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ORIGINAL ARTICLE

Proton-pump inhibitors do not influence serum magnesium levels in renal transplant recipients

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Abstract Severe hypomagnesemia has been reported with use of proton-pump inhibitors (PPIs). We assessed the effect, if any, of PPI use on serum magnesium level in a cross-sectional analysis of a large published cohort of renal transplant recipients (RTRs). Between February 2004 and February 2006, 512 consecutive prevalent RTRs were enrolled at two university hospitals in Belgium (Brussels and Ghent). Serum creatinine was 1.5 ± 0.7 mg/dl, and estimated glomerular filtration rate (eGFR) 53 ± 19 ml/min/1.73 m^2. Mean (and median) magnesium level was 1.91 ± 0.23 mg/dl. PPIs were prescribed in 20 % (n = 101) of cases. At multivariable analysis, PPI use was not an independent predictor of serum magnesium level or hypomagnesemia. The independent predictors of a lower serum magnesium level were the use of tacrolimus, cyclosporin and sirolimus, the absence of use of mycophenolate mofetil, lower levels of parathyroid hormone and higher eGFR. This study is the first to analyze the potential impact of PPIs on magnesium level in a large, representative cohort of RTR patients. Our results suggest that PPIs may be used without particular fear of favoring hypomagnesemia-related side effects in RTRs, an important finding in a population at high risk of hypomagnesemia.

Keywords Hypomagnesemia · Kidney transplantation · Magnesium · Proton-pump inhibitor

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Introduction

Hypomagnesemia is common, with an estimated prevalence in the general population ranging from 2.5 to 15 %. It may result from inadequate intake (alcoholism, malnutrition, etc.), decreased gastrointestinal absorption, increased renal loss or redistribution from extracellular to intracellular space. Proton-pump inhibitors (PPIs) are commonly prescribed for prolonged periods for peptic ulcer disease, gastroduodenitis and gastro-esophageal reflux disease. They have a good safety profile, although severe hypomagnesemia was reported by Epstein et al. [1] in 2006 for the first time. Approximately 40 cases of hypomagnesemia from PPI use have been reported [1–10].

The mechanism of PPI-induced hypomagnesemia remains unclear [3, 4, 6, 10]. Urinary magnesium (Mg) levels and fractional magnesium excretion are generally low suggesting a defect in intestinal absorption of magnesium or increased losses into the gut [1, 4, 5, 7, 9]. In the small intestine, there are two major pathways for magnesium absorption: a transcellular active transport operating through the transient receptor protein channel family member, TRPM6, and a paracellular passive transport modulated by the tight junction proteins claudin-16 and claudin-19 [4, 14]. In some published cases, hypomagnesemia was partially corrected by high-dose oral magnesium supplements [1, 4]. This suggests that the passive magnesium transport was intact, and that PPI impaired TRPM6 function, perhaps as a result of the higher pH of the bowel. Another hypothesis is that hypomagnesemia develops in patients heterozygous for mutations in the TRPM6 gene [4, 8]. However, these hypotheses remain unproven.

The prevalence and risk factors of PPI-induced hypomagnesemia are poorly defined [8, 10]. The purpose of our study was thus to assess the effect, if any, of PPI use on

serum magnesium levels in a cross-sectional analysis of a large published cohort of renal transplant recipients (RTRs) [11]. We aimed at establishing or rejecting a potential role of PPI use as an independent predictor of serum magnesium levels and of hypomagnesemia in this population.

Materials and methods

Patients

As detailed elsewhere [11], the study was conducted at two university hospitals in the Belgian cities of Brussels and Ghent. Consecutive prevalent RTRs with a functional graft attending the outpatient clinics of the Cliniques Universitaires Saint-Luc (Brussels) and the Ghent University Hospital (Ghent) for periodic evaluation between February 1, 2004, and January 31, 2006, were eligible for the study. Inclusion criteria were age $\geq$18 years and time after transplantation $\geq$3 months. Combined organ transplants and patients under treatment for malignancy (except non-metastatic cutaneous cancers) were excluded.

The study was approved by the local research ethics committees, and written informed consent was obtained from each participant.

Laboratory measurements

Serum levels of magnesium, creatinine, calcium, phosphorus, hemoglobin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and intact parathyroid hormone (iPTH) were measured using standard methodology.

The two laboratories had slightly different values for the normal range of magnesium level (lower limit of normal magnesium level 1.74 mg/dl at Brussels lab and 1.70 mg/dl at Ghent lab). Hypomagnesemia was defined as a Mg serum level <1.7 mg/dl. In order to make sure that the slight difference in the normal range did not impact the results, we performed a sensitivity analysis converting the values provided by the Brussels lab as 1.7/1.74* (Brussels Mg level).

Diabetes was defined according to the American Diabetes Association (ADA) criteria or intake of antidiabetic drugs. The glomerular filtration rate (GFR) was estimated (eGFR) by the abbreviated Modification of diet in renal disease (MDRD) equation. Hypertension was defined as a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg or the intake of antihypertensive drugs.

Statistical analysis

Data are presented as means, medians, or percentages, as appropriate. Univariate analysis was performed using Pearson's cross product correlation, t test, and χ^2 test when applicable. All variables reaching the $p < 0.2$ level at univariate analysis entered the multivariable models. Multiple stepwise linear regression was used to assess significant determinants of magnesemia. Logistic regression was used to identify the determinants of hypomagnesemia. The Hosmer–Lemeshow test was used to assess the goodness of fit in the logistic regression model.

Predictor variables included the following relevant demographic, anthropometric, hemodynamic and biochemical variables: age, gender, height, weight, body mass index (BMI), race, smoking status, diabetes, time since transplantation, time spent on dialysis, hemoglobin, creatinine, eGFR, serum levels of Ca, P, PTH, C-reactive protein (CRP), total cholesterol, HDL cholesterol, and mean arterial pressure (MAP). Additionally, treatment with PPIs, angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, calcium channel blockers, statins, antiplatelet agents, vitamin D substitution, Ca supplements, corticosteroids, tacrolimus, cyclosporin, sirolimus, mycophenolate mofetil (MMF) and azathioprine were also included in the regression analysis to assess their potential confounding effect.

The existence of an interaction between PPI use and diuretic use with a potential impact on the level of Mg was tested by introducing, in the multiple regression analysis, a multiplicative term between PPI and diuretic use, in addition to the use of each class separately.

Data were analyzed using PASW software. All tests were two-tailed, and a $p < 0.05$ was considered as significant.

Results

Patient characteristics

The demographic characteristics of the cohort were reported earlier [11]. Briefly, between February 2004 and February 2006, 512 RTRs were included. The population was 98 % Caucasian, 59 % male, aged 53 $\pm$ 13 years and time since transplant was 92 $\pm$ 79 months. Comorbidities included hypertension in 433 cases (85 %), diabetes in 79 (15 %) (type 1 in 6, type 2 in 73) and a history of cardiovascular (CV) events in 160 (31 %). Maintenance immunosuppressive regimens consisted of various combinations of azathioprine (25 %), MMF (55 %), cyclosporin (47 %), tacrolimus (35 %), and sirolimus (12 %). Steroids were part of the immunosuppressive regimen at inclusion in 84 % of patients. Antihypertensive drugs included angiotensin receptor

Table 1 Univariate analysis of the determinants of magnesium level

Variables	Mean ± SD or %	r with Mg	p
Age (years)	53 ± 13	0.06	0.18
Diabetes	15		0.11
Time of transplantation (months)	92 ± 79	0.14	0.002
Creatinine (mg/dl)	1.5 ± 0.7	0.13	0.004
eGFR (ml/min/1.73 m^2)	53 ± 19	−0.15	<0.001
CRP (mg/dl)	0.49 ± 0.86	−0.07	0.096
Total cholesterol (mg/dl)	208 ± 42	0.09	0.04
Phosphate (mg/dl)	3.1 ± 0.7	0.13	0.005
PTH (pg/ml)	73 ± 83	0.17	<0.001
Hemoglobin (g/dl)	13 ± 2	−0.11	0.02
Tacrolimus	35		<0.01
Cyclosporin	44		0.012
Sirolimus	12		0.10
Mycophenolate mofetil	55		0.02
Azathioprine	25		0.12
Angiotensin receptor blockers/ ACE inhibitors	64		0.12
Statins	41		0.16
Vitamin D	39		0.03
Ca supplements	50		0.08
PPI	20		0.31

Mg magnesium, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *PTH* parathyroid hormone, *ACE* angiotensin-converting enzyme, *Ca* calcium, *PPI* proton-pump inhibitor

blockers and/or ACE inhibitors in 64 % (n = 327), diuretics in 25 % (n = 128), beta-blockers in 42 % (n = 217), and calcium channel blockers in 32 % (n = 166). Proton-pump inhibitors were prescribed in 20 % of patients (n = 101), statins in 41 % (n = 210), antiplatelet agents in 7 % (n = 39) and vitamin D substitution in 39 % (n = 199). Serum creatinine was 1.5 ± 0.7 mg/dl (eGFR 53 ± 19 ml/min/1.73 m^2). Mean (and median) magnesium level was 1.91 ± 0.23 mg/dl.

Univariate analysis of the determinants of magnesium level

A positive significant correlation was found between serum magnesium level and time since transplantation, creatinine, total cholesterol, phosphate and PTH levels as well as MMF treatment. A negative correlation was observed with hemoglobin levels, tacrolimus and cyclosporin treatment as well as the intake of vitamin D supplements.

No significant association was observed between magnesium level and gender, age, history of diabetes or CV events, use of PPIs, diuretics, beta-blockers, calcium supplements and statins (Table 1).

Table 2 Multivariable regression analysis of the determinants of magnesium level

Factors	b	95 % CI	p
Tacrolimus	−0.38	−0.45; −0.03	<0.001
Cyclosporin	−0.22	−0.29; −0.15	<0.001
eGFR	−0.003	−0.004; −0.002	<0.001
PTH	0.001	0.00; 0.001	0.001
Sirolimus	−0.15	−0.23; −0.07	<0.001
Mycophenolate mofetil	0.05	0.008; 0.009	0.03
PPI	−0.02	−0.07; 0.03	0.47

CI confidence interval, *eGFR* estimated glomerular filtration rate, *PTH* parathyroid hormone, *PPI* proton-pump inhibitor

Table 3 Logistic regression analysis of the determinants of hypomagnesemia

Factors	Exp(B)	95 % CI	p
Hemoglobin	0.72	0.54; 0.97	0.03
Tacrolimus	4.62	1.75; 12.22	0.002
Vitamin D substitution	4.29	1.51; 12.20	0.006
eGFR	1.03	1.01–1.05	0.008
PPI	−0.84	0.26; 2.71	0.78

CI confidence interval, *eGFR* estimated glomerular filtration rate, *PPI* proton-pump inhibitor

Multivariable regression analysis of the determinants of magnesium level

At multiple linear regression, the independent predictors of a low magnesium level were the use of tacrolimus, cyclosporin and sirolimus, the absence of use of MMF, low levels of PTH and high eGFR. Proton-pump inhibitors intake was not an independent predictor of magnesium level (Table 2).

In addition, there was no statistical interaction (p: 0.87) between diuretic use and PPI use regarding the impact on serum magnesium concentration.

We further analyzed the predictors of hypomagnesemia at univariate, then multivariable logistic regression analysis. The results were quite consistent with the multiple linear regression and the trends identical although cyclosporin was not a predictor of hypomagnesemia (Table 3).

The sensitivity analysis accounting for the slight difference in the lower limit of the normal range of Mg level did not modify the above mentioned results.

Discussion

To the best of our knowledge, this study is the first to analyze the potential impact of PPIs on Mg level in a large,

representative cohort of RTR patients. Proton-pump inhibitors were taken by 20 % of patients and PPI use was not an independent predictor of serum magnesium level or hypomagnesemia. Our results thus suggest that PPI may be used without particular fear of favoring hypomagnesemia-related side effects in RTRs, an important finding in a population at high risk of hypomagnesemia. This study indeed confirms that hypomagnesemia is very common (20 %) in a Caucasian renal transplant population, more so than in the general population (2.5 to 15 %).

The independent predictors of a low magnesium level in our RTR cohort included the use of both tacrolimus and cyclosporin, or sirolimus, a high eGFR and a low PTH level.

Hypomagnesemia is a well-known side effect of tacrolimus, cyclosporin and sirolimus treatment, resulting from renal magnesium wasting [15–22]. Calcineurin inhibitor (CNI) treatment induces hypomagnesemia through a decreased expression of TRPM6, a channel kinase involved in active transcellular Mg transport in the kidney [22, 23]. In some studies, the magnesium level is lower in patients under tacrolimus than under cyclosporin treatment [24]. Sirolimus treatment has been shown to decrease the expression of NKCC2, the main sodium transporter in the thick ascending limb. By decreasing the NaCl transport, sirolimus probably affects the transepithelial voltage and thus the passive transport of magnesium, thereby accounting for the increased urinary excretion of sodium, potassium, and magnesium [25]. The relationship between MMF and magnesium level is less obvious. One study [26] analyzed the effect of MMF on plasma bioelements and found a positive correlation between magnesium plasma concentrations and mycophenolic acid (MPA) pharmacokinetic parameters, suggesting that higher exposure to MMF might increase Mg level, although causality may not be claimed in this cross-sectional observational study. It might result from higher dosages of CNI (leading to hypomagnesemia) in those without MMF. Clearly the impact, if any, of MMF on Mg level requires further study.

Renal function is also a classical determinant of magnesium serum level. Indeed, magnesium is largely eliminated by the kidney [27]. The relationship between magnesium and PTH levels is also well-known [28–30]. Severe hypomagnesemia induces both impaired PTH secretion and end-organ resistance to PTH.

Four other cohort studies very recently investigated the relationship between PPI use and hypomagnesemia. All of them included patients at the time of hospital admission or during hospital stay, in contrast to our outpatient cohort of RTRs. The first one [12] analyzed magnesium level in 487 patients aged 50 years or older and detected a moderately lower serum magnesium [PPI users: 1.91 (standard deviation (SD) 0.34) mg/dl versus 2.00 (0.30) mg/dl in non users; $p = 0.004$] and an increased risk of hypomagnesemia in PPI users [adjusted odds ratio (OR) = 2.50, 95 % confidence interval (CI) 1.43–4.36] after adjusting for confounders. The second one [13] screened 196 patients aged 65 years and older who were admitted to a Geriatric unit. In that study, patients with a GFR <60 ml/min/1.73 m^2 who were taking a PPI had significantly lower magnesium concentrations than those not taking a PPI (1.97 versus 2.11 mg/gl; mean difference 0.15 mg/dl; 95 % CI 0.024–0.26). The third study [14] examined serum magnesium levels and the likelihood of hypomagnesemia in 11,490 adults admitted to an intensive care unit, taking or not a PPI or histamine-2 receptor antagonist. Proton-pump inhibitors use was associated with a 0.012 mg/dl lower adjusted serum magnesium level but this effect was restricted to the subgroup of patients taking diuretics. The last one [2] compared 402 adults with hypomagnesemia at the time of hospital admission to medical services, age- and sex-matched with 402 control individuals with normal serum magnesium levels. In this hospital-based adult population, out-of-hospital PPI use was not associated with lower serum magnesium levels at the time of hospital admission. As the published cohorts are few and mostly report positive results, the question of a publication bias remains open.

Several points merit further discussion. Firstly, the duration of PPI use was not available in our cohort or in three of the four other studies [2, 12, 14]. In the third study [13], the mean duration of PPI use was 35.2 months (range 3 days–393 months), with 69.5 % on PPIs for longer than 12 months. Medication adherence was assumed to be 100 %. In most reported cases, patients had been on PPI therapy for at least 5 years, but hypomagnesemia occurring after only 1 year of PPI treatment has been described [7, 8]. Secondly, as in the previous cohorts, urinary magnesium levels were not available. In the reported cases, urinary magnesium levels and fractional magnesium excretion were low suggesting a defect in intestinal absorption of magnesium [4, 7, 9]. However, considering the variably decreased kidney function in our cohort, data on fractional magnesium excretion would be hard to interpret. Third, we did not have information on diet, alcohol use, over-the-counter medication use (such as magnesium supplements). Fourth, data on potassium levels, which often parallel magnesium levels, were missing which could confound the observed relationship. At least in RTRs, however, potassium and magnesium concentrations tend to diverge through the different dose-dependent tubular effects of calcineurin inhibitors leading, respectively, to hyperkalemia and hypomagnesemia. Finally, although our sample was large-sized, the current cross-sectional design remains a limitation.

In conclusion, to our knowledge, this study is the first to assess the effect of PPI use on serum magnesium levels in a

cross-sectional analysis of a large published cohort of renal transplant patients. Proton-pump inhibitors use was not an independent predictor of Mg level and hypomagnesemia was not associated with the use of PPIs. Thus, PPI, an important class of modern drugs, may be prescribed without particular fear of hypomagnesium-related side effects in RTR patients.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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