Transpl Int (2003) 16: 76–81
DOI 10.1007/s00147-002-0479-9

ORIGINAL ARTICLE

Brunello L. Mazzola
Simone D.P. Vannini
Anita C. Truttmann
Rodo O. von Vigier
Bendicht Wermuth
Paolo Ferrari
Mario G. Bianchetti

Long-term calcineurin inhibition and magnesium balance after renal transplantation

Received: 29 May 2001
Revised: 14 March 2002
Accepted: 22 August 2002
Published online: 14 January 2003

B.L. Mazzola · S.D.P. Vannini
A.C. Truttmann · R.O. von Vigier
M.G. Bianchetti (✉)
Division of Pediatric Nephrology,
University Hospital, 3010 Berne,
Switzerland
E-mail: mario.bianchetti@insel.ch

B.L. Mazzola · S.D.P. Vannini · P. Ferrari
Division of Nephrology,
University Hospital, Berne, Switzerland

B. Wermuth
Department of Clinical Chemistry,
University Hospital, Berne, Switzerland

Abstract Regulation of magnesium balance is achieved by a steady-state mechanism in which intake and output are maintained at an equal level. Dietary magnesium intake, total and ionized plasma magnesium levels, and urinary magnesium were assessed in 46 renal transplant recipients treated with cyclosporine, nine transplant recipients who had never been on cyclosporine, and 31 healthy volunteers. Dietary magnesium intake [13.5 (11.0–15.1) mmol/day vs 13.0 (11.1–16.0) mmol/day and 13.7 (11.4–16.7) mmol/day, respectively; median and interquartile range] and urinary magnesium excretion [4.31 (3.57–5.89) vs 4.39 (3.56–6.02) and 5.01 (3.73–6.01) mmol/day, respectively] were similar in renal transplant recipients treated with cyclosporine, transplant recipients who had never been on cyclosporine, and control subjects. Total [0.74 (0.70–0.78) vs 0.80 (0.74–0.84) and 0.81 (0.79–0.87) mmol/l], respectively] and ionized [0.49 (0.46–0.52) vs 0.53 (0.50–0.58) and 0.54 (0.52–0.59) mmol/l, respectively] plasma magnesium were significantly lower in renal transplant recipients on cyclosporine than in transplant recipients without cyclosporine, and healthy controls. These observations indicate a modified magnesium steady state in renal transplant recipients treated with cyclosporine.

Keywords Calcineurin · Cyclosporine · Kidney diseases · Magnesium deficiency · Organ transplantation

Introduction

Control of extracellular magnesium balance is achieved by urinary excretion of the amount that is absorbed, normally approximately one-third of nutritional magnesium. There are two major mechanisms through which hypomagnesemia can be induced: poor intestinal absorption (or low magnesium intake) and renal losses. The normal renal response to poor intestinal magnesium absorption or low magnesium intake is to lower magnesium excretion to very low levels. Consequently, the determination of urinary magnesium easily distinguishes renal from non-renal causes of hypomagnesemia, urinary magnesium being very low in patients with hypomagnesemia of extra-renal origin and inappropriately normal or increased in those with renal magnesium loss [1, 11, 20].

The use of the calcineurin inhibitors cyclosporine and tacrolimus is often associated with permanent and sometimes profound hypomagnesemia [2, 3, 4, 5, 6, 13, 14, 17]. Studies on renal handling of magnesium have hitherto been hindered by the use of circulating total magnesium concentration, which does not estimate the ultra-filterable fraction of circulating magnesium. Only recently have reliable techniques become available for the determination of ionized magnesium, that is, the main fraction of circulating magnesium available for glomerular filtration [16, 20, 21]. The

objective of this study was to assess dietary magnesium intake and its renal homeostasis in renal transplant recipients treated with the calcineurin inhibitor cyclosporine.

Patients and methods

Eligible for the study were the renal transplant recipients treated with cyclosporine on regular follow-up at the Division of Nephrology or at the Division of Pediatric Nephrology, University of Berne, Switzerland, who met the following criteria: stable functioning allografts for more than 12 months; circulating creatinine of less than 167 μmol/l; absent diabetes mellitus [21] (glycosylated hemoglobin A_{1c} of less than 0.057 and fasting plasma glucose of less than 6.10 mmol/l); no history of excessive alcohol intake [1, 11]; no treatment with any diuretic agent or supplementation with magnesium salts; and no recent (fewer than 8 weeks) urinary tract infection.

Forty-six patients (21 female, 25 male, aged between 16 and 76, median 45 years) entered the study between April and October 1999. Apart from cyclosporine micro-emulsion (Sandimmun; Neoral) b.i.d., the medication used for the patients is shown in Table 1. The subjects completed a 3-day food-intake record so that we could assess the amount of magnesium they consumed daily and provided urine over 24 h for determination of creatinine, phosphate, uric acid, calcium, magnesium, sodium, potassium, and chloride, and attended the outpatient clinic in the morning after approximately 10–12 h of fasting. Body weight, height, sitting blood pressure (first and fifth sound), and heart rate were measured, and venous blood specimens drawn anaerobically and without stasis for determination of hemoglobin, whole-blood cyclosporine, plasma creatinine, phosphate, uric acid, albumin, total magnesium, ionized calcium and magnesium, sodium, potassium, chloride, blood pH, and carbon dioxide pressure.

The protocol, except for the determination of cyclosporine level, was applied in two control groups. There were nine patients (seven female, two males aged 43 to 75, median 64 years) with renal transplants performed before 1987 who had never been on cyclosporine, and 31 healthy volunteers (14 female, 17 male, aged 21 to 52, median 29 years). The medication used for the renal transplant recipients without cyclosporine is given in Table 1.

The study was performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki and was authorized by the hospital's ethical committee. Informed written consent was obtained from the participants. All measurements were performed in duplicate. The whole-blood cyclosporine trough level was measured by specific monoclonal fluorescent polarization immunoassay [22]. Hemoglobin (sodium lauryl sulfate assay), creatinine (kinetic alkaline picrate assay), uric acid (allantoin-uricase assay), inorganic phosphate (ammonium molybdate reduction assay), albumin (bromocresol-purple assay), total magnesium (xylidil-blue assay), and urinary calcium (cresolphthalein complexone assay) were measured colorimetrically with an automated analyzer. Direct ion-selective electrodes were used for the measurement of pH, carbon dioxide pressure, sodium, potassium, chloride, and ionized calcium and magnesium. Ionized magnesium was determined in silicone-free tubes (heparin 1,000 units/l) using a magnesium electrode (ETH 7025), which had been characterized by this and other laboratories [16, 20, 21]. Dietary magnesium intake was calculated from Swiss food-composition tables and data obtained from the local industry, as previously reported [16].

We used plasma and urinary creatinine levels to calculate the glomerular filtration rate, and plasma and urinary electrolyte concentrations and creatinine levels to calculate the fractional clearance, using standard equations. We used urinary magnesium (U_{Mg}) and plasma and urinary creatinine (P_{Cr}, U_{Cr}) concentrations to calculate the excretion of magnesium corrected for glomerular filtration rate using the following equation:

$$\frac{U_{Mg} \times P_{Cr}}{U_{Cr}}$$

The clearance of magnesium and calcium was calculated from their plasma ionized concentrations. The maximal tubular re-absorption of phosphate was calculated from plasma (P_{Ph}) or urinary (U_{Ph}) phosphate and P_{Cr} or U_{Cr} as follows [8]:

$$P_{Ph} - \left(\frac{U_{Ph} \times P_{Cr}}{U_{Cr}}\right)$$

We used blood pH and carbon dioxide pressure to calculate plasma bicarbonate, using the Henderson-Hasselbach equation. The two-tailed Kruskal-Wallis test (non-parametric analysis of variance for independent samples) with the Bonferroni adjustment and simple regressions with the non-parametric coefficient of determination r_s^2 were used for analysis. Significance was assumed for P values of below 0.05. The results are given as median and interquartile range, which extends from the value at centile 25 to that at centile 75 and includes half of the data points.

Table 1 Medication other than cyclosporine b.i.d. given to 46 renal transplant patients with cyclosporine and to the control group of 9 renal transplant patients without cyclosporine. None of the 55 patients was on treatment with diuretics

Medication	Patients with cyclosporine	Patients without cyclosporine
Immunosuppressive agents		
Azathioprine	22	9
Mofetil mycophenolate	1	–
Prednisone	37[a]	9[b]
Cardiovascular drugs		
β-adrenergic antagonists	24	6
Calcium channel blockers	22	4
Converting enzyme inhibitors	14	3
Lipid-lowering drugs	4	2
Sedatives	5	3

[a]Dose ranging between 0.02 and 0.30 (median 0.09) mg/kg daily
[b]Dose ranging between 0.13 and 0.22 (median 0.14) mg/kg daily

Results

Basal data for the group of renal transplant recipients treated with the calcineurin inhibitor cyclosporine and for the two control groups are shown in Table 2. The group of transplant recipients treated with cyclosporine was studied 1.3–14 years, median 5.0 years, after transplantation; that of the transplant recipients without cyclosporine, 13–21 years, median 17 years, after transplantation ($P < 0.01$). For the patients on calcineurin inhibition, the cyclosporine dosage was 3.6 (2.2–4.4) mg/kg body weight daily, and the whole-blood concentration was 135 (110–148) μg/l.

The group of renal transplant recipients given cyclosporine and the two control groups did not significantly differ with respect to heart rate, circulating

Table 2 Basal data in renal transplant recipients treated with cyclosporine and in the two control groups. Results are given as median (interquartile range)

Characteristic	With cyclosporine	Without cyclosporine	Healthy subjects
Body weight; kg	62[a] (55–73)	70 (55–80)	74 (64–79)
Body height; m	1.70[b] (1.60–1.76)	1.62 (1.58–1.65)	1.81 (1.74–1.87)
Blood pressure; mmHg	128[b,e] (121–143)/83[b] (76–87)	140 (129–148)/90 (83–94)	120 (106–126)/71 (61–77)
Heart rate; /min	64 (62–70)	70 (60–76)	62 (60–72)
Hemoglobin; g/l	126[c] (114–137)	141 (135–151)	144 (139–150)
Plasma albumin; g/l	38[b] (37–40)	38 (36–39)	43 (41–45)
Plasma creatinine; μmol/l	126[c] (109–138)	100 (96–112)	92 (78–98)
Glomerular filtration rate; ml/(min×1.73 m^2)	83[c] (70–98)	98 (74–102)	123 (102–147)
Plasma uric acid; μmol/l	415[d] (360–474)	331 (303–387)	256 (210–291)
Plasma phosphate; mmol/l	1.25 (1.19–1.34)	1.28 (1.19–1.45)	1.27 (1.20–1.35)
Plasma sodium; mmol/l	141 (139–142)	140 (139–142)	140 (138–141)
Plasma potassium; mmol/l	4.29[d] (3.98–4.62)	4.02 (3.72–4.27)	4.0 (3.78–4.25)
Plasma chloride; mmol/l	105 (103–106)	105 (101–107)	104 (102–106)
Plasma total magnesium; mmol/l	0.74[c] (0.70–0.78)	0.80 (0.74–0.84)	0.81 (0.79–0.87)
Plasma ionized magnesium; mmol/l	0.49[c] (0.46–0.52)	0.53 (0.50–0.58)	0.54 (0.52–0.59)
Plasma ionized calcium; mmol/l	1.25 (1.22–1.29)	1.27 (1.25–1.29)	1.26 (1.24–1.29)
Plasma bicarbonate; mmol/l	24.5 (22.2–25.7)	25.5 (23.1–26.5)	26.4 (25.4–27.4)

[a] $P < 0.01$ vs healthy subjects
[b] $P < 0.05$ vs healthy subjects
[c] $P < 0.01$ vs renal transplant patients without cyclosporine and healthy subjects
[d] $P < 0.05$ vs renal transplant patients without cyclosporine and healthy subjects
[e] $P < 0.05$ vs renal transplant patients without cyclosporine

sodium, phosphate and calcium, and acid–base balance. Body weight, hemoglobin, the glomerular filtration rate, and total and ionized magnesium were significantly lower, and circulating creatinine, uric acid, and potassium higher, in renal transplant recipients on cyclosporine than in the two control groups. Blood pressure was significantly higher, and height and plasma albumin lower in renal transplant recipients on cyclosporine than in healthy controls. Body height was significantly higher, and body weight and blood pressure lower in patients with cyclosporine than in those without.

Information on renal tubule function and dietary magnesium is given in Table 3. Dietary magnesium intake and the 24-h urinary excretion of uric acid, phosphate, sodium, potassium, chloride, magnesium, and calcium were not statistically different in the three study groups. The fractional clearance of sodium, potassium, chloride, magnesium, and calcium was significantly higher in transplant recipients on cyclosporine than in healthy subjects. The maximal tubular phosphate reabsorption was significantly lower in transplant patients on cyclosporine than in the two control groups.

In transplant recipients on cyclosporine, no significant correlation was noted between circulating magnesium, either ionized or total, and the cyclosporine dosage or concentration. Furthermore, in the three study groups no correlation was noted between circulating magnesium and circulating creatinine, glomerular filtration rate, or age. The relationship between plasma ionized magnesium and the urinary excretion of this ion corrected for 1-l glomerular filtration rate is given in Fig. 1.

Discussion

In contrast to other ions, magnesium is treated by the body as an orphan: there are no known hormones that modulate U_{Mg} excretion, and bone, the principle reservoir of magnesium, does not readily exchange with circulating magnesium. The inability readily to mobilize magnesium stores means that, with negative magnesium balance, the losses primarily come from the extracellular fluid. Thus, circulating magnesium levels tend to fall with negative magnesium balance, leading to a marked reduction in U_{Mg} excretion unless U_{Mg} wasting is present [1, 11, 20]. In this study, the use of cyclosporine was associated with permanent and sometimes profound hypomagnesemia [2, 3, 4, 5, 6, 13, 14, 17]. Furthermore, dietary and U_{Mg} were similar in renal transplant patients treated with cyclosporine and in controls. It is therefore concluded that renal losses account for the tendency towards hypomagnesemia noted in renal transplant recipients treated with this calcineurin inhibitor.

The group of healthy subjects included in this study was younger than the groups of patients with or without cyclosporine. It might be argued that magnesium balance varies with age, but in the present study no significant correlation was noted between age and magnesium balance, either in patients or in control subjects, as previously reported for healthy subjects aged 10 to 75 years [23].

Circulating magnesium is present in three different states: ionized, bound to albumin, or complexed to phosphate, citrate, and other anions. The measurement

Table 3 Renal tubule function and dietary magnesium intake in renal transplant recipients treated with cyclosporine and in the two control groups. Results are given as median (interquartile range)

Parameter	Renal transplant recipients with cyclosporine	Renal transplant recipients without cyclosporine	Healthy subjects
Uric acid			
Excretion; mmol/day	2.68 (1.99–3.72)	2.78 (1.87–3.67)	2.89 (2.00–3.83)
Fractional clearance; 10^{-2}	8.51 (6.56–11.9)	10.5 (6.43–15.1)	7.36 (4.20–10.1)
Phosphate			
Excretion; mmol/day	38.9 (30.8–48.3)	35.7 (28.7–41.8)	40.6 (31.8–51.2)
Maximal tubular re-absorption; mmol/l	0.80[a] (0.63–0.89)	0.90 (0.71–1.09)	0.89 (0.83–1.05)
Sodium			
Excretion; mmol/day	168 (129–204)	176 (142–212)	169 (138–198)
Fractional clearance; 10^{-2}	1.40* (1.12–2.03)	1.40 (1.05–1.90)	0.91 (0.78–1.32)
Potassium			
Excretion; mmol/day	86 (76–121)	92 (62–103)	86 (77–121)
Fractional clearance; 10^{-2}	25.9* (19.8–37.9)	21.3 (17.5–33.6)	18.9 (14.1–23.5)
Chloride			
Excretion; mmol/day	156 (127–192)	170 (150–205)	159 (133–194)
Fractional clearance; 10^{-2}	1.72* (1.45–2.53)	1.83 (1.39–2.59)	1.24 (0.98–1.59)
Magnesium			
Intake; mmol/day	13.5 (11.0–15.1)	13.0 (11.1–16.0)	13.7 (11.4–16.7)
Excretion; mmol/day	4.31 (3.57–5.89)	4.39 (3.56–6.02)	5.01 (3.73–6.01)
Fractional clearance; 10^{-2}	11.6** (8.77–14.5)	7.65 (5.97–11.8)	6.75 (5.12–8.33)
Calcium			
Excretion; mmol/day	4.01 (2.94–4.40)	3.83 (2.89–4.70)	4.19 (2.91–4.68)
Fractional clearance; 10^{-2}	3.66** (2.74–4.4)	3.32 (2.47–4.32)	2.62 (1.87–3.00)

*$P < 0.01$, **$P < 0.05$ vs healthy subjects
[a]$P < 0.05$ vs renal transplant patients without cyclosporine and healthy subjects

of total circulating magnesium does not provide an estimate for the fraction available for glomerular filtration [14, 16, 20, 21]. In the present study, the key to advancing knowledge about renal magnesium handling in transplant recipients given calcineurin antagonists was that both total and ionized circulating magnesium were assessed [20].

In renal transplant recipients some further causes of hypomagnesemia deserve mention, including the use of diuretics, diabetes mellitus, excessive alcohol intake, and aldosteronism [1, 11, 20, 21]. In the present study, cyclosporine patients treated with diuretics, and those with diabetes mellitus or a history of alcohol abuse were excluded. Furthermore, we failed to disclose signs consistent with aldosteronism, as indicated by plasma and urinary potassium [19].

Renal function was moderately reduced in transplant recipients given cyclosporine, suggesting a possible association between the tendency towards hypomagnesemia and decreased renal function. No correlation between renal function and circulating magnesium was noted in our transplant recipients treated with cyclosporine. In addition, the literature demonstrates that moderately reduced renal function slightly decreases magnesium excretion [10]. In conclusion, the present data concur with those of the literature, demonstrating that cyclosporine induces hypomagnesemia by mechanisms unrelated to the glomerular filtration rate [1, 11, 20].

The present study did not address the renal site of action and the molecular mechanism of the pro-magnesiuric effect of calcineurin inhibitors. The re-absorption of magnesium predominantly occurs by para-cellular diffusion in the thick ascending loop of

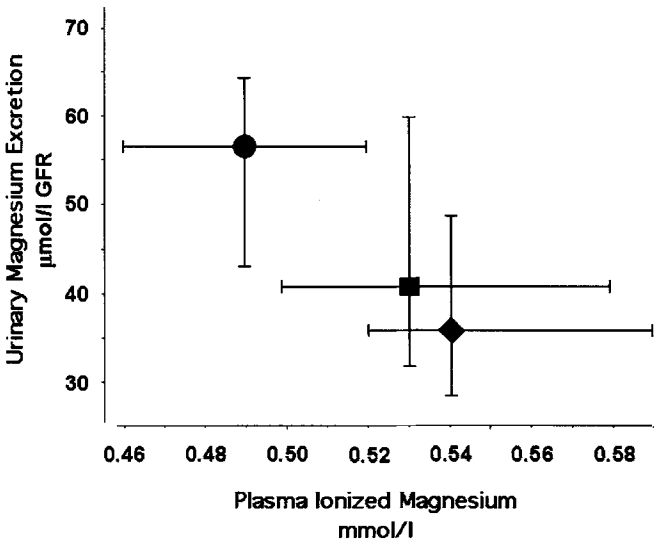

Fig. 1 Relationship between plasma ionized magnesium and its corrected urinary excretion in transplant recipients treated with (*circle*) or without (*square*) cyclosporine and in healthy subjects (*diamond*). The medians and the interquartile ranges are given. Plasma ionized magnesium levels were significantly lower ($P < 0.01$) in transplant recipients treated with cyclosporine than in transplant recipients without cyclosporine and in healthy subjects. The corrected U_{Mg} excretion was not statistically different in the three study groups (*GFR* glomerular filtration rate)

Henle [1, 11]. Loop diuretics produce hypomagnesemia but do not exacerbate the pro-magnesiuric effect of calcineurin inhibitors, suggesting a similar site of action [5]. These diuretics bind to the apical sodium–potassium-chloride co-transporter of the thick ascending loop of Henle and inhibit the generation of a lumen-positive gradient, that is, the driving force for the para-cellular re-absorption of magnesium [1, 5, 11]. Calcineurin inhibitors indirectly block the basolateral sodium–potassium pump in the loop, a further possible cause of a lumen-positive gradient, the aforementioned driving force for magnesium re-absorption [5]. It has therefore been assumed that both calcineurin inhibitors and loop diuretics decrease the para-cellular magnesium re-absorption in the thick ascending loop of Henle by inhibiting the generation of a lumen-positive gradient [5]. Circulating magnesium is mostly normal in patients lacking the apical sodium–potassium-chloride transporter [11]. Hence, the assumption remains unproved and deserves further confirmation.

This study confirms that calcineurin inhibitors impair renal potassium excretion in renal transplant recipients. Impaired potassium excretion induced by calcineurin antagonists is related to some degree of hypo-aldosteronism and defective electrochemical driving force for potassium secretion. Furthermore, these drugs decrease the activity of the basolateral sodium–potassium pump and that of the potassium channels in the principal cell of the distal nephron [19]. In addition, the study confirms that calcineurin inhibitors cause hyperuricemia. The specific mechanisms underlying this phenomenon are unknown [9, 15]. Experimental studies demonstrate ongoing phosphaturia in magnesium depletion. Metabolic alkalosis and hypokalemia are further causes of renal phosphate leakage that were not observed in our patients. These data, taken together with the observation that cyclosporine does not directly influence renal phosphate handling, support the assumption that magnesium depletion accounts for the tendency towards the decreased maximal tubular re-absorption of phosphate noted in our renal transplant recipients given cyclosporine [12, 15].

These results have substantial implications. Magnesium depletion is involved in settings such as arterial hypertension, cardiac arrhythmia, thrombosis, and atherosclerosis, which occur to an increased extent among renal transplant recipients. Apart from that, magnesium depletion is a risk factor for cyclosporine neurotoxicity [1, 15, 20].

We feel that the present observations document a phenomenon of steady state. U_{Mg} wasting caused by cyclosporine is initially associated with excretion exceeding intake. As the plasma magnesium level falls, the anti-magnesiuric effect of hypomagnesemia gradually lowers magnesium excretion until intake and output are again equal. At this point, the plasma magnesium concentration remains stable, although at a value below normal. Correcting the hypomagnesemia with magnesium supplements will partially remove the stimulus to magnesium retention, and most of the administered magnesium will be excreted in the urine, thereby limiting the degree to which the plasma magnesium concentration will rise. This fact, taken together with the poor intestinal absorption of magnesium and the associated potential of magnesium to produce diarrhea, accounts for the unsatisfactory effect of magnesium supplementation in this setting [7, 16, 18]. In conclusion, the study demonstrates that the most important cause of hypomagnesemia in renal transplant recipients given calcineurin antagonists is renal [5, 6].

References

1. Agus ZS (1999) Hypomagnesemia. J Am Soc Nephrol 10:1616–1622
2. Al-Khursany I, Thomas TH, Harrison K, Wilkinson R (1992) Reduced erythrocyte and leukocyte magnesium is associated with cyclosporin treatment and hypertension in renal transplant patients. Nephrol Dial Transplant 7:251–255
3. Allegra A, Corica F, Ientile R, Corsonello A, Sparacino V, Accettola F, Caputo F, Macaione S, Buemi M (1998) Plasma (total and ionized), erythrocyte and platelet magnesium levels in renal transplant recipients during cyclosporine and/or azathioprine treatment. Magnes Res 11:11–18
4. Almawi WY, Melemedjian OK (2000) Clinical and mechanistic differences between tacrolimus and cyclosporin A. Nephrol Dial Transplant 15:1916–1918
5. Arthur JM, Shamim S (2000) Interaction of cyclosporine and tacrolimus with diuretics in transplant recipients. Kidney Int 58:325–330
6. Barton CH, Vaziri ND, Martin DC, Choi S, Alikhani S (1986) Hypomagnesemia and renal magnesium wasting in renal transplant recipients receiving cyclosporine. Am J Med 83:693–699
7. Bettinelli A, Basilico E, Metta MG, Borella P, Jaeger P, Bianchetti MG (1999) Magnesium supplementation in Gitelman syndrome. Pediatr Nephrol 13:311–314
8. Brodhel J, Krause A, Hoyer PF (1988) Assessment of maximal tubular phosphate reabsorption: comparison of direct measurement with the nomogram of Bijvoet. Pediatr Nephrol 2:183–189
9. Clive DM (2000) Renal transplant-associated hyperuricemia and gout. J Am Soc Nephrol 11:974–979
10. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR (1969) The physiochemical state and renal handling of divalent ions in chronic renal failure. Arch Intern Med 124:302–311
11. Cole DA, Quamme GA (2000) Inherited disorders of renal magnesium handling. J Am Soc Nephrol 11:1937–1947
12. Katopodis K, Elisaf M, Siamopoulos KC (1996) Hypophosphatemia in a patient with Gitelman's syndrome. Nephrol Dial Transplant 11:2090–2092
13. Kim HJ, Ahn YH, Kee CS, Lee KS, Kwak JY (1994) Early short-term profile of serum magnesium in living donor renal transplant recipients on cyclosporine. Transplant Proc 26:2178–2180
14. Markell MS, Altura BT, Sarn Y, Barbour R, Friedman EA, Altura BM (1993) Relationship between ionized magnesium and cyclosporine level in renal transplant recipients. Ann N Y Acad Sci 696:408–411
15. Mason J (1990) The pathophysiology of cyclosporine in man and animals. Pediatr Nephrol 4:554–574, 686–704
16. Mullis P, Bianchetti MG (1998) High fiber diets may be responsible for hypomagnesaemia in diabetic patients. Nephron 78:238–239
17. Niederstadt C, Steinhoff J, Erbsloh-Moller B, Renner F, Sack K, Rob PM (1997) Effect of tacrolimus on magnesium homeostasis after renal transplantation. Transplant Proc 29:3161–3162
18. Oster JR, Epstein M (1988) Management of magnesium depletion. Am J Nephrol 8:349–354
19. Perazella MA (2000) Drug-induced hyperkalemia: old culprits and new offenders. Am J Med 109:307–314
20. Truttmann AC, Bettinelli A, Bianchetti MG (1997) Métabolisme du magnésium pour le clinicien: une mise au point actuelle et simple. Med Hyg 55:551–553
21. Vannini SDP, Mazzola BL, Rodoni L, Truttmann AC, Wermuth B, Bianchetti MG, Ferrari P (1999) Permanently reduced plasma ionized magnesium among renal transplant recipients on cyclosporine. Transpl Int 12:244–249
22. Wang P, Meucci V, Simpson E, Morrison M, Lunetta S, Zajac M, Boeckx R (1990) A monoclonal antibody fluorescent polarization imunoasssay for cyclosporine. Transplant Proc 22: 1186–1188
23. Yang XY, Hosseini JM, Ruddel ME, Elin RJ (1990) Blood magnesium parameters do not differ with age. J Am Coll Nutr 9:308–313