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The effect of long-term proton pump inhibitor use on the visceral adiposity index

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ABSTRACT

Objective: To investigate whether long-term proton pump inhibitor (PPI) use (≥3 years) is associated with changes in visceral adiposity index (VAI) and lipid profile

Patients and Methods: Between September 2020 and May 2022, 51 long-term PPI users (PG) and 75 age – and sex-matched controls (CG) were enrolled. Demographics, waist circumference (WC), body mass index (BMI), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and VAI (calculated via validated sex-specific formulas) were recorded. Statistical analysis was performed using SPSS 23.0 with independent t-test/Mann–tests and logistic regression.

Results: The PG exhibited significantly higher WC (97.1 ± 19.8 vs. 90.1 ± 16.7 cm; p=0.036), TG (148.8 ± 58.3 vs. 125.8 ± 48.6 mg/dL; p=0.018), and VAI (2.74 ± 1.59 vs. 2.12 ± 1.47; p=0.028) compared to controls. HDL-C and LDL-C differences were not significant. Male sex approached borderline significance as a predictor of elevated VAI in regression analysis.

Conclusion: Long-term PPI use is associated with increased WC, TG, and VAI despite no significant changes in HDL-C or LDL-C, suggesting a potential metabolic risk. Clinicians should consider this when prescribing PPIs; prospective large population based studies are warranted.

Keywords: Proton Pump Inhibitors, Triglycerides, Visceral Adiposity Index

1. INTRODUCTION

Proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide due to their potent acid-suppressive effects and favorable safety profiles. Commonly used in the management of gastroesophageal reflux disease (GERD), peptic ulcers, and Helicobacter pylori (H.pylori) eradication regimens, PPIs are often prescribed for long-term use, sometimes beyond the recommended duration [1,2].

Emerging evidence suggests that long term PPI use (LTPPIU) may not be entirely harmless. The US Food and Drug Administration and some authors have determined that LTPPIU should be used for > 3 years [3,4]. Recent studies have shown a possible association between LTPPIU and infections, osteoporosis, dementia, cardiovascular disease (CVD), changes in lipid metabolism, and insulin sensitivity [5,6]. However, the relationship between LTPPIU and Visceral Adiposity Index (VAI) has not been studied. VAI is a validated, sex-specific marker that indirectly estimates visceral fat function and distribution by integrating waist circumference (WC), body mass index (BMI), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels [7]. It has been widely used in epidemiological studies to predict cardiometabolic risk independent of total adiposity. While some studies have indicated potential links between LTPPIU and dyslipidemia, such as increased serum TG and low-density lipoprotein (LDL) levels and decreased HDL levels, the underlying mechanisms remain poorly defined [8,9]. Gastric acid suppression may impact nutrient absorption, gut microbiota composition, or hepatic metabolism, all of which could contribute to adverse metabolic outcomes [10].

In this study, we aimed to evaluate the effect of LTPPIU on serum lipid parameter specifically TG, HDL, and LDL levels as well as VAI values. Our objective was to determine whether LTPPIU is associated with measurable changes in metabolic risk markers, with a particular focus on visceral fat accumulation.

2. PATIENTS and METHODS

This case-control study was carried out between September 2020 and May 2022, including a total of 126 participants: 51 long-term PPI users (PPI group, PG) and 75 age and sex matched controls (control group, CG). Demographic data including age, sex, menopausal status, family history of CVD as well as WC, BMI, and lipid panel results were recorded. Information on PPI

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type and duration was collected from the PG, with inclusion criteria defined as daily use for at least 3 consecutive years (pantoprazole ≥40 mg/day, omeprazole 20 mg/day, lansoprazole 30 mg/day, esomeprazole 40 mg/day, or rabeprazole 20 mg/day) [3,4]. Control subjects had no PPI use in the previous five years. Exclusion criteria encompassed: renal dysfunction (serum creatinine ≥ 1.2 mg/dL), presence or history of hyperlipidemia, cardiovascular events, peripheral arterial disease, diabetes, chronic inflammatory or autoimmune diseases, atrophic/metaplastic gastritis, active infection, liver or kidney disease, smoking, alcohol use, lipid-lowering or other lipid-modifying drugs, and pregnancy.

Waist circumference was measured at the midpoint between the iliac crest and the costal margin. BMI was calculated as weight in kilograms divided by height in meters squared. Venous blood samples were obtained after ≥8 hours of fasting. Samples were collected for measurement of glucose, creatinine, magnesium, total cholesterol, TG, LDL-C, and HDL-C. Analyses were performed on an Abbott Architect c16000 analyzer (Abbott Park, IL), with LDL-C calculated using the Friedewald formula. Magnesium was measured spectrophotometrically via the Arsenazo method. All subjects underwent both endoscopic and histopathologic evaluation, and rapid urease testing plus biopsy-based H. pylori assessment was performed according to the Updated Sydney System [11]. Histological assessment included evaluation for intestinal metaplasia, gastric atrophy, H.pylori density, inflammation, and neutrophilic infiltration. Patients presenting with gastric atrophy and/or intestinal metaplasia were excluded from the study, as per the predefined criteria.

Visceral Adiposity Index was calculated using sex-specific formulas validated by Amato et al.:

- Males:

$$VAI = [WC / 39.68 + (1.88 \times BMI)] \times (TG / 1.03) \times (1.31 / HDL\text{-}C)$$

- Females:

$$VAI = [WC / 36.58 + (1.89 \times BMI)] \times (TG / 0.81) \times (1.52 / HDL\text{-}C)$$

All measurements and calculations were conducted in accordance with standard protocols and validated reference equations from Amato et al. [7].

The study was conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects. All participants provided written informed consent. The study protocol was approved by the Dokuz Eylul University Ethics Committee on November 3, 2020 (approval number: 60116787-020/66559).

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) for windows. The Kolmogorov–Smirnov test was employed to check the normality of continuous variables. Comparisons between these variables were made using either the independent sample t-test or the Mann–Whitney U test, depending on data distribution. Categorical variables were compared using either the chi-square test or Fisher's exact test, depending on expected cell frequencies. A linear logistic regression model was constructed to identify independent predictors of VAI levels. Variables included in the model were age, sex, menopausal status, PPI use, endoscopic findings, H.pylori status, H.pylori density, neutrophilic infiltration, familial CVD history, A p-value <0.05 was considered statistically significant.

3. RESULTS

Analysis of population characteristics, endoscopic findings and Helicobacter status of study groups

Baseline characteristics and H. pylori status of both groups are presented in Table I. There were no significant differences between PG and CG in age, sex, menopausal status, family history of CVD, BMI, or H. pylori positivity ($p > 0.05$). Within the PPI cohort, usage was distributed as: esomeprazole 41.2%, lansoprazole 29.4%, pantoprazole 25.5%, and rabeprazole 3.9%; none were on omeprazole. There was a statistically significant difference between the groups in terms of esomeprazole ($p=0.00$). Average duration of PPI use was 7.98 ± 4.90 years.

Endoscopic findings of PG were chronic gastritis in 39.2% (20/51) of patients, erosive esophagitis in 31.4% (16/51) of patients, duodenitis in 17.6% (9/51) of patients, erosive gastritis in 5.9% (3/51) of patients, and normal imaging in 5.9% (3/51) of patients. Endoscopic findings of CG were chronic gastritis in 40% (30/75) of patients, erosive esophagitis in 21.3% (16/75) of patients, normal imaging in 18.7% (14/75) of patients, duodenitis in 18.7% (14/75) of patients, and erosive gastritis in 1.1% (1/91) of patients. There was a no significant difference between endoscopic finding distributions between groups ($p=0.281$). In PG, H. pylori organisms were identified histologically in 60.8% (31/51) of patients. Mild H.pylori density were observed in 43.1% (22/51), moderate in 15.7% (8/51), while severe in 2% (1/51). Mild mononuclear infiltrates were observed in 54.9% (28/51), moderate inflammations in 25.5% (13/51) while severe mucosal infiltrates were recorded in 5.9% (3/51). Activity as determined by mucosal neutrophilic infiltrations is; mild 56.9% (29/51), moderate 23.5% (12/51) and severe 7.8% (4/51). In CG, H. pylori organisms were identified histologically in 62.7% (47/75) of patients. Mild H.pylori density were observed in 57.3%(43/75), moderate in 4.1 %(3/75), while severe in 1.3% (1/75). Mild mononuclear infiltrates were observed in 66.7% (50/75), moderate inflammations in 12% (10/75) while severe mucosal infiltrates were recorded in 1.3% (1/75). Activity as determined by mucosal neutrophilic infiltrations is; mild 72% (54/75), moderate 10.7% (8/75) and severe 1.3% (1/75). There were no significant differences in histopathological parameters between groups. The patients with gastric atrophy or intestinal metaplasia were excluded according to study exclusion criteria.

Analysis of lipid profiles, WC and VAI status of study groups

Serum glucose, creatinine, total cholesterol, TG, LDL-C, HDL-C and magnesium levels of the groups are shown in Table I. Briefly, TG, WC, and VAI values were significantly higher in the PG group than in the CG group ($p<0.05$). Although, statistically non-significant,

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serum magnesium levels in PG were measured lower than CG (2.07 ±0.42 mg/dL versus 2.13±0.45 mg/dL, p= 0.191).

According to the results of linear regression analysis, only male gender (odds ratio,0,300; 95% confidence interval, 1.059–1.201; p =0.07) was a predictor for elevated VAI. None of the other variables (Age, PPI use, endoscopic findings, H.pylori status, H.pylori density, neutrophilic infiltration, menopause, CVD family history) included in the analysis showed a significant association.

Table I. *The population and laboratory characteristics in PPI group (PG) and controls (CG)*

Parameter	PG (n=51)	CG (n=75)	P-value
Age[1]	50.67 ± 14.54	52.63 ± 15.53	0.477
Sex[2] (male/female%)	39.2	34.7	0.656
Menopause[2] (%)	33.3	30.7	0.331
Family history[2] (%)	13,7	9,3	0.697
H.pylori positivity[2] (%)	60.8	62.7	0.720
BMI[1] (kg/m^2)	25.68 ± 4.40	25.55 ± 3.84	0.865
Waist Circumference[1] (cm)	97.08 ± 19.83	90.12 ± 16.71	**0.036**
VAI[3]	2.74 ± 1.59	2.12 ± 1.47	**0.028**
Triglycerides[3] (mg/dL)	148.75 ± 58.26	125.83 ± 48.58	**0.018**
Total Cholesterol[3] (mg/dL)	187.92 ± 53.57	182.21 ± 48.51	0.535
HDL-C[1] (mg/dL)	48.46 ± 13.89	57.89 ± 54.14	0.227
LDL-C[1] (mg/dL)	113.38 ± 38.27	110.34 ± 38.29	0.662
Glucose[1] (mg/dL)	98.49 ± 16.69	97.63 ± 14.36	0.757
Creatinine[1] (mg/dL)	0.755 ± 0.136	0.750 ± 0.153	0.842
Magnesium[1] (mg/dL)	2.07 ±0.42	2.13±0.45	0.191

BMI: Body Mass Index, VAI: Visceral Adiposity Index, LDL-C: low-density lipoprotein, HDL-C: high-density lipoprotein. Subjects were considered Helicobacter pylori (H. Pylori) positive if the bacteria were histopathologically detected and/or the local rapid urease test was positive. 1 Student t-test was used. 2Chisquare test was used. 3 Mann–Whitney U test was used. Results were presented as mean ±SD. P<0.05 was considered to be statistically significant.

4. DISCUSSION

Proton pump inhibitors are among the most frequently prescribed medications worldwide. Nevertheless, inappropriate and prolonged use of PPIs remains a major health concern. While PPIs were long regarded as safe, emerging evidence has associated their long-term use especially in older adults, at high doses with several adverse outcomes, including gastric polyps, micronutrient malabsorption, infections, osteoporosis, dementia, chronic kidney disease, and cardiovascular complications [1,2,3]. The results of our study demonstrate that individuals with LTPPIU exhibited significantly higher values of WC, TG, and VAI compared to non-users, although differences in HDL and LDL levels did not reach statistical significance. These findings contribute to the growing body of literature questioning the metabolic safety of LTPPIU.

Several possible mechanisms may explain the observed associations. LTPPIU has been hypothesized to alter the absorption of key micronutrients, such as magnesium and vitamin B12, which are involved in lipid metabolism and mitochondrial function [12,13].

Furthermore, PPI-induced hypochlorhydria may disrupt gut microbial balance, favoring dysbiosis, which has been independently linked to visceral fat accumulation and increased triglyceride synthesis [14]. Studies have demonstrated that PPI users exhibit reduced microbial alpha diversity, with increased abundance of *Streptococcus* and *Veillonella*, and decreased beneficial genera such as *Faecalibacterium* and *Bifidobacteria*. Further, dysbiosis in metabolically unhealthy obese individuals is characterized by "leaky gut," reduced shortchain fatty acids (e.g. butyrate), and chronic lowgrade inflammation [15]. Relief of symptoms related to chronic gastritis, erosive oesophagitis, and duodenitis through PPI therapy may encourage patients to increase meal size and diversify their diets, thus elevating caloric intake and contributing to subsequent weight gain. Indeed, an analysis of NHANES data from 2005–2006 (n=3,073) showed male PPI users experienced a statistically significant average weight gain of approximately 1.5 kg over one year [16]. A limitation of our study is that dietary diversity and physical activity status were not assessed. Yoshikawa et al., conducted a casecontrol study of 52 GERD patients treated with PPIs (omeprazole, lansoprazole, rabeprazole) for a mean of 2.2 years. Patients gained on average 3.5 kg (~6%), and BMI rose from 23.1 to 24.0 ($p < 0.001$), whereas age and sexmatched healthy controls exhibited no such changes [17]. These results are in agreement with the findings of our study.

Visceral Adiposity Index is an important parameter associated with metabolic syndrome, cardiac and cerebrovascular events, which is used to detect an increase in atherogenic visceral adipose tissue [7]. The elevation in VAI values in the PPI user group is particularly noteworthy. VAI has been shown to correlate closely with insulin resistance, metabolic syndrome, and subclinical atherosclerosis [18]. The higher VAI in our cohort of PPI users, even in the absence of significant HDL or LDL alterations, suggests that PPIs may affect fat distribution and visceral fat function more profoundly than traditional lipid markers can reveal.

Our findings are consistent with those of a retrospective cohort study by Kim et al., who reported increased TG levels in patients undergoing long-term PPI therapy [19]. Similarly, a study by Imperatore et al. indicated that LTPPIU was associated with metabolic syndrome and hepatic steatosis in Coeliac disease [20]. Our findings are consistent with other studies in the literature that have observed the adverse effects of PPIs on the lipid profile [21-24]. The suppression of PPI-related gastric acid secretion and the associated increase in the lipolytic activity of gastric fluid, leading to excessive lipid absorption in the small intestine, may be the most likely cause of our observation.

However, it is important to interpret our results in light of certain limitations. This was a cross-sectional analysis, which precludes the establishment of causality. Moreover, dietary habits, physical activity levels, and the duration/type of PPI used were not standardized, which could act as confounders. Nevertheless, the consistency of our findings with prior literature, along with the inclusion of a robust metabolic index like VAI, strengthens the validity of our results.

Conclusion

In conclusion, our study suggests that LTPPIU may be associated with unfavorable changes in lipid metabolism and visceral adiposity, as evidenced by elevated TG and VAI levels. In clinical practice, it is important to prescribe PPIs with the correct indication and duration. This is particularly important in patients with metabolic syndrome or CVD. Further prospective studies are warranted to better understand the underlying mechanisms and to assess the long-term metabolic implications of prolonged acid suppression therapy.

Compliance with Ethical Standards

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki on biomedical research involving human subjects. All participants provided written informed consent. The study protocol was approved by the Dokuz Eylul University Ethics Committee (approval number: 60116787-020/66559, date: November 3, 2020).

Conflict of interest: The author declare that there is no conflict of interest.

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