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Thyroid and menopause

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ABSTRACT

Thyroid dysfunction is common in the general population especially in women. All thyroid diseases are in fact more common in women than in men and may interfere with the reproductive system. Thyroid function and the gonadal axes are related throughout the woman's fertile period. The relationship between the two glands is mutual. In particular, thyroid hormones affect the reproductive function both directly and indirectly through several actions. Studies on the relationship between menopause and thyroid function are few and do not allow to clarify whether menopause has an effect on the thyroid regardless of aging. With aging, the main changes regarding thyroid physiology and function are: a reduction of thyroid iodine uptake, free thyroxine and free triiodothyronine synthesis and catabolism of free thyroxine while reverse triiodothyronine increases; the level of thyroid stimulating hormone remains normal with sometimes a tendency to higher limits. These changes are present in both sexes without distinction between males and females. The complexity of the relationships can be summarized in three aspects: thyroid status does not influence significantly the climacteric syndrome; menopause may modify the clinical expression of some thyroid diseases, particularly the autoimmune ones; thyroid function is not directly involved in the pathogenesis of the complications of menopause. However, coronary atherosclerosis and osteoporosis may be aggravated in the presence of hyperthyroidism or hypothyroidism. The effects of postmenopausal estrogen replacement on thyroxine requirements in women with hypothyroidism should be considered.

INTRODUCTION

Menopause is defined as 1 year without menses in a woman who had menses previously[1]. Although some women may be asymptomatic, estrogen deficiency is associated with hot flushes, sweating, insomnia, and vaginal dryness and discomfort in up to 85% of menopausal women. Most women with menopausal symptoms will experience spontaneous cessation of the symptoms within 5 years after onset; a substantial proportion of women, however, continue to experience symptoms beyond 5 years[2].

Thyroid dysfunction is common in the general population, especially in women. All thyroid diseases are in fact more common in women than in men and may interfere with the reproductive system. Thyroid function and the gonadal axes are related throughout the woman's fertile period[3]. The relationship between the two glands is mutual[4]. In particular, thyroid hormones affect the reproductive function both directly and indirectly through several actions: they increase the synthesis of sex hormone binding globulin (SHBG), testosterone and androstenedione, reduce the clearance of estradiol and androgens and increase the conversion of androgens to estrone[5] (Figure 1). The direct effects are mediated by the presence of receptors for thyroid hormones at the level of oocytes where these hormones act synergistically with follicle stimulating hormone (FSH) (through FSH receptors present on granulosa cells) for the production of progesterone[6] (Figure 1).

The main role of estrogens in thyroid physiology is related to the increase of the serum concentrations of thyroxine binding globulin (TBG), a protein synthesized by the liver, with enhanced oligosaccharide chains of the type *N*-acetilgalactosamine that reduce its clearance[7] (Figure 1). Significant increases in TBG concentrations are present during pregnancy or when using the oral contraceptive pill[8].

The levels of serum TBG change immediately before and soon after menopause; this phenomenon is attributed to increased levels of TBG present in aging and offsetting the lack of estrogen[9].

Studies on the relationship between menopause and thyroid function are few and do not allow to clarify whether menopause has an effect on the thyroid regardless of aging. With aging, the

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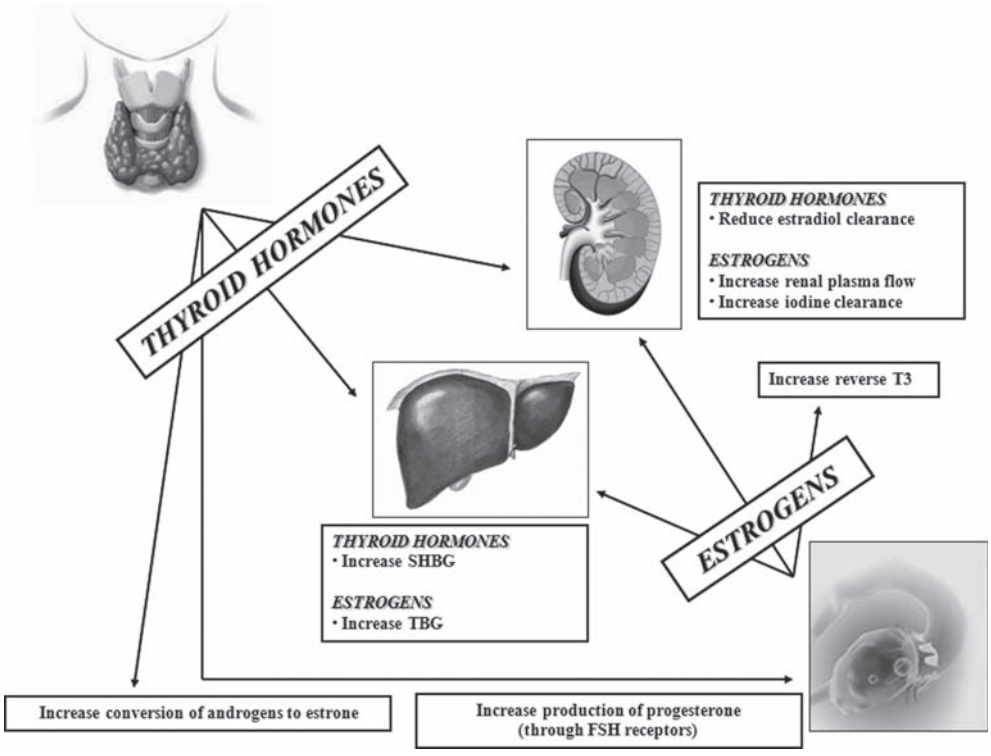

Figure 1 Schematic diagram explaining the relationship between thyroid, ovary, liver and kidney; actions of thyroid hormones, estrogens. T3, triiodothyronine; SHBG, sex hormone binding globulin; TBG, thyroxine binding globulin; FSH, follicle stimulating hormone

main changes regarding thyroid physiology and function are: a reduction of thyroid iodine uptake, synthesis of free thyroxine (FT4) and free triiodothyronine (FT3) and catabolism of FT4 while reverse triiodothyronine (rT3) increases; the level of thyroid stimulating hormone (TSH) remains normal, sometimes with a tendency to higher limits. These changes are present in both sexes without distinction between males and females[10].

Menopause *per se* is not related to an increased and/or decreased risk of different thyroid disorders and the complexity of the relationships can be summarized in three aspects: thyroid status does not influence significantly the climacteric syndrome; menopause may modify the clinical expression of some thyroid diseases, particularly the autoimmune ones; thyroid function is not directly involved in the pathogenesis of the complications of menopause. However, coronary atherosclerosis and osteoporosis may be aggravated in the presence of hyperthyroidism or hypothyroidism. The effects of postmenopausal estrogen replacement on thyroxine requirements in women with hypothyroidism should be considered. However, the final decision in treating menopause with estrogen/hormone therapy is not influenced by the concomitant presence of thyroid disorders and women should be treated according to the current guidelines[2].

Some manifestations of menopause are similar to the signs and symptoms suggestive of thyroid dysfunction. Hot flushes, intolerance to heat, sweating, palpitations, irritability, insomnia, and rapid changes in mood can be traced back to a status of hyperthyroidism, while skin atrophy, constipation, brittle hair, periorbital edema and increase of weight are shown in hypothyroid subjects[11]. Special considerations in diagnosing and treating perimenopausal and postmenopausal women with thyroid dysfunction include the difficulty of differentiating between menopausal symptoms and symptoms related to thyroid dysfunction; physicians in primary care, as well as endocrinologists, see many women who express considerable distress regarding symptoms such as weight gain, fatigue, mood swings, anxiety and other types of loss of well-being during the perimenopausal period.

In the Study of Women's Health Across the Nation[12], a community-based multiethnic study of the natural history of the menopausal transition, a 9.6% prevalence of TSH values outside the euthyroid range was found. Although TSH was associated with bleeding length and self-reported fearfulness, it was not associated with indicators of the menopausal transition, including menopausal stage defined by bleeding regularity, menopausal symptoms and reproductive hormone concentrations.

HYPOTHYROIDISM

An elevated serum TSH is the hallmark of hypothyroidism. Subclinical hypothyroidism represents a condition of mild to moderate thyroid failure characterized by normal serum levels of thyroid hormones with mildly elevated serum TSH, while in overt hypothyroidism, circulating FT3 and FT4 concentrations, but especially FT4, are below normal[13].

Etiology

The most common cause of hypothyroidism in the world's population is iodine deficiency[14]. In areas where the population is exposed to an adequate iodine intake, hypothyroidism is due to autoimmune thyroiditis[15,16]. Other causes of primary hypothyroidism are: destruction of thyroid tissue due to radioactive iodine therapy, external neck irradiation, total and subtotal thyroidectomy and infiltrative diseases (such as scleroderma and amyloidosis), defective thyroid hormone biosynthesis, excluding iodine deficiency, linked to therapies like lithium, iodine, iodine-containing drugs and radiographic agents. Central hypothyroidism is a rare disorder caused by hypothalamic–pituitary diseases. The causes of hypothyroidism are summarized in Table 1.

Epidemiology

All epidemiological studies that have been conducted over the years on the prevalence and incidence of thyroid disease by different authors are often incomplete or not comparable because of the differing definitions of the different clinical conditions (such as the definition of the various forms of hypothyroidism), the selection criteria used for the identification of patients, the influence of age and sex, the coexistence of environmental factors, and also the different techniques used for the measurement of the functional status of the thyroid (total or free thyroid hormone) or different techniques used for the diagnosis of thyroid disease (from ultrasound to palpation of the neck).

In populations living in areas with sufficient iodine intake, hypothyroidism is the most common disorder of thyroid function[17].

The prevalence of clinical hypothyroidism increases with age and especially in women[18]. In the Whickham survey[15], observing a large English cohort for 20 years (from the 1970s), subclinical hypothyroidism was found in 7.5% of adult women and the risk of developing hypothyroidism in women increased with age, reaching a value of 13.7/1000 per year between 75 and 80 years of age. Subclinical hypothyroidism was also more common in the elderly, with a prevalence in the female sex. In the Whickham study, the annual risk of progression to clinical hypothyroidism was 4.3% in women with autoantibodies against thyroid peroxidase and 2.6% in the presence of elevated TSH only. In the following 20 years, the risk rose to 55% in the first group and to 33% in the second one. In the Framingham Heart study[16], almost 12% of women over 60 were found to have at least subclinical hypothyroidism. The sample examined in the NHANES study[18] represented the geographic and ethnic distribution of the US population. Hypothyroidism was found in 4.6% of the US population (0.3% clinical and 4.3% subclinical); TSH levels and the prevalence of thyroid antibodies were greater in females and increased with age. The Colorado Thyroid Disease Prevalence Study reported subclinical and overt hypothyroidism in 16% of women aged 65–74 years and 21% of women aged over 74 yeara[19].

Clinical presentation

The symptoms of hypothyroidism are often non-specific and the onset may be insidious, especially in older women. In women in the perimenopausal and postmenopausal periods, the common features of moderate to severe hypothyroidism include easy fatiguability, muscle cramps, cold sensitivity,

Table 1 Causes of hypothyroidism

Primary
- Chronic autoimmune thyroiditis
- Iodine deficiency
- Iatrogenic: ^{131}I treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer
- Drugs: iodine excess (including iodine-containing contrast media and amiodarone), lithium, antithyroid drugs, *p*-aminosalicylic acid, interferon-α and other cytokines, aminoglutethimide
- Congenital hypothyroidism: absent or ectopic thyroid gland, dyshormonogenesis, TSH-receptor mutation
- Infiltrative disorders: amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis

Secondary
- Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
- Isolated TSH deficiency or inactivity
- Hypothalamic disease: tumors, trauma, infiltrative disorders, idiopathic

Transient
- Silent thyroiditis, including postpartum thyroiditis
- Subacute thyroiditis
- Withdrawal of thyroxine treatment in individuals with an intact thyroid
- After ^{131}I treatment or subtotal thyroidectomy for Graves' disease

TSH, thyroid stimulating hormone

weight gain, constipation, menstrual abnormalities, especially menorrhagia but also amenorrhea or oligomenorrhea in premenopausal women. Physical findings may include a cool, rough, dry skin, puffy face and hands, a hoarse, rusky voice, and slow reflexes. Reduced conversion of carotene to vitamin A and increased blood levels of carotene may give the skin a yellowish color.

Overt hypothyroidism, especially if protracted, has systemic consequences. Patients may present an increased systemic vascular resistance and decreased cardiac contractility[20] and dyslipidemia with elevated serum total cholesterol and low density lipoprotein cholesterol[21]. Overt hypothyroidism is also associated with psychiatric diseases, like depression and psychosis, cognitive dysfunction, bleeding disorders and, in its extreme form, hypothyroidism can evolve to myxedema coma and death[22].

The presence of symptoms in women with subclinical hypothyroidism is controversial[23]. It is very often difficult to distinguish euthyroid pre- and postmenopausal women from patients with subclinical hypothyroidism by using clinical symptoms. However, subclinical hypothyroidism has been associated with resting diastolic dysfunction and with systolic dysfunction on exertion[20,24]. Subclinical hypothyroidism could impair vascular function by inducing an increase in systemic vascular resistance and arterial stiffness and by altering endothelial function, thereby potentially increasing the risk of atherosclerosis and coronary artery disease[23]. Data on lipid profile and subclinical hypothyroidism are conflicting and probably related to differences in population studies such as cause of subclinical hypothyroidism, duration of thyroid dysfunction, TSH levels, age, and ethnicity of the subjects[22].

Treatment

Levothyroxine (L-T4) is the treatment of choice for hypothyroidism. L-T4 is converted to the bioactive hormone T3 in peripheral tissues. The replacement dose for adult women is estimated at 1.6 μg/kg of ideal body weight per day; in subjects older than 60 years, the dose should be reduced to 1.3 μg/kg[25]. However, L-T4 therapy should no longer be prescribed according to the commercially available dose size, but rather related to the patient's weight and age. In fact, the starting dose of L-T4 and its gradually increase are different depending on the patient's age and co-morbidities. In older patients or in the presence of cardiac disease, a gradual incremental dose is considered safer. In women without other pathologies aged between 40 and 60 years, the initial dose is 50 μg/day with increments of 25 μg every 3 weeks; in the case of a woman over the age of 60 years, the initial dose is lower (25 μg/day) and increases every 4 weeks. In cardiac patients, the initial dose is even lower (12.5 μg/day) and is increased every 6–8 weeks. Treatment with L-T4 reverses the signs and symptoms of hypothyroidism. The goal of therapy is to achieve serum TSH values in the normal range and an annual determination of TSH value is adequate for monitoring[26].

Subclinical hypothyroidism should be treated, especially when autoantibodies are present in the thyroid peroxidase test. L-T4 replacement therapy improves reversible coronary dysfunction and has favorable effects on dyslipidemia[27], and improves the health of the vascular system by decreasing systemic vascular resistance, endothelial function[28], and carotid intimal thickness, and might thereby prevent or reverse atherosclerosis and coronary artery disease. These beneficial effects are important in postmenopausal women who present a higher risk for the development of coronary atherosclerosis. Treatment with L-T4 does not increase the loss of bone mass if it is aimed at maintaining TSH values in the normal range[10].

Drugs such as ferrous sulfate, calcium carbonate, cholestyramine, sucralfate and proton pump inhibitors can interfere with the gastrointestinal absorption of L-T4[29]. Soy isoflavones, phytoestrogens currently used by many postmenopausal women as alternatives to conventional hormone replacement therapy, can decrease the absorption of L-T4 and may necessitate dose adjustments. The interaction can be lessened by ingesting the soy product and L-T4 at different times of the day[30].

In diagnosing and treating peri- and postmenopausal women, it is important to note the effects of estrogens on thyroid function tests. Because many postmenopausal women are also diagnosed and treated for hypothyroidism, the concomitant use of estrogen/hormone therapy and L-T4 is a relatively common occurrence in this population. Clinically equivalent doses of oral and transdermal estrogen/hormone therapy may affect TBG production differently. The oral administration of estrogens causes a dose-dependent increase of the serum levels of TBG as well as other hormone-binding proteins synthesized in the liver[31]. Oral administration exposes the liver to higher concentrations of estrogens delivered by the portal circulation, with respect to transdermal estrogen administration[32]. Therefore, the use of estrogen replacement can result in a drug interaction that may require L-T4 dose modifications. Arafah[33] investigated the effects of oral estrogen therapy (ET) on the thyroid function of 25 postmenopausal women with primary hypothyroidism. Oral ET produced a marked increase in TBG levels and in total T4, but serum FT4 decreased significantly and the average serum TSH increased; in 40% of these women, the L-T4 requirement increased. For this reason, the start of oral estrogen replacement therapy in a woman on thyroid hormone replacement requires frequent monitoring of her thyroid function parameters (TSH, FT4 every 6 weeks) and may necessitate multiple adjustments of her L-T4 dose to maintain a euthyroid state. Because transdermal estrogen therapy (with or without oral progesterone) does not significantly alter TBG levels, it would not be expected to alter thyroid function parameters and, for this reason, the transdermal route may be a preferable modality to use in hypothyroid women who require concomitant estrogen replacement treatment[32]. In postmenopausal women, the oral administration of androgens markedly reduces the levels of SHBG, whereas the transdermal administration of testosterone

produces a negligible effect[32]. In addition, the androgenic progestins used in some oral contraceptives (levonorgestrel and norethindrone) also lower SHBG levels markedly or attenuate the elevations induced by their estrogenic counterparts. In contrast, the non-androgenic progestins used in oral hormone replacement regimens (medroxyprogesterone acetate and micronized progesterone) have little to no effect on SHBG levels[32].

Tamoxifen is a selective estrogen receptor modulator (SERM) with estrogen-like effects on the liver and is used predominantly for the treatment and prevention of breast cancer. Studies have reported increased levels of serum TBG, through a reduced clearance, in postmenopausal women[34]. Furthermore, the clinical relevance of tamoxifen in thyroid function is controversial and characterized by a weak decrease in serum FT3 and FT4 and an increase in TSH, usually within the normal range[35]. Droloxifene and raloxifene are new SERMs that are currently available for prevention and treatment of osteoporosis and have been shown to cause a stronger increase in TBG than with tamoxifen, even if without a significant effect on serum TSH[36]. It has also been reported that raloxifene may decrease L-T4 absorption[37].

HYPERTHYROIDISM

Etiology

Overt hyperthyroidism is defined by undetectable levels of serum TSH and elevated FT3 and FT4 concentrations; in subclinical hyperthyroidism, the serum TSH level is low or undetectable but FT3 and FT4 concentrations are normal. Thyrotoxicosis is defined as the state of thyroid hormone excess and is not synonymous with hyperthyroidism, which is the result of excessive thyroid function. Hyperthyroidism, in iodine-sufficient areas, is most frequently due to Graves' disease, while toxic adenoma and toxic multinodular goiter are prevalent in areas where iodine intake is low[38]. Graves' disease is an autoimmune disorder caused by thyroid-stimulating immunoglobulin binding the TSH receptor and most commonly presents in the second to the fourth decade[39]. Thyrotoxicosis may develop in patients with toxic adenomas that are benign monoclonal thyroid tumors, present as single functioning nodules at thyroid scintigraphy, or toxic multinodular goiter, in which multiple functioning nodules are present in the same gland[40] and most commonly present in the fifth and sixth decades of life.

Other causes of thyrotoxicosis without an excess of thyroid hormone synthesis are: postpartum thyroiditis or subacute thyroiditis and exogenous thyroid hormone intake due to unintentional excessive replacement therapy in hypothyroid patients or to intentional TSH suppressive therapy for benign or malignant thyroid disease. The more uncommon etiology is due to hypersecretion of TSH from the pituitary, trophoblastic tumor, metastatic thyroid carcinoma, struma ovarii, drug-induced thyroiditis (amiodarone, interferon-α, lithium, iodine). The causes of thyrotoxicosis are summarized in Table 2.

Table 2 Causes of thyrotoxicosis

Primary hyperthyroidism
- Graves' disease
- Toxic multinodular goiter and toxic adenoma
- Functioning thyroid carcinoma metastases
- Activating mutation of the TSH receptor or protein G (McCune–Albright syndrome)
- Struma ovarii
- Drugs: iodine excess (Jod–Basedow phenomenon)

Thyrotoxicosis without hyperthyroidism
- Subacute thyroiditis
- Silent thyroiditis
- Other causes of thyroid destruction: amiodarone, radiation, infarction of adenoma
- Ingestion of excess thyroid hormone (thyrotoxicosis factitia) or thyroid tissue

Secondary hyperthyroidism
- TSH-secreting pituitary adenoma
- Thyroid hormone resistance syndrome: occasional patients may have features of thyrotoxicosis
- Chorionic gonadotropin-secreting tumors
- Gestational thyrotoxicosis

TSH, thyroid stimulating hormone

Epidemiology

Hyperthyroidism is far less prevalent than hypothyroidism. In an area where the population is exposed to adequate iodine intake, such as in the Whickham survey, hyperthyroidism was found in 2% and subclinical hyperthyroidism in 10% of adult women (with serum TSH concentrations less than 0.5 mIU/l), and ten times more common than in men[15]. In an older population over 60 years, in the Framingham study, 4% of women aged 60 or over had low levels of circulating TSH (< 0.1 mIU/l), even when half of the subjects were treated with L-T4[16]. In another US study of 3242 pre- and early perimenopause women, the prevalence of subclinical hyperthyroidism was 3.2%[12].

The prevalence of hyperthyroidism was assessed in the Pescopagano Survey, a study conducted in a southern Italian village located in an area of mild to moderate iodine deficiency that had never been submitted to any iodine prophylaxis program[41]. The overall prevalence of overt hyperthyroidism was twice as high as that found in the Whickham survey and, in contrast with iodine-sufficient areas in which hyperthyroidism was mainly due to Graves' disease, toxic nodular goiter accounted for the majority of thyrotoxic subjects, being twice as frequent as toxic diffuse goiter. Toxic nodular goiter occurred in older subjects especially in females. The prevalence of hyperthyroidism progressively increased from 0.7% in children to 15.4% in subjects more than 75 years old and was more frequent in subjects with nodular goiter. In another study, the risk of developing overt hyperthyroidism was 4% per year in patients with thyroid adenoma and 9–30% in the next 1–7 years in patients with nodular goiter[42].

Clinical presentation

Common manifestations of hyperthyroidism may be confused with perimenopausal symptoms including palpitations, nervousness, insomnia, easy fatiguability, excessive sweating and intolerance to heat (Table 3). Symptoms and signs more specifically present in women with hyperthyroidism are diarrhea, weight loss without loss of appetite, systolic hypertension, tremor, hyperreflexia and muscle weakness. Women with Graves' disease can also present goiter and eye signs and thyroid dermopathy.

In patients over the age of 60, cardiovascular and myopathic manifestations predominate; the most common presenting complaints are palpitations, dyspnea on exertion, tremor, nervousness, and weight loss.

Women with subclinical hyperthyroidism may have mild clinical symptoms or signs. Many studies have evaluated the cardiovascular effects of subclinical hyperthyroidism using ECG and Doppler echocardiography. An increase in the average heart rate and a higher prevalence of atrial premature beats were found in patients with subclinical hyperthyroidism than in controls[43]. In other studies, an increase in left ventricular mass or altered diastolic function were described. Different studies have also demonstrated an increased risk of atrial fibrillation in older women with subclinical hyperthyroidism[44].

Overt thyrotoxicosis favors resorption and bone formation, increasing osteoclast and osteoblast activity; however, the increase in bone formation is not able to compensate for the resorption[45]. The consequence is progressive bone demineralization. The reduction of bone density is largely reversible, restoring the euthyroid state[45]. In postmenopausal women, overt thyrotoxicosis is associated with increased bone resorption, low bone mineral density and possible fractures[46]. Cortical bone is more severely affected than trabecular bone. Whether subclinical hyperthyroidism causes low BMD or increases fracture rates in postmenopausal women is controversial[47]. In a recent 6-year prospective study[48], 1278 healthy euthyroid postmenopausal women were studied: this study demonstrated that physiological variation in thyroid status was related to bone mineral density (BMD) and fracture. Higher FT4 and FT3 levels were associated with reduced BMD, and higher FT4 was associated with increased bone loss at the hip. An increased risk of non-vertebral fracture was reported in women with higher FT4 and FT3 despite protection from non-vertebral fracture in women with higher TSH[48].

Table 3 Signs and symptoms common to both hypothyroidism/hyperthyroidism and menopause

Hypothyroidism	*Hyperthyroidism*
Skin atrophy	Hot flushes
Constipation	Heat intolerance and sweating
Brittle hair	Palpitations
Periorbital edema	Irritability
Weight gain	Insomnia
Constipation	

Thyroid hormone suppressive therapy in premenopausal women with nodular goiter or thyroid cancer yielded conflicting results. Early cross-sectional studies showed reduced bone density in the femoral neck and forearm but not in the lumbar spine as measured by single-photon or dual-photon absorptiometry[49]. However, in those studies high doses of L-T4 were used. In subsequent cross-sectional studies, L-T4 did not have significant adverse effects on bone in premenopausal women[50]. In the last 15 years, lower L-T4 doses have been used to obtain mild TSH suppression. Longitudinal studies of premenopausal women receiving suppressive doses of L-T4 report a decrease in BMD of the spine or forearm or no adverse effects on bone[51]. Similar conflicting results have been reported for postmenopausal women with subclinical hyperthyroidism. In two meta-analyses, L-T4 suppressive therapy was found to have no effect on BMD in premenopausal women[52,53]. In postmenopausal women, there was a loss of 0.77–1.3% in bone mineral per year and cortical bone was more affected that trabecular bone[52]. In postmenopausal women, L-T4 may accelerate bone turnover, depending on the degree of serum TSH suppression and dietary calcium intake. In a recent retrospective cohort study with a nested case–control design using a population health database, L-T4 treatment was associated with a higher risk of fractures in a dose–response manner in older women (70 years old or more)[54]; even in this work, serum TSH and thyroid hormone measurements were not available.

Treatment

Overt hyperthyroidism should be treated. Drug therapy with thionamides (methimazole or propylthiouracil) quickly reduces the synthesis of thyroid hormones[38]. Such therapy is not usually appropriate as a long-term therapy because of the possible occurrence of side-effects, such as rash and urticaria and, less frequently, agranulocytosis, and the possible recurrence of hyperthyroidism after discontinuation. Thionamide treatment for 12–18 months results in long-term remission in 40% of patients with Graves' disease[38]. Thionamide treatment may be used to restore euthyroidism in women with toxic nodular goiter but, because remission of this kind of hyperthyroidism almost never occurs in these patients, long-term thionamide therapy is not advised[55]. The two definitive treatment options for women with Graves' disease or toxic nodular goiter are ^{131}I and thyroidectomy. The first option, which cures hyperthyroidism after a single dose in 90% of patients, is preferable in women of advanced age. Thyroidectomy is especially useful for women with very large goiters and with Graves' ophthalmopathy, which may be worsened by ^{131}I therapy[56]. The most common adverse effects of thyroidectomy are injury to the parathyroid glands, resulting in hypocalcemia, and injury to the recurrent laryngeal nerves, resulting in hoarseness. Beta blockers can be used in women with hyperthyroidism to decrease tachycardia and improve symptoms such as anxiety, tremor and palpitations.

Treatment of subclinical hyperthyroidism is controversial. The recent Clinical Guidelines for hyperthyroidism[57] recommend therapy when TSH is persistently below the lower limit of normal, in women over 65 years of age and in patients with cardiac disease and in postmenopausal women. Treatment may decrease the risk of atrial fibrillation and the risk of low bone density in postmenopausal women[57].

NODULAR GOITER

Nodular goiter is the enlargement of the thyroid gland, usually associated with a normal thyroid function. It is mainly related to iodine deficiency. In general, nodular goiter can be divided into solitary nodular and multinodular thyroid disease[58]. In relation to thyroid function, nodular goiter is distinguished into non-toxic, with euthyroidism, or toxic multinodular goiter (multiple thyroid functioning nodules) or toxic thyroid adenoma (one hyperfunctioning nodule) with overt or subclinical hyperthyroidism[58].

Etiology and natural history

The natural history of nodular goiter is characterized by thyroid diffuse growth in the early phase, nodule formation and, in some patients, the development of functional autonomy[58,59]. Iodine deficiency is a major environmental factor contributing to goiters and, in iodine-deficient areas, subjects with long-standing nodular goiter tend to develop hyperthyroidism. A constitutional risk factor for the development of nodular goiter is gender, because the ratio of females to males in non-endemic goiter regions ranges from 5 : 1 to 10 : 1[58]. A strong genetic predisposition has been indicated by family and twin studies. Other risk factors are cigarette smoking, increased body mass index and certain drugs[60].

Hypotheses on the etiopathogenesis of functional autonomy have been formulated since 1989 by Dumont and colleagues; these hypotheses assumed the role of a relative hyperactivity of one of the elements involved in the cyclic adenosine monophosphate (cAMP) cascade such as TSH receptor, G protein, cyclase and protein kinase[61]. Subsequent studies confirmed that activating TSH receptor mutations are the main cause of thyroid toxic adenomas[62]. These data were corroborated in studies in Italy where it was observed that 73% of toxic thyroid adenomas had activating mutations of the TSH receptor[61]. Similarly to single toxic thyroid adenoma, mutations were found in single hyperfunctioning nodules within multinodular goiter in which non-functioning nodules also co-exist[63].

Epidemiology

Epidemiological studies of nodular goiter are hampered by problems such as selection criteria (e.g. age, sex), influence of environmental factors (e.g. iodine and drug intake, smoking and drinking habits), evaluation of size and morphology (palpation, sonography, scintigraphy), and determination of thyroid function[64]. A pattern of increased thyroid volume and nodularity in areas with iodine deficiency is the rule. A recent cross-sectional study using modern technologies on the spectrum of thyroid disorders occurring in a community with mild-to-moderate iodine deficiency in the South of Italy[40] clearly showed that the prevalence of goiter and thyroid nodularity increased with age. The prevalence of goiter increased from 16% in children to 60% in adults. Nodular goiter was negligible in the 15–25-year age class, but increased up to 29% in the 56–65-year age class[40].

In the Whickham survey, 15.5% of the participants had a palpable goiter (8.6% had a small goiter), with a female to male ratio of 4.5 : 1[15]. In Framingham, Massachusetts, where iodine intake was also sufficient, 1% of persons between 30 and 59 years of age had multinodular goiter by palpation[16]. In Connecticut, 2% of adults were reported to have nodular glands[65]. In Denmark, palpable goiter was demonstrated in 9.8% of a mildly iodine-deficient population and 14.6% of a moderately iodine-deficient population[66]. This frequency increased to 15.0% and 22.6%, respectively, when goiter was defined by sonographic determination of thyroid volume[65].

Clinical presentation

Non-toxic goiter is often asymptomatic with only cosmetic problems. The symptoms are highly variable and due to obstruction of the upper areas, with shortness of breath and cough, recurrent laryngeal nerve, with dysphonia, and esophagus with dysphagia. The paralysis of a recurrent laryngeal nerve is rare and, if present, especially if unilateral, is likely due to the presence of thyroid cancer with infiltration of the nerve itself.

THYROID AUTOIMMUNITY AND PREMATURE OVARIAN INSUFFICIENCY

Thyroid autoimmunity is more common in females than in males, probably because of the action that sex hormones, estrogens and androgens have on the immune system. In fact, the female/male ratio of patients with Graves' disease is reduced after 60 years and it has been observed that the presence of an early menarche or a late menopause is a risk factor for the development of an autoimmune thyroiditis, probably because of a greater exposure to estrogen during the reproductive life[67]. Sex hormones may modulate the mechanisms of thyroid autoimmunity, explaining why the clinical manifestations of these diseases are more evident in young subjects, while the prevalence of thyroid autoantibodies tends to increase with age[10].

Serum thyroid autoantibodies are detectable in up to 25% of women over the age of 60 years and autoimmune hypothyroidism is eight to nine times more common in women than in men and increases with age[17].

Premature ovarian insufficiency (POI) is defined as a primary ovarian defect characterized by absent menarche (primary amenorrhea) or premature depletion of ovarian follicles before the age of 40 years (secondary amenorrhea) with hypergonadotropism and hypoestrogenism[68]. POI is a disorder affecting approximately 1% of Caucasian women. POI affects approximately one in 10 000 women by age 20, one in 1000 women by age 30 and one in 100 women by age 40. The etiology of POI is highly heterogeneous[69]; it may be the consequence of environmental factors such as surgery, infections and chemotherapy, or it may be due to autoimmune disorders but it also has a major genetic component and is frequently found in families[70]. The premutated allele at the *FMR1* gene in Xq 27.3 has a more relevant role in the etiology of POI. A study conducted on 50 POI patients revealed that 8% had *FMR1* premutation[71]. The association between POI and other organ-specific autoimmune diseases has been documented for many years. Its prevalence has been evaluated variously, from 20% to 55%[72]. Autoimmune etiology constitutes approximately 5% of the total cases of POI and occurs in approximately 10% of patients who have Addison's disease[73]. In particular, in patients with autoimmune polyendocrine syndrome type-1, the frequency of POI is much higher, in the range of 50–60%. However, the diagnosis of autoimmune mechanisms in POI is difficult and remains controversial; the search for anti-ovarian antibodies relies on indirect immunofluorescence and seems to have low specificity. Adrenal autoimmunity is rare, but is the best-known association with POI. Thyroid autoimmune disease, most commonly autoimmune thyroiditis, is present in 14–27% of women with POI at initial diagnosis[74]. For this reason, it is recommended to measure TSH levels and test for the presence of thyroid peroxidase antibodies in these patients.

CONCLUSIONS

Thyroid dysfunction is common especially in women over the age of 50 years. Postmenopausal women are at increased risk of both osteoporosis and cardiovascular disease, and untreated thyroid disease may exacerbate these risks. Screening for thyroid dysfunction in asymptomatic individuals is controversial, but aggressive case-finding should be pursued. Serum TSH investigations can be justified in perimenopausal and postmenopausal women with symptoms such as fatigue, weight change, anxiety, depression, constipation or hyperdefecation, irregular menses, temperature intolerance, memory impairment; historical factors such as family history of thyroid dysfunction or other autoimmune disease, history of external neck irradiation or thyroid surgery, infertility, atrial fibrillation, use of amiodarone, lithium or interferon-α; signs like goiter, tachycardia or bradycardia, periorbital edema, exophthalmos laboratory abnormalities such as hyperlipidemia.

Women with overt thyroid dysfunction should be treated, but caution is required in diagnosing and treating thyroid dysfunction in women who are taking estrogens or SERMS; however, the final decision in treating menopause with estrogen/hormone therapy is not influenced by the concomitant presence of thyroid disorders and women should be treated according to the current guidelines[2].

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