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The association between clinical and laboratory parameters in thyroid disease and nonthyroidal illness in young women

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Abstract. – OBJECTIVE: Evidence from epidemiological and clinical studies strongly suggest that young women in the preconception period are a group at risk for thyroid disorders which may lead to further aggravation of pre-existing chronic thyroid disease and complications during pregnancy.

MATERIALS AND METHODS: This paper is a literature review focusing on articles published in English between 2014-2017 searched in Medline database using terms 'young women', 'subclinical hyperthyroidism', 'subclinical hypothyroidism', 'nonthyroidal illness syndrome', 'obesity', 'depression'.

CONCLUSIONS: Clinical assessment of young female patient including that of obtaining full medical history with a focus on the perceived changes in appearance, psychological symptoms and menstrual irregularities supported by laboratory tests indicative of metabolic status and characteristic changes in thyroid functions, may be the key to well-reasoned and justified individual therapeutic decisions.

Key Words:
Young women, Hyperthyroidism, Hypothyroidism, Nonthyroidal illness syndrome.

Abbreviations

HPT: hypothalamic-pituitary-thyroid; HPO: hypothalamic-pituitary-ovarian; TRH: thyrotropin-releasing hormone; T3: triiodothyronine; T4: thyroxine; TBG: thyroid hormone-binding globulin; LDL: low-density lipoprotein; HDL: high density lipoprotein; FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; TSH: thyroid-stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine; anti-TPO: anti-thyroid peroxidase; anti-TG: anti-thyroglobulin.

Introduction

Epidemiological and clinical studies have confirmed that young women in the preconception period are a group at risk for thyroid disorders[1]. Thyroid hormone abnormalities accompany both overt thyroid disease and the nonthyroidal illness syndrome and are a risk factor for complications during pregnancy[2]. There is a need to search for early predictors of disorders of thyroid homeostasis in the population of young women in order to prevent any potential risks and complications due to disease progression. Understanding the association between the characteristic clinical symptoms of thyroid disorders and the laboratory parameters of systemic alterations in the metabolic status and of the thyroid function, may be the key to the development of a well-reasoned panel of markers for early identification of young women who require specific diagnostic tests and proper therapy, especially when planning conception. The aim of this paper was the analysis of the articles published in English between the years 2014 -2017. The articles dealing with the use of laboratory parameters, calculated from the sera of young women to identify thyroid disease and nonthyroidal illness, were searched in Medline database using the terms 'young women', 'subclinical hyperthyroidism', 'subclinical hypothyroidism', 'obesity', 'depression'.

Pathomechanisms of Thyroid Dysfunction Development

Genetic Factors

Genetic factors predispose to the development of autoimmune disease[3].

Autoimmune Diseases

Autoimmune diseases are due to the abnormalities of the adaptive immune system, i.e. lymphocytes B and T, which maintains the equilibrium between a normal immune response against a foreign antigen and the avoidance of uncontrolled attacking of self-cells. Hashimoto's

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and Graves' diseases are the most common autoimmune thyroid disorders in women in the reproductive age and account for 30% of all autoimmune diseases in this group[4].

Environmental Factors

Stress may be responsible for the psychosomatic component of Graves' disease[5].

Iodine deficiency leads to decreases in the synthesis of thyroid hormones and can cause hypothyroidism in the mother and psychomotor disorders and ADHD in her child. Severe iodine deficiency predisposes to the development of cretinism[6].

Environmental chemical pollutants such as polychlorinated biphenyls may be endocrine disruptors and interfere with the regulation of the synthesis, secretion and transport of thyroid hormones[7].

Nonthyroidal Illness Syndrome

The nonthyroidal illness syndrome (euthyroid sick syndrome) is characterized by normal thyroid function with abnormal levels of thyroid hormones, resulting from the effect of additional peripheral and central mechanisms.

The peripheral mechanisms include disorders of thyroid hormone production, conversion and metabolism produced by the activity of the three selenodeiodinases (D1, D2, and D3) and by abnormalities in the production of thyroid hormone transport proteins. Proinflammatory cytokines (IL-6, IL-1, TNF-α) are thought to play an important role in the pathogenesis.

The central mechanism involves abnormalities in the hypothalamic-pituitary-thyroid axis which affect the secretion of thyroid hormones in the absence of any primary thyroid disease[2].

Impact of Intrauterine Thyroid Homeostasis on the Normal Fetal Development and Health in Adulthood

Abnormalities, due to the excess or deficiency of maternal thyroid hormones and transplacental transport of antithyroid antibodies in the course of maternal autoimmune thyroid disease, alter the intrauterine environment. They carry the risk for the development of hypo- or hyperthyroidism and other anomalies in the fetus, including disorders of neural tissue maturation, abnormal development of the skeleton and other tissues or neural tube defects that have been implicated in the pathogenesis of autism, Down's syndrome and Rett syndrome. Some of the defects may be lethal for the fetus or cause disabilities which may significantly affect the quality of the child's life[6]. Maternal thyroid dysfunction has been linked to numerous complications of pregnancy such as placental abruption, gestational diabetes mellitus, pregnancy-induced hypertension and pre-eclampsia. Overt hypothyroidism has been reported in 1.5-4.4% of pregnant women and subclinical hypothyroidism in 3-15% of them[3,4]. These conditions may also be responsible for postnatal neuropsychological complications in the child, including motor skills and sensory organization disorders, speech delay or learning and social interaction difficulties[6]

Impact of Thyroid Dysfunction on the Clinical Symptoms

The clinical picture of overt thyroid disease is various, with different clinical symptoms, depending on either deficiency or overproduction of thyroid hormones. In hypothyroidism (mostly in Hashimoto's thyroiditis), activated T lymphocytes, which are responsible for thyrocyte destruction, play a role in the development of chronic inflammation of the thyroid gland, while in hyperthyroidism (mostly in Graves' disease) activated B lymphocytes stimulate the specific receptors in thyrocytes with the resulting overproduction of thyroid hormones. Overt hypothyroidism occurs in 0.1-2% of the general population, its incidence increases with age and it is five-fold more common in women than in men[4,8].

Asymptomatic autoimmune thyroiditis does not show the characteristic clinical symptoms of thyroid dysfunction, but with raised serum concentrations of thyroid hormones and focal thyroiditis confirmed by biopsy[9].

Subclinical thyroid dysfunction is characterized by changes by the same factors which are responsible for overt thyroid disease, but it is asymptomatic, or the symptoms are vague. Subclinical hypothyroidism has been diagnosed in 15% of the female general population and subclinical hyperthyroidism in 2-3% of the adult population. The prevalence is 10-fold higher in women than in men[8,9].

Thyroid Disorders in Nonthyroidal Illness Syndrome

Abnormal thyroid hormone levels with different clinical diagnoses result from the underlying disease. These abnormalities observed in the course of various acute and chronic diseases have a common adaptive mechanism directed at the maintenance of energy homeostasis. Proinflammatory cytokines released during disease have a

key role in this process due to their capacity to regulate different genes involved in the metabolism of thyroid hormones. The pathomechanism of disordered thyroid homeostasis has been linked to local thyroid hormone metabolism in different target tissues, depending on the disorder duration, nature and acute vs chronic disease. Abnormal thyroid hormone levels are found in pneumonia, starvation, anorexia nervosa, sepsis, trauma, cardiopulmonary bypass, malignancy, stress, heart failure, hypothermia, myocardial infarction, chronic kidney disease, cirrhosis, chronic obstructive pulmonary disease, diabetic ketoacidosis and brain damage[2,11,12].

The Impact of Thyroid Hormones on the Increased Cardiovascular Risk

Thyroid hormones regulate the expression and activity of numerous proteins in cardiomyocytes and are important modulators of heart function, i.e. the heart rate, cardiac output and systemic vascular resistance. Thyroid hormone abnormalities are often observed in the setting of myocardial ischemia, congestive heart failure and after bypass surgery[2].

Mild and subclinical hypothyroidism is responsible for changes in the structure of heart muscle, impaired calcium homeostasis and myocardial contractility, increased arterial stiffness, endothelial dysfunction and development of arterial hypertension. It increases the risk for ischemic heart disease and myocardial infarction and for cardiovascular death[10,13].

Subclinical hyperthyroidism: direct and indirect action of thyroid hormones on the heart is a cause of cardiomyocyte proliferation, myocardial hypertrophy, accelerated atherosclerotic plaque growth in the arteries and increased incidence of stroke[10,14].

The Impact of Thyroid Hormones on Systemic Metabolic Processes

Thyroid hormones stimulate numerous metabolic processes including oxidation and thermogenesis as well as lipid metabolism[15,16].

The Impact on Body Mass Index (BMI)

Hypothyroidism slows basal metabolic rate which accounts for increases in body weight and BMI values[17].

Hyperthyroidism with elevated concentrations of thyroid hormones contributes to rapid weight loss and significant decreases in BMI[18].

The impact of low body weight and malnutrition on thyroid hormone concentrations is observed with low energy diets which alter the activity of the hypothalamic-pituitary-thyroid (HPT) axis and peripheral metabolism of thyroid hormones, by decreasing the synthesis and secretion of thyroid hormones[10].

The Impact on the Development of Diabetes and Glucose Intolerance

Thyroid hormones regulate carbohydrate metabolism in skeletal muscles and adipose tissue by acting on the transcription of the glucose transporter GLUT4 and stimulating lipolysis[7]. Thyroid disease is found in 30% of patients with type 1 diabetes and 12.5% of patients with type 2 diabetes. Frequent co-occurrence of type 1 diabetes and autoimmune thyroid disease and other organ-specific autoimmune diseases is accounted for by the common genetic predisposition to these diseases[7,19]. The pathomechanism of the association between type 2 diabetes and increased insulin resistance and thyroid hormone levels has been linked to abnormal deiodinase activity[2].

The Impact on the Development of the Metabolic Syndrome

Subclinical hypothyroidism has been linked to concomitant increases in a number of characteristic features, including abdominal obesity, glucose intolerance, hypertension and dyslipidemia. The metabolic syndrome, commonly considered a risk factor for cardiovascular disease, has been demonstrated in one in four patients with thyroid disorders[20].

The Impact of Thyroid Hormones on the Development of Depression

An association between depression and subclinical hypothyroidism results from the interdependence of the HPT axis and the serotonergic neurotransmission. Under physiological conditions, serotonin inhibits thyrotropin-releasing hormone (TRH) secretion in the brain while in depression, decreased serotonin concentrations in the brain tissue alter circulating thyroid hormone levels. Symptoms of depression have been diagnosed in 60% of patients with hypothyroidism[21,22].

The Impact of Thyroid Hormones on Fertility Disorders and Recurrent Pregnancy Loss

Both experimental and clinical studies have demonstrated that the hypothalamic-pituitary-ovarian (HPO) axis and the HPT axis are physiologically related and in some conditions may act as a unified system. Thyroid disease is four

to five-fold more frequent in women than in men. Both hypo- and hyperthyroidism have a significant impact on estrogen and androgen metabolism, menstrual disorders and fertility and cause characteristic clinical symptoms[23-25].

Hypothyroidism is associated with heavy menstrual bleeding (menorrhagia) which can cause blood loss anemia, anovulation and implantation failure, spontaneous miscarriage and infertility. Menstrual disorders are approximately three-fold more frequent in hypothyroid women than in euthyroid women. Hypothyroidism, especially Hashimoto's thyroiditis, is often associated with the polycystic ovary syndrome, an endocrine disorder with a negative impact on ovarian function[25-27].

Hyperthyroidism may cause a scant menstrual flow (oligomenorrhea)[28].

Thyroid Dysfunction and Polyglandular Immune Syndromes

Autoimmune thyroid disease often occurs in the same patient concomitantly with other organ-specific autoimmune diseases which is indicative of dysregulation of the immune system. In autoimmune polyendocrine syndromes, autoimmune thyroid disease may co-exist with other diseases, including type 1 diabetes, Addison's disease, primary hypoparathyroidism or non-organ specific autoimmune disorders such as lupus erythematosus, Sjögren's syndrome or rheumatoid arthritis[29].

Laboratory Parameters in Disorders of Systemic Metabolism Associated with Thyroid Dysfunction

Micronutrient Deficiency as a Cause of Disorders in Thyroid Homeostasis

Vitamin D deficiency: (1) hypothyroidism definitely increases the risk for thyroiditis by immunomodulatory effects on the immune response. Vitamin D by reducing lymphocyte T activation, lymphocyte Th1 proliferation, and cell cytokine synthesis may decrease the levels of autoantibodies that react with thyroid antigens[14,30]. (2) hyperthyroidism contributes to bone loss by altering skeletal homeostasis, i.e. coupling of bone resorption and bone formation during remodeling[31].

Iron deficiency: which occurs in 60% of patients with hypothyroidism interferes with the conversion of T4 to T3 and the activity of thyroid peroxidase[32,33].

Folic acid deficiency: (1) in hypothyroidism: decreased thyroid hormone concentrations reduce methylenetetrahydrofolate reductase activity thus inhibiting the formation of tetrahydrofolate which acts as a donor of methyl groups transferred from homocysteine to methionine. Such mechanism accounts for the less efficient conversion of homocysteine to methionine and for an increased risk for atherosclerosis development in subjects with hypothyroidism. (2) Hyperthyroidism is associated with high usage of folic acid stores and therefore with its decreased concentrations and subsequent subclinical deficiency. Hypermetabolic state found in hyperthyroidism is the reason of increased demands for folic acid[34,35].

Selenium deficiency: maintenance of thyroid homeostasis depends on the activity of selenoenzymes (type 1, 2, and 3 iodothyronine deiodinases). Also, two isoforms of selenium-dependent glutathione peroxidase are involved in the intracellular mechanisms of antioxidative protection of thyroid cells[8].

Disorders of Lipid Metabolism

Thyroid hormones affect the activity of enzymes responsible for lipoprotein metabolism. (1) Hypothyroidism: the total and low-density lipoprotein (LDL) cholesterol levels are elevated while high- density lipoprotein (HDL) cholesterol levels usually remain within normal limits or are elevated. In subclinical hypothyroidism, the total and LDL cholesterol levels are normal or slightly elevated while HDL cholesterol levels are decreased or remain within normal limits. (2) Hyperthyroidism: the total and LDL cholesterol levels are decreased while HDL cholesterol levels are low or remain unchanged[36,37].

Disorders of Sex Hormones

Hypothyroidism: elevated levels of TRH enhance the release of prolactin and thus suppress ovulation and production of gonadotropins (FSH and LH) and cause decreases in the sex hormone-binding globulin, a glycoprotein responsible for transporting dihydrotestosterone, testosterone, estradiol, estrone and progesterone. Defects in hemostasis caused by a deficiency of the coagulation factors VII, VIII, IX and X may be another cause of menstrual disorders in women with hypothyroidism[25].

Hyperthyroidism*:* low levels of TRH are accompanied by reduced prolactin production with increases in the concentrations of FSH, LH, SHGB, estradiol, testosterone and progesterone. Estrogen concentrations in women with hyperthyroidism may be two- to three-fold higher than in euthyroid women[2,15,29,38,39].

Specific Laboratory Parameters in the Diagnosis of Thyroid Disease and Nonthyroidal Illness

Specific biomarkers of thyroid function are the key element in the rational explanation of causes and pathomechanisms, underlying the development of thyroid disorders and the assessment of their activity.

Thyroid-stimulating hormone (thyrotropin, thyrotropic hormone, TSH). TSH is a glycoprotein hormone produced in the pituitary. It stimulates the production and secretion of the thyroid hormones T4 and T3. The pituitary release of TSH is regulated by a negative feedback loop by blood concentrations of thyroid hormones, both directly and indirectly via decrease in TRH release by the hypothalamus, to ensure adequate supply of thyroid hormones. Measurement of serum TSH is the most specific and sensitive laboratory parameter of thyroid function, the screening test for thyroid dysfunction, preceding any further diagnostic tests[40].

T3, T4, free triiodothyronine (fT3) and free thyroxine (fT4). The thyroid stores and releases T3 and T4 whose synthesis and secretion are stimulated by TSH. T3 and T4 diffuse into the blood and are bound to carrier proteins and hence not biologically active. Thus, measuring total T3 and T4 concentrations in the serum has a poor diagnostic value and, consequently, the measurement of fT3 and fT4 is preferable since only these free unbound forms can penetrate cells and directly act on metabolic processes. Decreased serum fT3 and fT4 confirm the diagnosis of hypothyroidism and high serum fT3 and fT4 are diagnostic of hyperthyroidism. In normal man, approximately 0.03% of the total serum T4 and 0.3% of the total serum T3 are present in the free form[41].

The Reference Range and the Association between the Concentrations of TSH and Thyroid Hormones

The normal serum TSH concentration has been controversial and the authors differ in their opinions proposing concentrations ranging from 0.2 to 4.5 IU/mL[38] and from 0.4 to 4.5 IU/mL[42]. This suggests that a cut-off value for TSH should be interpreted in the light of the patient's age, gender and specific clinical diagnosis[43]. Pregnant women are a group in which a gestational age-specific cut-off value for TSH should be used. TSH >2.5 mIU/L during the first trimester and >3.0mIU/L in the second and third trimesters are accepted as normal[44].

Reference ranges for thyroid hormones:
- fT3 3.15-5.61 pmol/L, 208-596 pg/dL[38]
- fT4 9.1-23.8 pmol/L, 0.7-1.8 ng/dL[38]
- total T4 57.9-169.9 nmol/L[42]
- total T3 1.3-2.9 nmol/L[42]

Subclinical hypothyroidism. TSH is elevated and free thyroid hormones remain within the reference range[40].

Subclinical hyperthyroidism. TSH is low and free thyroid hormones remain within the reference range[40].

Non-thyroidal illness. In most cases, T3 and fT3 are low while T4 and fT4 are normal. The relationship of TSH, fT3 and fT4 indicates local abnormalities in the production, metabolism and function of thyroid hormones determined by the action of peripheral deiodinases and the central nervous system. Low serum T3 and T4 concentrations and unchanged or abnormally low TSH may indicate significantly altered negative feedback loop in the pituitary and hypothalamus[2].

Specific Cut-Off Value for Serum TSH in Young Women

Altered TSH in euthyroid young women may be indicative of pre-existing complex health problems. The literature data show that serum TSH of 2.5 mIU/L is an important cut-off value to diagnose patients at risk for further aggravation of their disease. Young women with TSH >2.5 mIU/L and euthyreosis have a two-fold higher risk for developing metabolic syndrome than their peers with TSH <2.5 mIU/L. Increased TSH >2.5 mIU/L and high-level anti-thyroid peroxidase (anti-TPO) antibodies have a predictive value for the development of overt hypothyroidism[41]. Establishing a specific cut-off value for TSH is especially important for identifying the risk for cardiovascular disease, particularly in cases of insulin resistance, severe menstrual abnormalities or depression[21,25].

Antibodies against Proteins Specifically Synthesized by Thyroid Cells

These are organ-specific, although diagnostically non-specific parameters of thyroid function. The increases in their titers may be seen not only in thyroid disease, but also in other, organ-specific, autoimmune diseases. When the titers of anti-thyroid antibodies are elevated, a biopsy of thyroid tissue should perform for any morphological changes in the gland[9].

Anti-thyroid peroxidase (anti-TPO) antibodies. The normal function of thyroid peroxidase

is essential for the production of T3 and T4. Anti-TPO antibodies were found in 73% of cases of subclinical hypothyroidism and can predict the risk for overt hypothyroidism development[7].

Anti-thyroglobulin (anti-TG) antibodies. Thyroglobulin is a protein produced exclusively by the follicular cells of the thyroid. Anti-TG antibodies are present in over 50% of individuals with thyroid dysfunction, both hypo- and hyperthyroidism, and in approximately 10% of people without thyroid dysfunctions. Anti-TG antibodies are a tumor marker used in the diagnosis of thyroid cancer, monitoring of the treatment and possible recurrent disease[10,45].

Anti-TSH receptor (TSHR) antibodies. TSHR regulates thyroid function. By inducing secondary mediators in the thyrocyte cytoplasm, TSHR either stimulates or suppresses the synthesis of thyroid hormones and thyrocyte proliferation. Assays of anti-TSHR antibodies are especially useful for the diagnosis of hyperthyroidism and monitoring of its treatment[8,46].

Proteins Transporting Thyroid Hormones to Target Tissues

The three transport proteins are thyroid hormone-binding globulin (TBG), transthyretin (thyroxine-binding pre-albumin) and albumin. Under normal conditions, thyroid hormone concentrations are proportional to the concentrations of transport proteins, which allows to maintain constant the serum levels of free thyroid hormones. The T4 binding affinity of the transport proteins differs, being the highest in the case of TBG, whose binding affinity for T4 is 50-fold higher than that of transthyretin and 7,000-fold higher than that of albumin. Structural similarities and high affinity of some polychlorinated biphenyls and polybrominated diphenyl ethers for the thyroid hormone transport proteins cause competitive displacement of T4 and T3 at the binding sites of the transport proteins[7,41].

The Role of a Panel of Laboratory and Clinical Parameters in Screening for Thyroid Homeostasis Disorders in Young Women

A review of the medical history and characteristic anthropometric and biochemical findings serve as a screening tool to identify the need for more detailed laboratory investigations for thyroid dysfunction. In young women, thyroid dysfunctions may be occult, with vague clinical symptoms, the diagnostic laboratory parameters should be sensitive, and their choice theoretically justified. Appropriate laboratory assays play a very important role in the correct diagnosis of the non-thyroidal illness syndrome and in the avoiding a misdiagnosis of primary thyroid disease with the consequent wrong treatment. Knowledge of the many aspects of T3 and T4 activity and their impact on the function of numerous body organs confirms the need for additional laboratory data to diagnose the biochemical and hormonal abnormalities produced by disorders of thyroid homeostasis[21].

Table I summarizes the literature data on the association between the most characteristic clinical symptoms, identified from the medical history and the laboratory assays, by assessing the systemic metabolic disorders and thyroid dysfunction.

Obesity and emaciation are easy to identify and may indicate the need for further diagnostic investigations for thyroid dysfunctions.

The association between obesity and thyroid dysfunction is confirmed by the laboratory parameters of both altered systemic metabolism and local changes in adipocytes. A positive correlation between serum TSH and BMI in young women with hypothyreosis or euthyreosis and the association with an abnormal lipid profile is indicative of a predisposition to the development of atherosclerosis. Increased prevalence of obesity as well as increases in the levels of triglycerides, homocysteine and obesity-associated parameters of inflammation and CPR have been demonstrated in patients with high normal TSH values (2.5-4.5 IU/mL)[12,34]. Leptin stimulates TSH release which explains increased TSH levels in the obese. A positive correlation between the levels of serum TSH and leptin locally produced in adipocytes indicates the involvement of adipose tissue in the pathomechanism of altered thyroid hormone activity. In patients with hypothyroidism, leptin levels may be 230% higher than in obese euthyroid patients[12]. A negative correlation between fT4 and BMI has been demonstrated in obese patients, even if the fT4 levels are within normal limits and the T3 and fT3 levels are increased resulting from the high conversion of T4 to T3. Local increases in fT3 have been linked to decreased TSH expression and increased deiodinase activity in adipocytes[17,47].

Energy restrictions and caloric deprivation during prolonged fasting depress the thyroid axis, impair the feedback mechanism and peripheral metabolism of thyroid hormones leading to cellular hypothyroidism. The decreases in T3 levels with concomitant transient increases in free

T4 have been linked to the suppression of the hypothalamic-pituitary-thyroid axis with a decreased conversion of T4 to T3. The causes may include decreased synthesis and/or secretion of thyroglobulin, decreased leptin levels and impaired conversion of T4 to T3 by the deiodinase system. In anorexia nervosa, thyroid hormone abnormalities usually include normal or low TSH with low T3, T4, fT3, fT4 and T3/T4 ratio compared to healthy subjects[2,10].

In depression, the decreased serotonin levels in brain tissue could lead to increased TRH concentrations and the resulting blunted TSH response and T4 and T3 production by the thyroid. Decreased TSH and increased fT4 concentrations, which however remained within the normal range were commonly found in major depressive disorders[10,49]. TSH production in the hypothalamus is probably suppressed by the locally produced fT3 or controlled by T3 bioavailability in brain tissue. To date, there have been no laboratory markers for the use in the diagnosis of depression in young women. The association between the altered thyroid hormone homeostasis and the clinical symptoms of depression seems a valid argument for the use of appropriately adjusted cut-off values for serum TSH in the diagnosis of depression and monitoring its severity[2].

Reported studies have confirmed the association between thyroid dysfunction and menstrual abnormalities and anovulatory cycles. A negative feedback loop in the HP axis causes an increase in TRH secretion and consequently increases in TSH and prolactin levels. Serum TSH and prolactin act synergistically with FSH and LH. A history of menstrual abnormalities and fertility problems in young women indicate the need for hormone assays, i.e., TRH, TSH and prolactin levels as possible causes of reproductive disorders[50].

Autoimmune thyroid diseases due to an abnormal response to thyroid autoantigens often coexist with other autoimmune diseases, including polyglandular autoimmune syndromes, but tests for thyroid autoantibodies are not a routine screening tool. The literature data confirm the benefits of their use in the diagnosis and assessment of other non-thyroid autoimmune diseases. Anti-TPO assays have been used to assess the activity of rheumatoid arthritis. Other studies report the increased cardiovascular risk in patients with

Table I. The association between the clinical features and laboratory evaluation of systemic disease and thyroid function.

	Serum biochemical markers		
Clinical features	**Systemic**	**Thyroid-specific**	**References**
Obesity	- Markers for lipid and carbohydrate metabolism disorders; - ↑leptin; - ↑homocysteine; ↑proinflammatory cytokines and CPR	- ↑TSH - TSH positively correlated to BMI - fT4 negatively correlated to BMI - ↑T3 and fT3, - T4 to T3 conversion high	18, 19, 20, 51
Malnutrition	- ↓transthyretin - ↓hypothalamic deiodinase type 1 and type 2	- Low TSH - Low T3 and T4	51
Depression	- no specific serum biomarkers - ↓serotonin and ↑TRH in the brain	- ↑ weak TSH increase after TRH stimulation - low fT3 - ↑fT4	25, 42
Menstrual disorders	- ↑prolactin - suppressed gonadotropin synthesis and secretion	- ↑TSH	29
Co-existing metabolic disease(s)	markers for: - type 1 diabetes - Addison's disease - primary hypothyroidism - rheumatoid arthritis	↑antibodies: - aTPO - aTG - TSHR	32

↑=increased ; ↓=decreased.

the polyglandular autoimmune syndromes based on the confirmed association between the increasing severity of inflammation and the risk for cardiovascular disease[10,51].

Two mechanisms of drug action on thyroid hormones have emerged:

1) Suppression of TSH release and T4 to T3 conversion produced by corticosteroids and dopamine. Glucocorticoids in high doses can inhibit the peripheral conversion of T4 to T3 and, as a result, lower the serum T3 concentrations[40,52].
2) The impact of drugs on the binding of thyroid hormones to the transport protein TGB. Estrogens increase serum TBG levels with the resulting increases in total serum T4 without alterations in fT4[52].

Treatment and Prophylaxis in Disorders of Thyroid Hormone Homeostasis in Young Women

There is a general opinion that the use of levothyroxine is justified exclusively in overt thyroid disease while pharmacological treatments to regulate altered thyroid hormone ratios due causes other than thyroid disease are actually harmful[53,54].

- The management recommended for young women with nonthyroidal illness focuses on developing behavioral changes and searching for the underlying disease(s) which may be responsible for disorders of thyroid hormone metabolism. Patients with thyroid dysfunction may be at a greater risk for the development of cardiovascular disease, osteoporosis, overweight and obesity, celiac disease and diabetes. After early screening for thyroid disorders and identification of young women with disorders of thyroid hormone homeostasis the following approaches are suggested[2,9]:
- Reducing high TSH levels by appropriate treatments for overweight and obesity as even small decreases in TSH levels may lower BMI values and improve the lipid profile[17,36].
- A balanced diet providing adequate nutrients and energy, correcting deficiencies of micronutrients such as iodine, iron, selenium, zinc, folic acid and vitamin D[14,32,34].
- Including T3 and T4 measurements in the screening panel to identify the local conversion of the two hormones[2].
- Taking into consideration of the impact of pregnancy, inflammation or chronic disease on altered serum thyroid hormone ratios[53,54].
- Assessment for a tendency to depression[48].
- Diagnostic tests for sex hormone imbalance[50].
- Analysis of the effects of drugs on the levels of thyroid hormones[40,52,54].

Conclusions

The literature review reveals the profile of a young female patient with the dysfunctional levels of thyroid hormones and the characteristic set of clinical features and laboratory panel. Body weight, psychological assessment, and further laboratory tests may aid in the understanding of the impact of the thyroid dysfunction on complex health problems in young women, associated with the increased incidence of metabolic disorders, depression and sexual hormone disorders, complications of pregnancy, and an increased risk for the development of cardiovascular disorders and chronic disease.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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