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ORIGINAL

The prevalence of hyperprolactinaemia in overt and subclinical hypothyroidism

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Abstract. The aims of this study were to: 1) determine the prevalence of hyperprolactinaemia in patients with newly diagnosed subclinical and overt hypothyroidism, and 2) investigate the change in PRL levels with treatment. In this observational study, patients with a new diagnosis of hypothyroidism in our endocrinology clinic were approached for participation, as were healthy controls. Patients with medical reasons for having elevated PRL levels, lactating and pregnant women were excluded from the study. No patient had kidney or liver disease. After examination to determine if clinical causes of PRL elevation were present, serum levels of thyrotropin (TSH), free thyroxine, free triiodothyronine and PRL were measured and correlation of PRL levels with the severity of hypothyroidism (overt or subclinical) was performed. Fifty-three patients (45 women, 8 men, mean age 45.3±12.2 years) had overt hypothyroidism. One hundred forty-seven patients (131 women, 16 men, mean age 42.9±12.6 years) had subclinical hypothyroidism. One hundred healthy persons (85 women, 15 men, mean age 43.9±11.4 years) participated as controls. The same blood tests were repeated in patients after normalization of TSH levels with L-thyroxine treatment. PRL elevation was found in 36% of patients with overt hypothyroidism, and in 22% of patients with subclinical hypothyroidism. PRL levels decreased to normal in all patients after thyroid functions normalized with L-thyroxine treatment. In the hypothyroid patients (overt and subclinical) a positive correlation was found between TSH and PRL levels (r=0.208, p=0.003). PRL regulation is altered in overt and subclinical hypothyroidism, and PRL levels normalize with appropriate L-thyroxine treatment.

Key words: Hypothyroidism, Subclinical hypothyroidism, Hyperprolactinemia, Prolactin

HYPERPROLACTINEMIA is a common condition that can result from a number of causes, including medication use, hypothyroidism, and pituitary disorders. Depending on the underlying cause and consequences of the hyperprolactinemia, selected patients may require treatment. Hyperprolactinaemia may develop in patients with primary hypothyroidism through a variety of mechanisms. In response to the hypothyroid state, a compensatory increase in the discharge of central hypothalamic thyrotropin-releasing hormone occurs, which results in stimulation of prolactin (PRL) secretion. Furthermore, prolactin elimination from the systemic circulation is reduced, which contributes to increased prolactin concentrations [1-4]. Other reasons for increasing prolactin levels in hypothyroidism include a decreased sensitivity to the suppresant effect of dopamine on prolactin synthesis [5], and increased prolactin synthesis through increased prolactin messenger RNA levels in the presence of lower thyroid hormone levels [6]. While the prevalence of hyperprolactinaemia in overt hypothyroidism has been reported to be as high as 40%, its prevalence and clinical significance in subclinical hypothyroidism has only been reported in case reports and smaller studies [7, 8, 9, 10, 11]. Some have even found no relationship between the degree of hypothyroidism and prolactin levels [8].

Because of the variable results and low patient numbers in previous studies, we aimed in this study to: 1) measure the prolactin levels and determine the prevalence of hyperprolactinaemia in newly diagnosed subclinical and overt hypothyroidism patients, and 2) investigate the change in PRL levels with L-thyroxine replacement therapy.

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Materials and Methods

Our study protocol was approved by our University Research Ethics Committee. In a prospective fashion, consecutive patients newly diagnosed with hypothyroidism in our endocrinology clinic between January, 2006 and December, 2008 were approached for participation in the study. Patients with clear medical reasons for hyperprolactinemia, such as lactating and pregnant women, those with liver or kidney disease, and those taking antidepressants, estrogens, or antipsychotics, were excluded from the study. After consent was granted, they were examined to determine if clinical or pharmacological causes of PRL elevation were present, and serum levels of thyrotropin (TSH), free thyroxine, free triiodothyronine and PRL were measured. The same examination and tests were performed in 100 healthy persons (without a history of thyroid disease or conditions which affect prolactin levels) after consent was obtained.

Serum levels of TSH, free thyroxine (fT4), free triiodothyronine (fT3) and PRL were measured in all patients before and after TSH normalization with L-thyroxine treatment. Serum fT3, fT4 and TSH levels were measured by using a chemiluminescent assay method with Immulite 2000 commercial kits (Siemens Medical Solutions Diagnostics, Los Angeles, USA) on an Immulite autoanalyzer (Immulite, Bio-DPC, Los Angeles, USA). Immunoassay was also used (using the same analyzer equipment) to quantify serum autoantibodies against thyroglobulin and autoantibodies against thyroid peroxidase. Hypothyroidism was defined as subclinical if basal TSH was increased and if FT3 and FT4 were normal. Hypothyroidism was defined as overt if basal TSH was increased and FT3 or FT4 were decreased.

Serum prolactin was measured using a chemiluminescent assay method with the ACCESS® prolactin commercial kit (Access Immunoassay Systems, Beckman Coulter**,** Inc., Fullerton**,** USA). The normal ranges of serum PRL were 1.9-25 ng/mL for females and 2.5-17 ng/mL for males. We defined hyperprolactinaemia as serum PRL >25 ng/mL for females and >17 ng/mL for males. Correlation of PRL levels with the severity of hypothyroidism (overt or subclinical) was performed.

Statistical evaluation was performed with SPSS for Windows® using Student's t test, chi-square test, one-way ANOVA with Bonferroni test as a post hoc test for pairwise comparisons, and the Pearson correlation test. *P* values less than 0.05 were regarded as statistically significant. Results are reported as mean±SD.

Results

Of the 200 consecutive patients with newly diagnosed hypothyroidism seen in our clinic, 53 (45 women, 8 men, mean age 45.3±12.2 years) had overt hypothyroidism and 147 (131 women, 16 men, mean age 42.9±12.6 years) had subclinical hypothyroidism. The healthy controls were 85 women and 15 men with a mean age of 43.9±11.4 years. Patient groups (subclinical hypothyroidism and overt hypothyroidism) and control groups were similar in regard to age and gender. PRL elevation was found in 19 patients (36%) with overt hypothyroidism, and in 32 patients (22%) with subclinical hypothyroidism. Laboratory variables of the patients and controls are given in Table 1.

A statistically significant elevation of PRL levels was found in patients with overt hypothyroidism when compared to patients with subclinical hypothyroidism and controls, and in patients with subclinical hypothyroidism when compared to the control group ($p<0.001$) (Table 1). PRL levels decreased to normal levels after thyroid function normalised with L-thyroxine treatment, as shown in Table 2.

When the TSH levels of all hypothyroid patients (n=200) were compared to their PRL levels, a positive correlation was found ($r=0.208$, $p=0.003$, Fig. 1).

Discussion

In this largest study of subclinical hypothyroid patients to date, we found PRL levels to be elevated in both sublcinical and overt hypothyroidism, and that these levels normalize with L-thyroxine treatment. Elevation of PRL in overt hypothyroidism has been reported before [1-4, 8, 12], but studies on this subject in patients with subclinical hypothyroidism are few [9, 10, 11]. Several mechanisms have been proposed for the increase in prolactin levels in primary hypothyroidism. First, elevated prolactin levels can be attributed to increased PRL secretion under the influence of TRH, which stimulates TSH as well as PRL secretion [3, 4, 12, 13]. Second, prolactin clearance may be decreased in hypothyroid patients [3, 14]. Third, a study by Foord, *et al*. demonstrated that cultured anterior pituitary cells from hypothyroid rats have a reduced sensi-

Table 1 Demographic and laboratory values (mean±SD) in patients with subclinical and overt hypothyroidism and in healthy controls

	Subclinical hypothyroidism (n=147)	Overt hypothyroidism (n=53)	Control (n=100)	*P*
Age (years)	42.9±12.6	45.3±12.2	43.9±11.4	*P*=0.4 (one-way ANOVA)
Gender: Female n (%)/Male n	131(89.1%)/16	45(84.9%)/8	85(85.9%)/15	*P*=0.6 (Chi-square test)
FT_3 pg/mL (nv:1.5-4.7)	3.0±0.5	1.8±0.9	3.1±0.3	*P*<0.001 Overt<subclinical=control
FT_4 ng/dL (nv:0.8-1.9)	1.0±0.2	0.4±0.3	0.9±0.2	*P*<0.001 Overt<control=subclinical
TSH μIU/mL (nv: 0.27-4.2)	9.5±5.9	85.2 ±64.2	1.4±0.9	*P*<0.001 Overt>subclinical>control
Anti-T (nv: 0-115 IU/mL)				*P*=0.001 (Chi-square test)
High n (%)	82 (55.8%)	36 (67.9%)	0 (0%)	
Normal n (%)	65 (44.2%)	17 (32.1%)	100 (100%)	
Anti-TPO (nv: 0-34 IU/mL)				*P*=0.001 (Chi-square test)
High n (%)	94 (63.9%)	41 (77.4%)	0 (0%)	
Normal n (%)	53 (36.1%)	12 (22.6%)	100 (100%)	
Prolactin ng/mL (nv: 1.9-25 for females; 2.5-17 for males)	17.6±10.5	21.8±13.7	12.4±4.8	*P*<0.001 Overt>subclinical>control
Hyperprolactinemia n (%)	32 (22%)	19 (36%)	0 (0%)	*P*<0.001 (Chi-square test)
Female/Male	25/7	13/6		

nv=normal values

Table 2 Comparison of FT3, FT4, TSH and PRL levels (mean±SD) in subclinical and overt hypothyroidism patients after the patients became euthyroid after receiving treatment with L-thyroxine

	FT3 pg/mL	FT4 ng/dL	TSH μIU/mL	Prolactin ng/mL
Subclinical hypothyroid patients (n=147)	3.4±0.6	1.4±0.3	1.6±1.3	11.8±5.4
Overt hypothyroid patients (n=53)	3.3±0.7	1.5±0.3	1.5±1.3	11.1±4.2

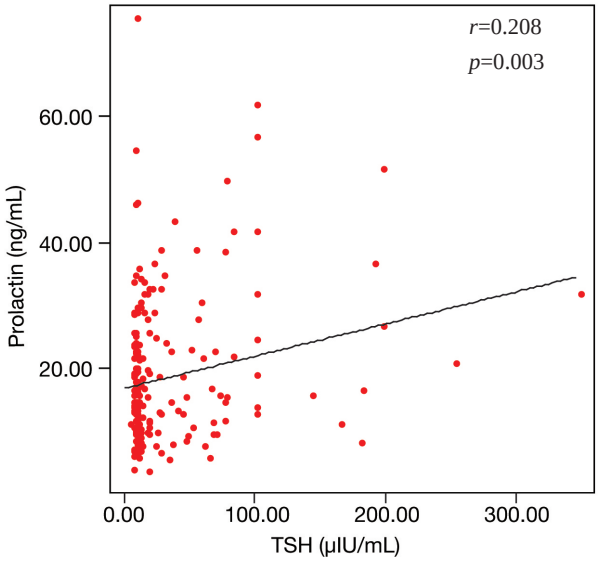

Fig. 1 Distribution of serum PRL concentrations in 200 hypothyroid patients (overt and subclinical). A positive correlation was found between TSH and PRL levels (r=0.208, p=0.003).

tivity to the inhibitory action of dopamine and dopamine agonists on prolactin production, possibly by a defect at the level of the dopamine receptor or at the post receptor level [5]. Fourth, thyroid hormone itself may also play an important role in the cause of hyperprolactinaemia. Davis, *et al*. [6] noticed that 3,5,3'-triiodothyronine reduces prolactin messenger RNA levels in rodent pituitary cells. Thus, decreased circulating thyroid hormone levels result in increased prolactin synthesis. Other pathophysiological factors leading to hyperprolactinaemia in primary hypothyroidism might involve actions on prolactin receptors as well as on prolactin gene expression.

Rarely, hyperprolactinaemia in primary hypothyroid patients is associated with an enlarged pituitary gland leading to diagnostic confusion with prolactinomas. This pituitary enlargement might be explained by lactotroph and/or thyrotroph hyperplasia, related to the severity and duration of hypothyroidism [13, 15-17].

Hyperprolactinaemia is not seen in all patients with hypothyroidism, but it has been reported to occur in 0-40% of hypothyroid patients [7-11]. Among women with overt hypothyroidism, hyperprolactinaemia was found in 39-57% [12, 18]. This is similar to the proportion (36%) of our overt hypothyroid patients with hyperprolactinaemia. In the study of 1003 hypothyroid (TSH >4.0 mU/L) patients by Raber, *et al*., hyperprolactinaemia was found in 84 (8%) patients, including 11 pregnant or lactating women. They also did not find a correlation between initial TSH and PRL levels [8].

In the study of 66 patients with subclinical hypothyroidism by Meier, *et al*. [11], 19% had high PRL levels. Patients were then randomly treated with placebo or L-thyroxine. Those treated with L-thyroxine became euthyroid and their PRL levels returned to normal. PRL levels remained high in those who received placebo. Notsu, *et al*. [10] measured PRL levels in 15 healthy controls and in 74 Hashimoto's thyroiditis patients: 42 were euthyroid, 18 had sublcinical and 14 had overt hypothyroidism. PRL was found to be elevated in 42% of the overt hypothyroid patients, 11% in the subclinical hypothyroid patients, and 14% or the euthyroid patients. Among those with high PRL levels, one had a prolactinoma, one had pseudotumor, and one had liver cirrhosis. Hyperprolactinaemia was more common in our overt hypothyroidism patients (36%) than in those patients with subclinical hypothyroidism (22%). The PRL levels in our subclinical hypothyroid group were higher than those in the reports mentioned above.

In several case series, normalization of serum PRL levels was observed after L-thyroxine treatment of patients with overt hypothyroidism [8, 10, 13, 15-17]. However, studies that show normalization of serum PRL levels after L-thyroxine treatment in patients with subclinical hypothyroidism are few [9, 10, 11]. In our study also, PRL levels returned to normal range in all patients after a euthyroid state was achieved with L-thyroxine treatment. If thyroid tests are normal a patient with high PRL levels, further (usually more expensive) tests should be done to determine the etiology of the hyperprolactinaemia. If hypothyroidism is diagnosed, PRL levels should return to normal with appropriate L-thyroxine treatment.

PRL regulation is altered, not just in patients with overt hypothyroidism, but in those with subclinical hypothyroidism as well. PRL levels return to normal with appropriate L-thyroxine treatment. Thyroid function tests should be performed on patients with hyperprolactinaemia before performing further tests or imaging studies.

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