

## Hyperprolactinemia in association with subclinical hypothyroidism

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### Abstract

**Background:** Hyperprolactinemia is the most common endocrine disorder in hypothalamic-pituitary axis and has been reported in variable levels in patients with overt primary hypothyroidism. We decided to determine the prevalence of hyperprolactinemia and clinical related symptoms in subclinical hypothyroidism patients.

**Methods:** In this cross sectional study, prolactin levels of 481 subclinical hypothyroid patients were assessed. Prolactin measurement was performed using chemiluminescent immunoassay. Data were collected and analyzed.

**Results:** Sixty-two (13%) patients were males and 419 (87%) were females. The mean age of the patients was  $32.53 \pm 10.13$  years. Ninety-eight patients (91 females 7 males) had high prolactin. Prevalence of hyperprolactinemia in subclinical hypothyroidism was 20.4% (11% in men and 22% in women,  $p=0.05$ ). There was no correlation between the serum TSH and prolactin level. Clinical symptom prevalence was not different between patients with and without hyperprolactinemia.

**Conclusion:** This study showed that prevalence of hyperprolactinemia in subclinical hypothyroidism is notable and this disorder is more common in female subclinical hypothyroidism than the men.

**Key words:** Hyperprolactinemia, Subclinical hypothyroidism, Clinical symptom.

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**H**yperprolactinemia is the most prevalent endocrine disorder in hypothalamic-pituitary axis (1). Pathologic hyperprolactinemia is generally applied for the situation in which prolactin level increases because of some reasons other than physiologic causes. Prolactin secretion is controlled by prolactin inhibitor factor that is secreted from hypothalamus, other factors like vaso active inhibitory peptide (VIP) and Thyroid releasing hormone (TRH) cause to increase prolactin secretion (1). In fact, TRH in addition to increasing TSH causes to rise prolactin level (2). In patients with primary hypothyroidism, increased levels of TRH can cause to rise prolactin levels and these patients may have galactorrhea (3). Different increased level of serum prolactin has been reported in 30% of patients with primary hypothyroidism (4). Subclinical hypothyroidism is defined by high TSH and normal thyroid hormones (5).

Although many studies had shown that this situation of thyroid never create a special symptom in people but most of the sub clinical hypothyroidism patients suffer from the symptoms of this disease like fatigue, musculoskeletal symptoms and cold intolerance (5). Some studies have reported musculoskeletal and cardiovascular metabolic disorders in subclinical hypothyroidism similar to primary hypothyroidism (6,7).

In 1988 for the first time, an increase of serum prolactin was reported in a woman with carpal tunnel syndrome and subclinical hypothyroidism (8). After that, one study showed the relationship between subclinical hypothyroidism, hyperprolactinemia and sterility (9). Although some studies reported that hyperprolactinemia is rare disorder in subclinical hypothyroidism (10).



Considering the clinical importance of hyperprolactinemia in ovulation disorders (11), sterility (12,13) and menstruation disorders (14,15), this study was done for the determination of hyperprolactinemia prevalence in subclinical hypothyroidism patients and clinical related symptoms in subclinical hypothyroidism patients in Sari , Iran.

### Methods

From April 2009 to June, 2010, this cross sectional study was done on 481 subclinical hypothyroidism patients aged 14-70 years were enrolled. Exclusion criteria of participation in this study were: pregnancy, lactation, renal failure {Creatinine(Cr)  $\geq 2$ }, history of hypophysis- hypothalamic disorders, using drugs affected on prolactin level, consuming thyroid hormone drugs from three months ago.

A questionnaire was designed for the evaluation of hypothyroidism symptoms for all qualified people. These symptoms were dry skin, cold weather intolerance, constipation, menstruation disorders, galactorrhea, hirsutism, alopecia, weight gain, muscle cramp. 7cc fasting blood sample was taken from each person and were preserved in -70°C and then TSH, T4 and serum prolactin were measured by Diasorin company kit manufactured by Spain and liazon apparatus and chemoimmuno luminance (CLIA) method. Coefficients variation of T4, TSH, and prolactin were 2.5%, 0.7%, 2.6%, respectively.

Collected data were analyzed by SPSS statistical software version 17 and frequency of hyperprolactinemia in patients with subclinical hypothyroidism were calculated. Clinical and demographic features were evaluated by quantitative variables and were shown by mean  $\pm$  standard deviation (meant  $\pm$  SD), t-test was used for the comparison of quantitative variables between two groups and  $\chi^2$  test was used for comparing qualitative variables. P value less than 0.05 was considered statistically significant.

### Results

Four hundred –eighty subclinical hypothyroidism patients were enrolled in this research. Thirteen patient were males and 87% were females. The mean age of these patients was 32 $\pm$ 10.1 years and most of the patients were between 20-40 years. Ninety-eight of 383 patients (20.4%) had hyperprolactinemia (91 female and 7 male). Prevalence of

hyperprolactinemia in men and in women with subclinical hypothyroidism were 11% and 22%, respectively (p=0.05).

The mean age of patient with normal prolactin was 34 $\pm$ 11 and in patients with prolactin level higher than normal was 31 $\pm$ 9 years (p=0.001).

In people with high level of prolactin 87.6% was in age group of 20-40 and 8.2 % was in less than 20 years and 13.3 % was in age group higher than 40 years. In patients with normal prolactin, 70 percent was between 20-40 years and 7.6 percent was younger than 20 years and 22.5 percent was older than 40 years.

In patient with hyperprolactinemia, 72 (14.9%) 19 (3.95%) and 7 patients had prolactin level higher than one, two and three times of normal range respectively.

Prevalence of fatigue was 23.6%, menstruation disorders 22.2% and alopecia 12.7%. Other symptoms such as dry skin (10.7%), constipation (7.7%), and cold intolerance (4.8%), weight gain (3.6%), galactorrhea (2.6%), hirsutism (1.5%) and muscle cramp (0.8%) were less common in 480 patients with subclinical hypothyroidism.

Comparisons of symptoms between two groups of patients with or without high prolactin were shown in table 1. In fact there was no statistically significant difference between these two groups for hypothyroidism symptoms (P>0.05).

**Table 1. Clinical symptoms in subclinical hypothyroidism patients with or without hyperprolactinemia**

Symptoms	Normal PRL 383 (68%)	High PRL 98(32%)	pvalue
Fatigue	92 (24)	22 (22.4)	0.7
Dry skin	39 (10.2)	12 (12.2)	0.5
Cold intolerance	17 (4.4)	6 (6.1)	0.5
Weight gain	14 (3.7)	3 (3.1)	0.8
Alopecia	49 (90.9)	12 (19.1)	0.9
Hirsutism	6 (1.6)	1 (1)	0.7
Muscle cramp	4 (1)	0 (0)	0.3

The comparison of hypothyroidism symptoms in subclinical hypothyroidism men and women was shown in table 2. Prevalence of alopecia was 1.6% in males and 14.4% in females (p=0.005). Prevalence of hyperprolactinemia was 11.3% and 21.7% in male and female respectively (p=0.05).

TSH level in 415 patients (86%) was  $\leq 10$  Iu/l and 60 patients (14%) had TSH levels higher than 10. Clinical symptoms between these two groups were not statistically significant (Table 3).

In comparison of clinical symptoms among the hyperprolactinemic women and women with normal prolactin level, we did not find statistically significant difference (Table 4).

**Table 2. The comparison of hypothyroidism symptoms in subclinical hypothyroidism male and female**

Symptoms	Female 367(76.3%)	Male 62(12.9%)	Pvalue
hyperprolactinemia	90 (21.7)	8 (11.3)	0.05
Fatigue	94 (24.8)	20 (16.1)	0.1
Dry skin	44 (11.2)	7 (6.5)	0.3
cold intolerance	19 (5)	4 (3.2)	0.5
Constipation	32 (8.1)	5 (4.8)	0.36
Weight gain	15 (4.1)	0 (0)	0.1
Galactorrea	11 (2.6)	1 (1.6)	0.6
Alopecia	60 (4.4)	1 (1.6)	0.005
Muscle cramp	4 (1)	0 (0)	0.4

**Table 3. The comparison of clinical symptoms in subjects with sub clinical hypothyroidism in two groups with TSH  $\leq 10$  and TSH>10**

Clinical symptoms	TSH>10 60 (13.7%)	TSH<10 415(83.6%)	Pvalue
High PRL	8 (21.1)	10 (21.7)	0.07
Fatigue	20 (30.3)	94 (22.7)	0.2
Dry Skin	7 (10.6)	44 (10.6)	1
Cold intolerance	4 (6.11)	19 (4.6)	0.6
Constipation	5 (7.6)	32 (7.7)	0.9
Weight gain	2 (3)	15 (3.6)	0.8
Muscle cramp	0 (0)	4 (1)	0.4
Menstruation disorder	11 (16.7)	96 (23.1)	0.2
Galactorrhea	2 (3)	10 (2.4)	0.8
Hirsutism	0 (0)	7 (1.7)	0.3
Alopecia	7 (10.6)	54 (13)	0.6

**Table 4. The comparison of clinical symptoms and TSH level in sub clinical hypothyroidism females with high or normal prolactin.**

Clinical symptoms	high prolactin 91 (%21.7)	normal prolactin 328 (%78.3)	P value
Weakness	21 (23.1)	83 (25.3)	0.6
Skin dryness	12 (13.2)	35 (10.7)	0.5
Coldness feeling	6 (6.6)	15 (4.6)	0.5
Constipation	5 (5.5)	29 (8.8)	0.3
Weight increase	3 (3.3)	14 (4.3)	0.7
Muscle cramp	0 (0)	4 (1.2)	0.3
Menstruation disorder	23 (25.3)	84 (25.6)	0.9
Galactorrhea	5 (5.5)	6 (1.8)	0.05
hirsutism	1 (1.1)	6 (1.5)	0.8
Alopecia	11 (12.2)	49 (14.9)	0.5
TSH $\leq 10$	83 (91.2)	279 (85.1)	0.1

## Discussion

We studied 481 newly diagnosed outpatients with subclinical hypothyroidism after the confirmation of subclinical hypothyroidism by repeated measurement of PRL. Conditions that caused physiologic and pathologic hyper prolactinemia were excluded. From 481 patients, 98 (20.4%) had hyperprolactinemia.

The estimated incidence of hyperprolactinaemia in hypothyroidism has been reported from 0% to 40% (16). Its prevalence in female with overt hypothyroidism was reported 39 to 57% (17,18). Researches in subclinical hypothyroidism are few and have different results. In Zeliha et al. study reported the prevalence of hyperprolactinemia in overt and subclinical hypothyroidism was 23.3% and was similar to the results of our study (19). This study was performed on 124 subclinical hypothyroidism patients and 43 overt hypothyroidism. The cause of low hyperprolactinemia prevalence in over thypothyroidism patients in this study may be the small sample size in a study that was conducted by Raber et al. hyperprolactinemia prevalence in overthypothyroidism and subclinical hypothyroidism was 10% and 8%, respectively (16). Pregnant and breast feeding women, patients with anti depression and anti psychotic drugs consumption and women using estrogen were not

excluded in this study. Additionally in this study prolactin was measured with immunoradiometric assay (IRMA).

The highest rate of hyperprolactinemia prevalence in our study was in age range of 20 to 40 years. It is expected that with increasing age, the prevalence of subclinical hypothyroidism will be increased. Perhaps one of the reasons of this different finding in our study was more evaluation of women in this age group for routine tests before pregnancy.

An important question is, whether hyper prolactinemia can create clinical symptom in these patients or not. Menstrual disorder was detected 45.2% in our study, 23.5% in hyperprolactinemic patients and 21.8% in normal prolactin groups. These findings were similar with the report of Raber et al. that menstrual disorder was seen in 26% of the hyperprolactinemia patients (16). This symptom was lower than overhypothyroidism with prevalence of 93% (20). Galactorrhea in hyperprolactinemia group was 5.1% and it was 1.8% in normoprolactinemic patients. This difference was not statistically significant. In Meier et al. a study that was performed on 66 female patients, no cases of menstruation disorders and galactorrhea was reported (21).

We have compared the prevalence of hypothyroidism symptoms in subclinical hypothyroidism on males and females. That showed the higher prevalence of hyperprolactinemia in subclinical hypothyroidism in female than male, this prevalence was 21.7% and 11.3%, respectively. In hypothyroidism patients, TRH is the stimulant factor of rising prolactin level. A previous study suggested that perhaps estrogen caused to increase prolactin response to TRH that caused higher prolactin level in woman than men (22). Meier et al. reported that women before menopause or menopausal women that received estrogen had higher level of prolactin compared to menopausal women without estrogen replacement (21).

Alopecia was significantly higher in women (14.4%) than men (1.6%). This result is similar to the findings of Zltautkr, et al. (19). It was mentioned that hypothyroidism and hyperprolactinemia have effective roles in stimulating androgenic alopecia, this may be a probable reason for our female androgenic alopecia. Hyperprolactinemia stimulates androgen production from adrenal and thyroxin effects on free and total testosterone with effect on thyroid binding globulin (TGB). So, coexistence of these two disorders can cause intensive alopecia. In this study, the comparison of symptoms between two groups with TSH higher and lower than 10 showed no statistical difference. Other study

showed that hypothyroidism symptoms were more prevalent in patients with higher TSH (5). In our study, patients with TSH lower than 10 was 87.3% and higher than 10 were only 13.7% and patients distribution may be the cause of this difference. In this study no correlation was found between TSH and prolactin levels (16,21,23) like the results of other studies. As we expected, TRH caused hyperprolactinemia in hypothyroidism, perhaps there is some unknown etiology that causes hyperprolactinemia in these patients.

In summary prevalence of hyperprolactinemia in subclinical hypothyroidism patients is considerable. Hyperprolactinemia causes reproduction disorders in women, early diagnosis and treatment of this disease is important.

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