Clinical, laboratory, ultrasound and FNAB aspects of subclinical thyroid diseases (hypo and hyperthyroidism)

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Abstract

The thyroid gland is the first gland to appear in the human embryo and is one of the largest glands in the human body, weighing 15 to 20 grams during adult life, containing two lobes 2 to 2.5 cm^3 in volume and about 3 million follicles of various sizes. Hypothyroidism is the syndrome induced by thyroid hormone (TH) deficiency and by increased levels of TSH and of thyroid antibody titers (anti-thyroperoxidase and/or anti-thyroglobulin) and is associated with Hashimoto's thyroiditis. Hyperthyroidism is the syndrome caused by excess TH, suppression of TSH, increased levels of antithyroid antibodies (anti-thyroperoxidase, anti-thyroglobulin and anti-TSH receptor) and is associated with Graves' disease. Subclinical thyroid dysfunctions are characterized by normal TH levels and altered (increased or decreased) TSH levels. They are highly prevalent in the general population and their significance and the need for drug treatment are topics of debate in clinical practice. The present study about Subclinical Hypo and Hyperthyroidism involved younger as well as older women who, on average, were younger than men. The number of men was smaller and men had worse TSH, T4L, T3L, Anti Tg and TRAB values than women. This fact suggests that thyroid diseases are less common among men, although subclinical thyroid disease is more marked and more compromising for this gland among them. Female patients had a higher number of thyroid nodules, but all nodules of both female and male patients were benign. No other systemic involvement was observed in the patients studied, except for the presence of diffuse or nodular goiter (single or multiple), with a predominance of this finding among women.

The present study evaluated and compared the clinical and laboratory data of two distinct populations with Hypothyroidism and Subclinical Hyperthyroidism, respectively.

Introduction

The thyroid gland is the first gland to appear in the human embryo, exhibiting a highly organized structure and being able to synthesize and excrete its secretion products, the thyroid hormones (TH) triiodothyronine (T3) and thyroxine (T4), which are important for the development, growth and maintenance of the quality of life of human beings. The thyroid is one of the largest glands in the human body, weighing 15 to 20 grams during adult life, containing two lobes 2 to 2.5 cm3 in volume and about 3 million follicles of various sizes [1].

The evaluation of thyroid dysfunctions is part of the investigation of many specialties. In general, thyroid function can be determined in a direct manner by palpation of the gland or using specific tests [2-5].

Non-thyroid diseases, pregnancy, various medications (especially amiodarone and lithium) and age may affect the extra-thyroid metabolism, the transport, absorption and/or action of TH, and may mimic dysfunction of this gland. The presence of anti-TSH or anti-TH antibodies results in abnormal findings [6-12]. The synthesis and secretory activities of TH are controlled or stimulated by thyrotropin hormone, which is produced by the thyrotropic cells of the anterior pituitary. These activities also involve the presence of iodine and of a glycoprotein – thyroglobulin (Tg) – which is responsible for 70 to 80% of the entire protein content of the thyroid and is the site of TH synthesis. Thyroglobulin levels increase in subjects with goiter by accompanying the increase in gland volume (goiter) [13,14].

Hashimoto's thyroiditis is associated with the presence of anti-thyroperoxidase and/or anti-thyroglobulin titers and is accompanied by diffuse or nodular goiter and/or by heterogeneity of the thyroid parenchyma, being the main cause of acquired hypothyroidism [15-18].

Hypothyroidism is the syndrome induced by TH deficiency and by increased levels of TSH and of thyroid antibody titers (anti-thyroperoxidase and/or anti-thyroglobulin) and is associated with Hashimoto's thyroiditis [19,20].

Hyperthyroidism is the syndrome caused by excess TH, suppression of TSH, increased levels of antithyroid antibodies (anti- thyroperoxidase, anti-thyroglobulin and anti-TSH receptor) and is associated with Graves' disease [21].

Subclinical thyroid dysfunctions are characterized by normal TH levels and altered (increased or decreased) TSH levels. They are highly prevalent in the general population and their significance and the need for drug treatment are topics of debate in clinical practice [22-24].

The increasing number of prospective population and meta-analysis studies about the effect of subclinical disease on the cardiovascular system and on life expectancy has led to a new consensus regarding the indications of treatment for these two clinical entities [29,30].

Cases and methods

The study was conducted on 142 patients (24 men and 118 women) with subclinical hypothyroidism (TSH value > 4.5 and < 10.0 IU/L and normal free T4 and T3 values) and 50 patients (8 men and 42 women) with subclinical hyperthyroidism (TSH value > 0.1< 0.27 IU/L and normal freeT4 and T3 values). Age ranged from 23 to 77 years (mean: 50.18 years) for hypothyroid men and from 20 to 80 years (mean: 41.61 years) for hypothyroid women, and from 54 to 80 years (mean: 70.75 years) for hyperthyroid men and from 27 to 86 years (mean: 62.37 years) for hyperthyroid women.

The following laboratory exams were carried out by electrochemiluminescence: TSH (thyrotropic hormone – RV: 0.27-4.5 IU/L; free T4 (free thyroxine - RV: 0.8-1.9 ng/dl), free T3 (triiodothyronine - RV: 2.0-4.4 ng/d), thyroglobulin (Tg – RV: 1.4-78 ng/ml)), anti-TPO antibody (anti-thyroperoxidase - RV: <34 IU/ml), anti-thyroglobulin antibody (Anti Tg- RV:<115 IU/ml), and anti-TSH receptor antibody (TRAB- RV: <0.55 IU/ml).

Ultrasound examination was applied to the patients with palpable or suspected thyroid nodules detected during routine physical exams and with an 8000 EX imaging system (Samsung Medson Co, Seoul, Korea). Lesions were classified as solid, cystic or complex nodules.

Ultrasound examination was also used to guide FNA of nodules larger than 10 mm and the aspirated material was stained with hematoxylin-eosin and submitted to histopathology examination (FNAB).

Results

Mean TSH values were 7.73 IU/L and 5.72 IU/L; 0.115 IU/L and 0.081 IU/L for hypothyroid and hyperthyroid men and women, respectively.

Among females with Subclinical Hypothyroidism, mean TSH was 6.12 IU/L for the 20-30 years age range (27 patients); 6.31 IU/L for the 30-60 years age range (74 patients); 6.95 IU/L for the 60-80 years age range (15 patients), and 8.48 IU/L for patients older than 80 years (N=2), results showing statistically significant differences (Table 1).

Among males with Subclinical Hypothyroidism, mean TSH was 5.68 IU/L for the 20-30 years age range (2 patients), 7.67 IU/L for the 30-60 years age range (15 patients), and 6.2 IU/L for the 60-80 years age range (5 patients).

Among females with Subclinical Hyperthyroidism, mean TSH was 0.02 IU/L for the 20-30 years age range (5 patients); 0.068 IU/L for the 30-60 years age range (18 patients); 0.096 IU/L for the 60-80 years age range (17 patients), and 0.115 for patients older than 80 years (N=2) (Table 2).

Among males with Subclinical Hyperthyroidism, mean TSH values were, 0.145 IU/L for the 60-80 years age range (6 patients) and 0.025 IU/L for patients older than 80 years (N=2).

Mean Free T4 values were 0.96 ng/dl and 1.11 ng/dl; 1.47 ng/dl and 1.27 ng/dl for subclinical hypothyroid and hyperthyroid men and women, respectively.

Mean free T4 values were 1.09; 1.06; 1.06 and 1.04 ng/dl for the 20-30, 30-60, 60-80 and older than 8 years age ranges, respectively, for women, and 1.39; 1.05 and 1.05 ng/dl for the 20-30; 30-60 years and 60-80 years age ranges for men, respectively.

Table 1. Distribution of hormone levels and other parameters studied.

HYPOTHYROIDISM											
FEMALES						**MALES**					
TSH	T4L	T3L	Tg	Anti-TPO	AntiTg	TSH	T4L	T3L	Tg	Anti-TPO	Anti-Tg
5.72	1.11	2.97	50.14	197.05	140.01	7.73	0.96	2.88	27.13	93	101.29

TSH= IU/L; T4L=ng/dl; T3L= ng/dl; Tg (thyroglobulin)= ng/dl; Anti-TPO= IU/m; Anti-Tg= IU/ml

Table 2. Distribution of hormone levels and other parameters studied.

HYPERTHYROIDISM											
FEMALES						MALES					
TSH	T4L	T3L	Tg	Anti-TPO	AntiTg	TSH	T4L	T3L	Tg	Anti-TPO	Anti Tg
0.08	1.27	3.19	50.14	112.54	78.09	0.115	1.47	2.71	29	54	161.25

TSH= IU/L; T4L=ng/dl; T3L= ng/dl; Tg (thyroglobulin)= ng/dl; Anti-TPO= IU/m; Anti-Tg= IU/ml

Table 3. Distribution of TRAB (TSH receptor stimulating antibody)

TRAB			
HYPOTHYROIDISM		HYPERTHYROIDISM	
FEMALES	MALES	FEMALES	MALES
0.66	0.82	4.55	4.34

TRAB= IU/ml

Mean Free T3 values were 2.88 ng/dl and 2.97 ng/dl; 2.71 ng/dl and 3.19 ng/dl for hypothyroid and hyperthyroid men and women, respectively.

Among females, free T3 values were 3.23; 2.85; 2.66 and 2.28 ng/dl for the 20-30; 30-60; 60-80 and older than 80 years age ranges. Among males, the values were 3.5; 3.09; and 2.92 ng/dl for the de 20-30 years; 30-60 years and 60-80 years age ranges.

Thyroglobulin values were 27.13 ng/dl, 50.14 ng/dl; 29 ng/dl and 112.54 ng/dl for hypothyroid and hyperthyroid men and women, respectively.

Anti-TPO values were 93 IU/ml, 197.05 IU/ml, 54 IU/ml, and 74.78 IU/ml for hypothyroid and hyperthyroid men and women, respectively. Anti-Tg values were 101.29 IU/ml, 140.01 IU/ml, 161.25 IU/ml, and 78.09/ml for hypothyroid and hyperthyroid men and women, respectively. TRAB values were 4.34 IU/ml and 4.55 IU/ml for hyperthyroid men and women, respectively (Table 3).

The following ultrasonography results were obtained for hypothyroid patients: 2 and 9 cases of a single solid nodule, 2 and 14 cases of multiple solid nodules, 4 and 7 cases of simple cysts, no case and 7 cases of solid nodules and cysts in the same gland, 15 and 36 cases of diffuse goiter, no case and 1 case of a micronodular gland, 1 case and no case of pseudo nodules, and 2 and no cases of reduced glands among male and female patients, respectively.

Among hyperthyroid patients, the results were: 1 and 5 cases of a single solid nodule, 1 and 15 cases of multiple solid nodules, 2 and 1 cases of simple cysts, none and 3 concomitantly solid and cystic nodules, and none and 1 case of diffuse goiter among hyperthyroid men and women, respectively. No malignant lesion was detected by cytopathological examination.

The number of nodules per gland of all patients ranged from one to seven, with sizes ranging from 0.3 cm to 1.6 cm. There was a very common association of solid nodules and small cysts in the studied glands.

TRADS study of these nodules showed values between 2 and 4, suggesting that all of them were benign.

Fifteen nodules of female patients and 7 nodules of male patients were classified as BETHESDA 2 by cytology. No case of malignancy was found in this study.

No patient was submitted to surgical excision of these lesions.

Discussion

Altered TSH levels in the presence of normal TH levels characterize subclinical thyroid dysfunctions, which may affect up to 20% of the adult population studied. Despite this high prevalence in the population and the increased diagnostic frequency, the significance of this condition and the need for its treatment continue to be controversial in clinical practice [22].

Among older people (more than 65 years of age), TSH values undergo a physiological elevation, the recommendation being to use the reference values for each age range [22].

Hypothyroidism is a highly prevalent condition regardless of the criterion used to define it. In a study conducted in England, 7.5% of the women and 2.8% of the men had TSH levels > 6 IU/L, and in an American study conducted in Colorado on 25,862 subjects, about 11.7% of the participants showed abnormal serum TSH. In Brazil, a study conducted in Rio de Janeiro using a cut-off value of TSH >4 IU/L detected altered values or treatment with levothyroxine in 12.3% of the 1298 female participants [4].

Subclinical hypothyroidism (SCHypo) commonly occurs in the population, with a higher prevalence and incidence than subclinical hyperthyroidism (SCHyper). The condition is usually asymptomatic and, when symptoms are present, the more frequent ones are dry skin, impaired memory, fatigue, muscle weakness, and intestinal constipation. However, there are no reports of worse quality of life, cognitive changes, depression or anxiety, even among older persons [22].

Thyroid hormones have positive inotropic and chronotropic effects, and similar effects have been reported among patients with SCHyper [22-24]. An increasing number of studies have associated persistent SCHyper with worsening of quality of life, cognitive changes, a higher risk of osteoporosis and fractures, as well as an increase in cardiovascular and mortality risk [23]. A risk association between SCHyper and atrial fibrillation has been observed in older patients with TSH <0.44 IU/L. It has also been confirmed that endogenous SCHyper, with TSH levels of 0.1 IU/L or less, is more frequently associated with the risk of atrial fibrillation [23].

The prevalence of SCHyper varies according to the population studied, iodine content in the diet, and patient sex and age. It is higher among older and black women and in iron-deficient populations, ranging from 1 to 3.2%, but in general being lower than 1%. In regions considered to be in transition in terms of dietary iodine content, the prevalence of SCHyper is high, with an estimated prevalence of 10% in the general population, varying according to sex, age, ethnicity, and dietary iodine content. No treatment has been established for either SCHypo or SCHyper, with controversy persisting about therapy.

A recent meta-analysis has shown a significant association between these conditions and an increased risk of coronary artery events and mortality due to any cause or to a cardiovascular cause after adjustment of correction factors. These data have been considered compelling and definitive about the persistent impact of SCHyper on cardiovascular risk, especially in the presence of TSH levels <0.1 IU/L [23-25]. SCHyper has also been associated with greater bone loss during menopause, with a higher risk of bone fractures and also with changes in cognitive function and mood and with anxiety, depression and dementia [24].

In the present study, women were younger and also some older ones were younger than men. Men showed worse TSH, T4L, T3L, Anti Tg and TRAB values, a fact possibly suggesting that subclinical thyroid disease is more marked and more compromising for this gland among males. No other systemic involvement was observed in the patients studied, except for the presence of diffuse or nodular goiter (single or multiple), with a predominance of this finding among women [25-27].

Conclusion

In the present study women were younger and also older ones, on average, were younger than men. The number of men was smaller and men had worse TSH, T4L, T3L, Anti Tg and TRAB values than women [28-30]. This fact suggests that thyroid diseases are less common among men, although subclinical thyroid disease is more marked and more compromising for this gland among them. Female patients had a higher number of thyroid nodules, but all nodules of both female and male patients were benign. No other systemic involvement was observed in the patients studied, except for the presence of diffuse or nodular goiter (single or multiple), with a predominance of this finding among women.

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