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Prevalence of Hyperprolactinemia in Patients Undergoing Long-Term Proton Pump Inhibitor Therapy

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ABSTRACT

Proton pump inhibitors used to treat gastrointestinal disorders cause various threatening effects and lead to an increase in serum prolactin levels. **Objectives:** To evaluate serum prolactin and macroprolactin levels in long-term proton pump inhibitor therapy patients. **Method:** An observational cross-sectional study was done between February 2023 and June 2024, at Niazi Welfare Foundation Teaching Hospital, Sargodha after approval from the institutional review board. Patients of either gender using proton pump inhibitors for ≥3 months, alone or in combination with histamine 2 receptor antagonists or pro-kinetics were included to measure serum prolactin levels. A duration of >3 months was taken as long-term therapy to see the impact on prolactin levels. The data were analyzed using SPSS version 25.0. **Results:** Out of the 166 patients, 102 (61.4%) were female, and 64 (38.6%) were male. The patient's mean age was 42.6 ± 14.3 years, and serum prolactin level was 23.2ng/mL. Among the participants, 97 (58.4%) had normoprolactinemia, while 69 (41.6%) had hyperprolactinemia. A significant increase in hyperprolactinemia with longer proton pump inhibitor treatment duration was revealed. **Conclusions:** It was concluded that prolonged use of proton pump inhibitors has the potential to raise serum prolactin levels, highlighting the importance of thorough evaluation for optimal clinical management.

INTRODUCTION

Proton pump inhibitors (PPIs) are frequently prescribed drugs, widely used to treat a variety of gastrointestinal (GI) problems like dyspepsia, peptic ulcer disease, gastroesophageal reflux disease (GERD), H. pylori eradication, and other disorders including Zollinger-Ellison syndrome. Over the past two decades, PPI usage has significantly risen due to their superior acid-suppressive effects [1, 2]. Combining PPIs with histamine 2 receptor antagonists (H2RAs) has shown greater benefits compared to using PPIs alone [3]. Additionally, PPIs are often paired with pro-kinetics in clinical practice, and this combination has proven effective in numerous studies [4]. Research studies have highlighted several threatening effects potentially linked to prolonged PPI use including risk of bone fractures, deficiencies in vitamin B12, and calcium, kidney disorders, a higher incidence of pneumonia, dementia, and cardiac events [5, 6]. Hyperprolactinemia can be classified as physiological, pathological, and pharmacological. Physiological hyperprolactinemia occurs due to natural processes such as pregnancy and stress, while pathological hyperprolactinemia is caused by hypothalamic-pituitary disorders, including tumors. The pharmacological form is triggered by medications like antipsychotics [7, 8]. In women, elevated prolactin levels can lead to symptoms such as infertility, painful intercourse, reduced libido, irregular menstrual cycles, oligo-menorrhea, amenorrhea, galactorrhea, and lower bone density. In men, hyperprolactinemia may result in

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erectile dysfunction, reduced sex drive, infertility, osteoporosis and weight gain. Additionally, results in galactorrhea and gynecomastia [9, 10]. PPI therapy's impact on endocrine hormones especially prolactin has been explored in various studies [11]. Many of these studies have found minimal or no effects on prolactin with short-term PPI use [12]. Some case studies noted a link of PPIs in causing hyperprolactinemia. These cases indicate that PPIs, whether used alone or in combination with pro-kinetics, can lead to varying increases in serum prolactin levels [13]. Studies have indicated an association of sexual and reproductive issues including gynecomastia with lansoprazole and omeprazole usage [14]. Moreover, there is a lack of studies on hormonal profiling with long-term PPI use, highlighting the need for such screening. Most research on the short-term effects of PPIs on endocrine hormones has focused primarily on male subjects. There is also a notable gap in information regarding long-term PPI use and hormonal issues in females. This underscores the necessity for studies that include both males and females to assess any gender-specific changes in biochemical hormonal profiles. Many medications, including PPIs, have been known to affect serum prolactin levels. Several studies conducted in tertiary care hospitals have identified PPIs as a common cause of drug-induced hyperprolactinemia [15, 16]. Proton pump inhibitors (PPIs) are frequently prescribed drugs, used to treat a variety of gastrointestinal (GI) problems. Although, PPIs are safe drugs research shows potential endocrine effects, particularly on prolactin levels. PPI usage is linked to raising serum prolactin levels by altering the gastric PH and affecting the dopamine bioavailability which has a role in inhibiting prolactin secretion. Drug-induced hyperprolactinemia leads to multiple comorbidities such as infertility, reduced libido, irregular menstrual cycles, oligo-menorrhea, amenorrhea, galactorrhea, and erectile dysfunction and impacts patients' quality of life. So, it's crucial to investigate the ill effects of PPI usage. However, the impact of long-term PPI use on serum prolactin levels has not been thoroughly investigated.

This study aimed to address this gap in the literature by evaluating serum prolactin and macroprolactin levels in patients of both genders undergoing long-term PPI therapy. It is imperative to understand the mechanism contributing to multiple ailments in the clinical area. This study will help clinicians in the early identification and management of complications associated with long-term PPI therapy.

METHODS

An observational cross-sectional study was done between February 2023 and June 2024, involving patients from the gastroenterology outpatient clinics at Niazi Welfare Foundation Teaching Hospital, Sargodha. The study was conducted after approval from the institutional review board documented with Ref No. IRB/NM&DC/173 and IRB No. NM&DC-IRB-64. The sample size was calculated using the Cochrane formula n=Z2 P(1-P)/d2 on open Epi software [17] based on 42% prevalence from a recent research study [14] employing a statistical power of 80% with 7% margin of error. The samples were gathered using a non-probability sampling technique. Participants included were # of either gender who had been using PPIs for ≥3 months, either alone or in combination with H2RAs or pro-kinetics to treat a variety of gastrointestinal (GI) problems like dyspepsia, peptic ulcer disease, gastroesophageal reflux disease (GERD), H. pylori eradication, and other disorders including Zollinger-Ellison syndrome. Those who consented to participate were enrolled after providing informed consent. Exclusion criteria included patients using PPIs for depression, renal diseases, hypertension, diabetes, or thyroid disorders, patients with pituitary tumors, pregnant women, and those taking PPIs along with medications other than H2RAs or pro-kinetics. A physical examination was conducted on all subjects, and relevant data were extracted from their medical records. Additional data were collected individually regarding socio-demographic characteristics, medical history, and PPI usage. Serum prolactin levels were measured for all enrolled patients at a single time point after 3 months of PPI therapy. All participants were regular PPI users. A 5ml blood sample was collected from each participant [18]. The standard reference range for serum prolactin in Pakistani male is reported to be 3-15 ng/ml, and in female, 4-25 ng/ml [19]. The institutional laboratory established a normal serum prolactin range of 2.3-18 ng/ml for male and 3.6-25 ng/ml for female. For the current study, serum prolactin levels of 100 ng/ml were considered a marked increase. Additionally, the cut-off for female was set at >25 ng/ml, while for male it was >18 ng/ml. The quantitative measurement of prolactin in human serum was performed using an enzyme-linked immunosorbent assay (ELISA) kit (Calbiotech, Inc., 1935 Cordell Ct, Cajon, CA 92020, US) following the manufacturer's protocol. Initially, direct serum samples were used to screen prolactin levels. Macro-prolactinemia screening was carried out using the polyethene glycol (PEG) precipitation method [20]. All serum samples were treated with an equal volume of 25% PEG solution (PEG 6000, ROTIPURAN® Ph.Eur., Carl Roth GmbH, Germany, w/v). The mixture was vortexed and then centrifuged at 3000 rpm for 15 minutes. The supernatants were subsequently analyzed for prolactin levels. The outcomes of the direct serum prolactin test referred to as total prolactin, and the post-PEG treatment assay, referred to as free prolactin, were compared as a percentage. Patients were classified as having macro-pro-lactinemia if their prolactin recovery after PEG treatment was 40% or less of the original value [21]. The data were analyzed using SPSS

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version 25.0. Continuous variables were expressed as mean and SD, while frequencies and percentages were calculated for categorical variables. Statistical analysis involved an independent t-test and Fisher's exact test. Univariate and multivariate logistic regression analysis for odds ratios (OR) at 95% confidence intervals (CI) were performed. A p-value of <0.05 was considered significant.

RESULTS

Out of the 166 patients, 102 (61.4%) were female, and 64 (38.6%) were male. The patient's mean age was 42.6 ± 14.3 years, and serum prolactin level was 23.2ng/mL. Among the participants, 97 (58.4%) had normo-prolactinemia, while 69 (41.6%) had hyperprolactinemia. Among the patients, 20 (12%) were receiving combination therapy, while the remaining were on PPI monotherapy. There were no significant differences between hyperprolactinemic and normoprolactinemic patients regarding age, gender, or body mass index (p>0.05). The majority of participants, 150 (90.36%), were married. However, a significant difference (p=0.02) was observed between the groups in terms of mean treatment duration. Independent t-test and Fisher's exact test analysis revealed significant associations in the demographic variables of participants (Table 1).

Table 1: Demographics of Normo-Prolactinemic and Hyper-Prolactinemic Participants

Characteristics	Normo-prolactinomas 97	Hyper-prolactinemic 69	p-value
Mean Age (years)	42.13 ± 13.9	42.9 ± 14.6	0.725
Mean Treatment Duration (Months)	25.2 ± 25.3	37.73 ± 37.1	0.002
Mean BMI (kg/m2	24.7 ± 3.7	24.5 ± 3.9	0.654
Gender			
Male	35	30	0.425
Female	61	40	
Other Characteristics			
Smoking	2 (1.20)	4 (2.41)	0.241
Smokeless Tobacco	19 (11.4)	10 (6.02)	0.412
Exercise	13 (7.8)	14 (8.4)	0.292
Working Women	5 (4.9)	4 (3.9)	0.656
Housewife	13 (7.8)	14 (8.4)	0.292
Menstruating Women	5 (4.9)	4 (3.9)	0.656

An increase in mean serum prolactin levels beyond the normal cut-off range was observed in female patients compared to male patients. The overall prevalence of hyperprolactinemia was 42%, with 24% (40 patients) in female and 18% (30 patients) in male (Figure 1).

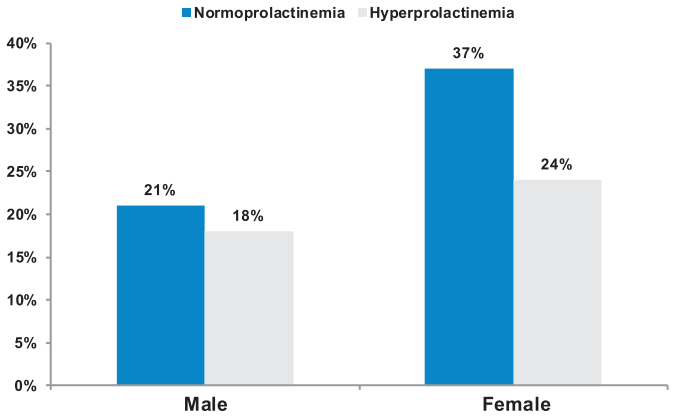

Figure 1: Prolactin Levels in Female and Male with Normoprolactinemia and Hyperprolactinemia

A high incidence of significantly elevated serum prolactin levels was observed in female patients. Macro-prolactinemia was detected in 21 (12.7%) patients, of whom 15 (9.1%) were female. Additionally, 49 (29.5%) patients had true hyperprolactinemia, with 25 (15%) being female (Figure 2).

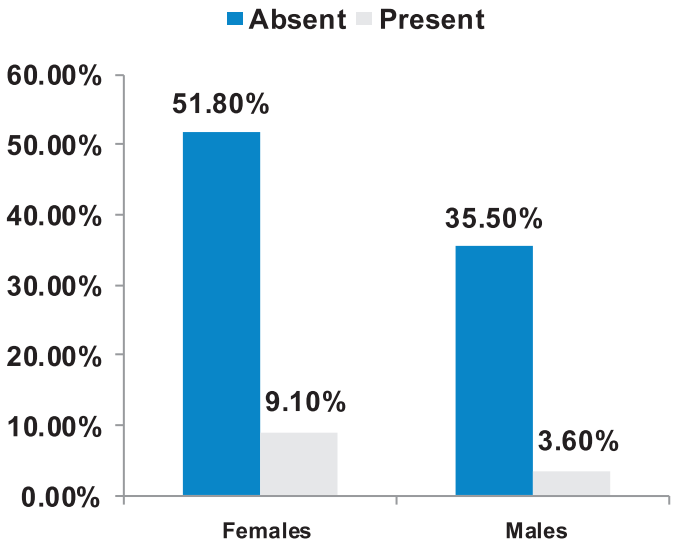

Figure 2: Frequency of Macroprolactinoma in Male and Female Using Long-Term PPIS

The mean serum prolactin level in the PPI monotherapy group was 30.7 ± 27.2 ng/mL, whereas, in the combination therapy group (PPI + pro-kinetics), it was 62.8 ± 41.02 ng/mL. Independent sample T-test shows that difference in prolactin levels between the PPI monotherapy group and the combination therapy group was statistically significant (p<0.05) (Table 2).

Table 2: Comparison of Mean Serum Prolactin Levels among Patients Using Proton Pump Inhibitors (PPI) Monotherapy and Combination Therapy

Variable	PPI Monotherapy (m + SD)	Combination Therapy (m + SD)	p-value
Prolactin Levels (ng/mL)	30.7 ± 27.2	62.8 ± 41.02	0.001

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In univariate analysis, compared to 3-10 months of PPI use, various subgroups with longer treatment durations were at significantly higher risk of developing hyperprolactinemia. The risk was elevated for patients using PPIs for 11-20 months (OR: 5.3; 95% CI: 1.8-15.5; p=0.002), 21-30 months (OR: 2.6; 95% CI: 1.0-6.7; p=0.05), 31-40 months (OR: 3.1; 95% CI: 1.0-9.5; p=0.048), and more than 40 months (OR: 5.6; 95% CI: 2.1-14.5; p=0.001), indicating a significant increase in hyperprolactinemia with longer PPI treatment duration (Table 3).

Table 3: Logistic Regression Analysis of Various Demographic and Clinical Characteristics Concerning Hyperprolactinemia

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender				
Female	Reference			
Male	1.3 (0.7-2.5)	0.4	1.7 (0.8-3.9)	0.18
BMI (Per Unit Increase)	1.04	0.150	1.03	0.210
Age (Years)				
≤30	Reference			
31-50	1.1 (0.5-2.5)	0.8	1.4 (0.5-3.5)	0.51
>50	1.8 (0.7-4.4)	0.2	2.1 (0.7-6.2)	0.18
Duration of PPI Use (Months)				
3-10	Reference			
11-20	5.3 (1.8-15.5)	0.002	4.9 (1.6-15.2)	0.006
21-30	2.6 (1.0-6.7)	0.05	2.2 (0.8-6.1)	0.15
31-40	3.1 (1.0-9.5)	0.048	2.6 (0.8-8.9)	0.13
>40	5.6 (2.1-14.5)	<0.001	6.3 (2.2-17.9)	0.001
Tobacco Use				
Smoking	2.8 (0.5-16.0)	0.2	3.2 (0.4-23.8)	0.25
Smokeless Tobacco	0.7 (0.3-1.6)	0.3	0.4 (0.1-1.0)	0.05
Clinical Characteristics				
Combination Therapy	6.2 (1.9-19.9)	0.002	4.6 (1.3-16.1)	0.01

DISCUSSION

This study was the first to find serum prolactin values in long-term PPI users. In both genders, mean serum prolactin levels were found to be elevated beyond their respective normal ranges. These findings suggest that long-term PPI use may be associated with increased serum prolactin levels. Similarly, medication-induced elevations in serum prolactin have been reported to varying degrees in other studies. In various case reports, elevated serum prolactin levels after PPI treatment have been reported to range from 32.9 ng/mL to 288 ng/mL [13]. In a recent study, the basal prolactin level was observed at 132 ± 68.7 ng/mL, and after discontinuing the medication, it decreased to 16.9±8.2 ng/mL. PPIs and pro-kinetics were identified as the primary contributors to hyperprolactinemia in 71.8% of the cases [15]. The exact mechanism by which PPIs raise serum prolactin remains unclear, and not all studies have depicted a significant relationship between PPI use and increased prolactin levels. The current study suggests that central stimulation may play a role in excessive prolactin secretion. Additionally, PPIs might interfere with prolactin clearance or excretion, contributing to higher serum prolactin levels. There were more cases of hyperprolactinemia among patients using PPIs for ≥3 months, whether alone or in combination with other medications. The prevalence observed in this study aligns with earlier findings [15]. However, comparing the results of this study with other research on drug-induced hyperprolactinemia is challenging for several reasons. Firstly, there is considerable variability in the cut-off points used to define hyperprolactinemia across different studies, which complicates direct comparisons. In this study, a cut-off point of >25 ng/mL for females and >18 ng/mL for males was used, which are commonly applied thresholds in hyperprolactinemia studies conducted in Pakistan [23, 24]. Secondly, different drugs vary in their potential to elevate serum prolactin levels, making direct comparisons challenging. This study is the first specifically designed to assess hyperprolactinemia in long-term PPI users, adding unique insights to the existing literature on drug-induced prolactin elevations. In the current study, 30% of patients were found to have macroprolactinemia, while 70% had true hyperprolactinemia among the total hyperprolactinemic patients, with no significant gender-specific variation. These findings are consistent with previous studies reporting a prevalence of 10-45% [22-24]. However, this study is the first to specifically screen for both macro-prolactin and monomeric prolactin in long-term PPI users, providing novel insights into the effects of prolonged PPI use on prolactin levels. The current study compared the mean serum prolactin levels between patients using PPI alone and those using it in combination with other medications. It was found that patients using PPI in combination may be more susceptible to elevated serum prolactin levels than those using PPI alone over a long-term duration. This observation was further supported by binary logistic regression analysis, which confirmed a higher likelihood of increased serum prolactin in individuals using combination therapy. These results reinforce previous findings, where the combination of PPIs and pro-kinetics accounted for 71.8% of all drug-induced hyperprolactinemia cases [15]. Understanding the impact of combination therapy on serum prolactin levels is crucial for a thorough evaluation of the potential hyperprolactinemic effects linked to long-term PPI use. This comprehensive approach helps clarify the increased risk associated with combination therapy compared to PPI monotherapy. In the current cross-sectional study, the majority of participants were using omeprazole and esomeprazole, with very few long-term users of other PPIs;

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notably, there were no users of rabeprazole. The low frequency of PPIs other than omeprazole and esomeprazole posed a limitation, preventing the study from adequately comparing mean serum prolactin levels among all PPI-treated groups. This necessitates the need for further research that includes a broader range of PPI medications to facilitate more comprehensive comparisons. The current study found no associations between various demographic variables—such as age, gender, body mass index (BMI), marital status, smoking, use of smokeless tobacco, exercise, employment status, and being a housewife when comparing normal prolactin and hyperprolactinemic groups. This suggests that none of these factors are likely to contribute to increases in serum prolactin levels.

CONCLUSIONS

It was concluded that a significant number of patients were found to have hyperprolactinemia, which was closely associated with the long-term use of PPIs. It is imperative to understand the mechanism contributing to multiple ailments in the clinical area. This study will help clinicians in the early identification and management of complications associated with long-term PPI therapy. Additionally, the duration of PPI use had a more pronounced effect on prolactin levels in male patients compared to female patients.

Authors Contribution

Conceptualization: MZ
Methodology: MZ, SN, SA, MIUH
Formal analysis: JA
Writing review and editing: SN, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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