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FREQUENCY OF OTHER ENDOCRINE DISORDERS IN HYPOTHYROIDISM

Abstract: Hypothyroidism is a condition of reduced production, distribution, or absence of action of thyroid hormones. Clinical diagnosis of hypothyroidism is not easily established due to the nonspecific clinical manifestations. Determination of serum TSH is the first-line test for the diagnosis of hypothyroidism. The aim of the study was to determine the presence of other endocrine disorders in patients with subclinical (TSH levels between 5 and 10 mIU/l), or clinical (TSH above 10 mIU/l) hypothyrodism. We analyzed 50 patients (35 with clinical hypothyroidism and 15 with subclinical form). In all patients anthropometric data (age, sex, weight, height, body mass index, blood pressure and heart rate), and clinical signs of hypothyroidism (skin changes, menstrual disorders) were determined. Blood was drawn in fasting state for measurement of FT4, sTSH, glucose, lipids, ionized calcium, PTH, cortisol, ACTH, prolactin, gonadotropins, estradiol in women of reproductive age, and testosterone in men. Skin lesions were rarely present. Oligomenorrhea was more frequent in subclinical hypothyroidism, and menopause in clinical hypothyroidism. Blood pressure was normal in all subjects. Patients with clinical hypothyroidism compared to those with subclinical form had higher TSH values (19.5 ± 5.7 vs. 5.9 ± 0.3 mIU/l), and higher doses of L-thyroxine (81.2 ± 4.6 vs. 21.4 ± 3.5 μg/day). Disturbance of glycemic control was present in 18% of patients. Total cholesterol and LDL were insignificantly higher in patients with hypothyroidism than in subclinical form of the disease. FT4, calcium, PTH, cortisol, ACTH, gonadotropins, estradiol and testosterone did not differ between groups. The proatherogenic relation of estradiol with triglycerides was established in women with clinical form of hypothyroidism.

Key words: hypothyroidism, subclinical hypothyroidism, TSH, FT4, endocrine disorders

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Introduction

Hypothyroidism is a condition caused by reduced production, distribution or absence of abnormal thyroid hormone action (1). Hypothyroidism can occur from the intrauterine period until old age, as a mild or subclinical and clinically manifest hypothyroidism (1, 2). Recent Scandinavian studies have shown that the incidence of manifest hypothyroidism ranges from 32 to 156/100.000 patient-years depending on country and age of the subjects (3). In contrast to clinically manifest hypothyroidism, prevalence of the subclinical hypothyroidism is 4 to 8.5% with an increase to 20% in women older than 60 years (4). Study by Diez and Iglesias analyzed the course of subclinical hypothyroidism and showed that 26.8% of patients developed manifest hypothyroidism, while 37.4% of patients normalized TSH (5).

Chronic autoimmune thyroiditis or Hashimoto's thyroiditis is nowadays considered the most common cause of acquired hypothyroidism. The disease is seven times more common in women than in men, and the incidence increases with age. The disease has a hereditary character whose nature is still not resolved (6).

While in clinical hypothyroidism signs and symptoms of the disease are associated with increased TSH and decreased thyroxine (T_4) and triiodothyronine (T_3), subclinical hypothyroidism is characterized by an increased concentration of TSH with normal total or free T_4 and T_3. Therefore, determination of TSH is fundamental for the diagnosis of subclinical hypothyroidism. Population studies have shown that normal reference range for TSH is from 0.4 to 4 mU/l (7). Some authors consider that the upper limit of the TSH concentration should not exceed 2.5 mU/l (8).

Disorders of lipid metabolism represent an important consequence of hypothyroidism. It is shown that substitution with levothyroxine in subclinical hypothyroidism decreases total cholesterol and LDL cholesterol, and without affecting HDL cholesterol and triglycerides. TSH concentrations above 10 mU/l are considered to be associated with adverse effects on lipid metabolism which is not clearly shown for TSH concentrations between 4 and 10 mU/l (4, 9). Electrolyte disorders in hypothyroidism are common but usually mild. The most common electrolyte disorder in hypothyroidism is decrease in sodium due to the lack of thyroid hormones on renal function and pituitary, and consequent change in excretion of water (2). It is known that in patients with hypothyroidism cortisol response to hypoglycemia during insulin tolerance test is damaged (10). In women, hypothyroidism can be associated with ovulatory dysfunction (11), while in men can cause erectile dysfunction and loss of libido (12).

Considering the above facts on the importance of thyroid hormones in the metabolic pathways and role in the functioning of the endocrine axis, the objective of this study was to determine the presence of other endocrine disorders in patients with subclinical or clinical form of hypothyroidism.

Material and methods

Clinical characteristics of the group

We included 50 patients that were referred for the endocrine outpatient examination at the Clinical Hospital Centre "Bežanijska kosa." Patients were under observation for having subclinical or clinical hypothyroidism, or for the regular monitoring and adjustment of therapy of the preexisting subclinical or clinical hypothyroidism.

Subclinical hypothyroidism was defined by the presence of clinical signs and symptoms, and TSH levels between 5 and 10 mIU/l. Clinical hypothyroidism was defined by using TSH level of more than 10 mIU/l.

In all subjects we determined gender, age, body weight, body height, calculated body mass index (BMI), determined systolic and diastolic blood pressure (systolic BP and diastolic BP) at the cubital fossa while seated, and determined the pulse. We assessed if the subject had changes in the skin (dryness, change in elasticity), and in women, if there is a change in menstrual regularity (oligomenorrhea or amenorrhea) or menopause.

Determination of the biochemical and hormonal parameters

In all patients fasting blood samples were drawn for the determination of biochemical and hormonal parameters. Glucose (mmol/l) were determined by enzymatic UV test (hexokinase method), manufacturer Beckman, USA. Cholesterol (mmol/l), HDL cholesterol (mmol/l) and triglycerides (mmol/l) were determined by enzymatic color test, manufacturer Beckman, USA. LDL cholesterol (mmol/l) was calculated using Friedwald formula. Ionized calcium (mmol/l) was determined using the ion selective electrode, AVL 9180 Electrolyte Analyzer Roche-Diamond Diagnostics, Germany. FT_4 (pmol/l), anti-microsomal antibodies (anti-TPO At, IU/l), anti-tireoglobulin antibodies (anti Tg At, IU/l), PTH (pg/ml) and testosterone (ng/ml) were determined using Roche electro-chemiluminiscence method, Germany. TSH (mIU/l), cortisol (nmol/l), ACTH (pg/ml), FSH (mIU/l), LH (mIU/l), prolactin (mIU/l), C-peptide (ng/ml), insulin (μIU/l) and estradiol (pg/ml) were determined using electro-chemiluminiscence method, DPC-Siemens, Germany. Antiovarian antibodies (IU/ml) were determined using ELISA method, Bioserv Diagnostics, Germany.

In the assessment of glycemic status, we performed categorization of fasting blood glucose on values between 6.0 and 6.9 mmol/l, and more than 7.0 mmol/l. The assessment of insulin sensitivity was performed using homeostatic model assessment or HOMA index that was calculated from the values of insulin and glucose (13).

Statistical analyzes

All calculations were performed using a standard software package SPSS (v.10.0.1) on a personal computer. In the text and tables continuous variables are presented as mean ± standard error (standard error, SE). In the statistical analysis of data, we used t-test, ANOVA and Spearman's correlation coefficient for the quantification of the correlations between variables. Statistically significant was considered $P<0.05$.

Table 1. Biochemical and hormonal characteristics of the whole group of patients and related to the type of hypothyroidism

	Whole group	Subclinical hypothyreosis (n=15)	Clinical hypothyreosis (n=35)	P (subclinical vs. clinical hypothyreosis)
Age (years)	53.4 ± 2.2	48.2 ± 5.0	55.7 ± 2.2	0.114
Weight (kg)	79.2 ± 2.6	79.3 ± 6.3	79.2 ± 2.7	0.982
BMI (kg/m²)	28.8 ± 0.8	28.0 ± 1.9	29.2 ± 0.9	0.569
Systolic BP (mmHg)	127.2 ± 2.4	125.0 ± 5.8	128.0 ± 2.5	0.581
Diastolic BP (mmHg)	80.9 ± 1.1	79.6 ± 2.3	81.4 ± 1.3	0.482
Puls (heart beats per min)	68.6 ± 1.7	71.1 ± 3.6	67.6 ± 1.9	0.363
Dose L-thyroxin (μg/day)	70.8 ± 5.3	21.4 ± 3.5	81.2 ± 4.6	<0.0001

Table 2. Biochemical and hormonal characteristics of the whole group of patients and related to the type of hypothyroidism

	Whole group	Subclinical hypothyreosis (n=15)	Clinical hypothyreosis (n=35)	P (subclinical vs. clinical hypothyreosis)
Glucose	5.7 ± 0.2	5.6 ± 0.3	5.8 ± 0.3	0.716
Cholesterol	6.1 ± 0.2	5.4 ± 0.3	6.5 ± 0.3	0.077
HDL cholesterol	1.3 ± 0.05	1.3 ± 0.08	1.3 ± 0.07	0.720
LDL cholesterol	4.0 ± 0.2	3.5 ± 0.3	4.3 ± 0.3	0.107
Triglycerides	1.6 ± 0.1	1.5 ± 0.2	1.6 ± 0.1	0.718
Ionized calcium	1.18 ± 0.007	1.16 ± 0.01	1.19 ± 0.007	0.103
FT_4	13.7 ± 0.7	14.2 ± 0.6	13.4 ± 1.0	0.640
sTSH	15.2 ± 4.0	5.9 ± 0.3	19.5 ± 5.7	0.118
Anti TPO At	522.4 ± 123.4	346.8 ± 88.3	596.9 ± 171.0	0.360
Anti Tg At	1067.9 ± 345.8	702.4 ± 362.8	1250.7 ± 486.8	0.462
Cortisol	462.5 ± 20.7	481.8 ± 47.2	454.5 ± 22.3	0.556
ACTH	28.0 ± 2.2	35.0 ± 6.0	25.4 ± 1.9	0.057

	Whole group	Subclinical hypothyreosis (n=15)	Clinical hypothyreosis (n=35)	P (subclinical vs. clinical hypothyreosis)
FSH	6.7 ± 1.1	6.7 ± 2.0	6.7 ± 1.3	0.993
LH	6.4 ± 1.4	7.9 ± 2.8	4.9 ± 0.9	0.332
PTH	48.1 ± 2.5	41.7 ± 3.6	51.2 ± 3.1	0.073
Prolactin	273.2 ± 15.5	310.5 ± 33.2	255.2 ± 15.9	0.096
Insulin	9.2 ± 1.1	12.7 ± 3.2	7.7 ± 0.7	0.044
C-peptid	0.9 ± 0.08	0.9 ± 0.09	1.0 ± 0.1	0.766
HOMA	2.6 ± 0.3	3.3 ± 0.9	2.2 ± 0.3	0.203
Estradiol	18.4 ± 3.3	13.4 ± 11.5	20.9 ± 0.3	0.351
Testosterone	5.7 ± 1.0	5.5 ± 2.5	5.9 ± 0.3	0.873
Antiovarian At	0.8 ± 0.1	0.6 ± 0.2	0.8 ± 0.1	0.368

Results

Clinical characteristics of the patients

From 50 subjects included in the study, 6 (12%) were males and 44 (88%) females. Fifteen (30%) subjects had subclinical hypothyroidism while 35 (70%) had clinical hypothyroidism. From patients with hypothyroidism, 7 (20%) were clinically newly diagnosed and 12 (34.2%) developed hypothyroidism after total thyroidectomy.

From total number of analyzed patients, 10 subjects (20%) had typical hypothyroid skin changes. From total number of women, regular menstrual cycle was found in 7 (14%), irregularity of menstrual cycle was found in 5 (10%) while 32 women (64%) were in menopause. When analyzed as subgroups of hypothyroidism, skin changes were found in one patient (6.7%) with subclinical hypothyroidism, and in 9 patients (25.7%) with clinical hypothyroidism. In subgroup with subclinical hypothyroidism, 2 women (13.3%) had irregular menstrual cycles (oligomenorrhea) and 6 (40%) were in menopause while in the subgroup with clinical hypothyroidism 2 women (5.7%) had oligomenorrhea, and 26 women (74.3%) were in menopause.

Anthropometric characteristics of the whole group of patients and subgroups are shown in Table 1. Presented dose of L-thyroxine in Table is in patients with subclinical hypothyroidism related to the dose at introduction of therapy, while in patients with clinical form of disease represents current dose. In patients with subclinical disease initial therapeutic approach considered only follow-up or use of small doses of L-thyroxine (12.5-25 µg). The decision on the therapeutic approach was brought individually. In clinical form of the disease applied therapeutic dose of L-thyroxine ranged from 25 to 150 µg.

Metabolic characteristics of the patients

Biochemical and hormonal characteristics of the whole group of patients and in relation to the type of hypothyroidism are presented in Table 2. Data for FSH, LH and estradiol are related to women in reproductive period.

According to the categorization of serum glucose level in the whole group, 5 patients (10%) had serum glucose level between 6.0 and 6.9 mmol/l while 4 (8%) had serum glucose level over 7.0 mmol/l, and that could represent glucose intolerance or diabetes. One patient had fasting glucose of 11.7 mmol/l.

Correlations in subgroups of the patients

In subgroup of patients with subclinical hypothyroidism, significant positive correlation was found between patient age and total cholesterol (r = 0.58, p = 0029) and ACTH (r = 0.58, p = 0.048), BMI and HOMA (r = 0.64, p = 0.023); diastolic BP and PTH (r = 0.64, p = 0.032), glucose and ACTH (r = 0.64, p = 0.023), FT_4 and testosterone (r = 0.78, p = 0.021), testosterone and heart rate (r = 0.86, p = 0012), testosterone and HOMA (r = 0.93, p = 0.002).

In subgroup of patients with clinical hypothyroidism, significant positive correlation was found between BMI and diastolic BP (r = 0.42, p = 0.020), BMI and blood glucose (r = 0.40, p = 0.032), BMI and triglycerides (r = 0.58, p = 0.002), glucose and triglycerides (r = 0.57, p = 0.001), triglycerides and HOMA (r = 0.53, p = 0.006), cortisol and total cholesterol (r = 0.51, p = 0.004). Significant negative correlation was found between total cholesterol and heart rate (r =- 0.36, p = 0.049), HDL cholesterol and blood glucose (r =- 0.57, p = 0.001), triglycerides and estradiol (r =- 0,911, p = 0.009); FT_4 and TSH (r =- 0.82, p <0.0001) and FT_4 and anti TPO At (r =- 0.42, p = 0.027), TSH and heart rate (r =- 0.39, p = 0.041).

Discussion

Several studies conducted in European countries with sufficient iodine intake had shown up to 7 fold higher incidence of hypothyroidism in women (14-17). When looking at the incidence of hypothyroidism among regions of the same country, it was shown that incidence could significantly vary due to differences in iodine intake (3). As our patients were age-compared to the subjects in the above mentioned studies, we concluded that our group had similar representation of hypothyroidism by sex. The limitations of our study were in small group of examined patients and the lack of data on iodine intake.

Rare skin changes in our patients may be explained by mild thyroid dysfunction in subclinical disease, or by treated hypothyroidism in clinical disease, or recent surgical removal of the thyroid gland when the skin signs have not developed yet.

In women of reproductive period hypothyroidism causes changes in menstrual cycle length and amount of menstrual bleeding. Change in the amount of menstrual bleeding is probably caused by estrogen breakthrough bleeding that is secondary to anovulation. In hypothyroidism, defects in hemostasis due to reduced concentrations of factors VII, VIII, IX and XI could contribute to the irregularities of the menstrual cycle (18). In contrary to the previous studies that indicated disruption of the menstrual cycle in 56-80% of the hypothyroid women (19, 20), Greek studies indicated irregularities of menstrual cycles in 23.4% of hypothyroid women. From those women, 42.5% had oligomenorrhea. Authors suggested that in hypothyroid women disturbances of the menstrual cycle were three times more frequent than in the general population (21). Genetic and other factors were taken into consideration for the explanation of such large differences among populations or prolonged period for the diagnosis of hypothyroidism (18). In our patients with subclinical and clinical forms of disease, oligomenorrhea was less frequently presented (13.3% and 5.7%).

Hypertension is more frequent in patients with hypothyroidism in comparison to healthy population (14.8 vs. 5.5%) (22). Higher values of systolic and diastolic blood pressure were found in women with subclinical form of disease in comparison to control euthyroid women (23). Potential mechanisms that might explain the occurrence of hypertension in hypothyroidism include increased peripheral vascular resistance and vascular stiffness (24), the absence of T_3 vasodilatative effect on smooth muscles of blood vessels (25) or the existence of higher levels of circulating norepinephrine and reduced the number of beta-adrenergic receptor (22). Thyroid hormone deficit may be associated with a decrease in glomerular filtration rate and blood flow through the kidneys (26). Finally, it was demonstrated that hypothyroid subjects often have an increased weight or were obese that lead to high blood pressure and increased cardiovascular risk (27). Values of systolic and diastolic blood pressure in our patients were within normal values and did not differ between subgroups of patients. However, this method of assessment of blood pressure did not represent an average daily values and possible changes in hypothyroidism. Therefore, more detailed analysis of the trends of diurnal blood pressure is needed in patients with hypothyroidism.

Average values of TSH were higher in our patients with clinical hypothyroidism compared to the patients with subclinical form of disease (19.5 ± 5.7 vs. 5.9 ± 0.3 mIU/l) but without reaching statistical significance. Higher TSH values obtained in patients with clinical hypothyroidism reflect the high value in the newly discovered, non-treated patients, or in patients with an unsatisfied supplementation of hypothyroid state. In 70-80% of healthy subjects, TSH level lies between 0.3 and 2 mIU/l, and

in 97% of cases it is less than 5.0 mU/l. If we exclude from the general population subjects with elevated antithyroid antibodies, it 95% cases TSH level is not greater than 2.5-3.0 mIU/l (28). Regardless of the upper normal limit is selected, it is necessary to monitor closely individuals with TSH levels of 3 to 5 mIU/l, and especially if they have positive anti-thyroid antibodies. In individuals older than 70 years, TSH values up to 6.0 or even 7.0 mIU/l in the absence of antibodies anti-thyroid antibodies, should not be criteria for the diagnosis of hypothyroidism (29). In our patients with subclinical hypothyroidism, TSH was between 5 and 6 mIU/l that represent the limit of biochemical criteria for the presence of thyroid dysfunction.

The dose of the applied L-thyroxine differed significantly between our patients with subclinical and clinical hypothyroidism (21.4 ± 3.5 vs. 81.2 ± 4.6 µg/day). The average applied dose of L-thyroxine in patients with clinical hypothyroidism was 1.6 µg/kg body weight and corresponded to the age-recommended doses (28). In subclinical form of disease, a small starting dose of 25 µg/day of levothyroxine is recommended, with control of TSH after 8 weeks and adjusting the dose. Some authors believe that due to the expected progression of thyroid weakness, a full daily dose of 50-75 µg can be applied from the beginning. In younger subjects on therapy, obtained TSH range from 0.3-3.0 mIU/l is considered satisfactory. After achieving these targeted TSH values, the following controls are set for 6 and 12 months (30).

Basal blood glucose values for the whole group and when analyzed by subgroups of patients, were within normal values and without differences between groups. However, when classification of glucose was performed, a significant presence of glucose disorders was found in our patients. Thyroid disease is often associated with type 1 and type 2 diabetes with a prevalence of 10 to 15%. It was shown that lower values of thyroid hormones enhance insulin-mediated glucose availability (31). Also, it was shown that patients with subclinical hypothyroidism and type 2 diabetes had more frequently manifested dyslipidemia or coronary heart disease (32) and increased cardiovascular mortality compared to patients with type 2 diabetes without subclinical hypothyroidism (33). Recently it was shown that subclinical hypothyroidism may reduce the non-cardiovascular mortality in type 2 diabetes (33). Disruption of glycemic control in our patients may be explained by an increased body mass index and consequent insulin resistance.

Hypothyroidism is among the most common causes of the secondary dyslipidemia that is characterized by elevated cholesterol, LDL cholesterol, apolipoprotein B, lipoprotein (a) or triglycerides. Tromsø study had shown the association of TSH levels, total cholesterol and LDL cholesterol, as well as decrease of those lipids after introduction of levothyroxine in hypothyroid patients (34). It appears that the effect of thyroxine substitution is significant only in patients with TSH over 10 mIU/l (35). Rotterdam study showed that subclinical form of disease represents a risk for atherosclerosis and myocardial infarction in elderly women (36). Subclinical hypothyroidism

is associated with congestive heart failure (37) but was not related to the development of stroke in these patients (38). Our patients had higher total cholesterol and LDL cholesterol only in hypothyroid subgroup, while HDL cholesterol and triglycerides did not differ between subgroups of patients. Relationship of lipid fractions with other clinical indicators confirmed the existence of well-known effect of age on the occurrence of dyslipidemia and a relation of body composition, glycemic control and dyslipidemia (39, 40).

The values of ionized calcium and parathyroid hormone in our study were within the normal range in both subgroups of patients. These results are consistent with data of other authors that markers of bone formation and resorption in hypothyroid patients and during thyroxine therapy did not differ from euthyroid controls (41).

It is known that thyroid hormones participate in regulation of the hypothalamic-pituitary-adrenal axis. As previously mentioned, cortisol response during ITT in hypothyroidism is damaged (10). There is also a reduced corticosterone response to ACTH after stimulation with corticotrophin-releasing hormone in hypothyroid rats (42). However, in patients with primary hypothyroidism an altered adrenal function was not shown (43). In our patients there was no difference in the values of morning cortisol and ACTH between the two groups which certainly can not exclude the existence of other functional disorders.

It was shown that long-term hypothyroidism may be associated with ovulatory dysfunction (11), and in 1-3% of cases associated with galactorrhoea (44). This is explained by increased production of TRH (45), reduced hypothalamic dopamine turnover (46) or possible change in TSH pulsatility that could affect GnRH pulse generator and ovulation. However, the study by Bals-Pratsch and colleagues showed that subclinical hypothyroidism does not disturb the function of the hypothalamic GnRH pulse generator, and does not change the normal appearance of LH pulses in the early follicular phase. Therefore, it is considered that women with subclinical hypothyroidism and some women with clinical hypothyroidism can have ovulatory cycles and normal function of the corpus luteum (47). In men, hypothyroidism can cause erectile dysfunction and loss of libido (12) as well as the reduction of circulating testosterone (48). Recently it was shown that in hypothyroid men decrease of serum testosterone may be caused by lower LDL cholesterol overtake by Leydig cells, subsequent decrease in the synthesis of progesterone and testosterone, higher conversion rate of testosterone to estradiol, decrease in serum T3 and by hyperprolactinemia (49). We did not show differences between FSH, LH, estradiol and testosterone in our hypothyroid patients. However, we found association of estradiol and triglycerides in women with clinical form of the disease, and that confirmed the existence of proatherogenic state in disturbed thyroid function (50).

Acknowledgement

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