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The Impact of Serum Magnesium Level and Use of Proton Pump Inhibitors on Cardiovascular Calcification in Participants with Chronic Kidney Disease

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Abstract:

Introduction: Cardiovascular calcification is a serious complication in both chronic kidney disease (CKD) and hemodialysis (HD) Participants. Proton pump inhibitors (PPIs) are frequently used in these Participants and may lower serum magnesium (Mg) levels, potentially affecting cardiovascular health.

Aim of the study: To measure the relationship of Mg, PPI use, and cardiovascular calcification in CKD and HD

Subjects and Methods: A retrospective cohort study of 100 Participants with CKD and ESRD undergoing HD at Fayoum University Hospitals and Om Masreen Hospital over six months. Participants were divided into four groups based on PPI usage: CKD Participants with and without PPI usage, and HD Participants with and without PPI usage. Data collection included demographic information, medical history, clinical and laboratory measurements. Cardiovascular calcification was evaluated using echocardiography and abdominal radiography

Results: No significant differences in demographics or baseline characteristics were observed between PPI users and non-users in the CKD group. However, PPI users had higher serum creatinine, cholesterol, and HDL levels, with lower serum Mg levels. They also showed increased abdominal aortic calcification and moderate left ventricular hypertrophy (LVH)

Conclusion: PPI use in renal disease and dialysis Participants resulted in hypomagnesemia plus higher cardiovascular risks, suggesting a need for careful monitoring and consideration of alternative therapies for these Participants.

Keywords: Chronic Kidney Disease; Hemodialysis; Hypomagnesemia; Proton Pump Inhibitors; Vascular Calcification.

1. Introduction

Cardiac disease (CVD) continues to be the major cause of mortality for people with chronic kidney disease (CKD), which affects around 9.1% of the world's population [1]. Vascular calcification is one of the best indicators of CVD, and those with chronic kidney disease (CKD) have a much greater disease load and a faster rate of vascular calcification development [2].

Vascular calcification, which mostly affects the medial layer of blood arteries but can also affect the intima, is typified by diffuse mineral deposition in CKD Participants. It mostly affects the aorta, although plain X-rays sometimes show a characteristic tramline pattern of calcification that reaches into the tiny capillaries on the periphery. Vascular calcification is more common when renal clearance deteriorates, and it often appears years sooner in renal disease than in controls [2,3].

Numerous severe side effects, such as ischaemic heart disease and an elevated risk of cardiovascular and all-cause death, are linked to vascular calcification. Vascular calcification plays a crucial part in these consequences, but there are presently no targeted treatments to halt its growth or undo its effects. Finding the risk factors causing vascular calcification and creating efficient preventative measures are crucial in light of this treatment gap. By addressing these issues, CKD Participants' cardiovascular load may be lessened, improving their prognosis and quality of life in the process [4, 5].

More recent studies have emphasized the important function of magnesium (Mg) in cardiovascular health, whereas earlier research concentrated on disordered mineral metabolism—more especially, abnormalities in calcium and phosphate—as major regulators of vascular calcification [6, 7, 8].

In clinical practice, proton pump inhibitors (PPIs) are frequently used for ailments such as GERD, gastric ulcers, and gastritis. PROTON- PUMPI usage has been associated with hypomagnesaemia in the general population, according to observational studies. There is, however, little information available about the connection between PROTON-PUMPI usage and hypomagnesaemia in dialysis Participants [9, 10, 11].

2. Subjects & Methods

2.1.*Subjects*

The material of this work comprised 100 hemodialysis or chronic kidney disease Participants who were followed up at or received hemodialysis at the Fayoum University Hospitals and Om Elmasryeen Hospital over six months.

The participants were divided into four groups:

- **Group A**: included 25 dialysis Participants using PROTON-PUMPIs.
- **Group B**: included 25 dialysis Participants not using PROTON-PUMPIs
- **Group C:** included 25 CKD Participants not on hemodialysis but using PROTON-PUMPIs.
- **Group D:** included 25 CKD Participants not on hemodialysis and not using PPIs.

Enrollment

- Regular hemodialysis for at least six months.
- CKD stage 2 or higher.

Exclusion

- Significant infection.
- Malignancy.
- Chronic diarrhea.
- History of parathyroidectomy.
- Unstable medical condition during the previous 30 days.
- Participants with rheumatic or congenital heart disease.
- Participants receiving drugs that may affect the serum Mg levels, for example, tonic/ vitamins and Mg-containing P binders.

2.2.*Study design*

This is a retrospective cohort study.

Sample size

The sample size was calculated using the G-power program with α. Error = 0.05 and power 80% and it was equal to 100 Participants.

2.3.*Statistical method*

The recruited data included age, gender, dialysis duration, diabetes, hypertension, drug history, clinical examination data, laboratory findings, ECG, Echo, and plain abdominal X-ray.

3. Results

Statistical analysis was performed using SPSS (version 21, Chicago, IL, USA). The statistical methods employed included the Chi-square (χ^2) test for comparing

nominal data, the Student t-test for measuring normally distributed quantitative data between two groups, and the Mann-Whitney test for comparing abnormally distributed quantitative data among two groups. Additionally, Analysis of Variance (ANOVA) was utilized to compare normally distributed data across more than two groups, while the Kruskal-Wallis test was applied for abnormally distributed qualitative data among multiple groups.

Non-statistically significant difference was found among the PPI and non-PPI groups among CKD Participants in terms of demographics (**Figures 1 & 2**), baseline medical conditions, systolic blood pressure, heart rate, or use of phosphate binders and calcimimetics. However, a significant difference was observed in diastolic blood pressure (p= 0.015) and vitamin D use, with more Participants in the PPI group using vitamin D (p= 0.04) (**Table 1**).

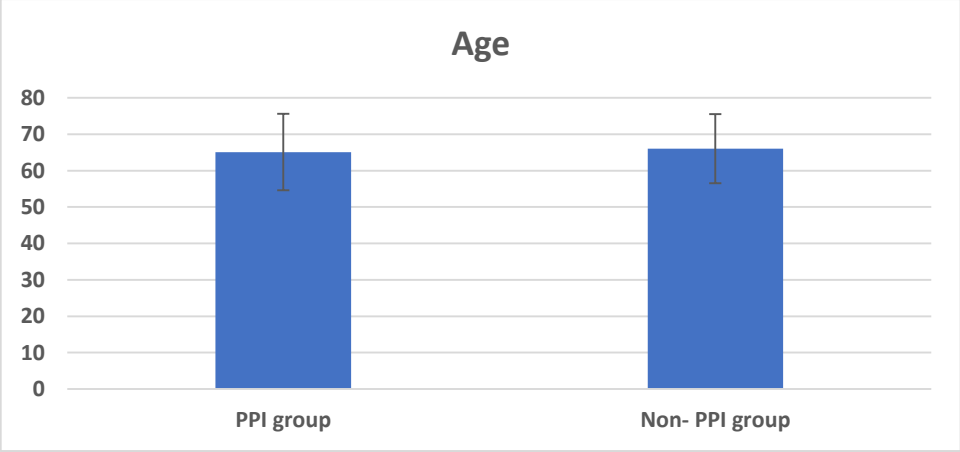

Figure 1: Age differences among PPI and non-PPI CKD groups.

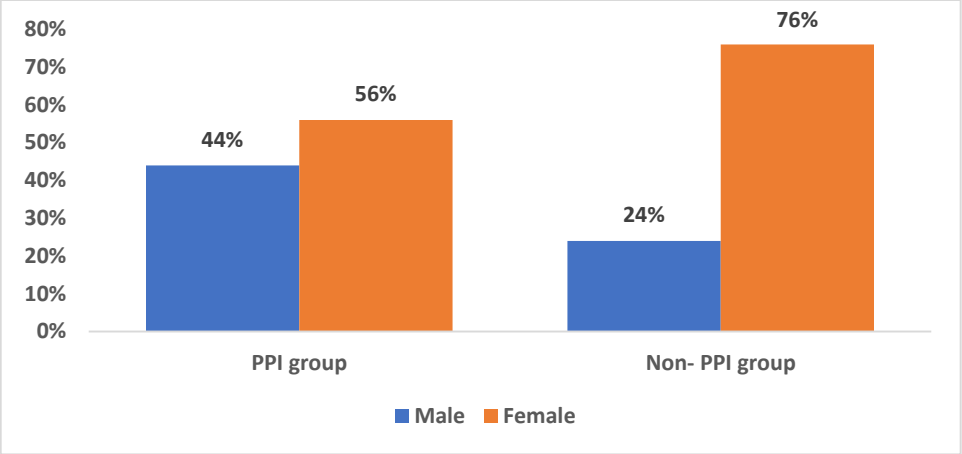

Figure 2: Sex differences among PPI and non-PPI CKD groups.

Table 1: Demographics and baseline characteristics among CKD Participants.

Variables	PPI group (n=25)	Non-PPI group (n=25)	*P*-value
Hypertension	22 (88%)	25 (100%)	0.07
Diabetes	11 (44%)	10 (40%)	0.77
Diabetes duration (years)	10.12±5.46	9.12±5.18	0.51
Systolic blood pressure (mmHg)	153.6±16.04	153.6±10.75	1.00
Diastolic blood pressure (mmHg)	86±8.16	92±8.66	0.015
Heart rate (beats/minute)	91±9.13	89±10	0.46
Phosphate binders No. (%)	11 (44%)	9 (36%)	0.56
Vitamin D No. (%)	17 (68%)	10 (40%)	0.04
Calcimimetics No. (%)	8 (32%)	4 (16%)	0.18

No significant differences were found among the PPI and non-PPI groups among CKD Participants in terms of CBC parameters, CRP, LDL, triglycerides, albumin, calcium, phosphorus, or iPTH. However, the PPI group had a statistically significantly higher serum creatinine (p=0.001), cholesterol (p=0.046), and HDL (p=0.003), while the non-PPI group had a statistically significantly higher alkaline phosphatase (p=0.03). Serum magnesium was significantly lower in the PPI group (p=0.021) (**Table 2**).

Table 2: Comparison of laboratory investigations among CKD Participants:

Variables	PPI group	Non-PPI group	*P*-value
Hemoglobin (g/dL)	9.9±1.089	9.68±0.87	0.43
Platelets (*10^3/mm^3)	147.7±32.8	155.56±35.7	0.42
White blood cells (*10^3/mm^3)	6.8±1.26	6.6±1.3	0.49
CRP	0.35±0.26	0.46±0.04	0.28
S. creatinine (mg/dL)	4.096±0.43	3.4±0.8	0.001
Cholesterol (mg/dL)	166.12±12.4	175.24±18.36	0.046
HDL (mg/dL)	40.36±9.05	49.68±11.69	0.003
LDL (mg/dL)	95.12±17.4	87.24±14.26	0.087
Triglycerides (mg/dL)	115.5±16.17	11304±18.99	0.62
Albumin (g/dL)	3.076±0.52	3.17±0.49	0.51
Alkaline phosphatase	213.4±42.96	242.4±52.85	0.03
Serum Calcium (mg/dL)	8.9±0.45	9.02±0.55	0.43
Phosphorus (mg/dL)	5.4±1.01	5.2±0.89	0.36
Magnesium (mg/dL)	1.7±0.4	2.02±0.5	0.021
Intact PTH (pg/mL)	245.9±53	261.2±61.67	0.35

Among CKD Participants, the PPI group exhibited a significantly higher volume of abdominal aortic calcification (p=0.005) and a greater percentage of Participants with aortic valve calcification (p<0.001). Additionally, while mild left ventricular hypertrophy (LVH) was more common in the non-PPI group, moderate LVH was significantly more prevalent in the PPI group (p=0.01) (**Table 3**).

Table 3: Echocardiography findings and calcification among the PPI and Non-PPI groups among CKD Participants:

Variables		**PPI group (n= 25)**	**Non-PPI group (n=25)**	***P*-value**
Volume of aorta calcifications (cm^3)		3.9±1.26	3.2±1.17	0.005
Aortic valve calcification No. (%)		25 (100%)	12 (48%)	<0.001
Degree of aortic valve calcification	Mild	10 (40%)	9 (36%)	<0.001
	Moderate	12 (48%)	3 (12%)	
	Severe	3 (12%)	0	
Left ventricular hypertrophy	Mild	9 (36%)	18 (72%)	0.01
	Moderate	16 (64%)	7 (28%)	
	Severe	0	0	

Insignificant variations were found among the PPI and Non-PPI groups among HD participants in terms of demographics, baseline medical conditions, systolic and diastolic blood pressure, heart rate, or phosphate binders, vitamin D, and calcimimetics, indicating that baseline demographic and clinical characteristics were largely comparable among both groups (**Table 4**).

Table 4: Demographics and baseline characteristics among HD participants:

Variables	**PPI group (n=25)**	**Non-PPI group (n=25)**	***P*-value**
Hypertension	22 (88%)	22 (88%)	1.00
Diabetes	15 (60%)	14 (56%)	0.77
Diabetes duration (years)	10.8±5.05	10.44±5.78	0.816
Hemodialysis duration (years)	19.56±5.8	19.88±6.6	0.857
Systolic blood pressure (mmHg)	154.8±14.46	154±17.55	0.86
Diastolic blood pressure (mmHg)	89.6±9.78	86.00±10	0.204
Heart rate (beats/minute)	86.68±10.09	91.6±10.02	0.08
Phosphate binders No. (%)	5 (20%)	5 (20%)	1.000
Vitamin D No. (%)	12 (48%)	9 (36%)	0.39
Calcimimetics No. (%)	5 (20%)	5 (20%)	1.000

Among HD Participants, Insignificant variations were found among the PPI and non-PPI groups regarding different laboratory investigations, except for magnesium, which was lower with a statistically significant difference among the PPI group *(p*=0.04*)* (**Table 5**).

Table 5: Comparison of laboratory investigations among the PPI and Non-PPI groups among HD Participants:

Variables	PPI group	Non-PPI group	*P*-value
Hemoglobin (g/dL)	9.6±1.06	9.6±1.14	0.94
Platelets (*103/mm3)	148.48±33.87	141.16±38.5	0.47
White blood cells (*103/mm3)	6.86±1.4	6.68±1.2	0.63
CRP	0.46±0.04	0.36±0.03	0.36
S. creatinine (mg/dL)	7.78±0.9	7.7±1.16	0.83
Cholesterol (mg/dL)	161.52±1 6.34	170.96±18.94	0.065
HDL (mg/dL)	46.8±9.4	49.7±11.9	0.35
LDL (mg/dL)	96.36±15	92.3±13.26	0.32
Triglycerides (mg/dL)	113.6±20.06	118.7±20.11	0.37
Albumin (g/dL)	3.2±0.54	3.1±0.49	0.59
Alkaline phosphatase	235.24±48.99	254.84±66.08	0.24
Serum Calcium (mg/dL)	8.9±0.51	8.94±0.55	0.792
Phosphorus (mg/dL)	5.59±0.99	5.4±0.8	0.56
Magnesium (mg/dL)	1.74±0.42	1.99±0.45	0.04
Intact PTH (pg/mL)	535.9±133.34	613.12±330.08	0.286

Insignificant variation among the PPI and non-PPI groups among HD participants regarding the volume of abdominal aorta calcifications or the presence of aortic valve calcification, as both groups had 100% aortic valve calcification. However, significant differences were noted in the degree of aortic valve calcification (p= 0.03) and the degree of LVH (p= 0.001), with the PPI group showing more severe calcification and LVH (**Table 6**).

Table 6: Echocardiography findings and calcification among HD Participants:

Variables		**PPI group (n= 25)**	**Non-PPI group (n=25)**	***P*-value**
Volume aorta calcifications (cm3)		3.44±1.5	3.33±1.77	0.815
Aortic valve calcification No. (%)		25 (100%)	25 (100%)	1.000
Degree of aortic valve calcification	Mild	1 (4%)	4 (16%)	0.03
	Moderate	4 (16%)	10 (40%)	
	Severe	20 (80%)	11 (44%)	
Left ventricular hypertrophy	Mild	2 (8%)	3 (12%)	0.001
	Moderate	2 (8%)	13 (52%)	
	Severe	21 (84%)	9 (36%)	

All factors were entered in one-step linear regression analysis to adjust for the confounders of the predictors of abdominal aorta calcification *(*R: 0.88, adjusted R: 0.506, *p*=0.009*)*. Four factors showed statistical significance as significant predictors, including: hemodialysis *(p*=0.02*)*, proton pump use *(p*=0.04*)*, diastolic blood pressure *(p*=0.028*)* and serum magnesium *(p*=0.029*)* (**Table 7**).

Table 7: Linear regression analysis to detect predictors of abdominal aorta calcification:

	Beta	**95% CI**		**t=**	***P*-value***
		Lower	**Upper**		
Hemodialysis	-0.413	-2.68	0.19	-2.9	0.02
Proton pump inhibitors	-0.412	-2.235	0.52	-2.85	0.04
Diastolic blood pressure	0.436	0.008	0.133	2.36	0.028
Magnesium	-0.405	-2.723	-0.161	-2.34	0.029

4. Discussion

The current study measured the relationship between magnesium levels and use of PPIs in cardiovascular calcification in Participants with chronic kidney disease. To achieve this aim, this study was conducted on 100 Participants (50 CKD Participants and 50 hemodialysis Participants) who were divided into two groups according to the use of PPIs as a part of their routine medications. In the current study, there was a statistically significant effect of PPIs on serum magnesium, as serum magnesium was lower among PPI users, either in the total cohort or each group separately. Following the current study, multiple reports found a relationship between proton pump and

hypomagnesemia among healthy volunteers [12,13].

Reduced magnesium levels have even been claimed in multiple studies of Participants dependent on hemodialysis. They also claimed that PPI use was associated with hypomagnesemia among CKD and hemodialysis Participants [14, 15, 16, 17]. Misara et al. claimed more hypomagnesemia among hemodialysis Participants who were receiving PPIs [15]. Other researchers found that serum magnesium was lower with a statistically significant difference among hemodialysis PPI users [7, 18]. Mikolasevic et al. claimed that the only difference among hemodialysis PPI users and non-users was the incidence of hypomagnesemia.

Otherwise, demographics, baseline characteristics and all other studied laboratory investigations were comparable [19]. Also, another Japanese study proved the same findings [20]. A relation was found among the use of PPIs and decreased urinary Mg excretion (a finding that likely reflects a decreased intestinal Mg uptake by PPIs) [21]. On the other hand, a low prevalence of hypomagnesemia was claimed among CKD Participants who were maintained on PPIs for an extended period, according to a study that included 500 CKD Participants followed for 5 years [22].

Regarding the cardiovascular effect of PPIs, abdominal aorta calcification (AAC) volume and aortic valve calcification frequency were higher with statistically significant differences among PPI users than non-users in the total cohort and in each group separately. Following the current study, Kosedo et al. claimed increased AAC and aortic valve calcification among hemodialysis Participants who were maintained on PPIs and the action was explained to be mediated by PPI-induced hypomagnesemia [23]. Another study proved that proton pump I are a risk factor for the development of aortic calcification in the HD population [7]. In an Italian study by Fusaro et al., PPIs augmented the known effect of warfarin on vascular calcification among hemodialysis Participants, and it has been shown that PPIs are solely considered risk factors for AAC after adjusting for other factors. He conducted his study on 18 hemodialysis units and 387 Participants [24]. Other studies claimed PROTON-PUMPI as a predictor for cardiovascular events and mortality in the dialysis population [25, 26]. Furaso et al., in their large cohort study, claimed increased coronary artery disease among hemodialysis

Participants who were maintained on PPIs [24]. Additionally, an increased incidence of heart failure has been claimed among hemodialysis Participants who use PPIs [27]. Furthermore, proton pump I in dialysis Participants has been associated with an elevated risk of cardiovascular adverse events and all-cause mortality [17]. Conversely, Arora et al. found that PPI users had a lower frequency of vascular and cardiac diseases [8, 28]. The effect of PPIs on the degree of LVH was obvious in both hemodialysis and non-hemodialysis CKD Participants, with an increased severity of LVH observed in PPI-dependent groups. Similarly, increased LVH has been found in the hemodialysis population receiving PROTON-PUMPI [29]. Additionally, hypomagnesemia induced by PPIs was considered a risk factor for the worsening of LVH in hemodialysis Participants [30]. A strong Relation between PPI use and the incidence of LVH has also been found in hemodialysis Participants with coronary artery disease [31]. Conversely, Lin et al. claimed that lansoprazole suppressed cardiac remodelling and alleviated left ventricular hypertrophy, resulting in the shortening of cardiac muscle in rats [32].

5. Conclusion

PPI use in the renal disease population resulted in hypomagnesemia and higher cardiovascular risks, suggesting a need for careful monitoring and consideration of alternative therapies for these Participants.

Acknowledgement: none.

Ethical approval and consent to participate: It was obtained by the hospital's ethical committee. Informed consent, both verbal and written, was obtained from all participants after clearly explaining the study's aims and procedures. Participants were provided with the researcher's contact information for any inquiries or clarifications.

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