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Fasting Urine Excretion of Magnesium, Calcium, and Sodium in Patients with Renal Calcium Stones

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Summary. 1. Urine excretion of magnesium (Mg), calcium (Ca) and sodium (Na) was studied in patients with renal Ca stones having normal kidney function (n = 60), and in matched controls (n = 60), on a free diet following an overnight fasting period. In stone formers, Mg was lower than in normals, whereas Ca was unusually high resulting in a significantly higher molar Ca/Mg ratio ($p < 0.001$).

2. In 3 out of 4 stone groups Na excretion was significantly elevated because of reduced tubular reabsorption. In normals, fractional Na excretion varied between 0.44 and 0.54% of endogenous creatinine clearance, whereas it exceeded 1% in the stone patients. Conversely, the molar ratio Na/Ca was equal in all groups.

3. Fasting urinary cyclic AMP was comparable in both populations supporting the assumption that in the majority of patients Ca- or Mg-wasting via urine may not be responsible for secondary hyperparathyroidism. In small selected groups, losses of divalent cations may act in concert, leading to stimulation of the parathyroid glands.

4. Correlations between minerals and Na reveal a close relationship between Na, Ca and Mg in terms of clearance and excretion rate in patients and controls. Fractional Na and Ca excretion are correlated in patients but not in normals. This suggests that in the absence of phosphaturia, factors other than extracellular volume expansion and/or hyperparathyroidism are operative in stone disease.

5. The origin of fasting natriuresis and relative hypercalciuria may be ascribed to a change, as yet not causally identified, in distal tubular Na reabsorption.

Key words: Urinary magnesium, Calcium, Sodium, Cyclic AMP, Creatinine clearance, Stone formers.

Renal excretion of magnesium (Mg), its urine concentration and possible inhibitory role in the formation of calcium (Ca)containing kidney stones has been the subject of numerous clinical reports, animal experiments and in-vitro studies since the first contribution by Hammarsten (10), but no final conclusion has been reached. More recent reports on the existence of absolute or relative hypomagnesiuria in Ca stone patients (in relation to simultaneously measurable Ca) are controversial. Mostly they are derived from investigation of populations which cannot be reasonably compared because of associated disorders, e. g. hyper- and normocalcaemic hyperparathyroidism (HPT), hypertension, diabetes mellitus etc. or which do not take into account dietary habits, age and sex differences or the mineral composition of stones formed during the time of evaluation (25, 6, 40, 23, 43, 22). Studies on Mg metabolism and balance were conducted in primary HPT by Heaton and Pyrah (11) and King & Stanbury (15) but not in common stone formers.

The best documented study on interrelations of urinary Mg and Ca in patients on a free diet also considers oxalic acid excretion and concentration (13) but not sodium (Na) excretion. From a nephrological point of view there is a direct dependency of Ca clearance on Na clearance and excretion rate under various basal and experimental conditions in animals and humans (41, 42). But there is less agreement as to a functional coupling of Ca and Mg clearance and that of Na and Mg aswell. In

primary HPT with Ca kidney stones an elevated urine Na is known to be a frequent occurrence, as is increased urine Ca in patients with uncomplicated Ca-lithiasis.

Very recently Coe, Canterbury, Firpo and Raisz (4) described elevated parathyroid hormone (PTH) in the peripheral circulation in a unexpectedly high percentage of such patients.

However, evidence is lacking for concomitantly increased Na and its possible coupling with the amount of Ca and Mg present in a given urine specimen. Examination of random 24-h urine samples would obviously yield misleading results in the context assumed interdependence of these urinary ions (see Table 2). Following an overnight 12 to 15-h fasting period, the influence of intestinal absorption processes upon urinary minerals can be discounted, i.e. the latter are almost exclusively determined by their serum concentration and kidney function.

Thus the present work was aimed at studying, under more rigidly controlled circumstances, urine excretion of Ca and Mg and their relationships to Na and cyclic adenosine monophosphate (cyclic AMP). The results indicate that stone patients excrete too little Mg in relation to Ca, despite the fact that fasting hypomagnesiuria and hypercalciuria are not common features of this disorder. The relatively high urine Ca could be ascribed to a regulatory role of simultaneously elevated Na.

SUBJECTS AND METHODS

All investigations were carried out on two populations of adults (controls, stone patients) from September 1973 through August 1974. They were closely matched as to age, sex and body surface. At the time of examination in the laboratory, all felt clinically healthy (no associated disorders included) and gave informed consent for the study. Physical examination and kidney function histories revealed no abnormalities in any subjects. Both populations were subdivided as shown in Table 1:

Controls (n = 60); comprising medical students, hospital and laboratory staff members. A routine biochemical screening programme (SMA 12-channel; Technicon-Autoanalyzer)

Table 1. Serum ion values in renal calcium stone patients and healthy control subjects

Groups Sex	Age	N	Body surface correction factor	Creatinine mmol/l	TP g/l	Mg_T mmol/l	Mg_T mmol/l	Ca_T mmol/l	Ca_D mmol/l	Ca^{++} mmol/l	Na mmol/l	K mmol/l
Controls ♂	24.9	15	0.909	0.087	73.3	0.83	0.59	2.52	1.47		144.7	
< 40	0.8		0.020	0.004	1.5	0.01	0.01	0.02	0.03		2.3	
Ca-stones ♂	33.7	15	0.926	0.083	74.5	0.79	0.55	2.53	1.49	1.18	144.6	4.39
< 40	1.5		0.015	0.004	1.0	0.02	0.01	0.02	0.03	0.02	1.2	0.07
Controls ♀	27.1	15	1.29	0.070	70.7	0.79	0.54	2.45	1.45		145.3	
< 40	1.4		0.010	0.003	0.8	0.01	0.01	0.02	0.01		0.7	
Ca-stones ♀	29.6	15	1.046	0.072	71.5	0.81	0.56	2.51	1.47	1.13	148.2	4.40
< 40	1.7		0.020	0.003	1.2	0.02	0.01	0.03	0.03	0.03	1.3	0.10
Controls ♂	54.2	15	0.971	0.075	69.9	0.86	0.59	2.43	1.43		146.7	
> 40	2.5		0.030	0.004	0.8	0.02	0.01	0.02	0.01		0.8	
Ca-stones ♂	55.1	15	0.934	0.088	74.5	0.79	0.55	2.48	1.47	1.11	144.3	4.34
> 40	2.2		0.013	0.004	1.3	0.02	0.01	0.02	0.03	0.04	1.1	0.08
Controls ♀	51.9	15	1.010	0.066	70.8	0.83	0.58	2.36	1.42		147.1	
> 40	1.7		0.016	0.003	1.0	0.02	0.01	0.02	0.02		0.4	
Ca-stones ♀	55.0	15	0.996	0.075	73.5	0.82	0.58	2.44	1.48	1.12	146.1	4.49
> 40	2.3		0.017	0.004	1.0	0.02	0.02	0.03	0.03	0.04	1.2	0.08

Each data point represents mean ± SEM. Abbreviations: < 40 = under 40 years; > 40 = over 40 years; TP: total protein; Mg_T, Mg_D: total and ultrafiltrable magnesium; Ca_T, Ca_D, Ca^{++}: total, ultrafiltrable and ionized calcium; Na, K: sodium, potassium; N: number of subjects

yielded normal values; Stone formers (n = 60): outpatient individuals with a well documented history of Ca stone formation (X-ray diffraction analysis: oxalate, phosphate and mixed composition) during the preceding 12 months necessitating either conservative treatment or surgical intervention. In most cases the daily excretion of calcium while on a free diet was higher than 220 mg. Patients with primary HPT were identified by careful follow-up examination of total serum Ca and its biological fractions (upper limit of normal ionised Ca (Ca^{++}): 1.25 mmol/l).

All individuals were requested by letter to maintain average dietary habits, i.e. to consume freely German "home-cooked" meals for two weeks prior to the investigation; only contraceptive drugs and those necessary for maintaining life were permitted. Following a strict overnight 12 to 15-h fasting period, endogenous creatinine clearance with normalisation of data (per 1.73 m^2 body surface) was performed as previously described (37). Venous blood samples were drawn at the midpoint of the 2h collection period, applying minimum stasis. Individual serum ion values are listed in Table 1, and urine excretion of Mg, Ca and Na per 24 h from representative groups in Table 2.

Analytical Techniques: Pressure ultrafiltration of anaerobically collected blood specimens was carried out by a modification of the method of Putman (31) using nitrogen (3 kg/cm^2), closed chambers (Millipore; Neu-Isenburg) and wet membranes (cellulose nitrate; Sartorius, Göttingen). Concentration of Mg and Ca in ultrafiltrate, serum and urine was measured by atomic absorption spectrophotometry (Zeiss PMQ II; Oberkochen) and EGTA-complexometric titration; Na was measured by emission flame photometry.

No correction factors were introduced in the calculation of clearance data for either specific volume of plasma proteins, total solutes or the Gibbs-Donnan effect. Creatinine was determined according to Bonsness and Tausky (2), and urinary cyclic AMP following Gilman's (9) competitive protein binding assay using filter separation of bound and free nucleotides.

Statistics: Morgan & Robertson (24) pointed out that values of urinary calcium output/day in both healthy humans and Ca stone formers do not follow a gaussian distribution, but that the frequency curve, is distorted in the region of lower values, probably because of a second type of distribution of limits. From the plot of urinary Na in controls on a probability scale (Fig. 1) and the logarithmic plot of Mg, Ca and cyclic AMP (Fig. 2) in patients, it appears that a non gaussian distribution also exists for other variables. For practical purposes we decided to index arithmethic means ± 1 standard error (SEM) unless otherwise indicated. Significant differences at the 5% probability level between groups of Table 3 arise from a two-tailed t-test. In all others the sign-rank test (Wilcoxon) was used. Coefficients of correlation were calculated (method of least squares) for 1 or 2 (multivariate analysis) independent variables.

Table 2. Urine volume, magnesium, calcium and sodium excretion per 24 h in younger (< 40 years) and older (> 40 years) stone patients and matched controls

Groups	N	Body surface correction factor	V_U ml	Magnesium mmol	Calcium mmol	Sodium mmol
Controls	11	0.942	1253	4.90	4.45	184
< 40	(7♂, 4♀)	±0.030	88	0.41	0.48	14
Ca-stones	11	0.985	1880	4.44	6.98	192
< 40	(7♂, 4♀)	±0.070	245	0.49	0.85	19
Controls	13	0.983	1078	3.79	4.00	132
> 40	(10♂, 3♀)	±0.021	112	0.33	0.63	14
Ca-stones	13	0.905	1844	3.83	5.95	180
> 40	(10♂, 3♀)	±0.013	190	0.58	0.60	25

Data denote mean ± SEM. V_U: urine volume/day

Table 3. Fasting urine excretion of magnesium, calcium and sodium in stone patients and healthy control subjects according to Table 1

	V_U	C_{CR}	Magnesium				Calcium				Sodium		
			Excretion rate	Excretion per unit nephron	Clearance ml/min	Fractional excretion	Excretion rate	Excretion per unit nephron	Clearance ml/min	Fractional excretion	Excretion rate	Clearance ml/min	Fractional excretion
	ml/min	ml/min	µmol/min	µmol/min 100 ml GFR			µmol/min	µmol/min/100 ml GFR			µmol/min		
Controls, ♂	0.81	112	2.23	2.62	3.9	3.47	2.43	2.14	1.6	1.45	73.8	0.5	0.49
< 40	± 0.09	7	0.19	0.18	0.4	0.32	0.32	0.27	0.2	0.17	10.7	0.1	0.07
											p<0.005	p<0.005	p<0.02
Ca-stones, ♂	2.36	118	1.85	1.63	3.4	2.98	3.16	2.74	2.1	1.84	128.5	0.9	0.79
< 40	± 0.38	8	0.18	0.19	0.4	0.36	0.27	0.22	0.2	0.15	12.3	0.1	0.09
Controls, ♀	2.62	136	1.96	1.57	3.6	2.95	2.22	1.72	1.5	1.18	101.0	0.7	0.54
< 40	± 0.43	10	0.27	0.26	0.5	0.52	0.44	0.36	0.3	0.25	18.3	0.1	0.10
Ca-stones, ♀	2.78	112	1.73	1.54	3.1	2.75	2.71	2.48	1.9	1.69	124.5	0.8	0.79
< 40	±0.43	13	0.28	0.21	0.5	0.36	0.34	0.24	0.2	0.17	14.1	0.1	0.10
Controls, ♂	1.94	109	1.28	1.25	2.2	2.10	1.85	1.64	1.3	1.15	81.0	0.6	0.51
> 40	±0.34	9	0.16	0.18	0.3	0.28	0.42	0.35	0.3	0.25	12.1	0.1	0.05
					p<0.05			p<0.05			p<0.005	p<0.005	p<0.001
Ca-stones, ♂	2.21	107	1.72	1.69	3.1	3.05	2.86	2.72	1.7	1.68	154.7	1.1	1.03
> 40	±0.33	8	0.20	0.22	0.4	0.38	0.38	0.30	0.2	0.18	18.4	0.1	0.11
Controls, ♀	1.88	106	1.72	1.65	2.9	2.87	1.74	1.64	1.5	1.56	71.1	0.5	0.44
> 40	±0.30	6	0.21	0.19	0.3	0.33	0.25	0.23	0.3	0.37	11.7	0.1	0.06
							p<0.025	p<0.02			p<0.01	p<0.02	p<0.005
Ca-stones, ♀	2.41	113	1.45	1.33	2.5	2.31	2.80	2.56	1.9	1.72	144.2	1.0	0.85
> 40	±0.41	11	0.21	0.14	0.4	0.25	0.36	0.29	0.2	0.19	23.6	0.2	0.10

Data denote mean ± SEM. Abbreviations: C_{Cr} : creatinine clearance, as a measure for glomerular filtration rate (GFR) V_U : urine volume/min; p: level of significance (t-test).

Table 4. Range and medians of fasting magnesium, calcium, sodium and cyclic AMP excretion rate (µmol/min) in younger (< 40 years) and older (> 40 years) stone patients and controls

	Magnesium excretion rate µmol/min		Calcium excretion rate µmol/min		Sodium excretion rate µmol/min		Cyclic AMP excretion rate nmol/min	
	< 40	> 40	< 40	> 40	< 40	> 40	< 40	> 40
Controls								
Range	0.66-4.21	0.30-3.58	0.25-5.13	0.33-5.15	17.3-286.6	14.4-202.8	2.8-13.0	3.9-11.1
Median	2.16	1.50	2.71	1.47	70.5	71.2	5.7	6.7
	(28)	(29)	(29)	(28)	(29)	(28)	(29)	(25)
	p < 0.01		N. S.		N. S.		N. S.	
ID_{80}	1.10-2.99	0.61-2.09	0.64-4.10	0.61-2.83	31.1-138.4	30.7-105.6	3.9-11.8	4.8-10.0
	(22)	(23)	(23)	(22)	(23)	(22)	(23)	(19)
	p < 0.01		p < 0.05		N. S.		N. S.	
Ca-stones								
Range	0.40-3.80	0.72-4.02	0.93-5.79	0.75-6.16	55.0-220.5	33.0-371.2	2.2-11.1	1.8-10.6
Median	1.59	1.32	2.81	2.56	119.4	139.9	5.8	5.3
	(30)	(30)	(30)	(30)	(29)	(29)	(29)	(27)
	N. S.		N. S.		N. S.		N. S.	
ID_{80}	0.64-2.69	0.81-2.58	1.41-4.35	1.21-4.65	58.7-188.0	52.2-227.2	3.1-8.6	3.7-7.5
	(24)	(24)	(24)	(24)	(23)	(23)	(23)	(21)
	N. S.		N. S.		N. S.		N. S.	

Abbreviations: ID_{80} = range remaining following elimination of 10% of each peak and nadir values; in brackets: number of individuals; p: level of significance (Wilcoxon sign-rank test)

RESULTS

1. Urine Mg, Ca, Na (Table 3): With the exception of older male patients (> 40 years) Mg was always lower in the stone patients than in the comparable control group. With increasing age a tendency toward lowering of Mg parameters can be observed in all groups under study. Conversely, the Ca excretion rate was generally higher in stone patients reaching a significant difference in older subjects only (> 40 years).

Obviously, this surplus in urinary Ca is not caused by a large increase in Ca in patients but rather its relative decrease in the control groups. Both Ca clearance and fractional excretion do not deviate greatly from the respective control group.

The most important electrolyte finding is that the majority of stone patients had a significantly higher urinary Na than control subjects, which contrasts with a rather unremarkable daily Na output (Table 2). Whereas fractional Na in the control groups varied between 0.44 and 0.54%, which is within the normal range, it was higher by 50 to 100% in stone formers. If Na excretion is classified according to increasing values and plotted against per cent cumulative frequency (Fig. 1), the result for the control group is a straight line which is somewhat distorted in the lower part. This might indicate a tendency toward low values in controls, whereas in stone patients this distortion is practically negligible. The slope of the regression line is identical in both populations but in stone formers the line is shifted to the right, confirming higher individual values.

2. Influence of Age upon Urinary Minerals and Cyclic AMP (Table 4): When all groups under study were subdivided roughly with regard to age, Mg ($p < 0.01$) and Ca excretion were found to be markedly lower in the older controls, which was not true for cyclic AMP excretion. Elimination from controls of 10% of each peak and nadir values (ID_{80}) also results in a Ca

Table 5. Correlations between urinary variables relevant for interpretation of tubular sodium, calcium and magnesium transport

Variables	Controls			Stone formers		
X : Y	N	R	p	N	R	p
Clearance (C): ml/min						
C_{Na} : C_{Ca}	54	0.356	<0.01	57	0.419	<0.001
C_{Na} : C_{Mg}	54	0.440	<0.001	58	0.276	<0.05
C_{Ca} : C_{Mg}	54	0.490	<0.001	59	0.531	<0.001
Fractional (F) excretion: per cent						
F_{Na} : F_{Ca}	54	0.187	N.S.	57	0.341	<0.01
F_{Na} : F_{Mg}	54	0.435	<0.001	57	0.326	<0.01
F_{Ca} : F_{Mg}	54	0.343	<0.05	59	0.377	<0.01
Mineral excretion/mmol creatinine						
Ca : Mg: <40	30	0.643	<0.001	30	0.104	N.S.
>40	30	0.304	N.S.	30	0.631	<0.001
Mineral concentration (mmol/l)						
Na : Ca	54	0.540	<0.001	59	0.616	<0.001
Ca : Mg	54	0.835	<0.001	60	0.671	<0.001
Relationship urine flow (ml/min) and mineral concentration (mmol/l)						
Flow : Ca	57	-0.565	<0.001	60	-0.611	<0.001
Flow : Mg	57	-0.659	<0.001	60	-0.657	<0.001
Flow : Na	57	-0.582	<0.001	59	-0.601	<0.001

Abbreviations: X = independent; Y = dependent variable; < 40 = younger; > 40 = over 40 years; N: number of individuals; R: correlation coefficient; p: level of significance.

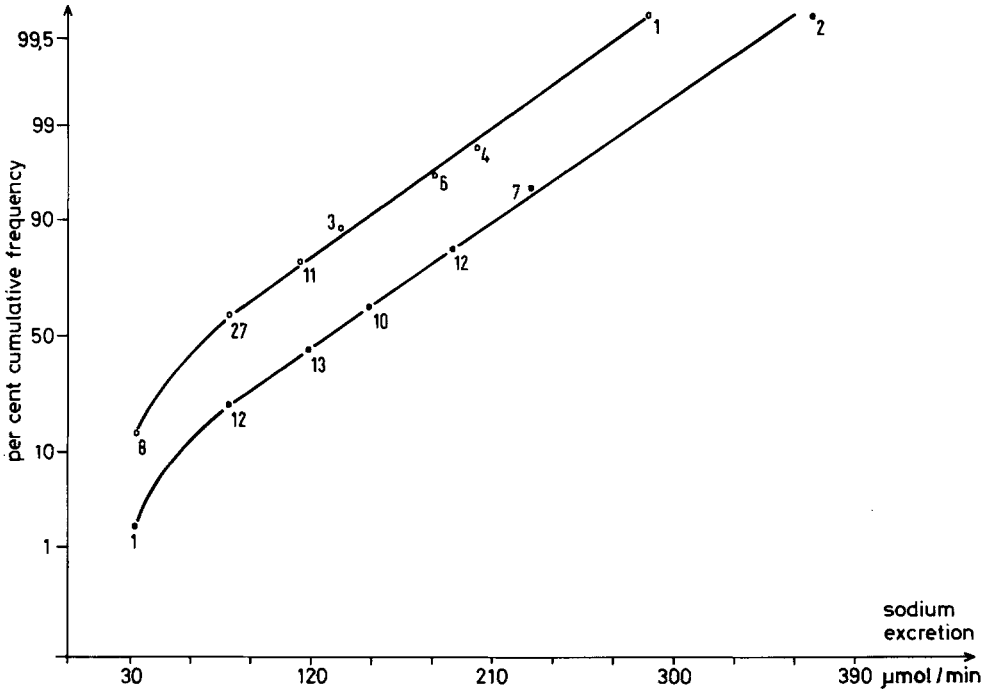

Fig. 1. Per cent frequency of fasting urinary sodium excretion rate in healthy control subjects (o) and stone patients (●) when plotted on a probability scale. Numerals on lines indicate total number of individuals per point

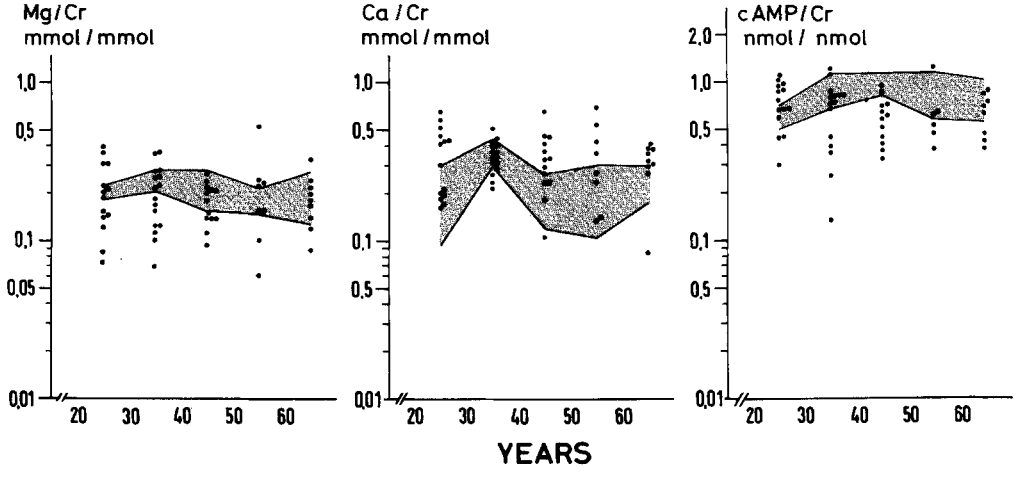

Fig. 2. Logarithmic plot of fasting urinary magnesium (Mg), calcium (Ca), cyclic AMP (cAMP) in relation to urinary creatinine (Cr) in stone patients (●) of 5 different age groups. Hatched area indicates 95% confidence limits of control subjects

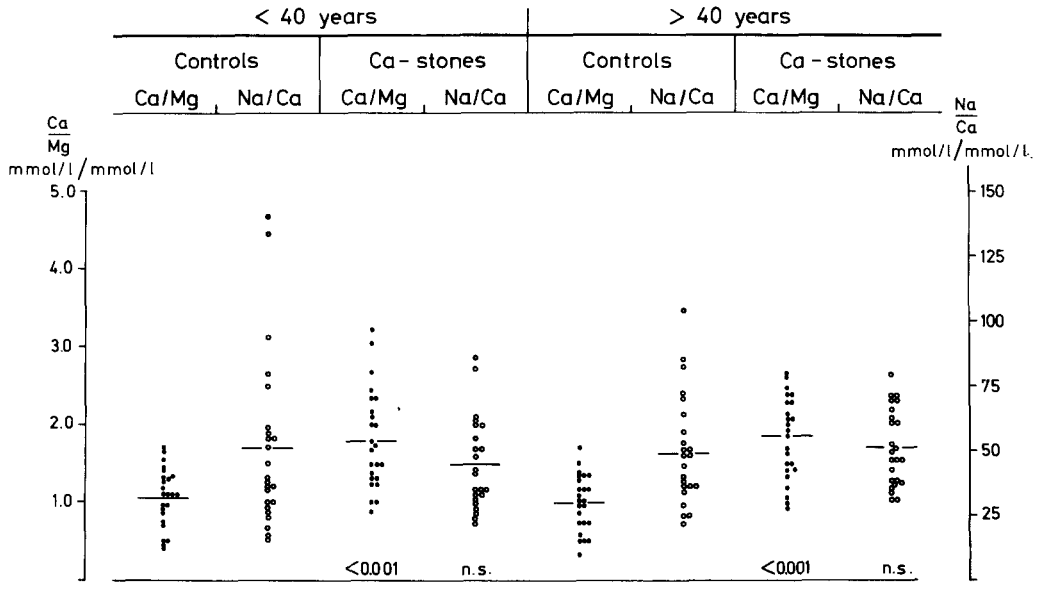

Fig. 3. Molar ratio calcium/magnesium (•) and sodium/calcium (o) in fasting urine of control subjects and stone patients. Each bulk of symbols represents ID_{80} of individual values (see table 4). Horizontal lines indicate mean values. Levels of significance in comparison to controls (Wilcoxon sign-rank test)

Table 6. Correlations between fasting urinary excretion of cyclic AMP and minerals (calcium and magnesium) or sodium

Variables	Controls			Stone formers		
X : Y	N	R	p	N	R	p
A. Mineral and cAMP excretion rate						
Ca : cAMP	46	0.012	N.S.	55	-0.076	N.S.
<40	27	0.146	N.S.	29	0.107	N.S.
>40	19	-0.193	N.S.	26	-0.348	N.S.
Mg : cAMP	48	0.346	<0.05	55	0.085	N.S.
<40	28	0.478	<0.01	29	0.172	N.S.
>40	20	0.295	N.S.	26	0.173	N.S.
Na : cAMP	47	0.148	N.S.	52	-0.148	N.S.
<40	28	0.310	N.S.	27	0.118	N.S.
>40	19	0.273	N.S.	25	-0.333	N.S.
B. Correlations between urine excretion of minerals and cAMP in stone formers outside 95 per cent confidence limit of controls (Fig. 2)						
Mg : cAMP				35	0.19	N.S.
Ca : cAMP				30	0.04	N.S.
(Mg + Ca) : cAMP				35	0.067	N.S.
C. Multivariate analysis (Mg = x_1; Ca = x_2; cAMP = y)						
All stone formers (see B.)				21	0.297	N.S.
<40				11	0.167	N.S.
>40				10	0.653	<0.05

Abbreviations: see Table 5

excretion significantly reduced by age, whereas in stone patients no age dependent reduction can be observed.

A more detailed classification of both population according to age (Fig. 2), with individual values of patients contrasting 95% confidence limit of controls, shows more clearly the tendency toward an increased Ca and a decreased Mg in urinary stone formers.

3. Interdependency of Urine Na, Ca and Mg, their Actual Concentrations and Relationships to Urine Flow (Table 5): With three exceptions, the data confirm conclusions drawn by earlier authors concerning functional coupling of tubular transport of these urinary ions (Walser; 42). There is no correlation between fractional Na and Ca in healthy controls. With increasing age the relationship between Ca and Mg excretion weakens severely, and there is a complete lack of correlation in younger stone formers, but not in the elderly. With comparable urine flow/min actual concentration of minerals and flow are linked by an inverse correlation. When Mg excretion is related to flow, a dependency of this ion on flow cannot be detected, as was earlier suggested (12).

4. Interrelationships between Urinary Jons and Cyclic AMP (Table 6): The correlation data argue against a direct relationship between urinary Ca losses and cyclic AMP and also between the amount of Na and cyclic AMP present. There seems to be a much more pronounced coupling between Mg and cyclic AMP at least in younger control subjects (< 40). Conversely in older stone patients a remarkable correlation can be calculated between excretion of divalent cations and cyclic AMP when Ca and Mg also range outside the 95% confidence limit of controls.

DISCUSSION

When amounts of ingested fluids were constant, urine flow/min (Table 3) and cyclic AMP (Table 4) in all groups were fairly comparable. But in stone patients the excretion of Mg was slightly lower than in controls, whereas Ca was higher and Na was significantly elevated. However, the critical evaluation of underlying pathophysiological factors is limited for two reasons. First, it must be assumed that during the two weeks preceding the study, all individuals maintained a diet with similar contents of Na, Ca and Mg. Second, neither the control nor the patient populations were considered to comprise cases with normo- or hypercalcaemic HPT.

The first point could be doubted since most physicians advise stone patients to prefer meals poor in Ca, i.e. to generally avoid dairy products but to drink an abundance of fluids in order to maintain higher daily urine volumes (Table 2). Despite the written instructions (see methods) a relative over-ingestion of carbohydrates and proteins might have occurred as well as a mild degree of expansion of extracellular volume. Other reports demonstrated that carbohydrates increase renal Ca and Mg excretion (13, 17) and that proteins lead in addition to phosphaturia (19, 1, 7) by virtue of a higher phosphate content. It is well known that volume expansion enhances urinary excretion of Na and phosphate (39) and uric acid (38) by preferential inhibition of proximal tubular reabsorption. The second point is presumably realised if normal concentration of ionised serum Ca (Table 1) and normal fasting cyclic AMP (Table 4) following a limited fasting period argue against hyperactivity of the parathyroids.

Coe and Kavalach (5) pointed to a tubular reabsorption leak of Ca (renal hypercalciuria) as the main cause of hypercalciuria and of secondary HPT in stone patients. Others (26, 27) concluded that this type of hypercalciuria would be associated with raised urinary cyclic AMP. From our data on fasting Ca and cyclic AMP (Fig. 2) it appears unlikely that secondary HPT as a result of Ca-wasting via urine had been frequently encountered in the stone groups, which would be further supported by the lack of correlation between both parameters (Table 6).

The slightly higher serum Ca in stone patients (total and ultrafiltrable; Table 1) does not contradict this interpretation as total proteins are also higher. Hence, normalisation to a given protein concentration of serum Ca would alleviate these differences between groups. Furthermore, no relationship between ultrafiltrable serum Ca and its urinary excretion can be detected ($r = 0.10$; not depicted) as might be expected in borderline hyperfunction of parathyroids.

Mg is predominantly localised within cells (18), and changes of its relatively low extracellular concentration in humans would be rapidly compensated. Therefore the lower ultrafiltrable serum Mg in stone formers (Table 1), described earlier by the present authors (36), could represent either a latent Mg deficiency or a higher affinity between plasma binders and ligand with the result of alterations in characteristics of renal tubular Mg transport. Whatever the cause of the former, the lower Mg load in proximal tubules of stone patients did not result in diminished net reabsorption as may be expected for maintenance of constant urinary Mg output. Most patients exhibit slightly increased fractional reabsorption (Table 3). Therefore, in the presence of moderate saluresis, lower urinary Mg suggests that tubular Mg reabsorption might also be controlled by mechanisms other than intratubular Na concentration, as

was described for the dog (3). Consequently, it seems clear from Fig. 3 that at any given level of urinary Ca and Mg, the molar ratio of both ions is significantly higher in stoneformers.

It is generally accepted that the limiting step for determination of the amount of phosphate present in urine is its proximal tubular reabsorption (16). The association of normal or even low phosphate levels especially in younger patients as reported in a parallel study (37), with raised sodium excretion as in the present work, also argues against involvement of natriuretic parathyroid hormone (8), unless one would assume a state of phosphate depletion in the bulk of stone formers.

Furthermore, in the face of normal serum protein concentration (Table 1), neither expansion of extracellular space itself nor subsequently stimulated parathyroids can sufficiently account for increased Na delivery to distal tubular reabsorption sites. Hence the distal tubule itself should be considered the site for compensation between high fasting Na and its rather unsuspicious excretion/day (Table 2). This thesis, on the other hand, would require either predominance of factors with Na retaining properties between early morning and evening or a sort of mineralocorticoid "escape" phenomenon as was reported for primary hyperaldosteronism during a moderate oral saline load (33). The first demand could be represented by raised plasma or tissue concentrations of hydroxylated metabolites of vitamin D_3 (25-(OH)D_3; 1,25-$(OH)_2$ D_3) with proven antinatriuretic effectiveness in dogs (29) and humans (30). Aside from this property those compounds facilitate parathyroid hormone effects on bone in vitro (32) and enhance intestinal Ca absorption from gut lumen in humans thereby mediating hypercalciuria (35). Since peak seasonal values of urinary Ca (34, 28) precede the peak seasonal values of serum 25-(OH)D_3 by 1 to 2 months (21), the idea that a significant role is also played by these substances in Na homeostasis of stone patients may be considered doubtful. Investigations directed toward the diurnal profile of these metabolites in stone disease are yet lacking. However, according to a recent report it might be possible that the critical determinant in achieving hypercalciuria is not their actual concentration but rather the pool size of 1,25-$(OH)_2D_3$ and its turnover rate which is confirmed to be a factor 2 to 3 higher in primary HPT than in normals (20).

Based on current knowledge, the assumption of a primary disturbance of metabolism of mineralocorticoids would be more reasonable in explaining the higher excretion level for Na and Ca and their stronger correlation in stone disease.

It is well known that following a defined oral Ca load the majority of patients exhibit enhanced intestinal Ca reabsorption and subsequently raised urine Ca. Recently published data of Ireland & Fordtran (14) document that, at least in normals, jejunal Ca transport is achieved against a concentration gradient and that its intensity is paralleled by an identically intensive Na flux in the same direction. Thus, with a comparable oral Na load, the assumption of the existence of a higher endogenous Na load as effected from its intestinal hyperabsorption would fit well into the concept of "absorptive hypercalciuria" (26). It may help to overcome the need for postulation of expanded extracellular space in stone patients as the single cause of their higher fasting natriuresis. In combination with higher Ca excretion the latter would result from diminished Na reabsorption at aldosterone-insensitive distal tubular sites where Na and Ca transport are closely coupled (33). Although at the present time such an interpretation must be extremely hypothetical, nevertheless the lack of correlation of fractional Na and Ca excretion in normals (Table 5) and the constant molar ratio Na/Ca among all groups (Fig. 3) lend support to it.

It can be concluded that with regard to higher Na excretion and the molar ratio Ca/Mg (Fig. 3) stone formers probably represent a homogenous population. This finding contrasts with less constant alterations of their renal excretion of uric acid, titratable acidity and inorganic phosphate (37) and their urinary pH, Ca and oxalic acid as well (13), which they have more in common with non-stone-forming controls. Further investigation of factors regulating Na homeostasis in this disorder are now in progress.

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Note added in proof: Since presentation of this manuscript a further report was published confirming normal plasma levels of parathyroid hormone in stone formers whether the subjects were hypercalciuric or normocalciuric. We agree with these authors (Posen, S., Kleerekoper, M., Ingham, J. P., Hirshorn, J. E. : Parathyroid hormone assay in clinical decision making. British Medical Journal 1, 16-19 (1975)) that surgical neck exploration only is justified in the presence of definitely elevated parathyroid hormone concentration in peripheral blood.