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REVIEW

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Thyroid disease in the perimenopause and postmenopause period

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ABSTRACT

The interpretation of thyroid function tests should be cautiously made during the perimenopause and postmenopause period bearing in mind that physiologic changes do exist in this group of women in terms of secretion and metabolism of thyrotropin and thyroid hormones. Moreover the incidence of thyroid disorders increases in postmenopausal and elderly women. There is no consensus for screening postmenopausal women even though there is well-known evidence about the effect of thyroid status on cognitive function, cardiovascular risk, bone turnover, and longevity. The diagnosis of any thyroid disorder is challenging in these patients because the symptoms are more subtle and attributed to menopausal symptoms. Management requires more attention in this population than that of younger groups, because high doses of L-thyroxine can lead to cardiac complications and increased bone turnover. Furthermore radio-iodine is preferred in treatment of hyperthyroidism in older patients. The risk of nodular thyroid disease and thyroid cancers increases in this group. Although the diagnostic approach is the same as for young patients, the risk of surgery is high and disease prognosis is worse. Women with any form of thyroid disease should be treated according to the current guidelines. Decision for menopausal hormonal therapy should be individualized regardless of the concomitant presence of thyroid disorders.

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Introduction

Postmenopause is defined as a permanent cessation of menstruation for 12 months due to the loss of ovarian function. There is an increasing prevalence of thyroid disorders with aging, particularly higher in postmenopausal women. The diagnosis is challenging in these patients due to symptoms like weight gain, dependent decline in free triiodothyronine (FT3) levels, and increase in reverse triiodothyronine (T3) levels. Sweating, insomnia, and palpitations can be attributed to both ovarian and thyroid dysfunction. The interpretation of thyroid function due to aging, other comorbidities, and use of multiple pharmaceuticals among these age groups makes decision-making more difficult.

There is a relationship between gonadal axes and thyroid function during the woman's fertile period. Thyroid hormones affect the reproductive function indirectly by increasing the synthesis of sex hormone binding globulin, testosterone, and androstenedione, reducing the clearance of estradiol and androgens, and also increasing the conversion of androgens to estrone. The direct effects are mediated via receptors for thyroid hormones at the level of oocytes. Thyroid hormones work synergistically with follicle stimulating hormone through follicle stimulating hormone receptors present on granulosa cells for the production of progesterone[1].

Estrogen is suggested to have a role in the pathogenesis of thyroid disease[2]. Estrogen causes an increase in the serum concentration of thyroxine-binding globulin by inducing sialylation of the protein, which decreases its clearance, and by enhancing its biosynthesis, resulting in an elevation of thyrotropin (TSH) by feedback. Due to insufficient adaptation of hypothyroid women taking hormone replacement therapy, the thyroxine (T4) dosage needs to be increased in these women. TSH levels should be checked at 12 weeks after administration of therapy[3].

Thyroid function has been investigated in different populations. Most studies have demonstrated an age-dependent decline in free triiodothyronine (T3) levels and an increase in reverse T3 (rT3) levels. The daily production of free thyroxine (FT4) decreases but its metabolism slows down due to the reduced activity of 5′ deiodinase 1; serum concentrations of FT4 remain stable[4]. Populations in which the most common thyroid pathology is thyroid deficiency secondary to Hashimoto thyroiditis display a trend for the TSH upper limit to increase with age[5–7]. On the contrary, an inverse relationship between TSH and age is seen in iodine-deficient populations in which the most common thyroid pathology is nodularity and increasing thyroid autonomy with age[8].

TSH values above 3.0 mIU/l occur with increasing frequency with age, elderly individuals (>80 years of age) having a 23.9% prevalence of TSH values between 2.5 and 4.5 mIU/l, and a 12% prevalence of TSH concentrations above 4.5 mIU/l[9]. Mild TSH elevations in older individuals may not

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reflect subclinical thyroid dysfunction, but rather be a normal manifestation of aging and thus the normal reference range may widen with increasing age[10].

Abnormal serum levels of TSH are observed in various non-thyroidal states which are more common in the elderly. Serum TSH may be suppressed in critically ill patients, especially in those receiving dopamine infusions[11] or pharmacologic doses of glucocorticoids[12]. In addition, serum TSH levels may increase to levels above the normal range during the recovery phase from any non-thyroidal illness[13]. Moreover, serum levels of T3 are low in the absence of thyroid disease in patients with severe illness because of reduced peripheral conversion of T4 to T3 and increased inactivation of thyroid hormone[14,15].

Treatment of hypothyroidism associated with adrenal insufficiency should be deferred until after glucocorticoid therapy has been instituted because TSH levels may be elevated in the presence of untreated adrenal insufficiency and may normalize with glucocorticoid therapy[16,17].

Progesterone supplementation in postmenopausal women has been found to decrease TSH levels[18]. Given the fact that TSH is higher in postmenopausal women[19], a lack of endogenous progesterone in the postmenopausal period may be one precipitating factor.

Non-hormonal menopause therapy may interfere with thyroid function. Neither fluoxetine nor sertraline was associated with clinically significant changes in thyroid function or thyroid autoimmunity in either primary hypothyroid or normal thyroid function patients with depression. However, results suggest that patients with normal thyroid function who were treated with fluoxetine are more susceptible to minor changes within the serotoninergic system than patients with hypothyroidism on the same selective serotonin reuptake inhibitor[20]. Baseline thyroid function, as measured by serum TSH, may predict a patient's response to antidepressant treatment with selective serotonin reuptake inhibitors. Optimal thyroid function, beyond simply being within the normal laboratory values, may be necessary for an optimal response to antidepressants[21].

Thyroid disorder may be found among older women aged >60 years who take gabapentin or clonidine and also take levothyroxine[22].

Screening for thyroid dysfunction

The American College of Physicians has recommended that women older than 50 years with one or more general symptom that could be caused by thyroid disease should be screened with serum TSH testing initially, followed by measurement of FT4 if the TSH level is undetectable or greater than 10 mIU/l[23]. The American Academy of Family Physicians has recommended routine thyroid function screening in asymptomatic patients older than 60 years[24]. The American Thyroid Association (ATA) has recommended screening in all adults beginning at age 35 years and every 5 years thereafter[25]. The American Association of Clinical Endocrinologists (AACE) has recommended routine measurement of TSH in older patients (age not specified)[20]. In contrast, the US Preventive Services Task Force has not recommended routine screening for thyroid disease in children or adults[26,27] and the Institute of Medicine has issued a statement that screening is not cost-effective in the Medicare population[28].

Hypothyroidism

Hypothyroidism is characterized with an elevated serum TSH which may be subclinical or overt. In subclinical hypothyroidism, serum TSH levels are mildly elevated in combination with a normal FT4. In the case of overt hypothyroidism there are markedly elevated TSH levels with decreased FT4. The National Health and Nutrition Examination Survey III has reported that a significantly greater number of women aged 50–69 years met criteria for subclinical and clinical hypothyroidism compared to men in the same age range[5]. The prevalence of subclinical disease was 4.3% and for overt disease was 0.3%. The Colorado Thyroid Disease Prevalence Survey reported a prevalence of 8.5% and 0.4% in people not taking thyroid hormone for subclinical and overt disease, respectively[29]. In the Framingham Study, 5.9% of women and 2.3% of men over the age of 60 years had TSH values over 10 mIU/l, 39% of whom had subnormal T4 levels[30]. In the British Whickham Survey, 9.3% of women and 1.2% of men had serum TSH values over 10 mIU/l[31,32]. The risk of developing hypothyroidism in women with positive antibodies and elevated TSH was 4% per year; whereas with only one abnormal parameter the risk was 2–3% per year[31,32]. The presence of antithyroperoxidase antibodies (TPOAb) predicts progression to overt hypothyroidism[25]. Up to 60% of suspected cases will regress to euthyroidism over 5 years, whereas 5–25% (perhaps more in those with positive TPOAb) will become frankly hypothyroid over a 5-year period[33].

Etiology

Environmental iodine deficiency is the most common cause of hypothyroidism on a worldwide basis[34]. In areas of iodine sufficiency, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Hypothyroidism may occur as a result of radioiodine or surgical treatment and after external beam radiation for non-thyroid-related head and neck malignancies, including lymphoma. A relatively new pharmacologic cause of iatrogenic hypothyroidism is tyrosine kinase inhibitors, most notably sunitinib[35,36], which may induce hypothyroidism through reduction of glandular vascularity and induction of type 3 deiodinase activity. Central hypothyroidism occurs when there is insufficient production of bioactive TSH[37,38] due to pituitary or hypothalamic tumors, inflammatory or infiltrative diseases, hemorrhagic necrosis (Sheehan's syndrome), or surgical and radiation treatment for pituitary or hypothalamic disease. In central hypothyroidism, serum TSH may be mildly elevated, but assessment of serum FT4 is usually low, differentiating it from subclinical primary hypothyroidism. Consumptive hypothyroidism is a rare condition that may occur in patients with hemangiomata and other tumors

in which type 3 iodothyronine deiodinase is expressed, resulting in accelerated degradation of T4 and T3[39,40].

Clinical presentation

Great attention is required for the diagnosis of hypothyroidism in postmenopausal and older adults because symptoms and signs including weakness, fatigue, constipation, dry skin, and intolerance to cold may be attributed to menopause manifestations and other diseases common in older patients, or side-effects of medications, or even aging itself. Subclinical hypothyroidism is generally asymptomatic in this population.

Management

Although L-thyroxine treatment is recommended in patients with primary hypothyroidism with elevated TSH levels over 10 mIU/l, treating a midlife woman with subclinical hypothyroidism is less certain.

Current evidence suggests that increased cardiovascular risk in patients having TSH <10 mIU/l is well established in the younger adult population (<70 years of age) but not in the elderly population (>75 years of age)[41]. Also, recent reports suggest that mild subclinical hypothyroidism could even be associated with longevity and could be beneficial for the elderly population (>70–85 years of age)[42–44].

The American Association of Clinical Endocrinologists/ATA guidelines suggest that treatment should be considered in patients whose TSH level falls between the upper limit of normal and 10 mIU/l, and who have symptoms of hypothyroidism, positive TPOAb, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors[25].

According to the European Thyroid Association guidelines, in patients with subclinical hypothyroidism and age <65–70 years, therapy with L-thyroxine should be instituted in the presence of symptoms or TSH ≥10 mIU/l. In the population over 70 years old and TSH ≥10 mIU/l, therapy may be considered when symptoms of hypothyroidism or cardiovascular risk exist. In patients >70 years of age and TSH <10 mIU/l, observation is all that is needed[44].

According to current data, it is comprehensible to raise the target levels of serum TSH to 4–6 mIU/l in patients over 70–80 years of age[29]. Avoiding overtreatment with L-thyroxine is crucial since the elderly patients are particularly prone to atrial fibrillation, while postmenopausal women are prone to accelerated bone loss.

When initiating therapy in patients older than 50–60 years with overt hypothyroidism and without evidence of coronary heart disease, a L-thyroxine dose of 50 μg daily should be considered. In patients with subclinical hypothyroidism, the initial L-thyroxine dosage is generally lower; a daily dose of 25–75 μg should be considered, depending on the degree of TSH elevation[25]. Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum thyrotropin at steady state, since such medications may alter the levothyroxine requirement by increasing thyroid binding globulin, which in turn reduces FT4[26].

Hyperthyroidism

Thyrotoxicosis is a condition resulting from high thyroid hormone action in tissues by virtue of inappropriately high tissue thyroid hormone levels. Hyperthyroidism is a form of thyrotoxicosis based on excessive thyroid function. Overt hyperthyroidism is defined as subnormal; generally undetectable serum TSH and elevated FT4 and FT3 levels. In subclinical hyperthyroidism, serum TSH levels are low in combination with normal FT4 and FT3 levels.

Hyperthyroidism is more common in women than in men (5:1 ratio). The overall prevalence of hyperthyroidism, which is approximately 1.3%, increases to 4–5% in older women[2]. Graves' disease (GD) is seen most often in younger women, while toxic nodular goiter is more common in older women.

In one prospective cohort study of adult women, the overall incidence of GD was 4.6 per 1000 during 10 years of observation[45]. Although GD is the most common cause of hyperthyroidism[46], toxic multinodular goiter (TMNG) is more common in older patients. Iodine-induced hyperthyroidism can be seen after an iodine load due to contrast agents or iodine-rich drugs such as amiodarone.

Subclinical hyperthyroidism is more frequent than overt hyperthyroidism in older adults. The prevalence of subclinical hyperthyroidism (SH) in an adult population depends on age, sex, and iodine intake. In a representative sample of US subjects without known thyroid disease, 0.7% had suppressed TSH levels (<0.1 mU/l) and 1.8% had low TSH levels (<0.4 mU/l)[2]. Similar rates have been reported in studies from Europe, with higher levels in women and older subjects[47,48].

The natural history of SH is variable[48], with annualized rates of 0.5–7% progression to overt hyperthyroidism and 5–12% reversion to normal TSH levels. Progression from SH to overt hyperthyroidism appears more likely if the TSH is suppressed (<0.01 mU/l), rather than low but detectable (0.01–0.4 mU/l)[49–51]. Patients with GD rather than a TMNG as the cause of SH may be more likely to spontaneously remit[48] therapy. In clinical series, TMNG is the most common cause of SH, especially in older persons[48,50,51].

Clinic presentation

Hyperthyroidism in older patients may be apathetic, rather than having hyperactivity, tremor, and other symptoms of sympathetic overactivity[52]. However, two-thirds of such patients have symptoms similar to those in younger patients[53]. In cross-sectional studies of patients with hyperthyroidism, older patients had a reduced risk for the presence of several classical symptoms (i.e. heat intolerance, tremor, nervousness) but a higher prevalence of weight loss and shortness of breath compared with younger patients[53,54]. Older patients also had a higher rate of atrial fibrillation and moderate to severe ophthalmopathy[55]. Tachycardia can be absent in older hyperthyroid patients, due to concomitant conduction system disease.

Management

Serum TSH is the initial test in order to diagnose and assess the severity of hyperthyroidism. Thyroid scintigraphy and a radioactive iodine (RAI) uptake test are used to determine the cause of hyperthyroidism.

Treatment modalities for overt and subclinical hyperthyroidism are the same. These include RAI ablation therapy, antithyroid medications, and thyroidectomy[55]. RAI ablation is often used for older adults because of its efficacy, safety, and cost-effectiveness[56].

Methimazole (MMI) treatment is preferred to propylthiouracil unless there is an allergy to MMI because of propylthiouracil's black box warning of several liver injury and acute liver failure[57]. Long-term MMI treatment of TMNG or toxic adenoma (TA) might be indicated in some elderly or otherwise ill patients with limited life expectancy, or in patients who are not good candidates for surgery or ablative therapy[57]. Depending on comorbidities, surgical approaches are less commonly used in older adults due to the perceived increased risk of morbidity[57]. They are reserved for large goiters with obstructive symptoms or known or suspected malignancy[58].

Management of subclinical hyperthyroidism

Although treatment of overt hyperthyroidism is always recommended, management of SH is less clear. Several studies showed similar deleterious effects in SH as in overt hyperthyroidism.

In studies investigating cardiovascular disease, an increased cardiovascular mortality was reported with SH[59]. There have been two recent meta-analyses[60,61] which both concluded that SH confers an increased risk of cardiovascular mortality. The risk was greater in subjects with TSH levels <0.1mU/l compared to those with TSH levels of 0.1–0.4mU/l. The most recent data indicate that SH subjects appear to be at particular risk for the development of heart failure[60,62], especially older subjects[62] and those with lower TSH levels[62].

Arrhythmias are another concern in SH. Absolute incidence rates of atrial fibrillation were much lower in younger subjects. Women under the age of 65 years had lower atrial fibrillation incidence rates when compared to women 65 years and older[63].

A further population-based study found that SH increased the risk for stroke in subjects over age 50 years with a hazard ratio of 3.39[64], although a recent meta-analysis of stroke risk in SH found insufficient number of events to draw definitive conclusions[65].

Regarding osteoporosis and fractures, a recent study reported that subclinical hypothyroidism had increased the risk for all major osteoporotic fractures. Risk increased with duration of SH, such that, after a median follow-up of 7.5 years, 13.5% of subjects with a low TSH level had experienced at least one major osteoporotic fracture, compared to 6.9% of subjects with a normal TSH level[66].

In studies investigating mood and cognition, approximately equal numbers of studies report significant associations between SH and measures of cognitive decline and the development of dementia, versus no associations[61–63]. Therefore, at this time, no conclusions regarding this issue can be reached. There appears to be no correlation between SH and depression[69–73].

The ATA has recommended treatment of SH in all individuals older than 65 years of age when TSH is persistently <0.1 mIU/l; in patients with cardiac risk factors, heart disease, or osteoporosis; in postmenopausal women who are not on estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms[54]. Treatment should be considered in asymptomatic individuals <65 years of age without the risk factors. Treatment of SH should be considered in individuals >65 years of age when TSH is persistently below the lower limit of normal but >0.1 mU/l, and in patients with cardiac disease, osteoporosis, or symptoms of hyperthyroidism[54]. Asymptomatic patients under age 65 years without cardiac disease or osteoporosis can be observed without further investigation of the etiology of the subnormal TSH or treatment[54].

The European Thyroid Association recently published guidelines for the treatment of subclinical hyperthyroidism[73], which are largely concordant with the ATA recommendations.

Thyroid nodules and thyroid cancer

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma. Palpable lesions that do not correspond to distinct radiologic abnormalities do not meet the strict definition of thyroid nodules. Non-palpable thyroid nodules detected on imaging studies are termed incidentalomas[74]. Thyroid nodules become more common with aging, especially in women. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men living in iodine-sufficient parts of the world[75,76]. In contrast, high-resolution ultrasound can detect thyroid nodules in 19–68% of randomly selected individuals, with higher frequencies in women and the elderly[77,79]. A large multinodular goiter is the most common presentation in adults. Thyroid cancer, which occurs in 7–15% of patients with thyroid nodules, should be excluded.

With the discovery of a thyroid nodule >1 cm in any diameter, a serum TSH level should be obtained. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained[79]. Since hyperfunctioning nodules rarely harbor malignancy, no cytologic evaluation is necessary. A higher serum TSH level, even within the upper part of the reference range, is associated with increased risk of malignancy in a thyroid nodule, as well as a more advanced stage of thyroid cancer[80,81]. Thyroid ultrasound has been widely used to stratify the risk of malignancy in thyroid nodules to decide whether fine needle aspiration (FNA) is indicated. The approach to the management of a solitary thyroid nodule in older adults is the same as that for younger patients[56]. Features with the highest specificity (median >90%) for the detection of thyroid cancer are microcalcifications, irregular margins, and tall shape, although the sensitivities are significantly lower for any single feature[82–89].

Diagnostic FNA of the thyroid is recommended for nodules ≥1 cm in greatest dimension with high and intermediate suspicion sonographic patterns and nodules ≥1.5 cm in greatest dimension with low suspicion sonographic pattern. It may also be considered for nodules ≥2 cm in greatest dimension with very low suspicion sonographic pattern (e.g. spongiform). Observation without FNA is also a reasonable option[74].

The Bethesda System for Reporting Thyroid Cytopathology is used to interpret FNA biopsy results[90]. If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not required. For a nodule with an initial non-diagnostic cytology result, FNA should be repeated with ultrasound guidance. If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended. If cytology is indeterminate, molecular testing may be used for differentiating benign from malignant thyroid nodules[74].

The mortality rates of patients with thyroid cancer increase starting at age 45 years, thus age is included in the American Joint Committee on Cancer TNM staging system of thyroid cancer[91]. The modalities used for the treatment of thyroid cancer in older adults are essentially the same as those used in younger patients. Frequently, the surgical approach for a thyroid cancer larger than 1 cm is near-total or total thyroidectomy. Thyroid lobectomy alone may be sufficient for tumors smaller than 1 cm[74]. Even though older patients may exhibit a higher surgical risk because of comorbidities, age by itself is not a contraindication to thyroidectomy[92].

Depending on the surgical pathology report, patients are stratified as low risk, intermediate risk, and high risk based on ATA guidelines[74]. Postoperative serum thyroglobulin can help in assessing the persistence of disease or thyroid remnants and predicting potential future disease recurrence[74]. RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk differentiated thyroid cancer (DTC) patients; however, RAI remnant ablation should be considered after total thyroidectomy in ATA intermediate-risk level DTC patients, and routinely recommended after total thyroidectomy for ATA high-risk DTC patients[74].

T4 suppression therapy is used for the treatment of DTCs. The beneficial effect of TSH suppression is a considerable reduction in recurrence rates of DTC, but this should be weighed against potential complications, especially in older adults[74].

Thyroid autoimmunity and premature ovarian insufficiency

Premature ovarian insufficiency 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 hypergonadotrophism and hypoestrogenism. Autoimmune etiology constitutes approximately 5% of the total cases of premature ovarian insufficiency. Thyroid autoimmune disease is present in 14–27% of women with premature ovarian insufficiency at initial diagnosis. Thus, determining TSH levels and the presence of thyroid peroxidase antibodies in these patients is recommended[1].

Conclusion

Thyroid dysfunction is common especially in women over the age of 50 years. Screening for thyroid dysfunction in asymptomatic individuals is controversial[23–28]. Clinical manifestations of hypothyroidism (e.g. weakness, fatigue, constipation, dry skin, and intolerance to cold), as well as of hyperthyroidism (e.g. heat intolerance, tremor, nervousness, weight loss, shortness of breath, atrial fibrillation, and moderate to severe ophthalmopathy), warrant further investigation. Such symptoms should not be confused with postmenopausal symptoms. Women with any form of thyroid disease, whether benign or malignant, should be treated according to the current guidelines. Decision for menopausal hormonal therapy should be individualized regardless of the concomitant presence of thyroid disorders.

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