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Hyperprolactinemia in Patients with Subclinical Hypothyroidism in Baghdad, Iraq, 2023

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ABSTRACT

Background: Hyperprolactinemia is the most prevalent endocrine disorder in the hypothalamic-pituitary axis. The common causes of hyperprolactinemia can be medications, hypothyroidism, and pituitary disorders. Hypothyroidism and hyperprolactinemia are found to be closely interrelated. Prevalence of hyperprolactinemia in subclinical hypothyroidism (SCH) has been reported in a wide range of 0%– 40% of hypothyroid patients. This study aimed to determine the prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism in Al-Kindy Teaching Hospital in Bagdad, Iraq. **Methods:** A cross-sectional study was conducted in the Department of Internal Medicine and in the diabetes and endocrinology center at Al-Kindy Teaching Hospital for nine months. A total of 95 patients who were diagnosed with SCH were recruited in this study. SCH was diagnosed when there are no specific symptoms or signs of thyroid dysfunction, but the patient has an elevated serum TSH in the face of normal circulating thyroid hormone levels. A study questionnaire was designed, and it included baseline characteristics and signs and symptoms of hypothyroidism. Seven ml of fasting blood samples was taken from all the studied patients and sent to the laboratory to measure the required biochemical parameters. Student t-test was used for comparison, and quantitative data were stated as the mean and standard deviation. Pearson correlation was calculated for the correlation between two quantitative variables. P value less than 0.05 was considered statistically significant. **Results:** The prevalence of hyperprolactinemia was 21.1%. The proportion of hyperprolactinemia was significantly higher among female patients compared to that in male patients. The mean level of TSH was significantly higher in patients with high prolactin levels when compared to those with normal prolactin levels. On the other hand, the mean levels of pulse rate, T3, and LH were significantly lower in patients with high prolactin levels than that in patients with normal prolactin levels.
Conclusions: Hyperprolactinemia is a considerable problem in patients who complained from SCH, especially in females. The most common signs and symptoms associated with hyperprolactinemia are dry skin, weight gain, constipation, psychosis madness, menorrhagia, and galactorrhea. Evaluation of serum prolactin levels in patients with SCH, especially those with the associated signs and symptoms, is recommended.

KEYWORDS: Hyperprolactinemia, Subclinical hypothyroidism, Prolactin, TSH.

INTRODUCTION

Hyperprolactinemia is a prevalent hormonal condition that impacts the hypothalamic-pituitary axis. The causes include substances such as prolactin inhibitor factor, VIP, and Thyroid Releasing Hormone (TRH). Primary hypothyroidism can result in elevated levels of thyrotropin-releasing hormone (TRH),

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which may contribute to the occurrence of galactorrhea. Subclinical hypothyroidism is defined as a condition when there is an elevated level of thyroid-stimulating hormone (TSH) in the blood, although the levels of thyroid hormones remain within the normal range.

Patients with subclinical hypothyroidism frequently encounter fatigue, musculoskeletal complaints, and cold sensitivity. Certain investigations have documented comparable metabolic problems to those observed in primary hypothyroidism.

In 1988, women diagnosed with carpal tunnel syndrome and subclinical hypothyroidism exhibited elevated levels of serum prolactin, a correlation that has been associated with hyperprolactinemia and infertility.

Hyperprolactinemia secondary to primary hypothyroidism has been recognized in the medical literature1-3. Its prevalence ranges between 29.5 4 and 57% 5. Elevation of prolactin (PRL) is very common, especially if thyroid hypofunction has been ongoing for a long time. Subclinical hypothyroidism (HScl) is defined by the finding of a normal basal level of TSH (Stage I) that hyperresponds to the administration of TRH or by elevated TSH (Stage II), with concentrations of circulating iodothyronines in physiological quantities, in the absence of obvious symptoms in most cases. However, Anglo-Saxon authors dismiss hyper-responses of TSH to TRH when basal thyrotropin is normal, considering the subclinical state when TSH has high basal levels.

The etiologies of this entity are the same as those that cause clinical hypothyroidism. This study aimed to determine the prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism at Al-Kindy Teaching Hospital in Bagdad, Iraq.

PATIENTS AND METHODS

Study Design and setting

A nine-month cross-sectional study was undertaken at Al-Kindy Teaching Hospital, namely in the Department of Internal Medicine and Diabetes and endocrinology centre. The study period spanned from November 1, 2022, to July 1, 2023. This study enrolled a total of 95 patients diagnosed with subclinical hypothyroidism who received medical care at the medical ward and endocrinology centre at Al-Kindy Teaching Hospital. The diagnosis of subclinical hypothyroidism was made using information from the patient's medical history, physical examination, and laboratory tests. The diagnosis is made when there are no distinct symptoms or indicators of thyroid malfunction. Yet, the patient has an increased serum TSH despite having normal levels of thyroid hormone in circulation (10). Patients who declined participation or had any of the following conditions were excluded from the study: pregnant and lactating women, patients taking medications that impact prolactin levels (such as oral contraceptive pills, antipsychotic drugs, antilipidemic drugs, and thyroid medications), patients with a history of thyroid surgery, patients who have been exposed to radiation, patients with chronic medical conditions (such as diabetes mellitus, congestive heart failure, chronic liver or kidney diseases, prolactinoma, and thyroid disorders).\

Data Collection Tools:

An interviewer-administered questionnaire was designed for this study. The questionnaire data was collected via face-to-face interviews with the study patients, and it included socio-demographic variables, previous medical, surgical, drug history, vital signs (pulse rate and blood pressure), and body mass index). Body Mass Index (BMI) was calculated by weight in (kilograms) divided by the square of height in

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(meters). Weight and height are measured by the same scale for all the subjects. BMI = Weight (Kg)/Square height (m²), then patients were classified as underweight or Normal (≤ 24.99 kg/m²), overweight (25 - 29.99 kg/m²), and obese (≥ 30 kg/m²) (11). In addition, the questionnaire encompassed the indicators and manifestations of hypothyroidism, such as general discomfort, exhaustion, difficulty with bowel movements, parched skin, sensitivity to low temperatures, irregular menstruation, abnormal milk production, excessive hair growth, hair loss, increase in body weight, mental instability, and muscle spasms. In relation to the studies, a fasting blood sample of 7 ml was collected from all the patients under study and sent to the laboratory for analysis. The serum levels of TSH, free thyroxine (T4), free triiodothyronine (T3), and prolactin, as well as serum levels of FSH and LH, were measured.

The data that was gathered was analysed using the SPSS statistical software, specifically version 25. The incidence of hyperprolactinemia in patients with subclinical hypothyroidism was determined. The data were confirmed to follow a normal distribution using a Shapiro-Wilk test. Hence, the Student's t-test was employed for comparison, and quantitative data were expressed as the mean and standard deviation. The statistical significance of the variation in percentages of qualitative data was assessed using the Pearson Chi-square test (χ2-test), with the use of Yate's correction or Fisher Exact test when appropriate. The Pearson correlation coefficient was computed to measure the correlation between two quantitative variables, along with its associated t-test, to determine the statistical significance of the correlation. The correlation coefficient (r) can be positive, indicating a direct correlation, or negative, indicating an inverse connection. Values below 0.3 indicate no correlation, values between 0.3 and 0.5 indicate weak correlation, values between 0.5 and 0.7 indicate moderate strength, and values over 0.7 indicate strong correlation. A statistically significant result was defined as having a p-value less than 0.05.

RESULTS

The sample for this study consisted of 95 adult patients diagnosed with subclinical hypothyroidism. The study patients' ages ranged from 21 to 63 years, with a mean age of 39.42 ± 10.93 years. The age group with the largest percentage of patients in the study was 30-39 years, with 38 patients (40%). This was followed by 29 patients (30.5%) in the age group of 40-49 years. In terms of gender, there were 74 individuals identified as female, accounting for 77.9% of the total, while there were 21 individuals identified as male, accounting for 22.1% of the total. This results in a male-to-female ratio of 1:3.5. The BMI calculation yielded an average of 28.56 ± 7.73 kg/m², with 42 individuals (44.2%) classified as overweight. Medical history was documented in 33 patients (34.7%). In relation to vital signs, the average pulse rate, systolic blood pressure, and diastolic blood pressure were 79.9 ± 26.5 beats per minute, 125.6 ± 10.3 mmHg, and 77.8 ± 8.4 mmHg, respectively. As depicted in (Table 1).

Table 1: Baseline characteristics of the studied patients

Patients' characteristics	**No. (n= 95)**	**Percentage (%)**
Age group (Years)		
> 30	18	18.9
30 – 39	38	40.0
40 – 49	29	30.6
≥ 50	10	10.5

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Gender		
Male	21	22.1
Female	74	77.9
BMI (kg/m²)		
Normal	37	38.9
Overweight	42	44.2
Obese	16	16.9
Past Medical History		
Yes	33	34.7
No	62	65.3
Vital Signs	**Mean ± SD**	**Range**
Pulse rate (Beats/mint.)	79.9 ± 26.5	64 - 171
Systolic blood pressure (mmHg)	125.6 ± 10.3	105 - 145
Diastolic blood pressure (mmHg)	77.8 ± 8.4	60 – 95

In this study, a high prolactin level was identified in 20 of the recruited patients, giving a 21.1% prevalence of hyperprolactinemia. As illustrated in (Figure 1).

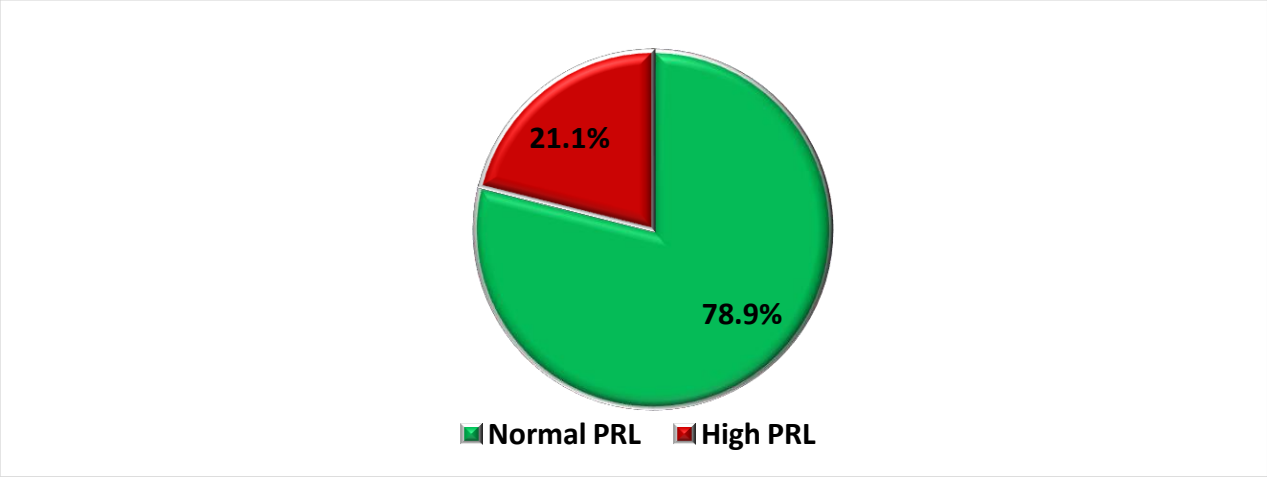

Figure 1: Distribution of study patients according to prolactin level

An analysis of the baseline characteristics of patients revealed a statistically significant correlation between prolactin levels and the gender of the patients. The prevalence of hyperprolactinemia was substantially greater in female patients compared to male patients, although no significant variation in prolactin levels was seen based on age and BMI.

Malaise was the most prevalent sign and symptom of hypothyroidism, observed in 87 patients (91.6%). Fatigue and cold intolerance were reported by 81 (85.3%) and 75 (78.9%) individuals, respectively. An analysis of symptoms in two groups of patients, one with high prolactin levels and the other without, revealed a substantial statistical difference in the occurrence of hypothyroidism symptoms. Specifically, the

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symptoms of dry skin, weight gain, constipation, psychotic madness, menorrhagia, and galactorrhea were found to be more prevalent in the group with high prolactin levels. As depicted in (Table 2).

Table 2: Comparison of demographic and clinical characteristics of study patients according to prolactin levels

Patients' characteristics	Prolactin Level		Total (%) n= 95	P- Value
	High (%) n= 20	Normal (%) n= 75		
Age (Year)				
< 30	5 (27.8)	13 (72.2)	18 (18.9)	**0.293**
30 – 39	7 (18.4)	31 (81.6)	38 (40)	
40 – 49	4 (13.8)	25 (86.2)	29 (30.5)	
≥ 50	4 (40.0)	6 (60.0)	10 (10.5)	
Gender				
Male	1 (4.8)	20 (95.2)	21 (22.1)	**0.038**
Female	19 (25.7)	55 (74.3)	74 (77.9)	
BMI Level				
Normal	6 (16.2)	31 (83.8)	37 (38.9)	**0.158**
Overweight	7 (16.7)	35 (83.3)	42 (44.2)	
Obese	6 (37.5)	10 (62.5)	16 (16.8)	
Signs and symptoms				
Malaise	17 (19.5)	70 (80.5)	87 (91.6)	**0.233**
Fatigue	16 (19.8)	65 (80.2)	81 (85.3)	**0.454**
Dry skin	19 (25.3)	56 (74.7)	75 (78.9)	**0.047**
Constipation	20 (27.4)	53 (72.6)	73 (76.8)	**0.005**
Weight gain	18 (26.5)	50 (73.5)	68 (71.6)	**0.039**
Muscle cramps	11 (26.8)	30 (73.2)	41 (43.2)	**0.289**
Psychosis madness	15 (29.4)	36 (70.6)	51 (53.7)	**0.031**
Menorrhagia	16 (42.1)	22 (57.9)	38 (40)	**0.001**
Galactorrhea	12 (66.7)	6 (33.3)	18 (18.9)	**0.001**

* Significant difference between percentages using Pearson Chi-square test at 0.05 level.

Comparing clinical parameters between patients with high prolactin levels and those with normal prolactin levels, it was shown that the average TSH level was substantially higher in patients with high prolactin levels (8.98 µIU/mL) compared to those with normal prolactin levels (7.12 µIU/mL, P= 0.002). In contrast, patients with high prolactin levels had significantly lower mean levels of pulse rate (70.11 b/m vs. 82.42 b/m, P= 0.039), T3 (1.57 pg/ml vs. 2.01 pg/ml, P= 0.001), and LH (5.57 IU/L vs. 6.97 IU/L, P= 0.024) compared to patients with normal prolactin levels. As depicted in (Table 3).

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Table 3: Comparison of clinical parameters according to prolactin levels

Clinical Parameters	Prolactin Level		P - V
	High Mean ± SD	Normal Mean ± SD	
T3 (pg/ml)	1.57 ± 0.32	2.01 ± 0.47	**0.001**
T4 (ng/dl)	93.84 ± 31.3	94.03 ± 29.23	**0.979**
TSH (µIU/mL)	8.98 ± 2.73	7.12 ± 0.96	**0.001**
FSH (IU/L)	8.91 ± 4.67	9.74 ± 5.68	**0.602**
LH (IU/L)	5.27 ± 1.98	6.97 ± 3.55	**0.024**
Pulse rate (Beats/mint.)	70.11 ± 13.50	82.42 ± 25.35	**0.039**
Systolic blood pressure (mmHg)	126.7 ± 8.9	124.6 ± 8.3	**0.324**
Diastolic blood pressure (mmHg)	76.88 ± 8.90	75.22 ± 9.13	**0.469**

* Significant difference of two means using student t-test at 0.05 level.

In the Pearson correlation analysis between prolactin level and thyroid function tests, this study found a significant positive correlation between prolactin level and TSH (r= 0.468, P= 0.001), while prolactin level was not significantly correlated with T3 and T4 levels. As illustrated in (Table 4).

Table 3.4: Correlations of prolactin level with thyroid function tests

Clinical parameters	Prolactin (ng/ml)	
	Correlation	P- Value
T3 (pg/ml)	- 0.173	0.169
T4 (ng/dl)	0.198	0.096
TSH (µIU/mL)	0.512	0.001

*Correlation is significant at the 0.05 level.

DISCUSSION

Twenty patients (21.1%) in this study had elevated prolactin levels. The Indian study from 2018 (7) and the Turkish study from 2010 (12) reported that 22% and 28% of patients with subclinical hypothyroidism had hyperprolactinemia, respectively, which was a close result. Lower figure was accounted for from a review

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directed in 2015, which detailed that prolactin height was seen as in 8% of patients with subclinical hypothyroidism (5). Because it is affected by pregnancy, breastfeeding, or using estrogen, the various sample sizes, age groups, and genders of patients who participated in the studies cited above may be to blame for the variations observed. Utilized medications, such as antidepressants and psychiatric medications, may also influence the prevalence of hyperprolactinemia.

The investigation approach, such as immunoradiometric assay, could also be to blame for the differences. While there was no significant difference in age or BMI, the present study found that the prolactin level of patients was significantly different depending on their gender, with female patients having a significantly higher level. Behar et al. reported a similar conclusion. A study in 2011 found that women had a higher prevalence of hyperprolactinemia in subclinical hypothyroidism, and there was a significant relationship between gender and prolactin level. The study also found that age was significantly related to prolactin level, with a high prolactin level occurring between the ages of 20 and 40 (8). Different finding was accounted for from a review led in 2015, which found that the distinction in the prolactin level as per the orientation of patients was not critical (5). Hypothyroidism alone is not sufficient to cause hyperprolactinemia; instead, another stimulus, such as estrogen, is required for this effect, which is why hypothyroid females have a higher prevalence of hyperprolactinemia than hypothyroid males do (13).

Our study found a statistically significant difference between two groups of patients with or without high prolactin levels in terms of hypothyroidism symptoms such as dry skin, weight gain, constipation, psychosis, menorrhagia, and galactorrhea. Different figure was accounted for from an Indian concentrate in 2018, as it observed that weakness and balding were altogether more normal in patients with high TSH (7). According to a 2014 Danish study, 81% and 4.15 percent of hypothyroid patients presented with fatigue and hair loss (14). In contrast, a 2015 Indian study found that patients with high prolactin levels had non-significantly higher percentages of fatigue, dry skin, cold intolerance, constipation, weight gain, alopecia, muscle cramps, and menstrual disturbances than patients with normal prolactin levels (5). The most common causes of the aforementioned differences are different sample sizes, the severity of the condition, and the conditions that are associated with it.

Patients with hyperprolactinemia had significantly higher mean levels of TSH than those with normal prolactin levels, and patients with hyperprolactinemia had significantly lower mean levels of pulse rate, T3, and LH than those with normal prolactin levels. In a 2015 Indian study, a different result was found: patients with subclinical hypothyroidism did not differ significantly in terms of total and free T3, total and free T4, or both. In contrast to the controls, patients with subclinical hypothyroidism showed a statistically significant increase in TSH and prolactin. One more unique outcome was gotten from a concentrate in 2011 that showed that patients with TSH < 10 was 87.3% and higher than 10 were just 13.7%, and no connection was found among TSH and prolactin levels (8).

Prolactin and TSH had a significant positive correlation in this study, but there were no significant correlations between prolactin and T3 or T4. In 2018, a study conducted in India found that the participants had a positive correlation between elevated serum PRL and elevated TSH levels. A 2016 study that found a significant positive correlation between TSH and prolactin levels in patients with subclinical hypothyroidism yielded another similarity. In contrast, Goel and colleagues' 2015 study found no significant correlation between TSH and prolactin levels in patients with subclinical hypothyroidism when TSH levels were compared to prolactin levels. The distinctions saw in the consequences of the referenced examinations may be ascribed to the different example sizes of each study's presence of conditions influencing hypothalamic-the

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pituitary pivot as drug cancers. Additionally, some patients alter the above results with a medication; different ages, different methods of estimating prolactin, and different genders enrolled—females were more affected than males due to the hormonal disruption caused by the condition.

CONCLUSION

This study showed that hyperprolactinemia is a considerable problem in patients who complained from subclinical hypothyroidism, especially in females. The most common signs and symptoms associated with hyperprolactinemia are dry skin, weight gain, constipation, psychosis madness, menorrhagia, and galactorrhea. Future larger-scale studies with larger sample sizes are needed to confirm the exact burden and the determinants of hyperprolactinemia in subclinical hypothyroidism. Evaluation of serum prolactin levels in patients with subclinical hypothyroidism, especially those who showed signs and symptoms such as weight gain, constipation, dry skin, psychosis madness, menorrhagia, and galactorrhea, is recommended.

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