Long Term Use of Proton Pump Inhibitor and Vitamin D Deficiency, A Survey-based study.

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Abstract

Vitamin D deficiency is a worldwide problem, it regulates the functions of over 200 gene and its essential for growth and development of human body, Vitamin D deficiency is linked to a wide range of several chronic and infectious diseases. Proton pump inhibitor (PPIs) were clinically introduced more than 25 years ago and have since proven to be effective and safe for the management and treatment of many types of gastrointestinal disorders, such as Helicobacter pylori infection, GERD, Zollinger-Ellison Syndrome. In conditions related to acidity, proton pump inhibitors (PPIs) are a common antacid medication. By inhibiting the H+/K+ ATPase enzyme, which regulates acid synthesis, they lower stomach acid secretion. In 2011 Food and Drug Administration USA, alarms the concomitant use of PPI for long time have been associated with risk of fracture. To Find the relationship between PPI and vitamin D deficiency, we performed a questionnaire-based survey among general population of Karachi Sindh, Questionnaire consists of age, sex, occupation, tea consumption, number of fractures, healing time of fracture and the vitamin D level.

This survey-based study was undertaken in the province of Sindh, Karachi, to check the impact of PPIs on vitamin D, A vitamin that can regulate different function in the body, the data collection form included demographic characteristics, Acidity and its duration, consumption of tea in a day, pain in bone and joints, bone fracture and its healing time, medicine used to overcome acidity, and their vitamin D level and status by the population. All the information were kept private and secure.

In this study, we expected that long-term use of proton pump inhibitors would lower vitamin D levels, resulting osteoporosis and other bone problems. Vitamin D aids calcium absorption in the bone, and low levels of vitamin D in the blood may have a mediating influence on these effects. If proper calcium absorption does not occur in the bone, it may result in a number of bone illnesses.

Keywords

Proton pump inhibitor (PPIs), Vitamin D deficiency, over-the-counter (OTC)

1. INTRODUCTION

The 25-hydroxy vitD, is associated with the absorption of calcium, bone metabolism, and to maintain its homeostasis in the body (Wakeman *et al*., 2021) inadequacy of vitamin D in the body can lead to demineralization of bone but several other chronic diseases have been associated with it such as, cardiovascular disease, cancer, multiple sclerosis, diabetes mellitus (Gröber *et al*., 2012) latterly, it has been found that the inadequacy of 25-hydroxy vitamin D in the body can lead to severity of covid-19 disease (Jiang *et al*., 2021). It has been estimated that almost one billion of world population are vitamin deficient and approximately 50% of the world population have 25-hydoxy vit D insufficiency (Siddiqee *et al*., 2021). However, it is necessary to find out that osteoporosis, osteoporotic fractures, rickets and osteomalacia have been linked to vitamin D deficiency (Riaz *et al*., 2016). Practically, deficiency of vitamin D in the body decrease the protection against fracture which have been provided by many drug used to treat osteoporosis among many patient (Bertoldo *et al*., 2022).The proper dietary status of vitamin D is significant for the preservation of bone health. Serum vitamin D is a crucial component in controlling the balance of calcium, phosphorus, and bone metabolism (Gu, P., *et al*., 2023).

In 1989, omeprazole has been introduced as a first PPI and it remain a mainstay in the treatment of Acidity, later on six PPIs have been approved by FDA till 2015 (Strand *et al.,* 2017). Proton pump inhibitor are the most commonly prescribed medicine in clinical practice, there mechanism is to bind irreversibly to the hydrogen potassium ATPase which can lead to reduce the gastric acid secretion from the parietal cell of stomach, and used to treat several gastrointestinal disorder such as Ulcers, H-pylori infection, Zollinger Ellison syndrome (Fournier *et al* ., 2009 ; Thong *et al*., 2020).The estimated sale of prescription and over the counter PPIs was 13 billion dollar in 2020 (Ghebre *et al*., 2020). PPIs affect the bone mineral metabolism, it can reduce the secretion of hydrochloric acid in the stomach which is an important precursor of calcium absorption in small intestine (Targownik *et al* ., 2008). In order to add new safety information about a potential increased risk of hip, wrist, and spine fractures with use of these drugs, the US Food and Drug Administration updated the prescription and over-the-counter (OTC) labels for PPIs in 2010 (Heidelbaugh *et al*., 2013). PPIs may raise your risk of fracture, however not all studies support this claim. Recent meta-analyses of observational studies reveal an increased risk of hip, spine, and other fractures, however the majority draw short-term, limiting findings (Kondapalli, A.*et al*., 2021).

To address this issue, we have performed a questionnaires-based study related to long term use of proton pumps inhibitors and deficiency of vitamin D in which different question have been asked by the participants, to find out the association between vitamin D and proton pump inhibitors. Finally, we will discuss the implications for clinical practice, and determine the need for future research.

2. MATERIALS AND METHOD

2.1. Study Design

This survey-based study was undertaken in the province of Sindh, Karachi, to check the impact of PPIs on vitamin D, a vitamin that can regulate different function in the body.

2.2. DATA COLLECTION

Data were collected through an online questionary from a general population of Karachi, from September 2022 to November 2022, the data collection form included demographic characteristics, Acidity and its duration, consumption of tea in a day, pain in bone and joints, bone fracture and its healing time, medicine used to overcome acidity, and their vitamin D level and status by the population. All the information were kept private and secure.

2.3. STATISTICAL ANALYSIS:

The data were analyzed using statistical package for social sciences (SPSS) version 16.0, Results were presented in the form of frequency and percentages as graphical and tabular presentations.

3. RESULTS AND DISCUSSION

3.1. Demographic Characteristics of participants:

The participant base-line demographics are shown in Table 1. In this study, 200 participants were included, the majority were females (N=131, 65.5%), the frequency of male were (N=69, 34.5%). Among 200 participants (N=81, 40.5%) were married and (N=118, 59%)were un-married. Among 131 females (N=73, 36.5%) was working women and from total males(N=54, 27.0) were working men.

Table 1. Demographic Characteristics of Participants

AGE	Frequency	Percent
15 to 25	64	32.0
25 to 40	119	59.5
40 to 60	17	8.5
Total	200	100.0

Table 1.1. SEX

SEX	Frequency	Percent
Male	69	34.5
Female	131	65.5
Total	200	100.0

Table 1.2 Marital status

Marital Status	Frequency	Percent
Married	81	40.5
Unmarried	118	59.0
Widow	1	.5
Total	200	100.0

Table 1.3 Occupation

Occupation	Frequency	Percent
Working women	73	36.5
Working men	54	27.0
House wife	12	6.0
Student	61	30.5
Total	200	100.0

3.2. Heart burn and tea consumption

The Participant history of getting heart burn and tea consumption shown in table 2.0 to 2.4.Among 200 participants, majority of them (N=140, 70%) were suffered from acidity and duration of acidity were found occasionally

(N=112, 56%) and total 22 participants(N=22, 11%) were suffering for more than one year. From total number of participants, eightyone of the participants (N=81, 40.5%) drunk tea twice a day and (N=42 ,21%) were drinking tea three times a day and (N=38, 19%) were drinking tea once a day and (N=28, 14%) didn't take tea. Among 140 of the participants suffered from acidity, in 48 of the participants (N=48, 24%) acidity normally happen, meanwhile (N=45, 22.5) of them got heartburn after having meal and (N=22, 11%) of them got acidity after drinking or having meal.However, (N=73, 36.5) of the participant didn't get heart heartburn after getting meal or drinking tea.

Table 2.0 Acidity Heart Burn

Acidity	Frequency	Percent
Yes	140	70.0
No	60	30.0
Total	200	100.0

Table 2.1 Duration of Acidity Heart Burn

Duration	Frequency	Percent
Occasionally	112	56.0
More than One Month	7	3.5
More than Six Month	7	3.5
More than Year	22	11.0
None	52	26.0
Total	200	100.0

Table No 2.2 Tea Consumption

Tea Consumption	Frequency	Percent
One time in a day	38	19.0
Two times a day	81	40.5
Three times a day	42	21.0
More than Three times	11	5.5
None	28	14.0
Total	200	100.0

Table 2.3 Acidity

Acidity	Frequency	Percent
After Having Meal	45	22.5
After Drinking Tea	11	5.5
BOTH	23	11.5
Normally happen	48	24.0
NONE	73	36.5
Total	200	100.0

3.3. Pain in bone, bone disease, bone fracture and healing time

The participants history of pain in bone, bone disease, bone fracture and the time required by the bone for healing has been shown in table 3. Among 200 participants, (N= 127, 63.5%) were feeling pain in their bone and joints, whereas (N= 73, 36.5%) didn't feel any pain. (N=185, 92.5) of the total individuals had no bone disease, where 4 of them had arthritis and 5 of them had osteoporosis. In total of 200 individuals, fifty people (N=50, 25%) had bone fracture in which 38 (N=38, 19%) of the individual their fracture healed within one to 3 month, where as 7 (N=7, 3.5%) of them required 3 to 6 months, Meanwhile, 2 of them required 6 month to 1 year and 3 of them required more than 1 year.

Table 3.0 (Pain in bone, Bone Disease, Bone Fracture and Healing)

Pain	Frequency	Percent
YES	127	63.5
NO	73	36.5
Total	200	100.0

Table 3.1 (Bone Disorder)

Bone Disorder	Frequency	Percent
Osteoporosis	5	2.5
Arthritis	4	2.0
NONE	185	92.5
OTHER	6	3.0
Total	200	100.0

Table 3.2 (Bone Fracture)

Bone Fracture	Frequency	Percent
YES	50	25.0
NO	150	75.0
Total	200	100.0

Table 3.3 (Healing Time)

Healed time	Frequency	Percent
1 month to 3 months	38	19.0
3 months to 6 Months	7	3.5
6 Months to 1 year	2	1.0
More than 1 year	3	1.5
NONE	150	75.0
Total	200	100.0

3.4. Duration of Medicine and Vitamin D lab results

The participants history of medicine usage, its duration and vitamin d levels and their vitamin D status shown in table 4 to 4.4. Among 200 participants, 143 individuals (N=143, 71.5) used omeprazole (Risek) to reduce their acidity, whereas 39 (N=39, 19.5%) of them used antacids(Mucaine), However 16 of the total individuals (N= 16, 8%), used esomeprazole (Nexum) to reduce their acidity. 119 of the total individuals (N=119, 59.5%) used occasionally when acidity occur, where as 13 of them (N=13, 6.5%) of them used medicine from 1 month, However, 11 of them used medicine from 1 to 6 months, meanwhile 9 of them took medicine from 6 month to one year, nevertheless it is found that 153 (N=153, 76.5) of the total individual, got medicine without doctor's prescription, whereas 47 (N=47, 23.5%) of them required prescription. 79 (N=79, 39.5%) of the total individual tested their vitamin D level, whereas 121 (N=121, 60.5%) of them didn't test their vitamin D test. 51 (N=51, 25.5%) had vitamin D deficiency, whereas 14 (N=14, 7) of them had vitamin D insufficiency, however 41 of them (N=41, 20.5) had normal vitamin D value.

Table 4. Medicine

Medicine	Frequency	Percent
Risek (Omeprazole)	143	71.5
Nexum (Esomperazole)	16	8.0
Zopent (Pantoperazole)	1	.5
Polypep (Famotidine)	1	.5
Ant Acid (Mucaine)	39	19.5
Total	200	100.0

Table 4.1 Duration of Medicine

Duration of Medicine	Frequency	Percent
0 to 1 Month	13	6.5
1 Month to 6 months	11	5.5
6 Month to 1 Year	9	4.5
Sometimes when Acidity occurs	119	59.5
None	48	24.0
Total	200	100.0
0 to 1 Month	13	6.5

Table 4.2 Doctor's Prescription

Doctor's Prescription	Frequency	Percent
YES	47	23.5
NO	153	76.5
Total	200	100.0

Table 4.3 Vitamin D Lab

Vitamin D	Frequency	Percent
YES	79	39.5
NO	121	60.5
Total	200	100.0

Table 4.4 Lab Result

Lab Result	Frequency	Percent
Deficiency	51	25.5
Insufficiency	14	7.0
Normal	41	20.5
None	94	47.0
Total	200	100.0

3.5. Association between PPI'S use and Vitamin D Deficiency

It has been found from as survey-based study that there is no association or risk between the long-term use of proton pump inhibitors and vitamin D deficiency. By using SPSS, it is found that the correlation between PPI's and vitamin D level is insignificance. $P > 0.05$.

Table 5.1 ANOVA

Model	Sum of Squares	Difference	Mean Square	F
1	Regression	1.212	1	1.212
	Residual	308.368	198	1.557
	Total	309.580	199	

Table 5.2 COEFFICIENTS

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig
		B	Std. Error	Beta		
1	(Constant)	2.983	.138		21.679	.000
	Medicine	-.049	.056	-.063	-.882	.379

Table 5.3 RESIDUAL STATISTICS

	Minimum	Maximum	Mean	Std. Deviation
Predicted Value	2.7361	2.9337	2.8900	.07805
Residual	-1.93374	1.26394	.00000	1.24482
Std. Predicted Value	-1.972	.560	.000	1.000
Std. Residual	-1.550	1.013	.000	.997

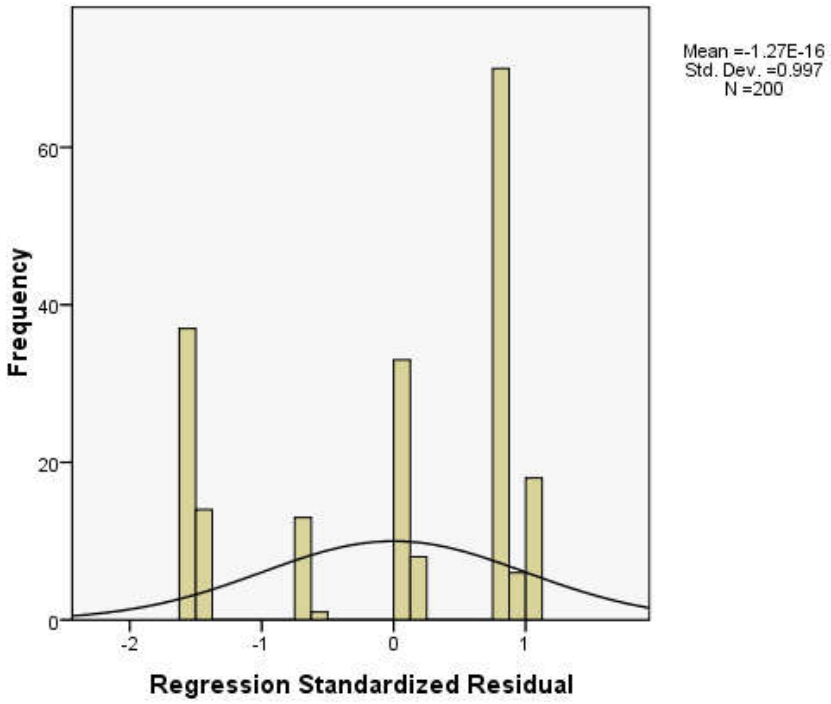

Fig.1: Regression

In this study, we expected that long-term use of proton pump inhibitors would lower vitamin D levels, resulting in osteoporosis and other bone problems. Vitamin D aids calcium absorption in the bone, and low levels of vitamin D in the blood may have a mediating influence on these effects. If proper calcium absorption does not occur in the bone, it may result in a number of bone illnesses.

Many pharmacological explanations have been put out to explain the link between PPI usage and fracture risk. A decrease in intestinal absorption of calcium has previously been postulated as a result of PPI therapy-induced hypochlorhydria and its impact on bone health (Abtahi *et al*., 2021).Studies examining how PPI medication affects bone mineral density have shown inconsistent findings. A slight drop in BMD levels has been linked to PPI use, according to certain studies , whereas other studies have revealed no differences in BMD scores and rates of BMD, which decline between PPI and non-PPI users (Fraser, L.A *et al*., 2013). Understanding the three-way interaction between calcium, parathyroid hormone, and magnesium is crucial. while having normal vitamin D levels, hypomagnesemia can reduce PTH or result in secondary hypocalcemia. When magnesium levels are corrected, PTH levels increase, which raises serum calcium (Gandhi, N.Y *et al*., 2012). In a dose-response relationship, the mortality risk among PPI users increased with continued usage. Compared to an SMR of 1.29 found during 1-2.9 years of follow-up, we saw a 38% increase in the risk of all-cause mortality at >5 years of usage (Ngwenya *et al*., 2018).

Limited experimental evidence suggest that PPIs may block the osteoclastic proton transport system, which could potentially reduce bone reso-

rption, even if PPI medication may impede insoluble calcium absorption when given without a meal (Yu-Xiao Yang 1, J.D.L *et al*., 2006).

Stewardship program's that are required to lessen incorrect prescribing, avoid complications, and save time and money can be put in place to reduce the inappropriateness of PPI prescriptions. To raise understanding the standards for appropriate PPI prescription, enhance staff practices and behaviors, and reduce the inappropriate use of PPIs, ongoing education programs and knowledge assessments of the healthcare workforce are also crucial (Abdallah Damin Abukhalil, O.A *et al*., 2023).

Limitations

This review has a number of restrictions. Regarding the determination of real drug exposure (including intermittent symptomatic use or over-the-counter availability) and the accuracy of fracture diagnosis, research' quality is often variable. Since all of the studies were observational in nature, residual confounding may still exist even after statistical correction. Patients who have been exposed to PPIs may have unmeasured risk factors, and confounding by indication is definitely a possibility.

Although a randomized trial involving patients receiving PPI medication would be ideal, it is uncertain whether such a trial will have the sample size and study period needed to record enough fracture instances (or to assess individual PPIs) to show this effect. Future research should present and modify for the analyses to take into account fracture risk variables and the need for PPI therapy.

4. CONCLUSION

Over all, this survey-based study found that long term use of proton pump inhibitor is not associated with vitamin D deficiency, However further studies will be necessary in order to find out the association between acid suppressants (PPI's) and vitamin D deficiency.

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