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THE IMPACT OF LONG-TERM USAGE OF PROTON PUMP INHIBITOR MEDICINES ON BLOOD LEVELS OF MAGNESIUM SALTS

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ABSTRACT

Introduction: Late 1980s proton pump inhibitors (PPIs) enhanced acidity-related disease treatment. They reduce stomach acid best.[1] PPIs work better than other anti-secretory drugs because they permanently inhibit the stomach H+/K+ ATPase, the final step of acid secretion. They are often recommended for GERD, peptic ulcer disease, and other stomach acid-related disorders.[2] PPIs are generally safe, however they may cause pneumonia, diarrhoea, iron and vitamin B12 deficiency, Clostridium difficile colitis, and hypomagnesemia.[3,4] Maintenance Patients with gastro-esophageal reflux illness often use PPIs. Some studies show that PPIs reduce GERD symptoms and treat esophagitis. A meta-analysis found that proton pump inhibitors relieved heartburn 11.5 percent of the time, compared to 6.4 percent for H2 receptor antagonists.[5] Esophagitis commonly returns, so acid suppression medicine is needed.[6,7] The speed of relapse after a trial off antisecretory medicines may indicate if maintenance medication is needed. Acute treatment may sustain remissions lasting more than three months, but recurring symptoms in less than three months indicate sickness best managed with continued medication.[8] Long-term drug usage (more than a year for PPIs) raises safety concerns.[9] Long-term safety concerns for proton pump inhibitors (PPIs) include stomach shrinkage, persistent hypochlorhydria and hypergastrinemia, and PPIs. Hypochlorhydria may lead to infections and malabsorption.[10] Numerous studies have connected PPI use to intestinal magnesium absorption-related hypomagnesaemia.[11] Magnesium is the body's fourth most abundant cation and second intracellular cation.[12] Magnesium is 1,000 mmols per adult (22-26gm). Healthy people have 1.5–2.0 mg/dl plasma Mg.[13] Bone contains 60% of the body's calcium, 30% of which is exchangeable and stabilises blood calcium levels. It also reinforces the skeleton. 20% is in skeletal muscle, 19% in soft tissues, and 1% in extracellular fluid.[14,15] Magnesium is needed for ATP transport and over 300 other metabolic processes. It improves heart rhythm, immunological function, muscle and neuron function, and bone density. It regulates blood pressure, sugar, protein, and energy metabolism.[16,17] The kidneys excrete Mg, the stomach absorbs it, and bone stores it.[18] Magnesium levels below 0.61 mmol/L (1.5 mg/dl) are low.[19] High-dose oral magnesium supplementation may treat hypomagnesaemia since urine magnesium excretion is low. Chronic usage of omeprazole and other proton pump inhibitors (usually over a year) may cause hypomagnesaemia (PPIs). Hypomagnesaemia disappears after PPI medication stops.[20,21] Reports indicate 38 hypomagnesaemia cases connected to PPI use.[22] The FDA issued a warning advisory acknowledging severe hypomagnesaemia connected to long-term PPI use after 15 further cases were recorded.[9] In March 2011, the FDA warned healthcare providers about hypomagnesaemia in long-term PPI users.[9] The FDA urges doctors to evaluate patients' blood magnesium levels while giving PPIs to long-term users or those on other hypomagnesemia-causing medicines (eg, digoxin or diuretics). The aim of this study was to examine the effect of the use PPIs for more than 3 months on serum magnesium level, and compare the result with serum Mg level of healthy control from adult people.

METHOD

A case control study consists of 97 subjects (50 control and 47 patients), with age range of 18-67 year. The study was conducted in the Medical City teaching complex, Baghdad from August 2013 to March 2014. The 47 patients included patient were using proton pump inhibitor (omeprazole, lansoprazole in the study) at least once daily for at least 3 months irrespective the reason of its use. Exclusion criteria included diabetes mellitus, dyslipidemia, heart failure, ischemic heart disease,

chronic kidney disease, thyroid disease, preeclampsia, Cushing syndrome, malabsorption syndrome, drugs that cause hypomagnesaemia like steroid, oral contraceptive pills, anabolic steroids, diuretics, aminoglycoside, laxatives, antacids, history of recent illness, recent use of multivitamins and tonics and alcoholism. All patient was assessed regarding their age, gender (male and female) and body mass index. All recruits were interviewed in outpatient clinic in Baghdad teaching hospital. Oral consent was given by each subject before participation in this study. Body weight, height and body mass index were measured, 10 cc of peripheral venous blood sample were taking without tourniquet, kept in plain test tube and sent to Baghdad teaching hospital laboratory to measure serum calcium, serum potassium, serum albumin, by using spectrophotometry at laboratory normal reference rang (serum calcium 8.5-10.0 mg/dl, serum potassium 3.5-5.3 mg/dl, serum albumin 3.5-5.4 g/l). Total serum Mg was measured by using Atomic Absorption Spectrophotometry (AAS) at private laboratory at normal reference rang 1.5-2.0 mg/dl.[23] Statistical Analysis method: Data of the study groups (patients and controls) were processed by computerized data base software (Microsoft excel software 2010), all variables were coded and transferred into statistical analysis computerized package; MINITAB ® 16.1.1 (2010) and SPSS (statistical package for social sciences) software for windows version 19 both were used for data management and analysis. ANOVA one-way method, multiple linear regression method, chi square was used to assess the significance of differences in between patients and controls in categorical variables. Level of significance (p value) ≤ 0.05 considered significant.

RESULTS

Table (1) show the demographic features of patients and controls, with gender, age and body mass index. Gender: Distribution of male and female was equivalent among patients and control (assessed using ANOVA one way) with p value of 0.4431. Age: Mean age between patients and control was not statistically significant (38.8 patients vs. 38.5 control), and its distribution among patients and control as distributed in table (1) was similar this was assessed using chi square test with p value of 0.879; so overall no difference in age of patients and control was found. BMI: Mean BMI was statistically difference among patients and control in which patient had BMI of 31.8 (obese) and control BMI of 29.5 (overweight), although their distribution as described in table (1) was no equivalent (assessed using chi square) in which the obese group (BMI > 30) had the highest proportion in both patients (75%) and control (52%).

Table 1: Demographic characteristics of study groups.

Variable		Patients		Control		*P*
		No.	%	No.	%	
gende	Male	29	61.7	27	54	0.443
	Female	18	38.3	23	46	
Age (years)	< 30	11	23.4	13	26	0.879
	30 – 39	13	27.6	12	24	
	40 – 49	16	34	15	30	
	≥ 50	7	14.9	10	20	
	Mean ±SD	38.83 ± 10.65		38.56 ± 12.81		0.911
	Range	**18 – 61**		**17 – 67**		-
BMI (kg\m^2)	< 25	1	2	6	12	0.039
	25 – 29.9	11	23	18	36	
	≥ 30	35	75	26	52	
	Mean ±SD	31.83 ± 3.409		29.58 ± 3.648		0.002

Table (2) Comparison between patients and control serum Mg level: Mean serum Mg levels has statistically significant difference between patient and control groups (assessed using t test) with p value 0.048, although both patients and control had a mean serum Mg level above 1.7mg/dl.

Table 2: Comparison between patients and control serum Mg mg/dl.

	Mean ± SD	Highest and lowest reading	P value
Patients	1.7191 ± 0.0798	1.96 - 1.60	0.048
Controls	1.7540 ± 0.0908	1.98 - 1.65	
Level of significance was 0.05 using t test			

Fig (1) shows relationship between serum Mg and age Pearson correlation of age vs serum Mg level = 0.118 (p value) meaning that there is no leaner relationship between them.

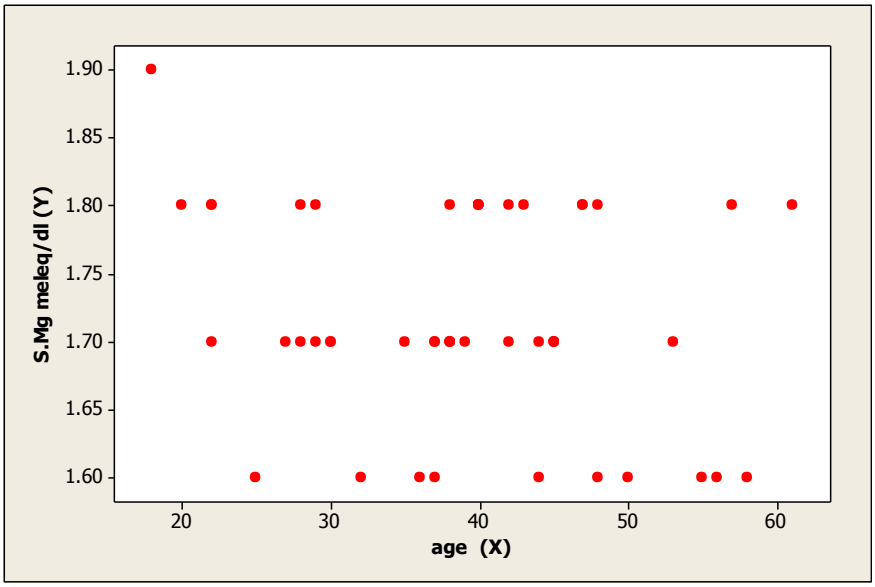

Fig. (1): Relation between age and serum Mg level.

Table (3) Effect of gender on serum Mg level: Gender had no effect on serum Mg level since it not statistically significant when assessed using t test with p value 0.114.

Table 3: Comparison between patients and control serum Mg distributed by gander.

	No.	Mean ± SD	P value
Patients (male)	29	1.7310 ± 0.0761	0.114 (not sig diff.)
Patients (female)	18	1.7000 ± 0.0840	
Controls (male)	27	1.7630 ± 0.0926	
Controls (female)	23	1.7435 ± 0.0896	
There was no statistical differences between each group, assessed using one way ANOVA with level of significance of 0.005			

Table (4) When assessing the effect of BMI on serum Mg level it was found that there is positive relation between BMI among patient and control and serum Mg level which mean that there is increase in serum Mg level associated with increase in body mass index with statistical significant p value 0.024.

Table 4: Relationship of BMI on serum Mg level.

BMI	**Patients**		**Control**		**P value**
	Mg (mean±SD)	**No.**	**Mg (mean±SD)**	**No.**	
< 25	1.7	1	1.6667 ± 0.0816	6	0.024
25 – 29.9	1.7 ± 0.0894	11	1.75 ±0.0707	18	
≥ 30	1.7257 ± 0.078	35	1.7769 ± 0.0951	26	
One way ANOVA was used, level of significance = 0.05					

Table (5) shows no statistical significant among patients and control regarding serum albumin, serum calcium and serum potassium.

Table 5: Serum electrolytes and albumin of patients and control.

Variable	**Patients**	**Control**	**P value**
Serum albumin mg/dl	41.223 ± 6.196	41.632 ± 6.223	0.747
Serum Calcium mg/dl	9.2894 ± 0.3364	9.284 ± 0.299	0.934
Serum Potassium mg/dl	4.4255 ± 0.4585	4.514 ± 0.3625	0. 293
Level of significant was 0.05, using t test			

Table (6) and fig. (2) multiple linear correlation between serum Mg and (albumin, calcium, and potassium) To assess the effect of calcium, potassium, and albumin on serum Mg level multiple linear regression method was used and was found no effect of these on Mg levels in patients.

Table 6: Effect of different variable on serum Mg levels using multiple linear regression method in patients.

Variable	B	Beta	P
Albumin	0.000025	0.01	0.99
Calcium	0.01623	0.41	0.685
Potassium	-0.00937	-0.34	0.733
B: coefficient, Beta: intercept, All variable had no effect on serum Mg level since there P value more than 0.05 (level of significance)			

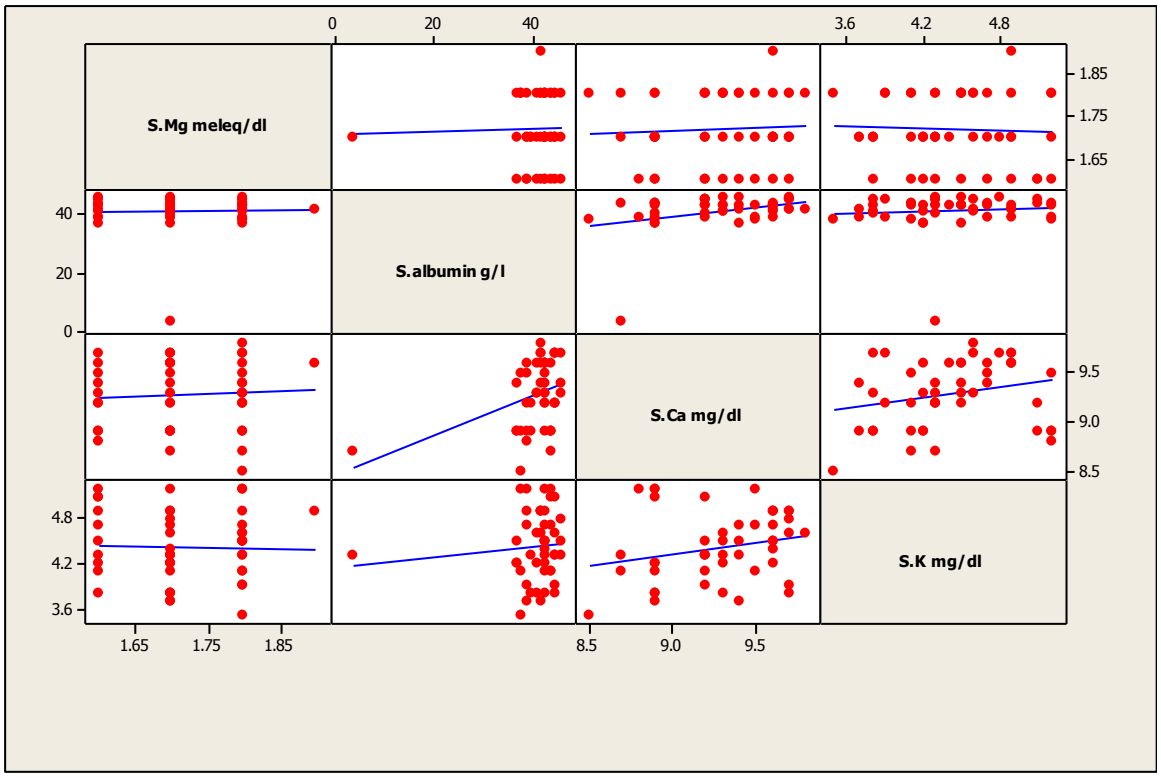

Fig. (2): multiple linear regression method between S.Mg, S. albumin, S.K and S.Ca.

Table (7) comparison between the effect of different type of PPI on serum Mg level in patients: there was no effect on serum Mg level since both PPI was not statistically difference when assessed using t-test, also the sample size for lansoprazole is small making its statistical predictability low.

Table (7): Distribution of serum Mg according to PPI used in patients.

PPI	No.	Mean ± SD	P value
Omeprazole	40	1.7150 ± 0.0834	0.4 (not sig.)
Lansoprazole	7	1.7429 ± 0.0535	
Level of significance was 0.05 using t-test			

Fig (3) relationship between serum Mg and duration of using PPI in months. There was a linear relationship between Mg level and duration of using PPI in months with p = 0.021, in which as the duration of therapy increased serum Mg were decrease by – 0.0106 for each month, but since the sample size was relatively small the regression equation had low prediction capability. Linear regression (correlation) was used to assess the existence of linear relationship between variable.

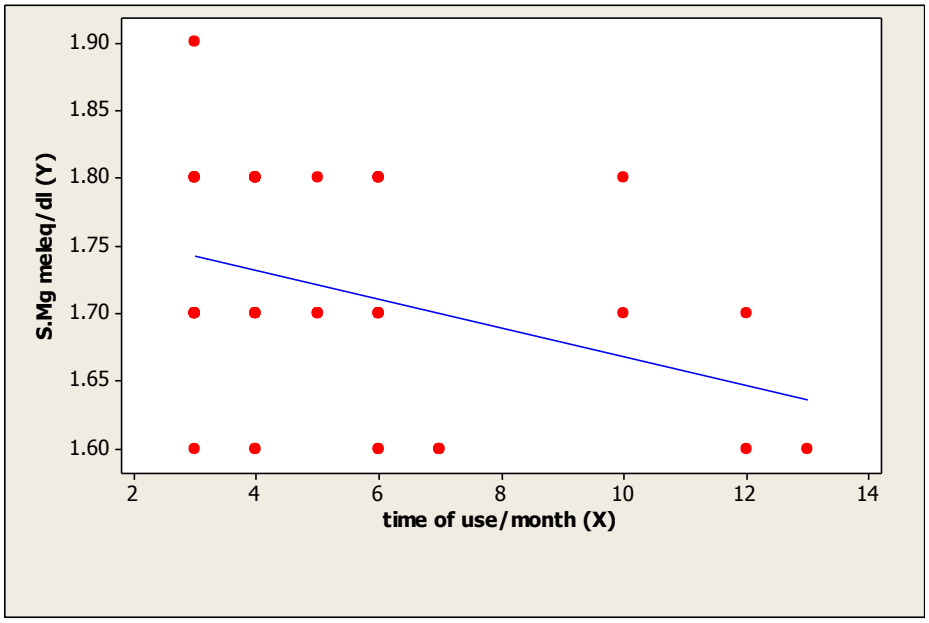

Fig. 3: Relation between S. Mg and duration of use PPI per month.

DISCUSSION

In this study, no patient had hypomagnesaemia, although 47 were using PPIs. This may be due to the exclusion criteria of this study, which withdrew patients with conditions or using drugs commonly associated to hypomagnesaemia, such as chronic diarrhea, vomiting, use of diuretics, gentamicin, cisplatin, cyclosporine, and others.[20] Data from this study suggest that the association between PPI use and hypomagnesaemia is uncommon. It is possible that hypomagnesaemia occurs in patients with genetic susceptibility, which may become clinically evident with PPI use. Several inherited diseases were described as causing low serum magnesium. Hypomagnesaemia with secondary hypocalcaemia is caused by a defect in TRPM6 channel, present in the intestine and renal tubules. The loss of function of TRPM6 leads to a reduction in intestinal absorption of magnesium, also accompanied by decreased renal reabsorption of this cation.[24] There are other hereditary causes of hypomagnesaemia that lead to renal losses, such as familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, where a mutation in the gene encoding claudin-16, a tight junction protein present in the kidney responsible for the paracellular transport of magnesium, decreases magnesium reabsorption. Gitelman's syndrome also affects renal transport, and is characterized by hypomagnesaemia and hypokalemia. Bartter's syndrome may have mutations of various proteins, and all these mutations affect the transport of magnesium through the thick ascending loop of Henle.[25] All patient included in the study were unintentionally have gastro-esophageal reflux disease GERD that result may be due to natural symptoms of disease and its chronicity make those patient more adherent to their drugs (PPI) than patient using PPI for different reason, also we find that percentage of male are more than female and body mass index BMI are significantly higher in patient group than control group with mean BMI 31.83 for patient and 29.58 for control p value 0.002, that can be explained by obesity as a risk factor for GERD.[26] Also there is no difference between patient and control group regarding mean age which is around 38 years in both group. We found that there was marginal statistical significance difference between mean serum Mg level of patient and control group (1.7191mg/dl for patient and 1.7540 for control) p value 0.048 this result are slightly different from the study done which reveal out-of-hospital PPI use was not associated with higher odds for a low serum magnesium level at the time of hospital admission.[27] this study was the second epidemiological investigation of the potential association between PPI use and hypomagnesaemia other than case series.[28] the difference in result may be because of difference in method of both studies as long as the Cambridge study concentrate only on patient already have hypomagnesaemia and they neglect the duration of use of proton pump inhibitor, in other word they were examining the prevalence of hypomagnesaemia due to PPI drugs. We find by regression equation method a linear relationship between serum Mg level and duration of PPI use in months with p value 0.021, that mean as duration of therapy increase serum Mg decrease month by month this effect was not change when we tack in to account the type of PPI. Although this finding have low prediction capability due to small sample size, it supports United State FDA concern about PPI, which depend for its announcement on case report around the world rather than randomized control study.[9] There was no statistical difference in comparison between patient and control group regarding serum albumin, calcium and potassium, also we use multiple linear regression method to examine the effect of albumin, calcium and potassium on serum magnesium in patient group and we find no statistical significant regarding these variables, this results are similar to results of Gustavo brazil.[29] except for association

between serum albumin and serum magnesium which is positively correlated in Brazilian study but not correlated regarding our study. There was no effect of gender on serum magnesium level in patient and control group was found that result was comparable to N. Bohnen and other studies that found no effect for gender on Mg level.[30] Also there is no effect for age on serum magnesium this result was similar to result of other study regarding this point.[31] Unexpectedly we find that there is positive relationship between BMI and serum magnesium which mean that increase in BMI associated with increase in serum magnesium level which is different than Francesco et al in his study found no effect of BMI on serum Mg.[32]

CONCLUSION

Patient using proton pump inhibitor drugs for 3 months and more have lower mean serum magnesium level in comparison with control group but still the mean serum magnesium in both group with in the reference rang further studies which includes more patient are needed.

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