

DOI: <https://dx.doi.org/10.18203/2319-2003.ijbcp20251067>

Original Research Article

Long-term use of proton pump inhibitors and its impact on glucose homeostasis: results of a prospective observational study

Arjemand Rangshoo¹, Shagufta Parveen², Nisar A. Shah^{3*}, Mariya A. Qurieshi⁴,
Umer Iqbal⁵, Shah Immad⁶

¹Department of Pharmacology, GMC Baramulla, Jammu and Kashmir, India

²Department of Pharmacology, GMC Srinagar, Jammu and Kashmir, India

³Department of Gastroenterology, GMC, Srinagar, Jammu and Kashmir, India

⁴Department of Social and Preventive Medicine, GMC Srinagar, Jammu and Kashmir, India

⁵Department of Anaesthesia, GMC Baramulla, Jammu and Kashmir, India

⁶3rd Phase Part-II MBBS Student, GMC Srinagar, Jammu and Kashmir, India

Received: 14 March 2025

Accepted: 10 April 2025

*Correspondence:

Dr. Nisar A. Shah,

Email: nisarshah19@gmail.com

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ABSTRACT

Background: Proton pump inhibitors (PPIs) being the commonly used medications in various gastrointestinal diseases, and were so far considered as most tolerated and safe medications with few, mild adverse effects associated with their use, but of late there have some concerns emerged on their long-term use and the one important observation is their impact on glucose homeostasis. Aim of the study was to measure the dysglycemic potential of proton pump inhibitors by estimating blood sugar and HbA1c at baseline, 6 months and 1 year follow up in patients put on long-term PPIs.

Methods: 150 patients of both the sexes, aged ≥ 18 years and diagnosed as gastroesophageal reflux disease (GERD), functional dyspepsia or ulcer dyspepsia were included in the study. Patients excluded from the study were those who didn't consent for their inclusion, known cases of diabetes, any liver or renal disease, pregnant ladies and the ones who were on medications like NSAIDs, steroids or any other hormone.

Results: Mean age of the studied subjects being 41.5 ± 14.6 years with the male: female ratio of 1.1:1. The mean body mass index (BMI) of the patients was 24.5 ± 2.7 kg/m². Prevalence of hypertension and hypothyroidism and hypercholesterolemia among the participants was 36%, 34.7% and 36.7% respectively and 18% participants had family history of diabetes.

Conclusions: The conclusions that can be drawn from the presents study are that in patients undergoing long-term more than 12 weeks treatment with PPI, there is a significant increase in overall blood glucose parameters, as measured by fasting blood glucose, random blood glucose, and glycosylated haemoglobin.

Keywords: PPIs, Dys-glycemia, ADRs of PPIs

INTRODUCTION

Proton pump inhibitors (PPIs) are among the top 10 most commonly used medications worldwide, and are used as a part of the management protocol for a large array of conditions, ranging from standalone treatment for conditions such as gastroesophageal reflux disease (GERD) and esophagitis to as an adjunct to antibiotics in

eradication of infections such as *H. pylori*.^{1,2} PPIs have emerged as the chief treatment for GERD and peptic ulcer disease due to their effectiveness and low toxicity and are thus being used as first choice drugs for these conditions for a period of 4-8 weeks.³ In combination with antibiotics, they are used for eradication of *H. pylori* infection and are also indicated as a simultaneous medication to prevent

aspirin and other NSAID related ulcers in high-risk patients.²

It is generally accepted that short-term use of PPIs for valid indications is safe, well tolerated, with mild and reversible side effects that include headache, diarrhoea, abdominal pain, nausea, constipation, skin rashes and dizziness.³ However, long-term use of PPIs has been linked to various adverse effects like pathological fractures, chronic kidney disease, enteric infections, pneumonia, gastric cancer, obesity, dyslipidemia, liver dysfunction and certain deficiencies like vitamin B12, vitamin C, calcium, and magnesium and long term use of PPIs has also been found to be associated with rebound hypersecretion syndrome and dysglycemia.^{4,5} These effects have led to warnings being issued against overuse of PPIs, and an increasing interest in research exploring the long-term effects of these drugs as India being currently considered the diabetes capital of the world, with 77 million of its population suffering from the disease, with the burden of the disease projected to increase even further in the coming years. In this context, the present study was conducted in order to identify the potential for dysglycemia among patients on long-term proton pump therapy and assess the socio-demographic correlates among them.

Aims and objectives

Aims and objectives of the study were to measure the dysglycemic potential of proton pump inhibitors by estimating blood sugar and HbA1c at baseline, 6 months and 1 year follow up in patients put on long-term PPIs, and also to estimate the time taken by PPIs to cause dysglycemia on their long-term use.

METHODS

The study was conducted by the Department of Pharmacology, Government Medical College, Srinagar, in collaboration with the department of Gastroenterology and Hepatology, Shireen Bagh super-specialty hospital Srinagar over a period of 18 months from June 2021 to November 2022 as an observational study with prospective longitudinal design on an adult population of 150 patients of both the sexes. Patients included were those aged ≥ 18 years and diagnosed as GERD, functional dyspepsia or ulcer dyspepsia. Patients excluded from the study were those who didn't consent for their inclusion, known cases of diabetes, any liver or renal disease, obesity, pregnant ladies and the those on medications known to cause dysglycemia like NSAIDs, steroids, thiazides, hormones etc.

After approval from the institutional ethical committee (No: GMCS/Acad/SS/9155-63/MC), adult patients presenting to the study institution and fulfilling the inclusion criteria and providing written informed consent were interviewed using a pre-designed, pretested proforma containing questions regarding their sociodemographic characteristics, medical and drug intake history. Following

their prescription of PPI by the physician, the regimen of the drug was noted down in the proforma. Each patient then underwent fasting blood sugar, random blood glucose and HbA1c assay before the start of the treatment, and the findings were noted down in the proforma. Then each of the patients were followed up for a period of 1 year, with reviews at 6 months and 1 year, where they underwent fasting blood sugar, random blood glucose and HbA1c assays again, and the results of those tests were again noted down in their individual proformas.

Data management and statistical analysis

The collected data were checked for consistency, completeness and entered into Microsoft excel (MS-excel, Microsoft Corp.) data sheet and analysed with the statistical program statistical package for the social sciences (IBM SPSS, version 22). Data were organized and presented using the principles of descriptive and inferential statistics. The data were categorized and expressed in proportions. The continuous data were expressed as mean $\pm$ SD. The data were graphically presented in the form of tables and bars. Where analytical statistics were performed, a p value of <0.05 was considered to be statistically significant for the purpose of the study. For analytical statistics, Chi-square test was used for categorical data and student's t-test was used for continuous data.

RESULTS

Most of the study participants were between 21 and 40 years of age with the mean age of the studied subjects being 41.5 ± 14.6 years with the male: female ratio of 1.1:1. Most of the participants had a BMI between 18.5 and 24.9 kg/m^2 , classifying them as 'normal' as per the World Health Organization (WHO) international classification of BMI. The mean BMI of the patients was $24.5 \pm 2.7 \text{ kg/m}^2$. Prevalence of hypertension, hypothyroidism and hypercholesterolemia among the participants was 36%, 34.7% and 36.7% respectively and 18% participants had family history of diabetes. Rabeprazole was the most commonly used PPI in more than 58%. After a follow up of six and 12 months, a significant increase in fasting blood sugar (FBS), random blood sugar (RBS) and HbA1c levels was observed.

Table 1: Distribution of study participants according to chief presenting complaint (n=150).

Chief presenting complaint	Frequency	Percentage
Burning sensation in upper abdomen	6	4
Dyspepsia	3	2
Epigastric discomfort	18	12
Epigastric fullness	4	2.7
Pain abdomen	119	79.3
Total	150	100

As is evident from Figure 1, most common were the cases of antral gastritis (30%), followed by duodenal ulcer (25.3%) and pangastritis was seen in 15.3% of cases.

Amongst the prescribed PPIs, most commonly prescribed was rabeprazole (58.1%) followed by pantoprazole in 31%, esomeprazole in 9% and least prescribed was the omeprazole (Figure 2).

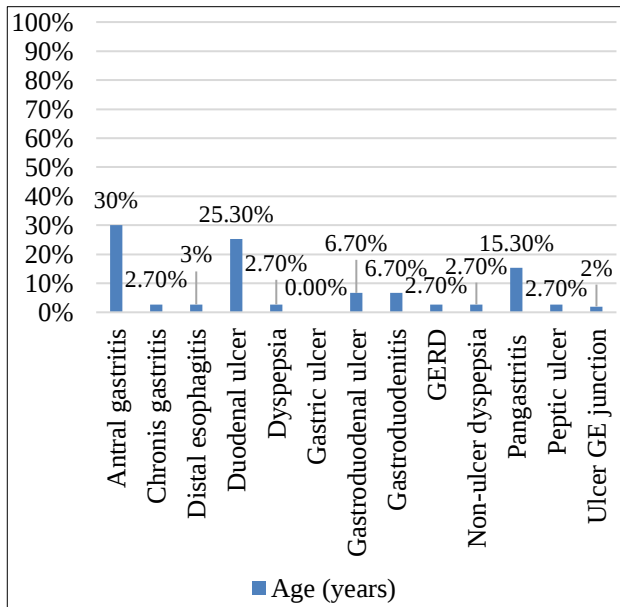


Figure 1: Distribution of study population as per clinical and endoscopic diagnosis.

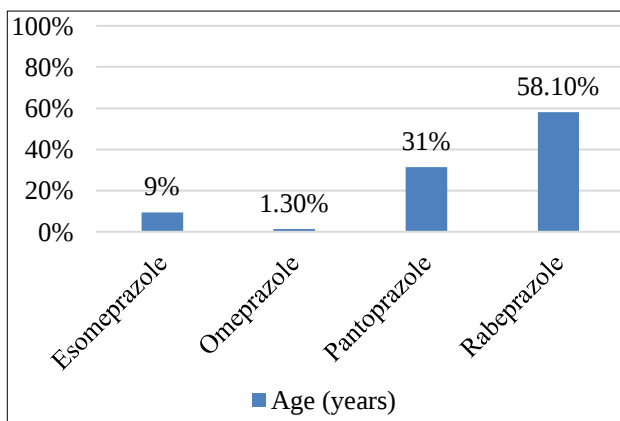


Figure 2: Distribution of study participants according to prescribed drug (n=150).

Table 2: Distribution of study participants according to mean blood sugar estimation parameters at baseline (n=150).

Blood glucose parameters	Mean	SD
FBS	87.6	10.4
RBS	138.5	15.7
HbA1c	5.1	0.3

Table 3: Distribution of study participants according to mean blood sugar estimation parameters at 6 months of follow-up (n=150).

Blood glucose parameters	Mean	SD
FBS	98.4	9.5
RBS	148.2	18.3
HbA1c	5.3	0.6

Table 4: Distribution of study participants according to mean blood sugar estimation parameters at 12 months of follow-up (n=150).

Blood glucose parameters	Mean	SD
FBS	105.6	10.6
RBS	159.9	21.3
HbA1c	5.5	0.5

DISCUSSION

The present study was used to explore the possibility of dys-glycemia with the long-term use of PPIs, though a serious yet an unexplored adverse effect. Among a group of patients, who had been prescribed and had been using PPI for a long-term period, the incidence of dys-glycemia was ascertained by following-them up for the study period.

Over the course of the study, a total of 150 patients were recruited, each being prescribed one of the commonly used PPI drugs (esomeprazole, omeprazole, pantoprazole, and rabeprazole) for long-term use (>6 months). These patients were examined at baseline, with follow-ups at 6 and 12 months to ascertain the dys-glycemic potential of the drugs by means of estimation of their serum blood sugar (fasting and random) and HbA1c levels.

It was seen that only 4% of the participants were below 20 years of age, with the mean age of the participants being 41.5 ± 14.6 years. It has been well-recorded in the existing literature that chronic gastrointestinal diseases that require long-term therapy with proton pump inhibitors are more common in older adults than their younger counterparts.⁶ Due to various physiological and metabolic changes, older adults often have impaired gastrointestinal function. This is especially pronounced in the elderly, who have impaired acid secretion, clearance, and saliva production. These make them prone to developing conditions that require chronic gastric acid suppression.⁷ This is also evident in the findings of the present study, where 42.7% of the participants were over 40 years of age. Similar age distribution in long-term PPI users have also been reported by Rajput et al and He et al in their studies on the topic.^{8,9}

While the proportion of male patients was found to be higher in the present study, it was marginal, with the male: female ratio being 1.1:1. This sex distribution is similar to what has already been reported in the published research. Abrahami et al reported that 48% of PPIs are prescribed in women.¹⁰ In separate research conducted by Hálfdánarson

et al, which looked into the nationwide usage of PPIs, findings indicated that although PPI prescriptions were more common among women, men were typically prescribed these medications for longer durations. Specifically, the study found that 55% of individuals who used PPIs on a long-term basis were men.¹¹

It was observed in the present study that the majority of the study participants had a BMI within the normal range as per the WHO international classification for BMI, while 45.3% were classified as being overweight. The mean BMI of the study participants was 24.5 ± 2.7 kg/m². It has been observed that a substantial proportion of PPI users are overweight, as compared to the general populace, by Hvid-Jensen in their research exploring the lifestyle factors among PPI users.¹²

The overwhelming majority of the patients presented with pain abdomen (79.3%), followed by epigastric discomfort (12%). When diagnoses were made (Figure 1), it was observed that the majority of the patients were suffering from antral gastritis (30%), followed by duodenal ulcers (25.3%) and other inflammatory conditions of the gastrointestinal system. Pain abdomen is a classical marker of the majority of these conditions, and a telltale sign of an ulceration. Most of the patients in the study sample had long-standing discomfort for which they did not seek treatment, so milder symptoms like abdominal discomfort or dyspepsia were under-represented in the present study. Gastritis and duodenal ulcers being the most common conditions for which long-term PPI therapy is indicated and has been reported by authors like Boj-Carceller, Hove et al, and Lin et al.¹³⁻¹⁵ In their meta-analysis, Gomez et al found that most patients on long-term acid suppression presented with abdominal pain precipitated either by gastric or by duodenal ulcers.¹⁶

Of the drugs prescribed (Figure 2), pantoprazole and rabeprazole were the most common. Rabeprazole and pantoprazole, among proton pump inhibitors (PPIs), are noted for their comparatively superior safety profiles. Notably, pantoprazole exhibits no drug interactions with a wide range of pharmacological agents, and the metabolism of rabeprazole is largely unaffected by the CYP2C19 and CYP3A4 cytochrome pathways.^{17,18} Furthermore, these drugs are relatively inexpensive and widely available in the study region. Therefore, they were the most commonly prescribed drugs for the management of the patients' conditions.

The primary goal of the present study was to evaluate the dys-glycemic potential of the long-term PPI therapy. It was measured by following-up the trends of change in the fasting and random blood glucose as well as the HbA1c levels of the participants over their yearlong treatment. At the baseline, the mean levels of fasting blood glucose, random blood glucose, and HbA1c levels were 87.6 ± 10.4 mg/dl, 138.5 ± 15.7 mg/dl, and $5.1 \pm 0.3\%$ respectively (Table 2). This was shown to increase statistically significantly to 98.4 ± 9.5 mg/dl, 148.2 ± 18.3 mg/dl, and

$5.3 \pm 0.6\%$ respectively at the end of 6 months of treatment (Table 3). A further statistically significant increase to 105.6 ± 10.6 mg/dl, 159.9 ± 21.3 mg/dl, and $5.5 \pm 0.5\%$ respectively was observed at the end of the 12-month follow-up (Table 4). The findings suggest that significant alterations in glucose metabolism occur in patients as soon as six months into treatment with PPIs, highlighting the drugs' potential to disrupt blood sugar regulation. This observed effect aligns with outcomes reported in other research studies focused on this subject.¹⁹

Hove et al in their study showed that there was an increase in the HbA1c levels of the patients after PPI therapy of 12 weeks, however, the increase was not found to be statistically significant.¹⁴ A significant increase in the fasting blood glucose levels of patients on long-term PPI therapy was observed by Imperatore et al in their study. The authors therefore reported that PPI therapy was an independent risk factor for the development of dysglycemia in patients without previously diagnosed metabolic syndromes.¹⁴ This alteration in glucose metabolism was asserted to be due to the alterations in the gut microbiota composition and functions that are precipitated by long-term exposure to PPI therapy in the patients. This increase in the blood glucose levels has been suspected to even progress to full-blown diabetes, as has been observed in the study conducted by Yuan et al, who reported that patients treated with PPI for more than 6 months had a 24% increased risk of developing diabetes mellitus.²⁰ Similar risk of developing or worsening of diabetes mellitus among patients treated with PPI for more than 6 weeks has been reported by He et al (OR 1.56, 95% CI 1.46, 1.66), and Ciardullo et al.^{9,19} Czarniack et al. found in their study that there was 1.69 times increased risk of developing type II diabetes mellitus among patients on long-term PPI use.²¹ Kuo et al further observed that among the PPIs, pantoprazole and lansoprazole were the most associated with an increased risk of type 2 DM.²² Finally, Guo et al conducted a systematic review and meta-analysis examining the association between PPI use and the incidence of diabetes among non-diabetics, and observed that there was a significant time-dependent association between the two.²³

On the other hand, not all research on the topic reported findings similar to the present study. In another sets of studies, such as those conducted by Moayyedi et al and Trang et al no statistically significant associations were observed between PPI use and development of dysglycemia.^{24,25} Furthermore, in their research, authors such as Crouch et al, Boj-Carceller et al, Lin et al and Naito et al observed that the use of PPI was associated with a lowering of HbA1c levels in the patients recruited to their samples.^{14,26,27} Lowering of blood glucose levels as a result of long-term PPI therapy have been observed by Villegas et al, Rajput et al, and Peng et al.^{8,28,29} However, most, if not all of these studies were conducted among diabetic patients, indicating that PPIs have different effects on the glucose metabolism in patients with and without diabetes. In those with diabetes, PPIs might have a beneficial effect

with respect to their glucose control, while in the general non-diabetic population; there is an increase in the blood glucose parameters. The observations made in the present study therefore indicate that the long-term use of PPI has a definite effect on the glucose metabolism, and in the general population, it is expressed as a statistically significant increase in the levels of serum glucose and HbA1c levels over the period of treatment, with the dysglycemic effects being evident within as early as 6 months of treatment with the medications.

CONCLUSION

The conclusions that can be drawn from the presents study are that in patients undergoing long-term more than 12 weeks treatment with PPI, there is a significant increase in overall blood glucose parameters, as measured by fasting blood glucose, random blood glucose, and glycosylated hemoglobin. This indicates to an increased dys-glycemic potential of these drugs when used over a long period, and thus an increased risk of DM. Though our results are consistent with some studies conducted earlier, there are few studies that have shown contradictory results in the form of improved glycemic control on long term use of PPIs in already diabetic patients. So before concluding that long term use of PPIs cause increase in incident diabetes and an improvement in glycemic control in already diabetic patients, further studies need to be conducted in this regard.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rangshoo A, Parveen S, Shah NA, Qurieshi MA, Iqbal U, Immad S. Long-term use of proton pump inhibitors and its impact on glucose homeostasis: results of a prospective observational study. *Int J Basic Clin Pharmacol* 2025;14:402-7.