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Original Article

Hyperprolactinemia in Subclinical Hypothyroid Patients at BPKIHS, Dharan

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Abstract

Background

Hyperprolactinemia and subclinical hypothyroidism may be associated and are usually accompanied by menstrual disorders in female patients. The objective of this study is to determine the prevalence and association of hyperprolactinemia in subclinical hypothyroidism and the associated clinical features.

Materials and Methods

This is a hospital-based descriptive cross-sectional study conducted from 1 July 2022 to 31 December 2022. Serum Prolactin level was measured in subclinical hypothyroid patients who met the inclusion criteria.Descriptive statistics such as frequency and percentage for categorical variables and mean with standard deviation for quantitative variables were calculated. Pearson's Chi-square test was used for statistical analysis and the p-value <0.05 was considered statistically significant for analysis.

Results

One hundred and forty-four newly diagnosed subclinical hypothyroid patients were enrolled; the mean age of the patients was 36.95±12.58 years. Female patients comprised 89.6% of the study participants. Hyperprolactinemia was prevalent in 23.6% of subclinical hypothyroid patients (23.4% in TSH 4.5-10 µIU/mL group and 24.3% in TSH >10 µIU/mL group). There was no significant association between subclinical hypothyroidism and prolactin levels.Menstrual irregularities were the most common clinical manifestations which account for 44.2% of female subclinical hypothyroid patients and menstrual irregularities were significantly associated with hyperprolactinemia.

Conclusion

The number of patients with hyperprolactinemia in subclinical hypothyroidism was substantial even though the association between them was not significant. Assessment of serum prolactin may be considered in subclinical hypothyroid patients who present with menstrual irregularities.

Keywords: *Hyperprolactinemia, Hypothyroidism, Menstrual irregularities, Prevalence*

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Introduction

Prolactin (PRL) belongs to the PRL/Growth hormone/placental lactogen family which is secreted from the anterior pituitary gland [1, 2]. Hypothyroidism may be associated with mild hyperprolactinemia due to increased prolactin secretion in response to thyrotropin-releasing hormone (TRH) [1, 3]. Subclinical hypothyroid patients are usually asymptomatic and diagnosed incidentally on laboratory workup [4].

Hyperprolactinemia and subclinical hypothyroidism (SCH) may occur together and a thyroid-stimulating hormone (TSH) level higher than 8 µIU/mL is highly specific in detecting hyperprolactinemia [5]. Elevated PRL causes alterations of the gonadotropic axis, inhibiting pulsatile gonadotropin-releasing hormone (GnRH) secretion which is associated with hypogonadism, galactorrhea, amenorrhea, decreased libido, and infertility inpremenopausal women [2, 5].

Hyperprolactinemia may be associated with menstrual irregularities and infertility in patients with SCH.This study aims to know the prevalence and association of hyperprolactinemia in subclinical hypothyroidism and the clinical features associated with it.

Materials and Methods

This is a hospital-based descriptive cross-sectional study conducted at B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal. Study participants were the newly diagnosed and treatment naïve subclinical hypothyroid patients attending the endocrine outpatient and inpatient department of the Internal Medicine from 1 July 2022 to 31 December 2022. The ethical approval was obtained from the Institutional Review Committee, BPKIHS (code no. IRC/2245/022). The patients were enrolled through a non-probability consecutive sampling technique. The sample size was calculated using the formula, z^2pq/ε^2; where n=sample size and z=z score at 95% confidence interval (1.96). p=population proportion of hyperprolactinemia in subclinical hypothyroidism. q = 1−p, ε = margin of error (0.07). Assuming a population proportion of 20.4% from Bahar et.al. [6]; and unlimited population size, the calculated sample size was 128. However, 144 subclinical hypothyroid patients were enrolled.

Patients with newly diagnosed subclinical hypothyroidism aged 18 years who had given consent were included. Subclinical hypothyroid patients taking levothyroxine, patients with a history of pituitary tumors, pregnant ladies, lactating mothers, patients with a history of chronic kidney disease, primary hypothyroidism, secondary hypothyroidism, chronic liver disease, and those patients taking dopamine receptor blocking agents were excluded from the study. The clinical features regarding hypothyroidism (e.g., fatigue, edema, infertility, menstrual irregularities including amenorrhea, menorrhagia, oligomenorrhea) and hyperprolactinemia (e.g., headache, infertility, galactorrhea), physical examination, and anthropometric measurements were documented. Serum prolactin and thyroid function test was measured using a sandwich chemiluminescence immunoassay (MAGLUMI 2000 Chemiluminescence Immunoassay) System.Three mL of blood was drawn using standard venipuncture technique using standard sampling tubes after an overnight fast and sent to the central laboratory of BPKIHS. Complete clot formation in serum specimens was ensured before centrifugation. Grossly hemolytic, lipemic, or turbid samples were avoided. The sample was tested within 3 hours when placed on board the MAGLUMI system. Hyperprolactinemia refers to the serum level of prolactin greater than the reference value of the biochemistry laboratory at BPKIHS (Male: 54-340µIU/ml Female: 66-490µIU/ml). Subclinical hypothyroidism is defined as elevated TSH with normal free T4 and free T3. Elevated TSH refers to the serum TSH greater than the reference value (0.3-4.5 µIU/mL)of the biochemistry lab at BPKIHS.Anti-Thyroid peroxidase antibody (TPO Ab) ≥ 30 IU/mL was considered positive.

The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 software for Windows. Numerical data for continuous variables wereexpressed in the form of mean ± standard deviation. The data for categorical variables were expressed either in number or percentage (n,%) and Pearson's Chi-square test was used to observe the association between the categorical variables. The test was considered statistically significant when thep-value<0.05.

Results

In this study, 144 newly diagnosed and treatment naïve subclinical hypothyroid patients were included. The mean age of the patients was 36.95±12.58 years. Female patients comprised 89.6% of the study participants. The mean TSH, fT4, and fT3 were 11.73±16.03 µIU/mL, 11.97±2.05 pg/mL, and 3.04±0.52 pg/mL respectively. Around 74% of patients had TSH 4.5-10 µIU/mL whereas 25.7% of patients had TSH >10 µIU/mL. More than half of the subclinical hypo-

thyroid patients had positive Anti-TPO antibody (TPOAb) (45.8% in TSH 4.5-10 IU/mL group and 67.6% in TSH >10 IU/mL group). There was a significant association between TSH level and TPOAb positivity ($p<0.05$). Hyperprolactinemia was prevalent in 23.6% of subclinical hypothyroid patients (23.4% in TSH 4.5-10 µIU/mL group and 24.3% in TSH >10 µIU/mL group) (Fig. 1). There was no association between subclinical hypothyroidism and prolactin levels (p=0.906) as well as TPOAb and prolactin levels (p=0.836) as shown in Table 2. Menstrual irregularities were the most common clinical manifestations which account for 44.2% of female subclinical hypothyroid patients. Overall, fatigue (20.1%), infertility (11.8%), paresthesia (11.1%), weight gain (8.3%), and body aches (7.6%) were other common clinical features. Goiter was present in nine patients and galactorrhea was present in three patients. Other clinical features of subclinical hypothyroidism are shown in Table 4. Menstrual irregularities were significantly associated with hyperprolactinemia (p=0.016). However, other clinical features did not haveanassociation with hyperprolactinemia in female patients as shown in Table 3 as well as in overall patients.There was a significant association between TSH level and menstrual irregularities. However, irregular menstruation was more common in mild subclinical hypothyroidism (TSH 4.5-10 µIU/mL). Other clinical features had no association with TSH levels except for body aches and depression (Table 4).

Table 1: Clinical characteristics of newly diagnosed and treatment naïve subclinical hypothyroid patients (n=144)

Variable	Mean ±SD	n (%)
Age (in years)	36.95±12.58	
Body mass index (in kg/m²)	26.29±4.28	
TSH (µIU/mL)	11.73±16.03	
fT4 (pg/mL)	11.97±2.05	
fT3 (pg/mL)	3.04±0.52	
Gender, female		129 (89.6)
Hyperprolactinemia, yes		34 (23.6)
TSH 4.5-10 µIU/mL		107 (74.3)
TSH >10 µIU/mL		37 (25.7)
Anti-TPOAb, yes		74 (51.4)
Diabetes mellitus		8 (5.6)
Hypertension, yes		13 (9.0)

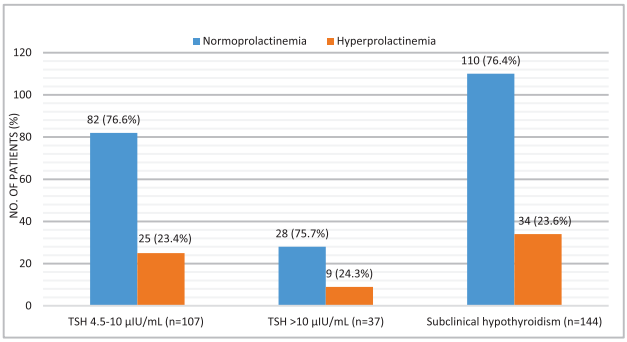

Figure 1: The proportion ofHyperprolactinemia in subclinical hypothyroidpatients

Table 2: Association of TSH & TPOAb with hyperprolactinemia (n=144)

	Normoprolactinemia n (%)	Hyperprolactinemia n (%)	p-value
TSH 4.5-10 µIU/mL	82(76.6)	25 (23.4)	0.906
TSH >10 µIU/mL	28 (75.7)	9 (24.3)	
TPOAb negative	54 (77.1)	16 (22.9)	0.836
TPOAb positive	56 (75.7)	18 (24.3)	

Table 3: Thecomparison of clinical symptoms and TSH levels in subclinical hypothyroidfemales with normalandhigh prolactin (n=129)

Clinical features	Normal prolactin (n=97) n (%)	Hyperprolactinemia (n=32) n (%)	p-value
Menstrual irregularities	37 (38.1)	20 (62.5)	0.016
Fatigue	17 (17.5)	8 (25.0)	0.354
Infertility	13 (13.4)	4 (12.5)	0.896
Paresthesia	15 (15.5)	1 (3.1)	0.066
Weight gain	9 (9.3)	3 (9.4)	0.987
Body ache	10 (10.3)	1 (3.1)	0.207
Edema	5 (5.2)	0 (0.0)	0.331
Goiter	7 (7.2)	1 (3.1)	0.405
Hair fall	4 (4.1)	2 (6.3)	0.637
Urticaria	3 (3.1)	1 (3.1)	1.000
Headache	1 (1.0)	3 (9.4)	0.047
Constipation	3 (3.1)	0 (0.0)	0.574
Depression	1 (1.0)	1 (3.1)	0.436
Galactorrhea	1 (1.0)	2 (6.3)	0.152
TSH<10 µIU/mL	74 (76.3)	23 (71.9)	0.616

Table 4: Clinical features in subclinical hypothyroidism segregated by TSH values 4.5-10 µIU/mL or > 10 µIU/mL (n=144)

Clinical features	TSH 4.5-10 µIU/mL (n= 107) n (%)	TSH>10µIU/ mL (n=37) n (%)	p-value
Menstrual irregularities(n=129)	48 (49.5)	9 (28.1)	0.035
Fatigue	22 (20.6)	7 (18.9)	0.830
Infertility	12 (11.4)	5 (14.3)	0.654
Paresthesia	14 (13.1)	2 (5.4)	0.200
Weight gain	10 (9.3)	2 (5.4)	0.455
Body ache	11 (10.3)	0 (0.0)	0.042
Edema	5 (4.7)	4 (10.8)	0.184
Goiter	5 (4.7)	4 (10.8)	0.184
Hair fall	6 (5.6)	1 (2.7)	0.479
Urticaria	3 (2.8)	3 (8.1)	0.176
Headache	3 (2.8)	2 (5.4)	0.603
Constipation	4 (3.7)	0 (0.0)	0.573
Depression	1 (0.9)	3 (8.1)	0.052
Galactorrhea	2 (1.9)	1 (2.7)	1.000

Discussion

The stimulation of lactotroph cells by thyrotropin-releasing hormone in response to low thyroid hormones causes hyperprolactinemia in SCH [1]. Hyperprolactinemia was prevalent in 23.6% of subclinical hypothyroid patients (23.4% in TSH 4.5-10 µIU/mL group and 24.3% in TSH >10 µIU/mL group) in this study. The prevalence of hyperprolactinemia in SCH varies from 18 to 36% with female predominance with a high prevalence in overt hypothyroidism than in SCH and is usually common in the early thirties [5-7]. A study done in India among 2848 individuals showed that the occurrence of hyperprolactinemia in subclinical hypothyroid females and males was 35.65% and 31.61%respectively [7]. Similarly, a cross-sectional study done by Bahar et al [6] in 481 subclinical hypothyroid patients had shown a prevalence of 20.4% (11% in men and 22% in women) which is similar to our study. The prevalence of hyperprolactinemia in subclinical hypothyroid patients was 18% in a study done by Sirohi et al [5] among which 90% were females as in our studyand the patients with a higher TSH level (7.5–10 µIU/mL) had a significantly higher prevalence of hyperprolactinemia (33%) than in patients with TSH (5–7.4 µIU/mL). A study done by Maskey et al [8] in Kathmandu, Nepal in 213 women with primary and secondary infertility found subclinical hypothyroidism as the most common disorder comprising 10.3% of cases with the prevalence of hyperprolactinemia being 15%.

Anti-TPO antibody (TPOAb) was present in 45.8% ofpatients with TSH 4.5-10 µIU/mL and 67.6% in patients with TSH >10 µIU/mL and the association between them were significant. The subclinical hypothyroid patients with positive thyroid antibodies had higher TSH levels; 80% of patients with TSH>10 µIU/mL had thyroid antibodies [9]. There was no association between subclinical hypothyroidism and prolactin levels in our study. Various studies showed a variable correlation between TSH and prolactin levels in subclinical hypothyroid patients. Bahar et al [6] showed no association between serum TSH and prolactin levels. However, another study revealed a significant positive correlation between TSH and prolactin levels in both subclinical and primary hypothyroid patients and had shownthat TSH≥7.51 µIU/mL in females and ≥8.33 µIU/mL in males had a sensitivity of~50% with a very high specificity of >90% in detecting hyperprolactinemia warranting the need of prolactin screening in subclinical hypothyroidism with TSH>7.5 µIU/mL[7]. Similarly, Sirohi et al [5] had also shown a positive correlation between TSH and prolactin levels.A significant elevation of prolactin was found in overt hypothyroidism in comparison to subclinical hypothyroidism; and in patients with SCH when compared to controls [10].

In our study menstrual irregularities were the most common clinical manifestations which account for 44.2% of female subclinical hypothyroid patients. Overall, fatigue (20.1%), infertility (11.8%), paresthesia (11.1%), weight gain (8.3%), and body aches (7.6%) were other common clinical features. Goiter was present in nine patients and galactorrhea was present in three patients. Menstrual irregularities were significantly associated with hyperprolactinemia (p=0.016). However, other clinical features did not have an association with hyperprolactinemia in female patients in this study. The clinical features in subclinical hypothyroid patients with or without hyperprolactinemia are similar [6]. As shown in other studies as well, menstrual disorders were the most common clinical manifestations of subclinical hypothyroidism with or without hyperprolactinemia. However, the frequency of other clinical features varied [5, 6]. The increased TRH in hypothyroidism causes a rise in PRL levels which leads to menstrual disorders. Similarly, the impairment of pulsatile secretion of GnRH interferes with ovulation which affects fertility in such patients [11]. Few studies done on infertile women in Nepal to seethe association of prolactin with TSH had shown prolactin to be posi-

tively correlated with TSH. Thus, hyperprolactinemia with thyroid dysfunction may be a contributory hormonal factor in a patient with menstrual irregularities and assessment of thyroid hormones and the levels of serum PRL has to be considered an important component in women with infertility [8, 12]. Hypothyroidism and hyperprolactinemia may occur together in infertile women; the association being higher with hypothyroidism in comparison to hyperthyroid or euthyroid patients [13]. Lowering of prolactin levels to normal or near normal is often necessary to permit ovulation inpatients with infertility associated with high prolactin [14]. Hyperprolactinemia associated with SCH may reverse on supplementation of thyroxine after 24 and 48 weeks [5, 15]. TSH and prolactin levels have to be assessed in women with menstrual irregularities as these patientsmay have significantly higher prolactin levels than euthyroid or hyperthyroid women [13]. There are certain limitations to the study. The number of subclinical hypothyroid patients in the study is less in number and it is a single hospital-based cross-sectional study. The diagnosis of SCH was based on a single blood test. There were no control patients for comparison.

Conclusion

In conclusion, the number of patients with hyperprolactinemia in subclinical hypothyroidism was substantialeven though the association between them was insignificant. Menstrual irregularities are usually associated with hyperprolactinemia in subclinical hypothyroid female patients. Hyperprolactinemia has to be considered in subclinical hypothyroid patients who present with menstrual disorders.

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Conflict of interest: None

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