



Frequency of Hyperprolactinemia in Patients with Overt and Subclinical Hypothyroidism

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Article Info

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Date Received:

30th December, 2023

Date Revised:

22nd September, 2024

Date Accepted:

25th October, 2024

Abstract

Objective: To see the frequency of hyperprolactinemia in patients with subclinical and overt hypothyroidism.

Methodology: This is a descriptive cross-sectional, was performed at the Department of Endocrinology, MTI Lady Reading Hospital, Peshawar, Pakistan. Patients with overt and subclinical hypothyroidism were included in this study. Pregnant or lactating women, patients with a history of renal or hepatic impairment, and patients taking medications that could cause hyperprolactinemia, such as antidepressants, antipsychotics, metoclopramide, and estrogen-containing oral contraceptive pills, were excluded from the study. The frequency of hyperprolactinemia was recorded in these patients.

Results: Among 377 patients who had subclinical or overt hypothyroidism, 140 (37.1%) patients were males, while 237 (62.9%) were females. Two hundred and ninety-five (78.2%) patients had subclinical hypothyroidism, while 82 (21.8%) patients were overtly hypothyroid. Among patients with hyperprolactinemia and subclinical or overt hypothyroidism, 25 (27.2 %) were males and 67 (62.8%) were females ($p=0.02$). Among patients with hyperprolactinemia, 25 (30.4%) were having hypothyroidism while 67 (22.7%) patients were having subclinical hypothyroidism ($p=0.14$).

Conclusion: Both subclinical and overt hypothyroidism is pretty prevalent in patients with high prolactin levels, especially in females.

Keywords: Hypothyroidism, Hyperprolactinemia, Subclinical hypothyroidism



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This article may be cited as:

Wazir N, Khan S, Ubaid M. Frequency of hyperprolactinemia in patients with overt and subclinical hypothyroidism. J Postgrad Med Inst. 2024;38(4):278-82. <http://doi.org/10.54079/jpmi.38.4.3384>

Introduction

In the hypothalamic-pituitary axis, one of the most common hypersecretion syndromes is hyperprolactinemia. Apart from prolactin-secreting pituitary tumors, its etiologies can be pituitary pathologies, medications, hypothyroidism and renal failure. Prolactin release is regulated from the hypothalamic peptides as they effect the secretion of the anterior pituitary gland. These secretions are delivered through the hypophyseal portal vessels. Dopamine is the dominant inhibitory signal that inhibits prolactin secretion. The signals from the hypothalamus regulates the secretion of prolactin through thyrotropin-releasing hormone (TRH).¹ In primary hypothyroidism, the main cause of hyperprolactinemia is through the effects of TRH.² In this primary hypothyroidism, TRH increases physiologically in response to a decrease in the serum levels of circulating thyroid hormones. The increased TRH levels can cause hyperplasia of thyrotrope and lactotroph cells, causing high basal prolactin levels and exaggerated prolactin response to intravenous TRH.²⁻⁴ Reduced renal clearance is another factor that can cause accumulation of prolactin in hypothyroid patients. Reduced dopamine sensitivity of prolactin secretion has also been observed in these patients, which may contribute to hyperprolactinemia.⁵ Estrogen also may be an important factor. Studies show that hyperprolactinemia is usually higher in females because of the effect of estrogen on the prolactin response to TRH.⁶

While the prevalence of hyperprolactinemia is studied in overt hypothyroidism and is 40%, its prevalence is not studied in cases of subclinical hypothyroidism (SCH). The prevalence of hyperprolactinemia in SCH varies from 8% to 34% in the literature.⁷⁻¹⁰ Some have even found no relationship between the degree of hypothyroidism and prolactin levels.¹¹ To the best of our knowledge, no study in Pakistan has been done to see the frequency of hyperprolactinemia in overt as well as sub-clinical hypothyroidism. Keeping in view the high frequency of hyperprolactinemia in patients with overt as well as subclinical hypothyroidism, expensive investigations such as MRI pituitary and expensive treatment such as Cabergoline exploited for the diagnosis and treatment of hyperprolactinemia, respectively, could be avoided. In hyperprolactinemia, secondary to overt or subclinical hypothyroidism, treatment with Levothyroxine therapy would reverse hyperprolactinemia instead. This gave us the reason to conduct this study, and thus, the objective of our study was to determine the frequency of hyperprolactinemia in patients with both overt and subclinical hypothyroidism.

Methodology

This study was conducted in the Department of Endocrinology Lady Reading Hospital Peshawar after approval from the Institutional Review Board on 25th Jan-

uary 2023, from September 2022 to June 2023, over 10 months. The reference number of the ethical approval certificate was 641/LRH/MTI. Non-probability consecutive sampling techniques were used. The sample size was 377 patients with overt or subclinical hypothyroidism, calculated on an open Epi sample size calculator with a 95 % confidence interval and 5 % margin of error using a 42.95 % prevalence of hyperprolactinemia in patients with hypothyroidism.¹² Written informed consent was taken from every patient included in the study. Patients with age > 16 years, any gender, and biochemically overt or subclinical hypothyroidism were included. Patients with total T4 levels less than 5.1 mcg/dl or Free Thyroxin (FT4) less than 0.8 ng/dl and TSH levels more than 4.2 mc/ml were diagnosed as overt hypothyroidism. Patients with T4 or FT4 within normal range and TSH levels between 5.0 and 10 mIU/L were labelled as subclinical hypothyroidism. Both overt and subclinical hypothyroid patients were treatment-naive. Pregnant or lactating women, patients with a history of renal or hepatic impairment, and patients taking medications that could cause hyperprolactinemia, such as antidepressants, antipsychotics, metoclopramide, and estrogen-containing oral contraceptive pills, were excluded from the study. Patients with serum prolactin levels (40 to 360 mIU/l) above the upper limit of the reference range were taken as having hyperprolactinemia. Blood samples from patients were sent to the hospital laboratory for measurement of serum prolactin (both macro prolactin and monomeric prolactin as the hospital laboratory lacks assay for measurement of macro prolactin), total T4, and TSH on a special chemistry analyzer using the Chemiluminescence Immunoassay technique. A well-structured questionnaire was used for the collection of data. Data was analyzed using SPSS version 20. Mean and standard deviations were calculated for age, T4, TSH, and prolactin level. Frequencies and percentages were calculated for gender, number of patients with hyperprolactinemia, number of patients with hypothyroidism, and subclinical hypothyroidism. Hyperprolactinemia was stratified among gender, hypothyroidism, and subclinical hypothyroidism. A post-stratification chi-square test was applied, with a p-value of less than 0.05 as significant.

Results

Mean for age was 29.4 ± 8.5 years, prolactin was 3.8 ± 523.6 mIU/l, T4 was 7.9 ± 3 μ g/dl, and TSH was 8.2 ± 2.2 mIU/ml. We had a total of 377 patients who had subclinical or overt hypothyroidism. In these 377 patients, 140(37.1%) patients were males while 237(62.9%) were females. Two hundred and ninety-five (78.2%) patients had subclinical hypothyroidism, while 82 (21.8%) patients were overtly hypothyroid (Table No 1). Among patients with hyperprolactinemia, 59 (64.1%) were aged between 15 to 30 years, 29(31.5%) between 31 to 45, and 4(4.3%) patients were aged more than 45 years ($p=0.88$) (table no 2). Among patients with hyper-

Table 1. Hyperprolactinemia

Frequency	Percent		
Hyperprolactinemia	Present	92	24.4
	Not present	285	75.6
	Total patients with SC or overt hypothyroidism	377	100.0

Table 2. Distribution of prolactin with respect to age

Hyperprolactinemia	Categories of age			Total	P-value
Present	59 (64.1%)	29 (31.5%)	4 (4.3%)	92 (100%)	0.88
Not Present	179 (62.8%)	96 (33.7%)	10 (3.5%)	285 (100%)	
Total	238 (63.1%)	125 (33.2%)	14 (3.7%)	377 (100%)	

Table 3. Distribution of hyperprolactinemia with respect to gender

Hyperprolactinemia	Gender sie distribution		Total	P-value
	Male	Female		
Present	25 (27.2%)	67 (72.8%)	92 (100%)	0.02
Not Present	115 (40.4%)	170 (59.6%)	285 (100%)	
Total	140 (37.1%)	237 (62.9%)	377 (100%)	

Table 4. Distribution of hyperprolactinemia in subclinical and overt hypothyroidism

Hyperprolactinemia	Distribution of hypothyroidism		Total	P-value
	Subclinical	Overt		
Present	67 (22.7%)	25 (30.4%)	92 (24.40%)	0.14
Not Present	228 (77.2%)	57 (69.5%)	285 (77.59%)	
Total	295 (78.2%)	82 (21.8%)	377 (100%)	

prolactinemia and subclinical or overt hypothyroidism, 25(27.2 %) were males and 67(62.8%) were females ($p=0.02$) (table no 3). Among patients with hyperprolactinemia, 25(30.4%) were having hypothyroidism while 67(22.7%) patients were having subclinical hypothyroidism ($p=0.14$) (Table 4).

Discussion

Our study found that the frequency of hyperprolactinemia in SC or overt hypothyroidism was 24.4%. Looking at hyperprolactinemia separately in SC and overt hypothyroidism, 22.7% of patients with SC hypothyroidism and 30.4% of patients with overt hypothyroidism had hyperprolactinemia. The difference in the frequency in these two categories was not statistically significant. Sharma et al. found these frequencies to be 35.6% and 42.9 %, respectively. Although the pattern of increased frequency of hyperprolactinemia in overt as compared to SC hypothyroidism was similar to that observed in

our study, the frequencies observed in the study were a bit more than those shown in our study.⁹ Other than a large sample size of 4950 patients compared to 377 in ours, we find no reason for this observation. Bahar et al. found the frequency of hyperprolactinemia in SC hypothyroidism to be 20.4%, which is similar to ours.¹⁰ Similarly, in line with our study, Hekimsoy et al. found the prevalence of hyperprolactinemia in SC and overt hypothyroidism to be 22% and 36 %, respectively.¹² A local study done in Lahore, which only looked at the frequency of biochemical hypothyroidism in hyperprolactinemia, found this to be 33%, a result very similar to ours.¹³ Similarly, an Indian study showed the prevalence of hyperprolactinemia to be 18% in subclinical hypothyroidism, a result near that shown in our study.¹⁴ Another Pakistani study showed that the severity of hyperproteinemia correlates with the TSH levels.¹⁵

Overall, 37.1 % of our study population was composed of males and 68.9 % was of females. This reflected a higher overall prevalence of SC or overt hypothyroid-

ism in the female gender in general.¹⁶⁻¹⁸ The most widely accepted reason for this is the higher prevalence of autoimmune diseases in general and of autoimmune thyroid disease, especially in women.¹⁸ Our study showed that the frequency of hyperprolactinemia in both overt and subclinical hypothyroidism is higher in females and that the difference in gender in this regard is statistically significant ($p=0.02$). This replicates the results of numerous other national and international studies.^{10,12-15} The reason behind this is that estrogen enhances the prolactin response to TRH.^{2,19} Shenberger and Klachko have previously reported that the production of Prolactin is stimulated by TRH, epidermal growth factor (EGF), dopamine receptor antagonists, and vasoactive intestinal peptide (VIP) making them conclude that primary hypothyroidism with high levels of TRH can lead to hyperprolactinemia.²⁰

The implication of the results, therefore, is to screen all the patients with hyperprolactinemia for any degree of hypothyroidism. This will improve cost-effectiveness to embark upon further expensive pituitary imaging (MRI in special) and also to avoid the harmful results of not treating subclinical and overt hypothyroidism in special populations such as children and infertile and pregnant women. Perhaps the most important of all is that patients with SC or overt hypothyroidism having hyperprolactinemia will receive appropriate therapy in the form of Levothyroxine instead of erroneous dopamine agonist prescriptions.

A relatively small sample size, cross-sectional nature of the study and no follow up of the patients when started on thyroxin were the main limitations. Population-wide studies are required to find the true prevalence and response to treatment of subclinical and overt hypothyroidism in hyperprolactinemia patients.

Conclusion

Both subclinical and overt hypothyroidism are quite prevalent in patients having high prolactin levels, especially in females, and all patients with hyperprolactinemia should be screened for these conditions. The difference in frequency of these conditions in hyperprolactinemia is not statistically significant.

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Authors' Contribution Statement

SK contributed to the conception, design, acquisition, analysis, interpretation of data, drafting of the manuscript, and critical review of the manuscript. NW contributed to the design, acquisition, analysis, drafting of the manuscript, and critical review of the manuscript. MU contributed to the design, analysis, data interpretation, manuscript drafting, and final approval of the version to be published. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Conflict of Interest

Authors declared no conflict on interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.