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Magnesium Status in Idiopathic Calcium Urolithiasis – An Orientational Study in Younger Males[1])

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Summary: With the aim of revealing a possible magnesium (Mg) deficiency in the aetiology of idiopathic recurrent calcium urolithiasis we studied the Mg content of red blood cells, serum total, protein-bound, ionised and complexed fractions of Mg, and urinary Mg after an overnight fast. The two study groups comprised 12 male recurrent calcium urolithiasis patients and 12 healthy male controls (mean age 31 and 29 years, respectively). In recurrent calcium urolithiasis, serum albumin and Mg of erythrocytes were significantly decreased, as was serum total and protein-bound Mg, whereas serum ultrafiltrable, ionised and complexed Mg were statistically indistinguishable from values in controls. Urinary Mg (per unit creatinine) in recurrent calcium urolithiasis (mean 0.188 vs 0.209 in controls; $p = 0.386$) was not statistically different, whereas urinary total protein, glucose, and pH were significantly increased. The renal clearances of Mg and glucose were positively correlated ($r = 0.56$; $p < 0.01$), with a steeper slope in recurrent calcium urolithiasis than controls. Further fractionation of serum and urinary Mg into ions and complexes in recurrent calcium urolithiasis subjects with identical creatinine clearance revealed no statistical difference between

1) Mg ions and complexes filtered by renal glomeruli;
2) Mg ions and complexes excreted in urine;
3) fractional Mg excretion.

Median urine supersaturation with respect to calcium oxalate was insignificantly lower (1.5 vs 2.2), with respect to hydroxyapatite insignificantly higher (3.3 vs 1.8), than in controls.

It is concluded that relatively young recurrent calcium urolithiasis patients exhibit a deficiency of Mg in erythrocytes and serum total Mg, but no alteration of renal Mg handling. Thus, in recurrent calcium urolithiasis, a role of Mg deficiency in urine as a factor initiating stone formation may be ruled out, whereas a possible link between cellular Mg deficiency and the impairment of renal tubular functions involved in reabsorption of glucose and proteins, and in urine acidification, deserves further studies.

1. Introduction

Magnesium (Mg) is an important element in biological calcification processes, where it can play a dual role. In skeletal tissue, for example, it may be a promotor of the maturation of hydroxyapatite prior to deposition (1, 2), and it may also be an inhibitor of calcium phosphate crystallisation (3), its actual role being determined by the prevailing physico-chemical environment. On the other hand, in alkaline urine, excess Mg can promote the formation of Mg-ammonium-phosphate stones, while the crystallisation of calcium phosphates and calcium oxalates is inhibited by Mg in acidic urine (4–6). With regard to calcium oxalate, the mechanisms contributing to inhibition are believed to be a Mg-induced decrease in both biosynthesis and urinary excretion of oxalate (for details see l. c. (7, 8)), but also complexation of urinary oxalate, and growth retardation of preformed calcium oxalate crystals (9, 10). In view of this situation, there is a clear need to determine whether or not patients with renal calcium stones have a Mg deficiency, especially in the urine. In so-called idiopathic recurrent calcium urolithiasis, comprising patients with calcium oxalate and mixed (mostly calcium oxalate and calcium phosphate) stones, earlier investigations in this area provided conflicting results (11–14). However, some of these are probably due to the fact that patients and controls in those studies were not, or only poorly, matched with respect to sex, age, body mass index, or lean body mass, the latter two as measures of obesity. Overweight is a frequent feature of males with recurrent calcium urolithiasis (15), and since these variables have a significant

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association with Mg deficiency (16), studies on Mg that neglect this may be seriously biased. Furthermore, because urinary Mg and the renal handling of Mg depend on the body stores of Mg, extracellular Mg included, it is essential that cellular content, serum fractions, and urinary content of Mg are investigated together. Since urinary Mg acts predominantly in its ionised form as an inhibitor of calcium oxalate crystal growth, renal handling of serum Mg, separately for ionised and complexed Mg filtered by glomeruli, is of major interest; similarly, also in urine, total Mg should be considered separately as free ions and complexes. Such work has not been carried out up to now in renal calcium stone research.

The present work was conceived as a pilot study with the aim of identifying a possible Mg deficiency in recurrent calcium urolithiasis by means of assessing the fasting Mg content of red blood cells, the biological fractions of Mg in serum, and the concomitant urinary excretion of Mg.

Materials and Methods

Study participants and procedures

Informed consent was obtained from all participants. Twelve male recurrent calcium urolithiasis patients (mean age 31 years, range 19–43) and twelve male healthy subjects (mean age 29 years, range 23–43) were studied, the latter serving as controls. The study participants were ambulatory, and all were on their usual home diet until 6:00 p. m. on the day before they entered the hospital.

In recurrent calcium urolithiasis, the absence of disorders characterised by concomitant stone formation, such as primary hyperparathyroidism, renal tubular acidosis, oxalosis, enteric hyperoxaluria, or gout was verified. Also, subjects with hypertension, diabetes, hyperthyroidism, or urinary tract infection were excluded. The duration of stone disease ranged from 2 months to 29 years. Stone analysis revealed calcium oxalate in nine, mixed stones (calcium oxalate plus calcium phosphate) in two, and some indeterminate calcium salt in one. At the time of laboratory examination (see below) stones were present in 7 of the 12 recurrent calcium urolithiasis patients.

The order of magnitude of several anthropometric and metabolic quantities was similar, and the mean values were as following:

body mass index was 23.9 [recurrent calcium urolithiasis] and 22.7 [controls] kg/(cm)^2;

serum creatinine 80.3 [recurrent calcium urolithiasis] and 85.5 [controls] µmol/l;

serum glucose 4.76 [recurrent calcium urolithiasis] and 4.79 [controls] mmol/l;

plasma citrate 0.11 [recurrent calcium urolithiasis] and 0.11 [controls] mmol/l;

the median urinary sodium was 7.83 [recurrent calcium urolithiasis] and 7.70 [controls] mol/mol urinary creatinine.

The latter value makes it unlikely that excess salt had been taken by recurrent calcium urolithiasis patients with the daily home diet. In both patients and controls, serum potassium and blood gases were within normal limits, the creatinine clearance exceeded 1 ml/min · kg body weight, the fasting urinary calcium/creatinine ratio was normal (< 0.34 mmol/mmol creatinine), except for three recurrent calcium urolithiasis patients who showed fasting hypercalciuria but whose other quantities were within the range of the normocalciuric stone formers. None of the participants was hyperoxaluric (upper limit of normal in this laboratory 0.39 mmol per day), and none was on long-term anti-stone medication or using any daily Mg supplementation via food or drinks.

On the day of the examination the following steps [part of a standardised programme developed to investigate disturbances of mineral metabolism (17) and yielding reproducible results upon repeat application (unpublished data)] were taken in the clinical laboratory after an novernight 12–14 h fasting period: 7:30 a. m. bladder voiding, stimulation of mild diuresis (approx. 1 ml urine per minute) by drinking demineralised water, followed by collection of a timed (2 h) fasting urine, puncture of a forearm vein and aspiration of blood without statis.

Physical exercise during the laboratory procedure was kept to a minimum in all participants to rule out unspecifically stimulated proteinuria (18).

Analyses

Routine methods were employed for blood gases (Blood Gas Analyser, Instrumentation Laboratory, Milan; Italy), urinary pH (pH meter 691, Metrohm, Filderstadt, Germany), and creatinine, sodium, potassium (Autoanalyser 747, Hitachi, Japan), calcium (by complexometry, using Calcium analyser 940, Corning, Halstead; UK) and phosphorus (as inorganic phosphate, Kit No. 3331, Merck, Darmstadt; Germany) in serum and urine. Oxalate in urine was measured by ion chromatography (19). Additional variables investigated were haematocrit, total protein [in serum by refractometry, in urine by colorimetry (reagents from Bio-Rad Laboratories, Munich; Germany)], albumin [in serum by colorimetry, in urine by nephelometry (using the monoclonal antibody, OSAL 14, Behring, Marburg; Germany)]. Atomic absorption spectrophotometry [FL 6, Zeiss, Oberkochen; Germany (inter-assay coefficient of variation = 0.6%, based on n = 29 control serum samples)] was used to determine undiluted serum Mg, Mg in ultrafiltrate of anaerobically handled serum samples [pressure filtration (nitrogen, 3 bars) through a M_r 10 000 cellulose triacetate membrane; Sartorius, Göttingen, Germany], and Mg in heparinised plasma and whole blood, containing 17–20 · 10^3 IU Na-heparin per litre sample. Ionised Mg in heparinised whole blood was determined using a sensitive electrode (CRT 8, Nova Biochemical, Rödermark; Germany), as described by *Altura* et al. (20). Serum human intact parathyroid hormone was measured using a commercial kit (Nichols, Bad Nauheim; Germany). Serum and urinary citrate (21), and serum and urinary glucose (Glucose Analyser 2, Beckman, Fullerton; USA) were determined enzymatically.

Calculations and statistics

The concentration of Mg in erythrocytes (expressed in mmol/l) was calculated as

P + [100 (W-P) : H],
where P is plasma Mg,
W is Mg in haemolysed whole blood, and
H is the haematocrit (22).

The serum protein-bound and the complexed Mg fractions were taken as the difference between the concentration of the serum total and ultrafilterable fraction, and the serum ultrafiltrable and ionised fraction, respectively. The renal filtered load of total Mg, Mg ions, and Mg complexes was taken as the product of the respective concentration in the ultrafiltrate and the creatinine clearance. Equil-2 software (23) was used for the calculation of urinary ionised and complexed Mg, and the relative supersaturation products of calcium oxalate, brushite, and hydroxyapatite in urine. To prevent errors in bladder voiding, substances in urine were factorised for urinary creatinine. The results in urine are expressed as arithmetic means (range), in blood as arithmetic means (SEM), if not otherwise indicated. Differences between groups were tested for significance ($p < 0.05$) by the t- or U-test, as appropriate. For several variables *Spearman*'s correlation coefficient was assessed.

Tab. 1 Baseline clinical chemistry data of patients with recurrent calcium urolithiasis and controls (healthy non-stone-forming individuals). Mean values (SEM, or range of values). S: serum; P: plasma; U: urine. *: $p < 0.05$ vs Controls.

	Recurrent calcium urolithiasis n = 12		Controls n = 12		p-value
S-Total protein; g/l	70.3	(3.9)	69.8	(3.6)	0.740
S-Albumin; g/l	47.5*	(10)	49.7	(1.8)	0.001
S-Total calcium; mmol/l	2.30	(0.018)	2.29	(0.020)	0.808
S-Phosphate; mmol/l	1.03	(0.05)	1.10	(0.06)	0.362
P-Parathyrin; ng/l	26.7	(9.79)	25.6	(16.6)	0.157
U-pH	6.02*	(4.8–6.9)	5.43	(4.8–6.6)	0.025
U-Creatinine clearance; ml/min	125	(91–188)	106	(66–167)	0.107
U-Protein; g/mol creatinine	3.76*	(1.0–21.3)	2.11	(0.7–3.7)	0.026
U-Albumin; µmol/mol creatinine	7.65	(0–15.0)	4.03	(0–11.9)	0.207
U-Glucose; mol/mol creatinine	0.049*	(0.02–0.13)	0.020	(0.01–0.04)	0.005
U-Calcium; mol/mol creatinine	0.309	(0.06–0.95)	0.157	(0.02–0.38)	0.214
U-Magnesium; mol/mol creatinine	0.188	(0.08–0.45)	0.209	(0.14–0.3)	0.386
U-Potassium; mol/mol creatinine	5.73	(2.3–12.6)	4.56	(2.1–11.02)	0.341
U-Citrate; mol/mol creatinine	0.144	(0.05–0.35)	0.154	(0.04–0.30)	0.863
U-Phosphate; mol/mol creatinine	0.97	(0.41–2.42)	1.39	(0.58–2.2)	0.069
U-Oxalate; mol/mol creatinine	0.012	(0.01–0.02)	0.013	(0.01–0.02)	0.707
U-Glucose clearance; ml/min	0.10*	(0.05–0.22)	0.04	(0.02–0.06)	0.001
U-Magnesium clearance; ml/min	3.48	(1.28–5.65)	3.00	(1.60–4.68)	0.442

Results

General data

The baseline clinical chemistry data in recurrent calcium urolithiasis patients and controls, matched for sex, age, body mass index, renal function (see Material and Methods), are shown in table 1. Except for serum albumin, the mean value of which in recurrent calcium urolithiasis was 4.4 per cent less than in controls, there were no statistically significant differences detectable in serum or plasma.

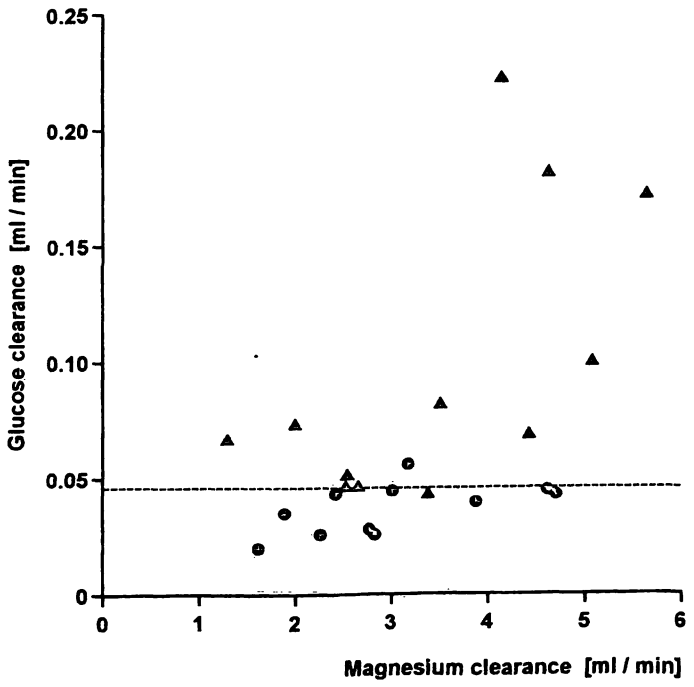

Fig. 1 Interrelationship of the clearances of total magnesium and glucose in fasting urine of male recurrent calcium urolithiasis patients (▲; n = 12) and healthy controls (●; n = 11). The dashed line denotes that in the majority of recurrent calcium urolithiasis subjects glucosuria is > 0.046 ml/min. For further details see text.

In fasting urine of recurrent calcium urolithiasis patients, the pH was significantly elevated, as were protein and glucose; the creatinine clearance, albumin, sodium, and potassium all tended to show higher, phosphate and Mg lower values than in controls. The degree of proteinuria and albuminuria was not different between recurrent calcium urolithiasis patients with stones in situ and those without stones at the time of examination. There was a significant positive correlation between the urinary clearances of Mg and glucose ($r = 0.56$, $p < 0.01$), with a steeper slope of the regression line for the patients ($n = 12$, $r = 0.62$, slope = 0.03) than for the controls ($n = 11$, $r = 0.575$, slope = 0.006) (fig. 1). Applying a cut-off point of 0.046 ml/min glucose clearance to the plot largely separates the two groups, only a single individual being definitively common to both. No other correlations with urinary glucose as the dependent variable could be detected.

Mg in erythrocytes, biological Mg fractions (tab. 2)

Mg in erythrocytes of recurrent calcium urolithiasis patients was about 9.5% lower than in controls, with the difference being very close to the level of significance (for reference values see l. c. (24, 25)). Also in recurrent calcium urolithiasis, the serum total and protein-bound Mg concentrations were about 7 and 13% lower ($p < 0.05$, and of borderline significance, respectively), and the mean values of ultrafilterable and ionised Mg

Tab. 2 Magnesium (Mg) in red blood cells and Mg fractions in serum, all in mmol/l, of stone patients and healthy subjects (controls). Mean values (SEM). For further details see text. *: $p \leq 0.05$ vs controls.

	Recurrent calcium urolithiasis n = 12		Controls n = 12		p-value
Erythrocyte Mg; mmol/l	1.902*	(0.055)	2.102	(0.082)	0.054
S-Total Mg; mmol/l	0.794*	(0.022)	0.858	(0.020)	0.042
S-Protein-bound Mg; mmol/l	0.172	(0.037)	0.197	(0.019)	0.058
Fraction of total (%)	21.7	(1.2)	22.9	(0.4)	0.366
S-Ultrafilterable Mg; mmol/l	0.622	(0.020)	0.662	(0.016)	0.141
Fraction of total (%); mmol/l	78.3	(1.2)	77.1	(0.4)	0.366
S-Ionised Mg; mmol/l	0.417	(0.017)	0.440	(0.022)	0.406
Fraction of total (%)	52.9	(2.5)	49.6	(4.8)	0.325
S-complexed Mg; mmol/l	0.205	(0.018)	0.237	(0.017)	0.222
Fraction of total (%)	25.4	(1.9)	27.4	(1.8)	0.455

were each about 5% lower than in controls. In both recurrent calcium urolithiasis and controls the protein-bound and ultrafilterable Mg concentrations as a percentage of total serum Mg were similar to those reported for healthy individuals (25). There was no significant correlation between erythrocyte Mg and serum total Mg (recurrent calcium urolithiasis, $n = 12$, $r = 0.092$, $p = 0.789$; controls, $n = 12$, $r = 0.296$, $p = 0.351$) or ultrafilterable Mg (recurrent calcium urolithiasis, $n = 12$, $r = 0.140$, $p = 0.681$; controls, $n = 12$, $r = 0.331$, $p = 0.294$).

Urinary Mg, protein and glucose at comparable creatinine clearance in recurrent calcium urolithiasis and controls (tab. 3)

To rule out the possibility that differences in the filtered load of Mg interfere with the amount of Mg in the final urine, we selected eight individuals from each of the twelve recurrent calcium urolithiasis patients and controls, who had almost identical creatinine clearance. This resulted in practically the same values for the Mg excretion rate and urinary Mg/creatinine ratio in recurrent calcium urolithiasis and controls; also with all other Mg variables studied significant difference between the groups. However, in recurrent calcium urolithiasis, the excretion rate of free Mg ions was slighly higher, and that of complexed Mg slightly lower than in controls; in addition, the mean fractional clearance of total and ionised Mg in these eight recurrent calcium urolithiasis patients was also higher, indicating the presence of some factor able to influence net tubular reabsorption of Mg. Urinary protein was 3.3-fold higher, and urinary glucose 2.8-fold higher in recurrent calcium urolithiasis patients than in controls.

State of supersaturation of urine (tab. 4)

In recurrent calcium urolithiasis as a whole group (12 patients) the mean relative supersaturation products of calcium oxalate was apparently lower than in controls (12 subjects), the difference being of borderline significance. In contrast, the mean relative supersaturation products of hydroxyapatite in recurrent calcium urolithiasis was 1.8- to 2-fold higher than in controls, due mainly to their higher urinary pH (see table 1), whereas

Tab. 3 Renal handling of magnesium (Mg) in 8 recurrent calcium urolithiasis patients and controls, respectively, with comparable mean creatinine clearance (as a marker of glomerular filtration rate). Mean values (range). Fractional excretion is synonymous with fractional clearance. For other abbreviations and details see table 1 and text. *: $p < 0.05$ vs Controls.

	Recurrent calcium urolithiasis n = 8		Controls n = 8		p-value
Creatinine clearance; ml/min	119	(91–154)	119	(86–168)	0.943
U-Protein; g/mol creatinine	6.36*	(0.98–21.3)	1.91	(0.68–3.72)	0.041
U-Glucose; mol/mol creatinine	0.054*	(0.02–0.13)	0.019	(0.01–0.036)	0.003
Mg; mol/mol creatinine	0.24	(0.08–0.45)	0.23	(0.14–0.40)	0.713
Filtered load of ionised Mg; µmol/min	51	(41–66)	52	(30–71)	0.832
Filtered load of complexed Mg; µmol/min	25	(7–42)	29	(21–42)	0.478
Filtered load of total Mg; µmol/min	75	(49–98)	80	(55–96)	0.523
Ionised Mg excretion; µmol/min	1.5	(0.5–2.7)	1.3	(0.7–2.0)	0.713
Complexed Mg excretion; µmol/min	1.0	(0.3–1.7)	1.2	(0.6–1.8)	0.431
Mg excretion; µmol/min	2.5	(0.9–4.3)	1.5	(1.6–3.4)	0.958
Fractional excretion of ionised Mg; %	3.0	(0.8–5.4)	2.5	(1.4–2.9)	0.603
Fractional excretion of complexed Mg; %	4.0	(1.6–7.4)	4.2	(2.7–7.5)	0.846
Fractional excretion of total Mg, %	3.2	(1.0–5.0)	2.9	(1.9–3.8)	0.954

Tab. 4 Relative supersaturation products for calcium oxalate, brushite, and hydroxyapatite in recurrent calcium urolithiasis patients and controls, respectively. Mean values (range).

Relative supersaturation products of	n	Recurrent calcium urolithiasis	Controls	p-value
Calcium oxalate; ΔG*	12	1.5	2.2 (1.0–3.3)	0.083
Hydroxyapatite; ΔG	12	3.3	1.8 (−1.6–5.1)	0.133
Brushite; ΔG	12	−1.0	−0.9 (−3.5–0.5)	0.977

*: free energy (see l. c. (22))

the mean relative supersaturation product of brushite was comparable in recurrent calcium urolithiasis and controls.

Discussion

Current understanding of Mg status in recurrent calcium urolithiasis

We assessed the Mg status in male recurrent calcium urolithiasis patients, strictly matched with controls for age, weight, and body mass, and we included in the examination erythrocyte Mg, serum total Mg and its protein-bound, ultrafilterable, ionised, and complexed fractions, as well as ionic and complexed urinary Mg. Erythrocyte Mg was examined because Mg concentration in these cells is genetically controlled (26), and therefore is largely independent of intestinal Mg uptake and acute changes in extracellular Mg (see below). Furthermore, the Mg content of nuclei-containing skeletal muscle cells did not differ between renal stone patients and healthy controls (12). Thus, in the synopsis our data probably correctly reflect the Mg status during the chosen time segment of a daily cycle, viz., 2 hours in the morning, after a prior 12–15 hours nocturnal fast.

The frequency of recurrent calcium urolithiasis is greatest in the fourth and fifth decade of life (27), with a maximum around the age of 40 years. Our data on Mg demonstrate that even younger recurrent calcium urolithiasis patients exhibit signs of an impaired Mg status. This situation may have escaped detection by previous investigators, because age was not conceived as a possibly biasing factor (12, 13). Thus, in our laboratory, male normocalciuric patients older than 40 revealed similar tubular handling of Mg, yet there was no evidence of Mg deficiency in erythrocytes or serum (unpublished data); independency of blood cell and total serum Mg from age was also found for healthy humans (28). However, intestinal transport of Mg decreases with age, but is maintained at near normal levels at the expense of regulatory hyperparathyroidism (29), thereby masking the presence of a generalised abnormal Mg status.

Another reason for the discrepant data on the state of Mg, especially magnesiuria, in the literature (for review see l. c. (14)), may be sought in the degree of the associated calciuria. Thus, many hypercalciuric stone patients, who show a filtered load of Mg similar to that of normocalciuric stone patients, are unable to increase Mg reabsorption appropriately; consequently they excrete even more Mg than controls (unpublished data). Similar findings were reported by others who examined Mg in 4 h fasting urine and 24 h urine of renal calcium stone patients (30–33). In the present work three recurrent calcium urolithiasis patients were classified as having idiopathic hypercalciuria (see Materials and Methods); they were not omitted but instead further studied although all Mg values were at the upper limit of the range observed for the normocalciuric patients.

Magnesium in blood

In the literature the values of erythrocyte Mg in healthy controls are generally higher, probably due to the use of different methodology (22, 24). Erythrocyte Mg is determined during maturation of the erythrocytes in bone marrow (34). There are conflicting reports regarding the mobility of Mg in erythrocytes. While Mg in blood cells in general was found to represent a more mobile pool, in contrast to parenchymatous organs like the liver and probably the kidney (35), a recent report states that in human erythrocytes the transmembrane Mg fluxes are slowed (36).

Consistent with the latter view would be the absence of a correlation between erythrocyte Mg and serum or ultrafilterable Mg in both recurrent calcium urolithiasis and controls (see Results). Therefore, the decrease of erythrocyte Mg in recurrent calcium urolithiasis as a whole group may be due to a long-term Mg deficiency of the whole body, probably resulting from an inadequate supply of exogenous Mg rather than enhanced Mg losses (see also below). Mg depletion of food in Western civilisation is supected of being one cause of low serum total Mg (37), and our findings of low serum total and protein-bound Mg in recurrent calcium urolithiasis would be compatible with this view. Alternatively, low serum total Mg as a consequence of impaired intestinal Mg uptake in recurrent calcium urolithiasis deserves consideration, but its occurrence in the relatively young individuals studied by us is unlikely. It should be noted that although the protein-bound fraction of serum Mg is reduced in proportion to the low serum albumin (see tab. 1), it is not alone responsible for the low total Mg; to a

certain extent all serum fractions contribute to the deficit of total Mg (tab. 2). This situation is similar to that reported by others, in that changes of serum albumin within the normal limits did not account for changes of serum total Mg (38).

In controls, the mean value of ionised Mg was about 20 per cent lower than that reported by *Altura* and coworkers (25), although in the laboratory of these workers and our own the same Mg sensitive electrode was used. The reason for this discrepancy is not readily recognizable. However, the subjects studied by these workers were on average older [29 years (present work) vs 59, (25)] and their blood pH was an average higher [7.392 (present work) vs 7.465 (25)], suggesting that either an age-related increase of free ions in plasma, decreased complexation or protein-binding of ions, or some combination of these two effects was responsible (see below). As these authors (25) provided no further information on serum total protein, albumin, and citrate, the true state of ionised Mg, an important biological property, remains unclear. Free ionised Mg in plasma results from the balance of Mg bound to macromolecules and complexed by small molecules, such as citrate or fatty acids. In our recurrent calcium urolithiasis patients, albumin was low (tab. 1) and citrate was indistinguishable from controls (see Material and Methods), so that ionised Mg in recurrent calcium urolithiasis should not have been low – thereby contrasting with the values reported by other authors (25) – but should have remained normal or even high. Thus, from the available data, the factor underlying the mean lower concentration of serum ionised Mg in recurrent calcium urolithiasis is not discernable, but may in part reflect the mean higher Mg ion exretion via urine (see below, and tab. 3).

Renal function and Mg in recurrent calcium urolithiasis

Recurrent calcium urolithiasis patients exhibited a number of abnormalities so far not generally recognised (tab. 1; fig. 1). In fasting urine these abnormalities include hyperproteinuria, hyperglucosuria, less acidic pH, and a trend toward higher creatinine clearance and higher albuminuria. Hyperproteinuria and hyperglucosuria persist after correction for creatinine clearance (see tab. 3). These findings support the contention that some abnormality of the nephron, be it functional, morphological, or both, is present in recurrent calcium urolithiasis. In searching for the origin of these, a somewhat disordered Mg, or some other disorder not studied here, may be considered as the critical factor(s).

Dietary Mg deficit is discussed as causing abnormalities in blood lipids in the rat (39), and disturbances of lipids are a constant feature of kidney diseases in humans, especially glomerular lesions (40). Thus, lipid-induced but Mg-dependent injury of both glomeruli and tubules might exist in the recurrent calcium urolithiasis patients in the present work, and may have facilitated the appearance in urine of proteins, whose access to the tubular lumen is normally prevented by intact tissues. On the other hand, the composition and metabolism of lipids may be primarily altered in recurrent calcium urolithiasis (41); also alteration of lipids has been discussed as one possible cause of increased Mg retention, which itself reflects the body's need to conserve Mg (42). Work related to such possibilities is currently in progress in our laboratory.

With the technical tools presently available it is not feasible to probe in situ, i. e. inside renal tubular cells, the state of Mg, to determine the cytosolic free Mg ion concentration or the concentration of Mg bound to subcellular structures. If low erythrocyte Mg reflects low renal cell Mg, regardless of the aetiology of Mg deficit, then events adversely affecting intracellular processes may be the consequence. Cellular Mg deficiency would lead to impaired phosphorylation due to the uncoupling of Mg-substrate binding, thereby preventing the reaction of the complex with hexokinase (43, 44), the key enzyme in transmembrane flux of (phosphorylated) glucose. Thus, in our recurrent calcium urolithiasis patients without overt signs of diabetes and insulin deficiency, the increased glucosuria should arise from decreased glucose uptake by the luminal structures of proximal tubular cells. Moreover, inappropriately high phosphaturia, as was found in Mg-deficient rats devoid of parathyroid glands (45), should also occur in recurrent calcium urolithiasis with normal parathyroid gland function; in the long-term such a situation should lead to some degree of phosphate deficiency. In fact, the latter may be recognised in both the low phosphate of fasting serum (46) and low urinary phosphate (46, 47; this work); both of these phenomena are lesser known features of recurrent calcium urolithiasis, as is exaggerated phosphaturia in response to a carbohydrate- and calcium-rich test meal, i. e. during a postprandial period with calcium-induced suppression of the phosphaturic component of parathyroid hormone (48).

Mg deficiency causes increased oxidative stress to various tissues, reflected in an increased lipid peroxidation (49, 50). One of the manifestations of oxidative stress is injury to endothelial cells (49) and, if Mg deficiency is severe, loss of the integrity of unspecified renal cell membranes (50). The steep blood-lumen pH gradient normally achieved by proton secretion into the distal tubule is linked to the activity of a Mg^{2+} ATPase of the luminal membrane (51). Thus, impaired acidification of fasting urine in Mg-deficient males with recurrent calcium urolithiasis (table 1), already previously described by us (52), may reflect an inadequate enzyme activity due to renal tubular cell damage, hence dimin-

ished proton generation. Viewed together, these interrelationships appear to show that Mg deficit is a potential common denominator of several abnormalities seen in recurrent calcium urolithiasis.

Calcifications and Mg

In pre-lithotripsy patients we found that the surface of stones in situ is smaller in the presence of high urinary Mg ion concentration, and vice versa (53); however, these patients were older, and obesity and calciuria were not strictly controlled. In the present work, a role of Mg in the aetiology of crystals or stones remains uncertain, considering the unaltered Mg in urine (tab. 3), and the associated supersaturation products of calcium oxalate and brushite (tab. 4). However, the higher protein and the trend to higher albumin in urine of recurrent calcium urolithiasis may lend research interests into promising directions. Although the degree of hyperproteinuria is small, the finding is reminiscent of preclinical signs in human individuals at risk of developing atherosclerosis (see l. c. (53)) and non-insulin-dependent diabetes mellitus, the latter being frequently associated with a cellular Mg deficit (55). Several proteins bind calcium; hence, even a small excess of proteins and possibly albumin, which is a constituent of stone matrix (56), may help to glue crystals together. The diameter of such crystallised particles, not single crystals, determines whether obstruction of the tubular lumen and formation of microliths occur (57).

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