AHOT | Acta Haematologica Oncologica Turcica

Acta Haematol Oncol Turc 2024;57(3):97-100

DOI: 10.4274/ahot.galenos.2024.2024-10-4

Original Article

Proton Pump Inhibitors: Effects on Magnesium and Arterial Stiffness in Renal Transplant Recipients

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ABSTRACT

Aim: Hypomagnesemia predicts cardiovascular outcomes in renal transplant recipients (RTRs). Proton pump inhibitors (PPIs) and H_2 receptor blockers (H_2RBs) are the most commonly used agents in RTRs. Previous studies have detected an association between hypomagnesemia and PPIs in patients undergoing ongoing hemodialysis. The current study aimed to evaluate the effects of PPIs on serum magnesium levels and arterial stiffness in RTRs.

Methods: We retrospectively analyzed 354 maintenance RTRs (mean age: 38.6±10.7 years) with stable allograft function who had undergone transplantation at least 36 months previously. All acute cellular and humoral rejections were excluded. According to the use of stomach-protecting agents (SPAs), patients were divided into the following three groups: PPIs (group 1, n=164), H_2RBs (group 2, n=96), and a control group that did not receive SPAs (group 3, n=94). Clinical and laboratory parameters (complete blood count, creatinine, calcium, phosphorus, magnesium, vitamin B12, folic acid, lipid profile) were noted from recorded data. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD4 equation. The pulse-wave velocity (PWv) was determined by pressure tracing over the carotid and femoral arteries using the SphygmoCor system.

Results: The groups were similar in terms of demographic characteristics (age, gender, duration of dialysis before transplantation) and biochemical parameters (serum calcium, phosphorus, parathyroid hormone, C-reactive protein, lipid profile, and eGFR). The mean serum magnesium level was significantly lower in group 1 but similar in groups 2 and 3. The PWv values were significantly higher in group 1 but similar in groups 2 and 3. In the linear regression analysis; types of SPA, serum calcium, and magnesium were detected as predictors of PWv.

Conclusion: We concluded that PPIs inhibit magnesium absorption independent of calcium metabolism in RTRs. Moreover, PPIs increase arterial stiffness and cardiovascular risk in RTRs. Thus, physicians should be aware of the side effects of PPIs to reduce cardiovascular morbidity and mortality.

Keywords: Biochemistry, cardiovascular risk, hypomagnesemia, kidney transplantation

Introduction

Cardiovascular disease is frequently observed in patients with end-stage renal disease (ESRD), and the risk of mortality among cardiac diseases in these patients has been shown to be 10-20 times grater than general population [1]. Renal transplantation (RT) is the standard treatment for patients with ESRD because it significantly prolongs patient life, largely by decreasing the progression of cardiovascular disorders. Renal transplant recipients (RTRs) have up to a 10-fold reduced rate of cardiac death compared with dialysis recipients [2].

Magnesium depletion is considered the missing link between cardiovascular risk factors and atherosclerosis in ESRD. Magnesium modulates calcium uptake and distribution in vascular smooth muscle cells and directly affects the vascular tone, thereby reducing peripheral resistance [3]. Hypomagnesemia predicts cardiovascular morbidity and mortality in the general population and accelerated loss of kidney function in RTRs [4].

Proton pump inhibitors (PPIs) are frequently used both to prevent and treat various gastrointestinal disorders after radiotherapy (RT) [5].

Cite this article as: Gürlek Demirci B, Karakan MŞ. Proton Pump Inhibitors: Effects on Magnesium and Arterial Stiffness in Renal Transplant Recipients. Acta Haematol Oncol Turc. 2024;57(3):97-100

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Received: 14.10.2024 **Accepted:** 24.11.2024 **Epub:**12.12.2024 **Published Date:** 18.12.2024

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Previous studies have highlighted the association between hypomagnesemia and PPIs in healthy individuals and patients undergoing ongoing hemodialysis. It is assumed that these observations are due to possible effects of hypomagnesemia on left ventricular size, hypertension, endothelial function, and insulin resistance [6].

The current study aimed to evaluate the effects of PPIs on serum magnesium levels and arterial stiffness in RTRs.

Methods

We performed a retrospective study of 354 maintenance RTRs (mean age: 38.6±10.7 years) with stable allograft function who had received their transplant at least 36 months previously were selected cross-sectionally according to the following exclusion criteria; 1) lack of regular follow-up data 2) malignant, rheumatologic or chronic inflammatory disease of unknown origin, systemic vasculitis history, 3) acute rejection 4) heart failure (ejection fraction <50%) or diastolic dysfunction of the heart 5) ischemic heart disease history (myocardial infarction, need for cardiac revascularization) or coronary bypass before or after transplantation, 6) peripheral artery disease, 7) tobacco use. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision no: 2-24-69, date: 20.03.2024).

According to the use of stomach-protecting agents (SPAs), patients were divided into the following three groups: PPIs (group 1, n=164), H2RBs (group 2, n=96), and a control group that did not receive SPAs (group 3, n=94).

Immunsuppressive Treatment Protocol

In most patients, maintenance immunosuppressive treatment included prednisone with a gradual tapering, mycophenolate mofetil, and cyclosporine or tacrolimus. Target through levels at 3 months were 150-200 ng/mL for cyclosporine and 8-10 ng/mL for tacrolimus. All patients were under 5 mg prednisolone treatment within the maintenance immunosuppressive regimen.

Biochemical Parameters

The standard clinical and biochemical parameters of all patients were analyzed. Physical examination and routine laboratory measurements (complete blood count and biochemical parameters as described below) were examined. In all participants, venous blood samples were collected after an overnight fast to measure the biochemical parameters.

The estimated glomerular filtration rate was calculated based on the CKD-Epi formulas; $141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] *1.159 [if black] [7].

Pulse-wave Velocity

The aortic pulse-wave velocity (PWv) was measured with the same device by sequentially recording electrocardiogram-gated carotid and femoral artery pressure waves using the intersecting tangent algorithm to determine the characteristic points. The PWv was calculated as the path length divided by the transit time (m/s) [8].

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software (v 15.0, IBM, Armonk, NY, USA). All numerical data are expressed as the mean±standard deviation. Data normality was analyzed using the Kolmogorov-Smirnov test. Normally distributed numeric variables were compared with independent-samples Student's t-test, and skew distributed numeric variables were compared using the Mann-Whitney U test. A p value of 0.05 was considered statistically significant.

Results

Demographic characteristics and laboratory data for the study population and data classified by group are summarized in Tables 1 and 2, respectively.

The mean daily PPI dose was 24±8.4 mg. The median duration of PPI use was 47±4.4 months. There were no significant differences between the two groups in terms of age, duration of transplantation, and presence of comorbid conditions.

The mean serum magnesium levels were significantly lower in group 1, but were similar in groups 2 and 3 (1.1±0.4 mg/dL, 1.7±0.2 mg/dL and 1.6±0.1 mgdL, respectively) ($p<0.05$) (Figure 1). The PWv values were significantly higher in group 1 ($p<0.05$), whereas they were similar in groups 2 and 3 (7.3±0.2 cm/sec, 6.3±0.1 cm/sec and 6.2±0.1 cm/sec, retrospectively) (Figure 2).

Using linear regression analysis with serum Mg as the dependent variable, PPI use was significantly associated with serum Mg ($p=0.008$) after adjusting for age, dialysis duration, and plasma albumin.

Table 1. Demographic and clinical characteristics of the study population

Gender (male/%)	196 (55%)
Age Mean±SD (years)	38.6±10.7
Etiology of ESRD [number (%)] Diabetes mellitus Hypertension PCKD Glomerulonephritis Unknown	 173 (49) 95 (27) 21 (6) 14 (4) 51 (14)
Duration of transplantation (months)	38.2±0.8
Fasting glucose, mean±SD (mg/dL)	88.7±12.4
Total cholesterol, mean±SD (mg/dL)	244.0±32.0
LDL- cholesterol, mean±SD (mg/dL)	128.8±24.5
Triglyceride, mean±SD (mg/dL)	189.7±12.5
Serum creatinine, mean±SD (mg/dL)	1.2±0.7

ESRD: End stage renal disease, LDL: Low-density lipoprotein, SD: Standard deviation, PCKD: Polycystic kidney disease

Discussion

The metabolism of magnesium is regulated by gastrointestinal absorption and renal excretion. It has been shown that PPI use is associated with impaired intestinal absorption of dietary Mg by disrupting active transport by TRPM 6/7 channels [9]. Moreover, hypomagnesemia is known to predict cardiovascular outcomes in both the general population and RTRs [4]. To our knowledge, this is the first in the literature that showed PPIs are linked to increased arterial stiffness and cardiovascular risk by decreasing Mg levels in RTRs.

A study by Recart et al. [10], which included 236 patients on PPI treatment, showed that patients on long-term PPI use were frequently prone to hypomagnesemia. On the other hand, some studies have reported that PPI use does not affect serum magnesium levels. Biyik et al. [11] detected serum magnesium levels of outpatients receiving long-term PPI treatments to be within the normal range in the absence of other factors affecting serum magnesium levels. The serum magnesium levels of outpatients who have and have not been using PPIs were found to be similar. However, the situation in patients undergoing ongoing hemodialysis is slightly different from the general population. Hypomagnesemia was reported to be linked to PPI use among patients undergoing hemodialysis. In a previous study, the dialysate magnesium level was 0.5-0.375 mmol/L. They reported that hypomagnesemia might occur with PPI use in hemodialysis patients with dialysate magnesium level was 0.5-0.375 mmol/L [12]. Another cross-sectional study of patients on ongoing hemodialysis showed that serum Mg levels among patients receiving PPIs were significantly lower than those who were not on PPIs [13,14]. Besides, by multivariate analysis, they found that the use of PPIs was a strong and independent predictor of low Mg levels, similar to the present study.

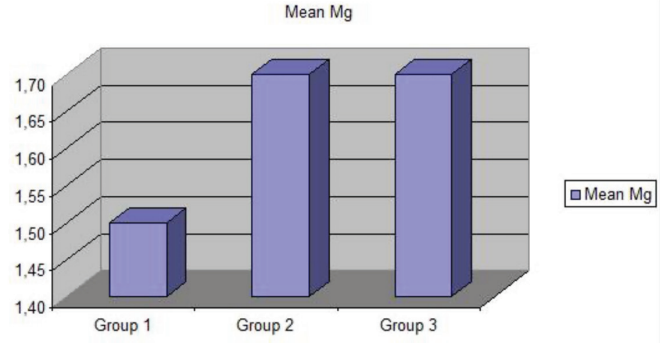

Figure 1. Mean serum magnesium level in group 1

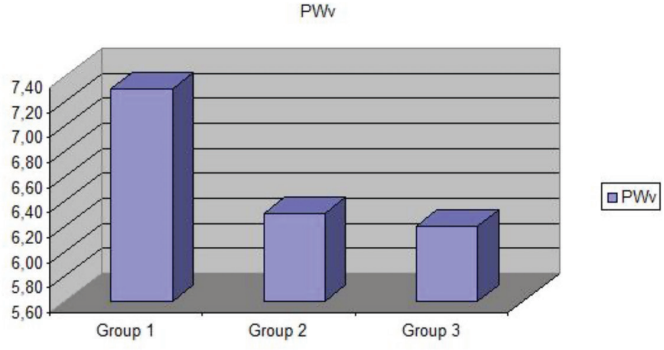

Figure 2. Mean PWv was significantly higher in group 1 than in group 2
PWv: Pulse-wave velocity

Vascular calcification is highly prevalent in patients who are on ongoing hemodialysis and continue after RT [15]. Previous studies have shown that hypomagnesemia may be related to atherosclerosis and arterial stiffness. The underlined mechanism may be associated with mitochondrial dysfunction and Ca transient suppression. A retrospective study on patients undergoing ongoing hemodialysis detected that serum Mg level was an independent factor for arterial stiffness [16]. Similar to our study, the relationship between hypomagnesemia and vascular stiffness was investigated in a previous study on RTRs. Our results were consistent with those of a previous report, as serum Mg level was an independent risk factor for arterial stiffness [17].

A previous study demonstrated that PPIs directly damage vascular endothelial cells [18]. Yepuri et al. [19] demonstrated that PPIs result in impaired endothelial function. Another recent study reported that PPIs decrease the levels of anti-atherogenic molecules in endothelial cells [20]. The present study, we showed PPI are associated with increased arterial stiffness and cardiovascular risk by decreasing Mg levels

Table 2. Demographic and clinical characteristics of the study groups

	Group 1 (n=164)	Group 2 (n=96)	Control group (n=94)	p value
Age, mean±SD (years)	38.4±4.6	41.1±3.1	39.7±9.7	NS
Duration of dialysis before tx, mean±SD (months)	76.4±1.8	83.2±1.6	77.6±2.4	NS
Duration of transplantation (months)	38.1±9.4	37.6±8.7	39.6±7.6	NS
Hemoglobin (g/dL) mean±SD	11.6±1.7	11.2±2.4	11.8±0.9	NS
Serum albumin (g/L) mean±SD	3.8±0.7	3.6±0.4	3.8±1.1	NS
Serum phosphate (mg/dL) mean±SD	4.2±0.4	4.6±0.6	4.4±0.7	NS
Serum creatinine (mg/dL) mean±SD	1.24±0.1	1.22±0.2	1.30±0.1	NS
Serum magnesium level (mg/dL) mean±SD	1.1±0.4	1.7±0.2	1.6±0.1	**<0.05**
PWv, mean±SD (m/sec)	7.3±0.2	6.3±0.1	6.2±0.1	***<0.01***

NS: Not significant, PWv: Pulse wave velocity, tx: Transplantation, SD: Standard deviation

in RTRs. These findings suggest that PPIs may increase calcification induced by vascular endothelial injury.

Study Limitations

The limitations of the present study include, first, we studied serum Mg levels, but did not specifically look at the ionized Mg fraction and we did not give information on PPI duration and baseline magnesium levels prior to PPI initiation, second, the lack of pretransplant measurements of PWv in recipients, third, we did not measure dietary Mg intake, markers of nutritional status, and finally, we did not distinguish the PPI types and we did not specify immunosuppressive drug levels.

Conclusion

In conclusion, we detected that PPIs may inhibit magnesium absorption independent of calcium metabolism in RTRs. Moreover, PPIs are linked to increased arterial stiffness and cardiovascular risk in RTRs. Thus, physicians should be aware of the side effects of PPIs to reduce cardiovascular morbidity and mortality. On the other hand, because of its cross-sectional design, this study has limited the ability to assess the long-term effects of PPI use on magnesium levels and cardiovascular risk, and prospective studies are needed to assess long-term impacts.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision no: 2-24-69, date: 20.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ş.K., Concept: M.Ş.K., Design: M.Ş.K., Data Collection or Processing: B.G.D., Analysis or Interpretation: B.G.D., Literature Search: B.G.D., Writing: B.G.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112-S119.
2. Meier-Kriesche HU, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. Am J Transplant. 2004;4:1662-1668.
3. Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. Cell Mol Biol Res. 1995;41:347-359.
4. Dey R, Rajappa M, Parameswaran S, Revathy G. Hypomagnesemia and atherogenic dyslipidemia in chronic kidney disease: surrogate markers for increased cardiovascular risk. Clin Exp Nephrol. 2015;19:1054-1061.
5. Lau YT, Ahmed NN. Fracture risk and bone mineral density reduction associated with proton pump inhibitors. Pharmacotherapy. 2012;32:67-79.
6. Gau JT, Yang YX, Chen R, Kao TC. Uses of proton pump inhibitors and hypomagnesemia. Pharmacoepidemiol Drug Saf. 2012;21:553-559.
7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.
8. Mac-Way F, Couture V, Utescu MS, Ignace S, De Serres SA, Loignon RC, et al. Advanced glycation end products, aortic stiffness, and wave reflection in peritoneal dialysis as compared to hemodialysis. Int Urol Nephrol. 2014;46:817-824.
9. Bai JP, Hausman E, Lionberger R, Zhang X. Modeling and simulation of the effect of proton pump inhibitors on magnesium homeostasis. 1. Oral absorption of magnesium. Mol Pharm. 2012;9:3495-3505.
10. Recart DA, Ferraris A, Petriglieri CI, Alonso Serena M, Bonella MB, Posadas-Martinez ML. Prevalence and risk factors of long-term proton pump inhibitors-associated hypomagnesemia: a cross-sectional study in hospitalized patients. Intern Emerg Med. 2021;16:711-717.
11. Biyik M, Solak Y, Ucar R, Cifci S, Tekis D, Polat İ, et al. Hypomagnesemia Among Outpatient Long-Term Proton Pump Inhibitor Users. Am J Ther. 2017;24:e52-e55.
12. Alhosaini M, Walter JS, Singh S, Dieter RS, Hsieh A, Leehey DJ. Hypomagnesemia in hemodialysis patients: role of proton pump inhibitors. Am J Nephrol. 2014;39:204-209.
13. Mikolasevic I, Milic S, Stimac D, Zaputovic L, Lukenda Zanko V, Gulin T, et al. Is there a relationship between hypomagnesemia and proton-pump inhibitors in patients on chronic hemodialysis? Eur J Intern Med. 2016;30:99-103.
14. Losurdo G, Caccavo NLB, Indellicati G, Celiberto F, Ierardi E, Barone M, Di Leo A. Effect of Long-Term Proton Pump Inhibitor Use on Blood Vitamins and Minerals: A Primary Care Setting Study. J Clin Med. 2023;12:2910.
15. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension. 2001;38:938-942.
16. Ishimura E, Okuno S, Kitatani K, Tsuchida T, Yamakawa T, Shioi A, et al. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. Clin Nephrol. 2007;68:222-227.
17. Van Laecke S, Maréchal C, Verbeke F, Peeters P, Van Biesen W, Devuyst O, et al. The relation between hypomagnesaemia and vascular stiffness in renal transplant recipients. Nephrol Dial Transplant. 2011;26:2362-2369.
18. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the cardiovascular risk factor asymmetric dimethylarginine. Circulation. 2013;128:845-853.
19. Yepuri G, Sukhovershin R, Nazari-Shafti TZ, Petrascheck M, Ghebre YT, Cooke JP. Proton Pump Inhibitors Accelerate Endothelial Senescence. Circ Res. 2016;118:e36-e42.
20. Costarelli L, Giacconi R, Malavolta M, Basso A, Piacenza F, Provinciali M, et al. Different transcriptional profiling between senescent and non-senescent human coronary artery endothelial cells (HCAECs) by Omeprazole and Lansoprazole treatment. Biogerontology. 2017;18:217-236.