

## Long-term proton pump inhibitors therapy and prevalence of hyperprolactinaemia: A cross-sectional study in outpatient gastroenterology clinics

Muhammad Ashfaq<sup>1</sup>, Adil Naseer Khan<sup>2</sup>, Yasser MSA Alkahraman<sup>3</sup>, Muhammad Zeeshan Haroon<sup>4</sup>

### Abstract

**Objective:** To evaluate serum prolactin and macroprolactin levels in patients on long-term proton pump inhibitors therapy.

**Method:** The cross-sectional study was conducted from January 2018 to November 2019 after approval from the ethics review committee of the Commission on Science and Technology for Sustainable Development in the South University, Abbottabad, Pakistan. The study included patients from two gastroenterology outpatient clinics in the Khyber Pakhtunkhwa province using proton pump inhibitors for  $\geq 3$  months either alone or in combination with either histamine receptor antagonists or prokinetics. Blood samples were collected from each patient for hormonal screening. Data was analysed using SPSS 25.

**Results:** Of the 166 patients, 101(60.8%) were females and 65(39.2%) were males. The overall mean age was  $42.5 \pm 14.2$  years, and the median serum prolactin level was 23.2ng/ml (interquartile range: 14.0-38.0ng/ml). There were 96(58%) patients with normoprolactinaemia and 70(42%) with hyperprolactinaemia. There were 19(11.4%) patients using combination therapy, while the rest were on proton pump inhibitors monotherapy. There was a significant increase in serum prolactin level with combination therapy compared to monotherapy ( $p=0.001$ ). Patients having treatment duration 11-20 months ( $p=0.006$ ) and  $>40$  months ( $p=0.001$ ) were at high risk of developing hyperprolactinaemia.

**Conclusion:** Long-term use of proton pump inhibitors could increase serum prolactin levels, and appropriate evaluation is essential for clinical management.

**Keywords:** Proton pump inhibitors, Long-term therapy, Hyperprolactinemia, Omeprazole, Prolactin.

(JPMA 74: 1067 2024) DOI: <https://doi.org/10.47391/JPMA.9541>

### Introduction

Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications, used for various gastrointestinal (GI) disorders, including dyspepsia, gastro-oesophageal reflux disorder (GERD), peptic ulcer disease, non-steroidal anti-inflammatory (NSAIDs)-induced ulcers, H-pylori eradication, and other hypersecretory disorders, like Zollinger-Ellison syndrome. In the past couple of decades, the use of PPIs has enormously increased due to its better acid-suppressive properties.<sup>1,2</sup> The combined use of PPI + histamine 2 receptor antagonists (H2RAs) has been shown to be beneficial compared to PPI use alone.<sup>3</sup> Similarly, PPIs are used in clinical practice with prokinetics, and this regimen has been successful in many studies.<sup>4</sup>

Observational studies have identified some serious side effects that may be associated with long-term PPI use.

<sup>1,3</sup>Department of Pharmacy, COMSATS University Islamabad, Abbottabad Campus, Pakistan; <sup>2</sup>Department of Gastroenterology, MTI Ayub Medical Complex, Abbottabad, Pakistan; <sup>4</sup>Department of Community Medicine, Ayub Medical College, Abbottabad, Pakistan.

**Correspondence:** M. Zeeshan Haroon. e-mail: zeeshanharoon@yahoo.com

ORCID ID: 0000-0002-5313-5318

**Submission complete:** 01-07-2023

**Review began:** 18-08-2023

**Acceptance:** 09-03-2024

**Review end:** 31-01-2024

Some potentially serious side effects seen in the studies include increased risk of bone fractures, vitamin B12 deficiency, calcium and magnesium deficiencies, renal disorders, increased risk of dementia, pneumonia, and cardiovascular events.<sup>5,6</sup> Hyperprolactinaemia is classified into physiological pathological and pharmacological types. Physiological hyperprolactinaemia stems from normal processes, like pregnancy and stress, while pathological hyperprolactinaemia arises from hypothalamic pituitary disorders, including tumours. The pharmacological type is induced by medications, like antipsychotics.<sup>7,8</sup>

In women, symptoms related to high prolactin levels may appear, ranging from sterility, loss of libido, painful intercourse, irregular menstruation, amenorrhoea, oligomenorrhoea, galactorrhoea and decreased bone mass. In men, hyperprolactinaemia can provoke decreased sex drive, erectile dysfunction, infertility, weight gain and osteoporosis. Gynaecomastia and galactorrhoea may also be present.<sup>9,10</sup>

The effects of PPI therapy on endocrine hormones, including prolactin, have been the subject of multiple studies. Many studies have reported little or no effects on prolactin with short-term use of PPIs.<sup>11-15</sup> However,

multiple case studies have been reported on the connection between PPIs and the development of hyperprolactinaemia with varying degrees of increase in serum prolactin levels when used either alone or in combination with prokinetics.<sup>16-21</sup>

Some cohort studies have also reported a relative risk of developing sexual and reproductive outcomes, such as gynaecomastia, with the use of lansoprazole and omeprazole.<sup>22,23</sup> In addition, studies related to hormonal profiling with long-term use of PPI are lacking, and justify the need to conduct such a hormonal screening. Studies conducted in connection with the short-term use of PPI and its effect on endocrine hormones are mainly conducted on male volunteers. There is also a scarcity of information related to hormonal profiling as well as subsequent sexual and reproductive outcomes in females after long-term use of PPI thereby, indicating the need to conduct the study in both males and females to evaluate any gender-specific changes in biochemical hormonal profiling.

Many drugs, including PPIs, have been shown to cause changes in serum prolactin levels. Numerous studies conducted in various tertiary care hospitals revealed that PPIs are frequently implicated as common contributor of drug-induced hyperprolactinemia.<sup>24-25</sup> However, the long-term use of PPIs and their effect on serum prolactin levels, to our knowledge, have not been studied yet. The current study was planned to fill the gap in literature by evaluating serum prolactin and macroprolactin levels in patients of both genders on long-term PPI therapy.

## Patients and Methods

The cross-sectional study was conducted from January 2018 to November 2019, and comprised patients from two gastroenterology outpatient clinics in the Khyber Pakhtunkhwa (KP) province.

After approval from the ethics review committee of the Commission on Science and Technology for Sustainable Development in the South (COMSATS) University, Abbottabad, Pakistan, , Cochrane formulae were used to estimate the sample size.<sup>26,27</sup>

$$n = \frac{Z^2 P(1 - P)}{d^2}$$

The sample was raised using nonprobability consecutive sampling technique. Those included were patients of either gender using PPIs for  $\geq 3$  months alone and in combination with either H2RA or prokinetics. Those who agreed to volunteer were enrolled after taking informed consent. Patients using PPI for  $< 3$  months and/or with a history of hormonal abnormalities, or comorbidities, such as

depression, renal diseases, hypertension, diabetes and thyroid disorders, patients with pituitary tumours, pregnant women, and patients using PPIs with concomitant drugs other than H2RA and prokinetics were excluded.

Physical examination of the subjects was done, and relevant data was extracted from the patient file. Data was also collected individually about socio-demographic characteristics, medical history, and PPI use. Serum prolactin and serum macroprolactin levels were measured for all recruited patients at a single time point. All the participants were regular users of PPIs.

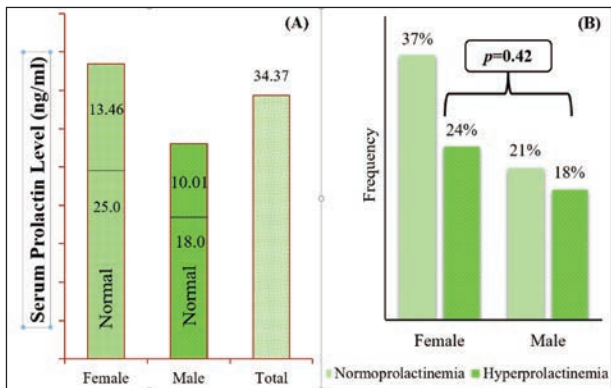
A 5ml blood sample was taken from each participant in line with literature.<sup>28</sup> The standard range for serum prolactin in Pakistani males has been reported to be 3-15ng/ml, and in females 4-25ng/ml.<sup>29,30</sup> The normal range of serum prolactin established in the institutional laboratory was 2.3-18ng/ml for males and 3.6-25ng/ml for females. In the current study, serum prolactin levels  $< 50$ ng/ml were considered mild, 50-100ng/ml were considered moderate, and  $> 100$ ng/ml were considered marked increase. Besides, the cut-off point used for females was  $> 25$ ng/ml, and it was  $> 18$ ng/ml for male patients.

The quantitative measurement of prolactin in human serum was done using an enzyme-linked immunosorbent assay kit (Calbiotech, Inc. 1935 Cordell Ct, Cajon, CA 92020 US) as per the manufacturer's protocol. Initially, direct serum was used to screen prolactin levels. The screening for macroprolactinaemia was performed by the polyethylene glycol (PEG) precipitation method.<sup>31</sup> All serum samples were precipitated with an equal PEG volume of 25% (PEG 6000, ROTIPURAN® Ph.Eur. Carl Roth GmbH, Germany) solution w/v) The mixture was vortex-mixed and subjected to centrifugation at 3000rpm for 15 minutes. The supernatants were then screened for prolactin levels. The results of direct serum prolactin assay, termed total prolactin, and post-PEG treatment assay results, termed free prolactin, were compared in percentage terms. Macroprolactinaemia was assigned to the patients whose prolactin recovery after PEG treatment was at least 40% or less of the initial value.<sup>31,32</sup>

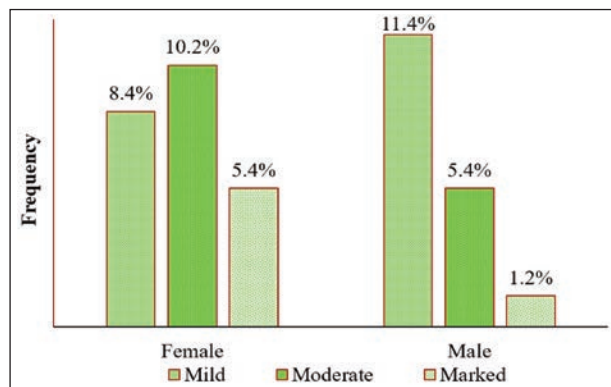
Data was analysed using SPSS 25. Data was reported as frequencies and percentages for categorical variables, and mean $\pm$ standard deviation, or median with interquartile range (IQR) for continuous variables. Mann-Whitney U test, Chi-square test, Fisher exact test and Spearman correlation tests were used, as appropriate. Univariate and multivariate logistic regression analyses were conducted with binary variables as outcomes considering various exposure and confounding factors. Odds ratio (OR) with 95% confidence interval (CI) calculated.  $P < 0.05$  was considered significant.

**Results**

Of the 171 patients enrolled, 5(2.9%) were excluded for being lactating mothers, and the study was completed by 166(97.1%) patients; 101(60.8%) females and 65(39.2%) males. The overall mean age was 42.5±14.2 years, and the median serum prolactin level was 23.2ng/ml (IQR: 14.0-38.0ng/ml). There were 96(58%) patients with normoprolactinaemia and 70(42%) with



**Figure-1:** (A) Mean serum prolactin of the sample, and (B) gender-wise frequency of hyperprolactinaemia.

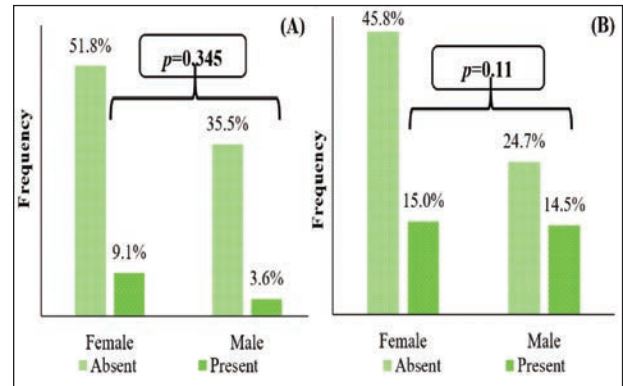


**Figure-2:** Gender-wise distribution of different levels of hyperprolactinaemia in long-term users of proton pump inhibitors (PPI).

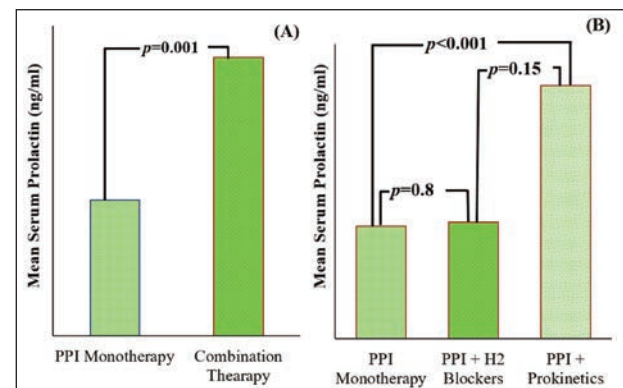
**Table-1:** Comparison of different variables in normoprolactinemic and hyperprolactinemic patients.

Variable	Total n (%)	Normoprolactinaemia (n=96) n (%)	Hyperprolactinaemia (n=70) n (%)	p-value*
Mean Age (years)	42.5±14.2	42.13±13.9	42.9±14.6	0.725 <sup>a</sup>
Mean Treatment Duration (months)	30.5±31.4	25.2±25.3	37.73±37.1	0.002 <sup>c</sup>
Mean BMI (kg/m <sup>2</sup> )	24.6±3.8	24.7±3.7	24.5±3.9	0.654 <sup>c</sup>
Gender				0.425 <sup>b</sup>
Male	65	35	30	
Female	101	61	40	
Smoking	6(3.61)	2(1.20)	4(2.41)	0.241 <sup>b</sup>
smokeless tobacco	29(17.5)	19(11.4)	10(6.02)	0.412 <sup>b</sup>
Exercise	27(16.3)	13(7.8)	14(8.4)	0.292 <sup>b</sup>
Working women	9(8.9)	5(4.9)	4(3.9)	0.656 <sup>b</sup>
Housewife	87(86.1)	51(50.5)	36(35.6)	0.522 <sup>b</sup>
Menstruating women	76(75.2)	44(43.6)	32(31.7)	0.482 <sup>b</sup>

BMI: Body mass index; \*p≤0.05 was considered statistically significant: a – p-value was calculated using Independent Sample t-test; b – p-value was calculated using Fischer Exact test; c – p-value was calculated using Mann Whitney U-test.



**Figure-3:** (A) Frequency of macroprolactinaemia in long-term users of proton pump inhibitors (PPI), and (B) the frequency of true hyperprolactinaemia in long-term PPI users.



**Figure-4:** (A) Comparison of mean serum prolactin levels among patients using proton pump inhibitors (PPI) monotherapy and combination therapy, and (B) comparison of serum prolactin levels in different PPI-treated groups.

hyperprolactinaemia. There were 19(11.4%) patients using combination therapy, while the rest were on PPI monotherapy. There were no significant differences between hyperprolactinaemic and normoprolactinaemic patients related to age, gender and body mass index ( $p>0.05$ ). Most of the subjects were married 150(90.36%). There was a significant difference ( $p=0.02$ ) between the groups with respect to mean treatment duration (Table 1).

An increase in mean serum prolactin from the normal cut-off range was observed in female patients compared to male patients (Figure 1A). The overall prevalence of hyperprolactinaemia was 42% ((40)24% in female and (30)18% in males) (Figure 1B). Using a gender-specific cut-off range, a higher prevalence was observed in males 30(46.2%) compared to 40(39.6%) females ( $p=0.42$ ).

A high incidence of a marked increase in serum prolactin was found in females (Figure 2).

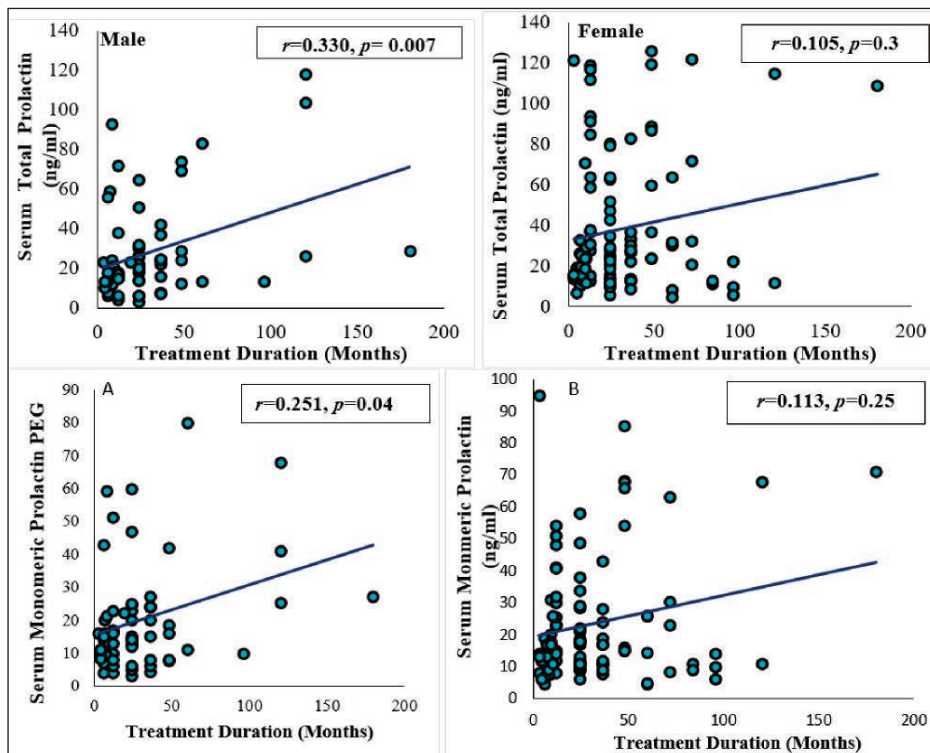


Figure-5: Treatment duration and gender factors in relation to serum prolactin values.

Table-2: Logistic regression analysis of various demographic and clinical characteristics with respect to hyperprolactinemia.

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Gender</b>				
Female	Reference			
Male	1.3 (0.7-2.5)	0.4	1.7 (0.8-3.9)	0.18
<b>Age (years)</b>				
≤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
<b>Duration of PPI Use (months)</b>				
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
<b>Tobacco Use</b>				
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
<b>Clinical Characteristics</b>				
Combination Therapy	6.2 (1.9-19.9)	0.002	4.6 (1.3-16.1)	0.01

OR: Odds ratio; CI: Confidence interval; PPI: Proton pump inhibitors; \* $p \leq 0.05$  was considered statistically significant.

Macroprolactinaemia was found in 21 (12.7%) patients, among which 15 (9.1%) were female (Figure 3A). Besides, 49 (29.5%) patients had true hyperprolactinaemia, and 25 (15%) were female (Figure 3B).

The mean serum level in PPI monotherapy group was

$30.7 \pm 27.2$  ng/ml, and it was  $62.8 \pm 41.02$  ng/ml in the combination therapy group (Figure 4A). The difference was significant between PPI monotherapy and PPI + prokinetics (Figure 4B).

Correlation analysis suggested a significant moderate positive correlation between serum total prolactin levels and treatment duration ( $r=0.330$ ,  $p=0.007$ ) in male patients. However, this correlation was not significant in case of female patients ( $r=0.105$ ,  $p=0.3$ ). Likewise, for monomeric prolactin, correlation analysis indicated a significant positive correlation between treatment duration and serum monomeric prolactin levels ( $r=0.251$ ,  $p=0.04$ ) in male patients. The correlation between treatment duration and serum monomeric prolactin was non-significant ( $r=0.113$ ,  $p=0.25$ ) in female patients.

In univariate analysis, compared to 3-10 months of PPI use, various subgroups in treatment duration, such as 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;  $p=0.048$ ), >40 months (OR: 5.6; 95% CI: 2.1-14.5;  $p<0.001$ ) were significantly associated with hyperprolactinaemia. The presence of combination therapy was also significantly associated with respect to PPI monotherapy with hyperprolactinaemia (OR: 6.2; 95% CI: 1.9-19.9;  $p=0.002$ ). Multivariate analysis revealed that patients using combination therapy were more likely to develop hyperprolactinemia (OR: 4.6; 95% CI: 1.3-16.1;  $p=0.018$ ). Patients with treatment duration 11-20 months (OR: 4.9; 95% CI: 1.6-15.2;  $p=0.006$ ) and >40 months (OR: 6.3; 95% CI: 2.2-17.9;  $p=0.001$ ) were at high risk of developing hyperprolactinaemia (Table 2).

## Discussion

To our knowledge, the current study is the first to investigate serum prolactin levels in long-term PPI users in

the region. In both genders, mean serum levels were found raised from their respective normal serum values. These findings suggested that long-term PPI users may have a raised level of serum prolactin. Different degrees of medication-induced increase in serum prolactin levels have been reported. In different case reports, the increase in serum prolactin levels after PPI treatment was reported to range from 32.9ng/ml to 288ng/ml.<sup>116-19,21</sup> In a recent study, the basal prolactin observed 132±68.7ng/ml and after discontinuing the medication, the prolactin level decreased to 16.9±8.2ng/ml, in which PPIs and prokinetics were the leading causes (71.8%) of hyperprolactinemia.<sup>24</sup> The exact mechanism by which PPIs increase serum prolactin levels is not fully understood, and not all studies have found evidence of significant association for PPIs causing an increase in serum prolactin levels. The current proposed that a central stimulation may be involved in the excess secretion. In addition, PPIs may interfere with prolactin excretion, leading to higher serum levels.

There was a high prevalence of hyperprolactinaemia among patients who were using PPI for ≥3 months either alone or in combination. The prevalence in the current study was in line with earlier findings.<sup>24</sup> However, it is complicated to compare the results of the current study with other drug-induced hyperprolactinaemia studies due to multiple reasons. First, there is a vast variability in the cut-off points for defining hyperprolactinaemia in various studies. The current study used a cut-off point of >25ng/ml for females, and >18ng/ml for male patients, which were commonly used in various studies related to hyperprolactinemia in Pakistan.<sup>29,30</sup> Secondly, different drugs have a varying degree of potential to increase serum prolactin levels, and the current is the first that was specifically designed to evaluate hyperprolactinaemia in long-term PPI users.

In the current study, 30% patients had macroprolactinaemia. Similarly, 70% of patients had true hyperprolactinaemia in total hyperprolactinaemic patients with no gender-specific variation. These findings are consistent with other studies (10-45%).<sup>33,34</sup> However, the current study was the first attempt to screen macroprolactin and monomeric prolactin in long-term PPI users.

The current study compared the mean serum prolactin levels in patients who were using PPI alone and in combination. It has been revealed that people using PPI in combination may be more exposed to increased serum prolactin than those using PPI alone for long-term duration. Binary logistic regression also confirmed the likelihood of increased serum prolactin in people using PPI in combination. These results strengthen the earlier findings<sup>25</sup>

in which the combination of PPIs and prokinetics was the leading cause (71.8%) of the total drug-induced hyperprolactinaemia cases. Understanding the impact of combination therapy on serum prolactin levels was crucial for a comprehensive evaluation of the potential hyperprolactinaemic effects associated with long-term PPI use.

In the current cross-sectional study, most participants were using omeprazole and esomeprazole. The frequency of long-term use for other PPIs in the study was very small, and there was no user of rabeprazole. Such low frequency of PPIs other than omeprazole and esomeprazole was one of the limitations, and, consequently, the study was unable to properly compare between the mean serum values among all PPI-treated groups.

The current study did not identify any relation for different demographic variables, including age, gender, BMI, marital status, smoking, use of smokeless tobacco, exercise, working status, and being housewife, between normal prolactin and hyperprolactinemic groups, thereby excluding the possibility of any of these variables increasing serum prolactin.

Correlational analyses for both genders showed significant association with treatment duration in male patients, but not in female patients. This could be due to the reason that many reproductive hormones are interrelated with each other, and female sex hormones have a role in the modulation of prolactin levels in the body. All the female participants were of different ages and within different phases of their reproductive cycles and variations in sex hormones. In addition, another contributing factor may be the fact that both males and females showed different responses to the same drug, and in a study done in Pakistani, females exhibited genetic variations in pharmacokinetic behaviour towards PPIs.<sup>35</sup>

The current study has limitations. First, due to its cross-sectional design, the study was unable to collect an adequate number of samples for pantoprazole, lansoprazole, dexlansoprazole, and rabeprazole within the study time period. Second, owing to financial constraints, the study was unable to generate large-scale data. Finally, no control group without PPI/H2 antagonist/combination therapy use was involved. A control group would have provided a clear baseline and more valuable information on the association between prolonged use of PPI and prolactin increase.

## Conclusion

A high number of patients were found to have hyperprolactinaemia, and the condition was significantly

linked to the long-term use of PPIs. The intensity of raised serum prolactin was almost doubled when PPI administration was accompanied by prokinetics. The duration of PPI use had a greater impact on prolactin levels in male patients compared to female patients.

**Acknowledgment:** We are grateful to gastroenterologist Dr Muhammad Naeem, from Mardan, for facilitating the study and granting permission to conduct the study in his outpatient clinic, and to Dr Qasim Khan, Dr Syed Mobasher Ali Abid and Dr Muhammad Junaid Hassan Sharif for providing statistical and other assistance, as well as to staff nurse Ms Saima and Ms Maryam Arif for their assistance in interviewing the female patients.

**Disclosure:** None.

**Conflict of Interest:** None.

**Source of Funding:** The Commission on Science and Technology for Sustainable Development in the South (COMSATS) University, Islamabad, Pakistan.

## References

- Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep.* 2008; 10:528–34. doi: 10.1007/s11894-008-0098-4.
- Yu LY, Sun LN, Zhang XH, Li YQ, Yu L, Yuan ZQY, et al. A Review of the Novel Application and Potential Adverse Effects of Proton Pump Inhibitors. *Adv Ther.* 2017; 34:1070–86. doi: 10.1007/s12325-017-0532-9.
- Abdul-Hussein M, Freeman J, Castell D. Concomitant Administration of a Histamine<sub>2</sub> Receptor Antagonist and Proton Pump Inhibitor Enhances Gastric Acid Suppression. *Pharmacotherapy.* 2015; 35:1124–9. doi: 10.1002/phar.1665.
- Xi L, Zhu J, Zhang H, Muktiali M, Li Y, Wu A. The treatment efficacy of adding prokinetics to PPIs for gastroesophageal reflux disease: a meta-analysis. *Esophagus Off J Jpn Esophageal Soc.* 2021; 18:144–51. doi: 10.1007/s10388-020-00753-6.
- Haastруп PF, Thompson W, Søndergaard J, Jarbøl DE. Side Effects of Long-Term Proton Pump Inhibitor Use: A Review. *Basic Clin Pharmacol Toxicol.* 2018; 123:114–21. doi: 10.1111/bcpt.13023.
- Kinoshita Y, Ishimura N, Ishihara S. Advantages and Disadvantages of Long-term Proton Pump Inhibitor Use. *J Neurogastroenterol Motil.* 2018; 24:182–96. doi: 10.5056/jnm18001.
- Capozzi A, Scambia G, Pontecorvi A, Lello S. Hyperprolactinemia: pathophysiology and therapeutic approach. *Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol.* 2015; 31:506–10. doi: 10.3109/09513590.2015.1017810.
- Holt RIG. Medical causes and consequences of hyperprolactinaemia. A context for psychiatrists. *J Psychopharmacol Oxf Engl.* 2008; 22:28–37. doi: 10.1177/0269881107087951.
- Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci.* 2013; 6:168–75. doi: 10.4103/0974-1208.121400.
- Verhelst J, Abs R. Hyperprolactinemia: pathophysiology and management. *Treat Endocrinol.* 2003; 2:23–32. doi: 10.2165/00024677-200302010-00003.
- Dammann, Burkhardt, Wolf. The effects of oral rabeprazole on endocrine and gastric secretory function in healthy volunteers. *Aliment Pharmacol Ther.* 1999; 13:1195–203. doi: 10.1046/j.1365-2036.1999.00545.x.
- Dammann HG, von zur Mühlen A, Balks HJ, Damaschke A, Steinhoff J, Hennig U, et al. The effects of lansoprazole, 30 or 60 mg daily, on intragastric pH and on endocrine function in healthy volunteers. *Aliment Pharmacol Ther.* 1993; 7:191–6. doi: 10.1111/j.1365-2036.1993.tb00089.x.
- MacGilchrist AJ, Howden CW, Kenyon CJ, Beastall GH, Reid JL. The effects of omeprazole on endocrine function in man. *Eur J Clin Pharmacol.* 1987; 32:423–5. doi: 10.1007/BF00543980.
- Meikle AW, Sanders SW, Tolman KG, Jennings DE, Karol MD, Ringham GL. Effect of Lansoprazole on Male Hormone Function. *Drug Investig.* 1994; 8:191–202.
- Thanoon IAJ, Mahmood AQ. Effect of omeprazole on reproductive hormonal levels and sexual function in male patients with peptic ulcer disease. *Al-Qadisiyah Med J.* 2011; 7:190–8.
- Duwicquet F, Gras-Champel V, Masmoudi K. [Hyperprolactinemia with galactorrhoea induced by lansoprazole: A case report]. *Therapie.* 2017; 72:691–3. doi: 10.1016/j.therap.2017.06.002.
- Izquierdo Prieto OM, Alía EM, González AR. [Galactorrhoea induced by lansoprazole]. *Aten Primaria.* 2004; 34:325–6. doi: 10.1016/s0212-6567(04)79506-2.
- Jabbar A, Khan R, Farrukh SN. Hyperprolactinaemia induced by proton pump inhibitor. *J Pak Med Assoc.* 2010; 60:689–90.
- Pipaliya N, Solanke D, Rathi C, Patel R, Ingle M, Sawant P. Esomeprazole induced galactorrhoea: a novel side effect. *Clin J Gastroenterol.* 2016; 9:13–6. doi: 10.1007/s12328-015-0622-7.
- Prikis M, MacDougall J, Narasimhadevara N. Proton Pump Inhibitor-Induced Galactorrhoea in a Kidney Transplant Recipient: A Friend or Foe? *Case Rep Transplant.* 2020; 2020:8108730. doi: 10.1155/2020/8108730.
- Rajgadhi H, Makwana H, Malhotra S, Patel P. Levosulpiride and Esomeprazole Induced Hyperprolactinemia Case Report of Drug Induced Hyperprolactinemia. *Natl J Integr Res Med.* 2010; 8:158–60.
- Daniels IR, Layer GT. How should gynaecomastia be managed? *ANZ J Surg.* 2003; 73:213–6. doi: 10.1046/j.1445-1433.2002.02584.x.
- He B, Carleton B, Etminan M. Risk of Gynecomastia with Users of Proton Pump Inhibitors. *Pharmacotherapy.* 2019; 39:614–8. doi: 10.1002/phar.2245.
- Venkataranasu A, Boddula R, Basavaraju S, Chinte C, Tickoo V. Drug Induced Hyperprolactinemia. *J Endocr Soc.* 2021; 5:A626–7. doi: 10.1210/jendso/bvab048.1277
- Mohanty BK, Choudhury AK, Baliarsinha AK. Study of Clinical Presentations of Patients with Hyperprolactinemia visiting a Tertiary Care Hospital. *J Evid Based Med Health Care.* 2016; 3:2745–7.
- Arya R, Antonisamy B, Kumar S. Sample size estimation in prevalence studies. *Indian J Pediatr.* 2012; 79:1482–8. doi: 10.1007/s12098-012-0763-3.
- Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench.* 2013; 6:14–7.
- WHO Guidelines on Drawing Blood: Best Practices in Phlebotomy [Internet]. Geneva: World Health Organization; 2010. (WHO Guidelines Approved by the Guidelines Review Committee). [Online] [Cited 2023 February 2]. Available from: URL: <http://www.ncbi.nlm.nih.gov/books/NBK138650/>
- Azeemuddin M, Nai R, Wasay M. Descr Study Find Possible Correl MRI Find Pituit Gland Serum Prolactin Level. *J Pak Med Assoc.* 2013; 63:739–42.
- Sherazi NA, Baig MZ, Khan AH. Frequency of Macroprolactin in

- Hyperprolactinemia. *J Coll Physicians Surg Pak*. 2018; 28:93–7. doi: 10.29271/jcsp.2018.02.93.
31. Olukoga AO, Kane JW. Macroprolactinaemia: validation and application of the polyethylene glycol precipitation test and clinical characterization of the condition. *Clin Endocrinol (Oxf)*. 1999; 51:119–26. doi: 10.1046/j.1365-2265.1999.00757.x.
  32. Šostarić M, Bokulić A, Marijančević D, Zec I. Optimizing laboratory defined macroprolactin algorithm. *Biochem Medica*. 2019; 29:020706. doi: 10.11613/BM.2019.020706.
  33. Suliman AM, Smith TP, Gibney J, McKenna TJ. Frequent Misdiagnosis and Mismanagement of Hyperprolactinemic Patients before the Introduction of Macroprolactin Screening: Application of a New Strict Laboratory Definition of Macroprolactinemia. *Clin Chem*. 2003; 49:1504–9. doi: 10.1373/49.9.1504.
  34. Vaishya R, Gupta R, Arora S. Macroprolactin; A Frequent Cause of Misdiagnosed Hyperprolactinemia in Clinical Practice. *J Reprod Infertil*. 2010; 11:161–7.
  35. Nazir S, Iqbal Z, Ahmad L, Ahmad S. Variation in pharmacokinetics of omeprazole and its metabolites by gender and CYP2C19 genotype in Pakistani male and female subjects. *Pak J Pharm Sci*. 2016; 29:887–94.
- 

**Author Contribution:**

MAS: Data concept, acquisition, analysis, drafting, final approval.

AK: Data acquisition, analysis, drafting, final approval.

FN: Data acquisition, drafting, final approval.

NMA: Concept, critically reviewing, intellectual input and final approval.