

Association between Cretinism and Prolactin Secretion

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ABSTRACT

Objective: To compare the serum prolactin level in hyperthyroid and normal control females. Hyperthyroidism is a mutual disease. Even though a direct relation has been demonstrated amid hypothyroidism and increased prolactin levels, this association has not been established for hyperthyroidism.

Materials and Methods: Cross sectional study was carried out on cases and control groups. To select the cases, all women referred to the laboratories of Saudi National Hospital with a thyroid-stimulating hormone (TSH) level ≤ 0.5 mIU/L and met the inclusion criteria were entered in the study. A total of 62 women aged 16 to 49 years were enrolled. The case group included 24 hyperthyroid women, and the control group included 38 women with normal thyroid function matched by age.

Results: The mean (SD) serum level of prolactin was 16.4 (0.96) ng/mL (95% confidence interval [CI], 15.39 ng/mL to 15.69 ng/mL) in the controls and 23.02 (1.47) ng/mL (95% CI, 22.7 ng/mL to 23.4 ng/mL) in the case subjects. Hyperprolactinemia was more common in the hyperthyroid group (16.4 [0.96] ng/mL versus 23.02 [1.47] ng/mL; $P < .001$). The prolactin level decreased with age. Hyperthyroidism and estradiol increased the prolactin level. After adjusting for age and estradiol, hyperthyroidism increased the serum prolactin level ($P < .001$).

Conclusion: The outcomes of the present study showed that hyperprolactinemia is more frequent in hyperthyroid females. Serum prolactin level can be increased in hyperthyroidism.

Keywords: Prolactin secretion, hyperthyroidism, Hyperprolactinemia.

INTRODUCTION

Prolactin (PRL) is a lactogenic hormone secreted by the anterior pituitary. Hyperprolactinemia is a case where the baseline or fasting level of PRL in the morning and in the absence of pregnancy and lactation is >25 ng/mL^[1]. PRL levels begin to increase as a result of a range of reasons, comprising the following:

- Physiologic reasons (sleep, exercise, physical stress, emotional stress, breast stimulation, and high-protein diet);
- In hypothyroid patients and patients with chronic kidney and liver diseases;
- In patients with prolactinomas, destructive lesions of hypothalamus or pituitary stalk;
- Use of certain medications, such as estrogen, neuroleptic drugs, metoclopramide, antidepressants, cimetidine, methyl dopa, reserpine, verapamil, risperidone).

As a result, in the study of hyperprolactinemia, drug causes and diseases, for example, hypothyroidism should be considered^[1].

It has been reported that hypothyroidism can cause an increase in PRL by increasing the

thyrotropin-releasing hormone (TRH) level^[1]. Nevertheless, the direct influence of hormones on serum PRL levels and the association amid hyperthyroidism and PRL is uncertain^[2,3], as thyroxine (T4) did not alter prolactin level in other studies^[4,5]. PRL levels in chronic hyperthyroidism was found to be normal or marginally above normal^[6,7]. Even though PRL production increases in hyper- and hypothyroidism, as a result of increased clearance in hyperthyroidism, an elevated blood level of PRL was found in patients with hypothyroidism^[8]. Baseline PRL levels in hyperthyroid patients were higher than in normal subjects^[9]. One of the significant points regarding thyroid hormones is their contribution in the regulation of pituitary sensitivity and function, as receptors of the pituitary gland surface are regulated by thyroid hormones. Therefore, thyroid hormones standardize the number of TRH receptors on anterior pituitary mammothrophs^[2].

A noteworthy association has been demonstrated amid autoimmunity and reduced levels of PRL in autoimmune diseases^[10]. PRL secreted by the anterior pituitary and prolactin-like polypeptides that are localized in the joints are effective in

modulating the chondrogenic differentiation of synovial cell function, and there is mild hyperprolactinemia in patients with rheumatoid arthritis^[11]. The study of Parker *et al*^[12] on the association between PRL and autoimmune ailments presented that PRL levels are increased in autoimmune diseases such as lupus. Remarkably, elevated blood levels of PRL have been shown in patients with Hashimoto disease^[13]. Based upon our observations and experience in which PRL and thyroid tests are demanded for patients with menstrual cycle disorders, when the patient is hyperthyroid, the patient's PRL is high and returns to its normal level after treatment for hyperthyroidism. As hyperprolactinemia requests additional expensive evaluation, for example, magnetic resonance imaging of the pituitary gland, based on a literature review and to the best of our knowledge, there are only few studies that have been conducted on the levels of PRL in women with hyperthyroidism, and the results have been contradictory^[4-9, 14]. Therefore, the current study was designed to compare the PRL levels in healthy women and patients with hyperthyroidism, for the reason that proving any association between hyperprolactinemia and hyperthyroidism can cause delay of requirements for time-consuming and costly procedures.

MATERIALS AND METHODS

This cross-sectional study was carried out on 62 premenopausal women aged 16 to 49 years. Patients were divided into 2 groups after meeting the inclusion criteria and providing informed consent; the case group (n = 24) included women with hyperthyroidism and a thyroid-stimulating hormone (TSH) level of <0.5 mIU/L, and the control group (n = 38) included women with normal thyroid function and TSH in the normal range of 0.5 to 4.5 mIU/L. To select the case group, throughout 3 months of study, all 16- to 49-year-old hyperthyroid women who were referred to the laboratories of Saudi National Hospital and met the inclusion criteria were selected. Consistent with the different experimental methods used in determining the samples, to ensure full reliability, all tests were repeated through electro chemilumino-metric assay in the reference laboratory. To choose the control group, serum samples from euthyroid age-matched eligible women were selected from a sample pool. Study inclusion criteria included the following: (1) primary hyperthyroidism (case group), (2) age between 16 and 49 years, and (3) female gender. Study exclusion criteria included: (1) use of medications for example, dopamine-receptor blockers including phenothiazines, chlorpromazine, butyrophenones, perphenazine,

thiothixenes, haloperidol and metoclopramide; dopamine-synthesis inhibitors such as methyl dopa; catecholamine tippers such as reserpine; opiates; H2 blockers such as cimetidine and ranitidine; imipramine, amitriptyline; serotonin re-uptake inhibitors such as fluoxetine; calcium channel inhibitors such as verapamil; hormones such as estrogens, anti-androgens, TRH; (2) breastfeeding; (3) pregnancy; (4) chronic kidney disease; (5) polycystic ovary syndrome; and (6) liver diseases.

The blood samples of eligible participants were sent to the laboratory. Samples were kept at -70°C until analysis. Serum concentrations of TSH, T4, PRL, and estradiol were determined. The investigators were blinded regarding subject identity and group. Serum levels of thyroid hormones and PRL were determined using an Elecsys analyzer 2010 and commercial kits (Roche). Patients with PRL levels >25 ng/mL were considered as having hyperprolactinemia. Serum concentrations of 4.6 to 11.2 $\mu\text{g/dL}$ were considered normal for T4, and 0.5 to 4.5 mIU/L was considered the normal range for TSH. All subjects with T4 >11.2 $\mu\text{g/dL}$ and TSH <0.1 mIU/L were classified as having hyperthyroidism.

SPSS ver. 18 (IBM Inc) software was utilized for statistical analyses. The concentration of each hormone and data for each patient in the case and control groups were coded. Data were assessed using descriptive statistics. Hormone levels were compared using t tests. To investigate the correlation between PRL and T4, the Pearson correlation test was used. The frequency of patients with hyperprolactinemia in both the case and control groups was compared using the chi-square test. A P value <.05 was considered significant for all tests.

RESULTS

The mean age (SD) of participants was 34.4 (1.09) years and 33.8 (0.79) years in the case and control groups, respectively. The TSH level in the case group was 0.077 (0.011) mIU/L and 3.79 (0.051) mIU/L in the control group (P<.001). The T4 level in the case group was 13.31 (1.49) mIU/L and 6.02 (2.09) mIU/L in the control group (P<.001). The estradiol level was 541.7 (72.39) pg/mL in the case group and 184.5 (16.8) pg/mL in the control group. The PRL level was 23.02 (1.47) ng/mL in the case group and 16.4 (0.96) ng/mL in the control group. PRL levels were significantly different between the two groups (P<.001). In the case group, 17 patients (70.8%) had normal PRL levels, and 7 patients (29.2%) had hyperprolactinemia; the maximum concentration of PRL in the case group was 60 ng/mL. In the control group, 97 patients (85.5%) had normal PRL levels, and only 16 patients (14.2%) had hyperprolactinemia. The frequency of

hyperprolactinemia was significantly different between the two groups (chi-square test, P = .011).

Demographic and laboratory characteristics of the study subjects are shown in Table 1.

Table 1. Demographic and Laboratory Characteristics of the Study Subjects

	Control	Hyperthyroid	P value
Age (years)	33.8 ± 0.79	34.4 ± 1.09	0.97
Thyroid-stimulating hormone (µIU/mL)	3.79 ± 0.51	0.077 ± 0.011	<.001
Thyroxine (µg/dL)	6.02 ± 2.09	13.31 ± 1.49	<.001
Estradiol (pg/mL)	184.5 ± 16.8	541.7 ± 72.39	<.001
Log(estradiol)	4.8 ± 0.09	6.01 ± 0.17	<.001
Prolactin (ng/mL)	16.4 ± 0.96	23.02 ± 1.47	<.001
Normal prolactin (n)	33 (86.8%)	17 (70.8%)	.010
Hyperprolactinemia (n)	5 (13.2%)	7 (29.2%)	.010

Receiver operating characteristic (ROC) curves were used to determine the cut off values for thyroxine and thyroid-stimulating hormone.

For thyroid-stimulating hormone, the area under the curve was 0.61 (0.363), a value with no clinical significance. For thyroxine, the area under the ROC curve was 0.053 (0.629) (P<.013), providing a cut point for thyroxine of 11.1 µg/dL.

Based on this area, the thyroxine value was reported as Youden = 1.2, sensitivity = 0.59, and specificity = 0.58. The outcomes of univariate regression analyses showed that all the three variables (age, hyperthyroidism, and estradiol) induced a significant effect on the PRL level; this means that hyperthyroidism and estradiol had a significant direct effect, but age presented a significant negative effect. The average PRL level in the hyperthyroid group was 6.49 ng/mL, which was significantly higher than the control group (P<.001).

The results of multivariate linear regression analyses showed that after removing the effects of age and gender, the effect of hyperthyroidism on PRL level was significant. In other words, the level of PRL in the hyperthyroid group increased by 18.9 units comparing with the control group (P<.001). These data show that the hyperthyroidism effect on serum PRL level is independent of the effects of age and estradiol.

The effect of age in the multivariate test was still significant and was inversely associated with PRL. The level of PRL declined by 0.23 ng/mL per year,

but estradiol in the multivariate analysis caused non significant effect on PRL (Table 2).

Table 2. Effect of Hyperthyroidism, Age, and Gender on Serum Prolactin Level, as Determined Using Multivariate Regression Analysis

	Unadjusted		Adjusted	
	β	P value	B	P value
Hyperthyroidism	6.49	<.001	18.9	<.001
Age	-0.25	.015	-0.23	.041
Estradiol (log)	5.80	<.001	1.9	.13

The outcomes of univariate logistic regression analyses revealed that the variables of hyperthyroidism and estradiol directly and significantly increased the chance of hyperprolactinemia. However, people who suffer hyperthyroidism had a statistically significant (P = .011) increased chance of hyperprolactinemia by (odds ratio, 2.49; 95% confidence interval, 1.19 to 5.29).

The outcomes of multivariate logistic regression analyses showed that after removing the effects of age and gender, hyperthyroidism still induced a significant positive impact on hyperprolactinemia (adjusted odds ratio, 70.2; 95% CI, 8.1 to 607.2) (P<.001). In this test, the effects of age and estradiol on serum PRL were not statistically significant (Table 3).

Table 3. Logistic Regression Analysis of the Effects of Hyperthyroidism on Prolactin

	Unadjusted		Adjusted	
	OR (95% CI)	P value	OR (95% CI)	P value
Hyperthyroidism	2.49 (1.19–5.29)	.011	70.2 (8.1–607.2)	<.001
Age	0.98 (0.94–1.02)	.56	0.98 (0.91–1.04)	.54
Estradiol (log)	2.83 (1.62–4.95)	<.001	1.39 (0.68–2.82)	.35

DISCUSSION

The results of this study showed that the serum PRL level in patients with hyperthyroidism is higher compared to normal individuals, and similarly a greater percentage of patients with hyperthyroidism suffer from hyperprolactinemia. Moreover, the concentration of serum PRL drops with age and increases with hyperthyroidism and raised estradiol level. The consequence of hyperthyroidism on the increase in PRL level is independent of the effects of age and estradiol. Nevertheless, these changes are minor and do not improve the PRL level to the same extent in patients with a prolactinoma. Cooper *et al*^[8] inspected the metabolic freedom rate of PRL in 6 patients with hyperthyroidism and 4 patients with hypothyroidism. The consequences of their investigation demonstrated that freedom is expanded in hyperthyroidism and diminished in hypothyroidism. The PRL level contrasted from the control amass just in patients with hypothyroidism, a discovering which isn't predictable with those of the present examination. Cooper *et al*'s examination included a littler and more constrained example contrasted and the present investigation. Malarkey *et al*^[5] inspected the impact of recommending T4 on serum PRL levels. The after effects of their examination demonstrated that PRL discharge does not change after organization of T4. As our examination was not interventional and was performed on hyperthyroid patients, the distinction in think about outline can mostly clarify the diverse discoveries, albeit more research is required around there.

In vitro studies on the impact of thyroid hormones on PRL discharge from foremost pituitary cells of rats demonstrated that the PRL emission rate is decreased by applying thyroid hormones^[2,3]. These discoveries are not reliable with those of the present examination. In spite of the fact that this examination varies from those shown above, different reasons, for example, the viability of hormones and distinction amongst intense and constant medicine of thyroid hormones, might be a clarification for these discoveries, as **Malarkey *et***

al.^[5] have demonstrated that the measure of PRL in people following the solution of T4 can't be changed. Then again, a reduction in the PRL pool and end of the PRL reaction to concealment tests (L-DOPA and bromocriptine test) and incitement tests (test with thyrotropic hormone) were accounted for by Stokić^[15].

It is conceivable that hoisted PRL level possibly a result of irritating arrival of PRL from the secretory granules amid the hyperthyroid state, prompting a decline in the substance of these granules. Delitala *et al*^[16] and Snyder *et al*^[17] showed that the PRL level in chronic hyperthyroidism was normal or slightly above normal, though the difference was not statistically significant. In our study, however, the PRL level was higher than normal compared to the control group. The main reasons for this difference are the selection of samples (gender, inclusion/exclusion criteria) and method of PRL measurement. Kramer *et al*^[18] demonstrated that the PRL level increments in immune system ailments, for example, lupus, and the investigation of Onishi *et al*^[9] likewise demonstrated that the PRL level increments in patients with Hashimoto thyroiditis. Lamentably, in the present investigation, the purpose behind the hyperthyroidism couldn't be separated.

The current study presented that hyperthyroidism can increase PRL independent of the effect of estradiol, but as a result of an increase in gender hormone-binding globulin in hyperthyroidism and measuring total estradiol in this study, the lack of increase in the free fraction of estradiol may be the reason for the lack of the effect on PRL.

Limitations

This was a cross-sectional study that could not determine a cause and effect relationship; therefore, the second phase of the study is being carried out as a clinical trial in order to assess the effect of hyperthyroidism treatment on the serum PRL level. Macroprolactin was not evaluated in our study. Since the present study was directed only on women, further studies on both sexes seem necessary. Unfortunately, the anti-thyroid peroxidase antibody

status of the patients was not known. Also, broader areas of studies with a focus on differentiating the different causes of hyperthyroidism on PRL level are recommended.

In the case of high PRL level, hyperthyroidism ought to be considered as one of the factors raising the PRL in the range of <40 µg/L. Nevertheless, owing to the fact that patients in this study were selected from those who had increased T4 and therefore, suppression of TSH, and since the ROC curve showed the T4 level more than 11/1 µg/dL leads to an increase in PRL, it seems that the recommendation is not practical for patients with subclinical hypothyroidism. In patients with subclinical hyperthyroidism, high PRL level require more investigation.

CONCLUSION

In patients with mild hyperprolactinemia, it is advisable to consider overt hyperthyroidism as an adjustable underlying cause.

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