was elevated in group A and B after 24 weeks, and in group B after 48 weeks in those patients only, who stopped medication; these differences were not significant.

d. Values of 24 h Urine. The calcium excretion either did not decrease or decreased only slightly during treatment in both groups. When the calcium excretion of those patients who stopped medication after 36 weeks was compared with the excretion of those who continued medication, no differences were found either within these groups before treatment and after 48 weeks of treatment, or between both groups. There was no difference between patients with AHC and NC (not shown) in the ability of exchange resin to lower urinary calcium excretion.

The excretion of oxalate decreased in group A during treatment (not significant). In group B the excretion of oxalate was low before treatment when compared with normal subjects, rose after 12 and 24 weeks to normal values (none of these differences were significant) and was elevated after 48 weeks in those patients who continued medication with 7.5 g twice a day (0.45 ± 0.02 mmol; $p < 0.05$). The excretion of potassium and citrate increased in both groups, but these differences were not significant. All other measured values (uric acid, sodium, magnesium, phosphate, pH) remained unchanged (not shown). When the urinary values are presented as concentrations then in group B a significant increase of

Table 1. Results of CaA and various substances in the serum, the 2 h and 24 h urine of patients with recurrent calcium lithiasis before and during long-term treatment with the cation exchange resin. Values as means ±1 SEM, except the control group (means ±2 SD). Control group : n = 42, if not otherwise indicated in brackets. A: patients with 2 x 7.5 g of the resin per day, n = 6; B: patients with 4 x 7.5 g of the resin per day, n = 6. Abbreviations: $Calcium_t$ = total calcium, $Calcium_i$ = ionized calcium. For other abbreviations see Methods section. ^{x} = fractional clearance (calculated as percent of 100 ml endogenous creatinine clearance), ^{xx} = range

	Normal values patients	Pre-treatment		After 6 weeks		After 12 weeks		After 24 weeks	
		A	B	A	B	A	B	A	B
Serum									
Creatinine; µmol/l	83±35	98±5	105±5	97±10	108±6	99±3	100±4	84±5	108±4
$Calcium_t$; mmol/l	2.44±0.20	2.40±0.04	2.42±0.02	2.39±0.04	2.46±0.05	2.42±0.03	2.44±0.05	2.42±0.03	2.54±0.04
$Calcium_i$; mmol/l	1.13±0.20	1.12±0.01	1.16±0.02	1.10±0.04	1.02±0.04	1.07±0.03	1.13±0.05	1.13±0.05	1.16±0.03
TmP; mmol/l	1.49±0.29	1.28±0.10[b]	1.24±0.03[a]	1.12±0.06	1.24±0.07	1.20±0.07	1.34±0.14	1.25±0.07	1.23±0.12
PTH; pg-Eq/ml	400-1000[xx]	544±30	789±29	644±39[c]	722±123	659±34[c]	975±121	559±37	721±110
CaA; % of dose	57.1±11.6 (8)	61.5±5.0	63.1±7.4	56.3±2.5	67.3±5.6	53.0±2.1	70.1±9.4	73.7±4.6	73.0±6.9
2 h fasting urine									
cAMP; nmol/min	2.66±0.60 (12)	2.13±0.40	3.12±0.40	2.89±0.20	3.26±0.20	2.79±0.40	3.52±0.50	2.25±0.26	2.87±0.15
Potassium; %[x]	14±10	13±3	12±2	16±2	20±2	21±3	18±3	18±3	19±2
24 h urine									
Volume; ml	1378±840	1305±242	1667±205	-	1964±262	1092±55	1410±284	1340±297	1795±124
Calcium; mmol	4.58±4.38	4.68±0.95	6.89±1.08	-	5.35±1.00	4.73±0.43	5.05±0.78	5.15±0.35	5.75±0.65
Oxalate; mmol	0.39±0.25	0.39±0.04	0.22±0.06	-	0.24±0.06	0.24±0.05	0.36±0.07	0.25±0.05	0.36±0.08
Citrate; mmol	2.48±1.77	1.33±0.20[b]	2.44±0.55	-	3.02±0.90	2.21±0.34	3.85±0.33	3.18±0.76	3.09±1.10
RSP-CaOx	0.97±0.34	0.94±0.16	0.84±0.14	-	0.71±0.11	0.95±0.06	1.04±0.04	0.92±0.09	0.85±0.13
RSP-CaP	0.34±0.88	0.37±0.22	0.31±0.12	-	0.28±0.14	0.22±0.19	0.56±0.20	0.75±0.20	0.47±0.22
Potassium; mmol	69±42	57±4	61±4	-	84±11	70±11	92±16	69±11	73±9

[a] $p < 0.05$, [b] $p < 0.01$ vs control values, [c] $p < 0.05$ vs pre-treatment values

oxalate (mmol/l) is found from 0.12 ± 0.02 to 0.26 ± 0.02 ($p < 0.01$) after 12 weeks, and to 0.25 ± 0.02 ($p < 0.05$) after 24 weeks (not shown).

e. BMC. In all patients BMC did not differ from age matched controls and remained unchanged during treatment.

f. Further Laboratory Determinations. No abnormal values of routinely performed blood cell counts and screening tests (blood sugar and triglycerides, tests of liver function) were found during treatment.

g. New Stone Formation During Treatment. In group A one patient spontaneously passed a kidney stone between 6 and 12 weeks of treatment, one between 12 and 24 weeks, and two patients passed stones between 36 and 48 weeks (after stopping medication). In group B two spontaneously passed stones were seen in the same patient between 6 and 12 weeks and between 24 and 36 weeks.

3. Influence of the Long-Term Administration of the Resin on the CaA During a Test Meal and on the Mineral Metabolism of Patients (Table 2)

a. CaA and Urinary Calcium Excretion During the Test Meal. Before treatment one patient with AHC absorbed 63.5% of dose from the test meal without resin and 52.7% with 7.5 g of the resin (normal value of CaA during the test meal 31 ±18, mean ±2 standard deviations SD). In all patients (n = 4) the mean amount of calcium absorbed from the test meal in the presence of the exchange resin rose during the 12 months of treatment and the same was observed for the calcium excretion (expressed as calcium-creatinine ratio). These differences were not significant. There was a significant correlation between the two parameters ($r = 0.69$, $n = 12$, $p < 0.01$).

b. Fasting Serum and 24 h-Urine. Ultrafiltrable calcium was elevated after 12 months ($p < 0.05$), and TmP was already low before the beginning of treatment when compared with normal values ($p < 0.05$). PTH decreased after 12 months (not significant). The urinary excretion of calcium and oxalate decreased slightly, and excretion of citrate increased during treatment (not significant). Urinary potassium was low before treatment in comparison with normal values ($p < 0.05$) and rose during treatment (not significant). All other measured values (serum: magnesium, uric acid, sodium, potassium, bicarbonate, chloride, alkaline phosphate, cAMP, pH) remained unchanged.

c. BMC and Other Laboratory Determinations. See Table 2 e, f.

Table 2. Influence of long-term resin treatment on the CaA and the calcium excretion during a test meal and on various serum and 24 h urine values of patients with recurrent calcium lithiasis. Values of serum and 24 h urine in control subjects see Table 1. Abbreviations: $Calcium_u$ = ultrafiltrable calcium, Ca/Creat = calcium-creatinine ratio. For other abbreviations see Table 1

	Pre-treatment	After 3 months	After 12 months
CaA; % of dose	43.8±5.8	46.4±6.9	48.1±7.3
Ca/Creat; mg/mg	0.21±0.05	0.22±0.04	0.26±0.09
Serum			
$Calcium_t$; mmol/l	2.49±0.14	2.47±0.05	2.47±0.06
$Calcium_u$; mmol/l	1.48±0.02	1.48±0.02	1.56±0.02[b]
$Calcium_i$; mmol/l	1.08±0.04	1.17±0.03	1.16±0.04
PTH; pg-Eq/ml	949±68	962±154	696±88
TmP; mmol/l	1.28±0.04[a]	1.32±0.10	1.36±0.12
24 h urine			
Volume; ml	1710±320	1755±297	2098±168
Calcium; mmol	8.15±1.85	6.35±1.43	7.68±1.40
Oxalate; mmol	0.38±0.06	0.32±0.07	0.35±0.05
Citrate; mmol	2.27±0.91	2.49±0.98	3.46±1.19
RSP-CaOx	1.05±0.10	0.96±0.06	0.86±0.04
RSP-CaP	0.43±0.20	0.02±0.24	0.22±0.23
Potassium; mmol	45±7[a]	54±4	68±4

[a] $p < 0.05$ vs control values;

[b] $p < 0.05$ vs pre-treatment values

d. New Stone Formation During Treatment. One patient had a spontaneously passed kidney stone after 3 months of treatment.

DISCUSSION

This study was performed under home diet, i.e. the values reflect outpatient conditions and are, therefore, interesting for the judgement of results, which can be obtained under ambulatory conditions in patients with calcium lithiasis. An exact control of the intake of the resin by the patients was not possible, but the elevated urinary excretion of potassium may prove that the resin was taken. In general, however, investigations on drug effects such as in the present study are largely hampered by the lack of objective control criteria regarding patient's compliance.

Although cation exchange resins should be restricted only to patients with AHC, patients with NC were also studied since in the first clinical study with this exchange resin patients with and without hypercalciuria, i.e. without precise classification, were included (11). Furthermore no particular recommendations were given by the manufacturer regarding the type of calciuria which should be treated by the resin.

In the former study the most marked decrease in urinary calcium was found in patients with extreme hypercalciuria (11). As this effect of the resin was not always found until some time after treatment had begun one cannot exclude that changed habits of life and/or food intake by the patients caused by the medical care, might have induced this favourable but nonspecific effect of the resin.

Our investigations show that the acute administration of the resin reduced the CaA in five healthy subjects and one patient. However we did not investigate for how long this beneficial effect would continue, which portion would be bound from greater amounts of calcium or from other calcium compounds, and what reduction of CaA would be achied during the simultaneous intake of the home diet.

Although our calculated in vivo exchange capacity of the resin is smaller than that indicated by the manufacturer for the in vitro binding, an effective reduction of the urinary excretion of calcium could have been expected. The continuous reduction of urinary calcium which has been reported was not seen in this study during long-term treatment; even with double the normal dose of resin no substantial changes in calcium excretion were found either in patients with AHC or with NC.

The rise of serum calcium, PTH, urinary cAMP, CaA and the small decrease of TmP (Group A, Table 1) indicate the development of a mild but transient hyperparathyroidism, most likely caused by the continuous reduction of absorbable calcium from the gut. A portion of the calcium excreted during treatment might be, therefore, of resorptive nature and might mask the real decrease of calcium caused by the resin. Although no signs of hyperparathyroidism were found after 24 weeks of treatment, urinary calcium excretion remained unchanged compared with the pre-treatment values. Thus it seems unlikely that the decrease, which was not observed during the first 12 weeks of treatment, was masked by overactivity of the parathyroid glands only.

Corresponding to animal experiments, which prove a PTH-independent increase of 1,25-$(OH)_2D_3$ during low calcium diet (2), the elevated fasting CaA observed after 24 weeks of treatment (Table 1) might have been responsible for the absence of a decrease in urinary calcium. A similar phenomenon was observed in protocol III (increase of the CaA from the test meal during long-term administration of the resin, Table 2). Equally seasonal variations in the CaA (9, 19) might have influenced our results. This uncertainty might have been excluded, had a control group without the resin medication been studied simultaneously.

The long-term administration of cation exchange resins coupled with phosphorus causes hyperoxaluria by means of increased oxalate absorption in the gut. This effect is caused by the intraluminal binding of calcium and the consecutive augmented free oxalate, which is no longer precipitated as CaOx (4). Thus the activity product of CaOx remains nearly unchanged with this secondary hyperoxaluria (5). Since in our study a raised urinary oxalate excretion was found only during acute administration of the resin and a small increase in group B during chronic administration, we might conclude either that only a small amount of calcium is bound to the resin or that normal oxaluria is possible when certain drugs, such as exchange resin studied, increase the CaA. But this observation needs more specific controlled studies.

Although, despite the increased phosphate excretion, cation exchange resins coupled with phosphorus decrease the oversaturation of the urine with CaP, but not with CaOx (see above), these two activity products remain unchanged in our study. The reduced recurrence rate of kidney stones during the treatment with phosphorus coupled exchange resins is said to be caused solely by the decrease of the activity product of CaP, as the urinary excretion of inhibitors of stone formation as well as the formation product and the crystal growth of CaOx and CaP remain unaltered (5). Thus consequently only patients with pure calcium phosphate lithiasis should be treated with exchange resins, although Pak (6) has proposed a CaP nidus as the onset of the development of CaOx lithiasis. As recurrent stone formation reportedly occurs during treatment with both types of exchange resin (1, 6; our study), none of these resins may eliminate all causes of stone formation. The observation period of this study (1 year) is too small to speculate on the recurrence rate during long-term administration of this resin.

The obviously greater reduction of urinary calcium by the phosphorus coupled exchange resin reported until now, might be caused by the following principles: a) the greater intraluminal precipitation of calcium-phosphate; b) the correction of a possible pre-existing phosphate deficiency, which leads to increased CaA (16) resulting in a lowered urinary calcium excretion during phosphate supply; c) a theoretically increased urinary excretion of inhibitors (pyrophosphate, citrate), which could not be proven until now (5), but needs repeated investigation.

The ideal method of intraluminal calcium exchange requires an additional mechanism in order to lower urinary calcium excretion for a longer time period. We suggest that this latter effect can only be achieved in combination with e. g. phosphorus or an unknown principle. The administration of phosphorus salts has already years ago been proven to be very effective in the prophylaxis of calcium lithiasis.

Acknowledgements. We are grateful to K. Schwille, M. L. Rasenack, I. Goldberg, and B. Schreiber for technical assistance and secretarial help.

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