Update on subclinical thyroid disease

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Abstract

Subclinical thyroid disease is commonly encountered now as more patients with vague, non-specific symptoms are being evaluated with ultra-sensitive, third generation TSH assays. The clinical significance of mild thyroid over-activity and under-activity is uncertain, which has led to controversy over the appropriateness of diagnostic testing and possible treatment. In this article, we discuss the definition, differential diagnoses, risks of progression, potential health outcomes and management of subclinical thyroid dysfunction.

Introduction

Subclinical thyroid disease is defined as a biochemical disorder with abnormal serum thyrotropin (TSH) and normal serum free thyroxine (T4). These changes of TSH are thought to be due to mild thyroid dysfunction.

Subclinical hypothyroidism

It is defined biochemically as normal free T4 in the presence of an elevated TSH. In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 to 15%, being higher in females. It's prevalence rises with age (1).

Subclinical hypothyroidism is more prevalent in areas of iodine sufficiency. A high prevalence of goiter and autoimmune thyroiditis has been observed in Sri Lanka following the salt iodization program, which makes subclinical hypothyroidism a more commonly encountered problem for the clinicians (2).

The causes of subclinical hypothyroidism are the same as those of overt hypothyroidism. Most patients have chronic autoimmune (Hashimoto's) thyroiditis with high serum concentrations of antithyroid peroxidase (AntiTPO) antibodies (3).

Diagnosis

The diagnosis of subclinical hypothyroidism is based upon biochemical testing alone, with high TSH and normal free T4. Most patients have serum TSH levels <10 mU/L and are asymptomatic.

If the serum TSH concentration is elevated on initial evaluation, it should be repeated along with a free T4 after 3 to 6 months to confirm the diagnosis. However, in circumstances where there is a strong indication for thyroxine therapy, such as, the presence of a goiter, positive anti TPO antibodies, pregnancy, infertility or planning a pregnancy, diagnosis and treatment can be initiated earlier.

Differential diagnosis

There are several causes of a high serum TSH concentration that do not properly fit the definition of subclinical hypothyroidism. One such instance is during the period of recovery from nonthyroidal illness, where a transiently elevated serum TSH can be detected. Also following the hyperthyroid phase of thyroiditis, a transient, mild hypothyroidism is usually seen. Assay variability and rarely, the presence of heterophilic antibodies must also be considered. Untreated adrenal insufficiency is another important diagnosis to exclude. In central hypothyroidism up to 25% of patients have a mildly elevated TSH and a low or low-normal free T4 and rarely, thyroid hormone resistance can give a similar biochemical picture.

Evaluation

Some patients with subclinical hypothyroidism have mild non-specific symptoms such as fatigue and constipation. Thus, patients with subclinical hypothyroidism should be questioned about symptoms of hypothyroidism, past treatment for hyperthyroidism and use of medications that may impair thyroid hormone absorption or function. Drugs such as lithium, amiadarone,

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interferone alfa and radiographic agents can interfere with thyroid functions. Antithyroid peroxidase antibodies are not routinely measured in patients with subclinical hypothyroidism, however, the presence of antibodies may be useful when deciding either to treat or to monitor.

Management

Although virtually all experts recommend treatment of patients with serum TSH concentrations >10 mU/L, the routine treatment of asymptomatic patients with TSH values between 4.5 and 10 mU/L remains controversial. The clinical guidelines by the Endocrine Society of Sri Lanka recommends to repeat TSH in 3 to 6 months in patients with TSH between 4.5-10 mU/L prior to commencement of thyroxine (4). In view of data linking subclinical hypothyroidism with atherosclerosis and myocardial infarction, young or middle aged patients with TSH between 4.5 and 10 mU/L can be treated in the presence of symptoms, a goiter, high titers of antithyroid peroxidase antibodies and dyslipidaemia.

One should be cautious about over-treatment with T4 which may result in adverse consequences, such as cardiac arrhythmia, especially in the elderly.

Synthetic thyroxine is the treatment of choice for correction of hypothyroidism. For elderly patients and those with underlying cardiovascular disease, the initial dose of thyroxine is typically 25 to 50 mcg/day. This approach will avoid over-treatment. Younger patients, without a history of thyroid autonomy, can be initiated at a dose slightly below full replacement (1.6 mcg/kg/d).

Initiating thyroxine replacement should be done early in women with TSH values >4.5 mU/L who are either pregnant, wish to become pregnant or have ovulatory dysfunction and infertility.

The goal of therapy is to reduce the patient's serum TSH to the normal reference range. Many experts recommend a therapeutic TSH target of 0.5-2.5 mU/L in young and middle-aged patients while a TSH target of 3 to 5 mU/L may be appropriate in patients over 70 years.

Subclinical hyperthyroidism

Subclinical hyperthyroidism is biochemically defined as low serum TSH concentrations (<0.5 mU/ml) with normal serum free T4 and triiodothyronine (T3).

It is caused by either exogenous or endogenous disease. Exogenous disease is more common due to the widespread use of thyroxine for treatment of thyroid disease. Autonomously functioning thyroid adenomas and multinodular goiters are the most common causes of endogenous subclinical hyperthyroidism. Among patients over 55 years, hyperthyroidism due to multinodular goiters was subclinical in 57% of patients, while hyperthyroidism due to Graves' disease was subclinical in only 6% of patients (5). Subclinical hyperthyroidism can occur in patients with thyroiditis and in patients with early Graves' disease prior to the onset of more overt hyperthyroidism.

It is more common in females, smokers, elderly and in areas of the world with mild to moderate iodine deficiency (6). Progression to overt hyperthyroidism is uncommon but in patients with large nodular thyroids and subnormal TSH, the development of overt hyperthyroidism may occur after iodine exposure.

Diagnosis

If the serum TSH concentration is below normal, the TSH measurement should be repeated along with serum free T4 and T3 to exclude overt hyperthyroidism and T3 toxicosis. The diagnosis is based upon the combination of a low serum TSH and normal serum free T4 and T3.

As the serum TSH concentration can be transiently reduced, a repeat TSH, free T4 and T3, should be performed after 3 to 6 months to confirm the diagnosis.

Differential diagnosis

The combination of low serum TSH and normal free T4 and T3 concentrations are seen in three other conditions;

Central hypothyroidism – Some patients with central hypothyroidism have low serum TSH and normal (but usually low or low-normal) free T4 and T3 concentrations.

Non-thyroidal illness – Euthyroid patients with nonthyroidal illness, especially those receiving high-dose corticosteroids or dopamine, may have low serum TSH and low-normal free T4 and T3 concentrations.

Recovery from hyperthyroidism – Serum TSH concentrations may remain low for up to several months after normalization of serum T4 and T3 concentrations in patients treated for hyperthyroidism or recovering from hyperthyroidism caused by thyroiditis.

Pregnancy

The diagnosis of true subclinical or overt hyperthyroidism during pregnancy may be difficult because of the changes in thyroid function that occur during normal pregnancy. Transient subclinical hyperthyroidism in the first trimester of pregnancy is considered a normal physiologic finding. True subclinical hyper-

thyroidism may occur, but it is not typically associated with adverse outcomes during pregnancy and does not require therapy (7). Furthermore, in pregnant women with overt hyperthyroidism, the goal of therapy is to maintain serum free T4 concentrations in the high-normal range and serum TSH concentrations in the low-normal or suppressed range (8).

Evaluation

Patients with subclinical hyperthyroidism should be questioned about symptoms of hyperthyroidism in addition to a past history of thyroid disease, exposure to iodine containing radiographic contrast media, herbal products or medications that may suppress TSH (T4, high dose corticosteroids). Women of childbearing age should be questioned about the possibility of pregnancy as high hCG in pregnancy can give rise to low TSH. All patients should be examined for the presence of thyroid gland enlargement and nodularity.

In patients who are considered for treatment, it is useful to obtain a radioactive iodine uptake scan to help determine the etiology. For example some patients with subclinical hyperthyroidism due to Graves Disease may remit spontaneously without therapy, so that continued observation without therapy is reasonable. Women of childbearing age should have a negative pregnancy test prior to undergoing radioactive iodine scanning. If the scan shows one or more focal areas of increased uptake, this could account for a toxic solitary or multinodular goiter. In patients with low or no uptake on radioiodine scan, the etiology of subclinical hyperthyroidism may be thyroiditis or recent iodine exposure (9).

In postmenopausal women or other patients at risk of osteoporosis, a bone densometry study is useful in making a decision to treat subclinical hyperthyroidism.

Management

There is little data to guide clinical decisions regarding the treatment of patients with endogenous subclinical hyperthyroidism. Potential benefits of treatment with normalization of TSH, include improvement in certain cardiovascular parameters and bone mineral density. However, there are no studies evaluating the long-term benefits of correcting subclinical hyperthyroidism, particularly studies with clinically important endpoints, such as cardiovascular disease and fractures.

The American Thyroid Association divides patients into high risk and low risk categories prior to treatment (8). The recently published clinical guidelines by the Endocrine Society of Sri Lanka recommends treatment as follows (4).

Factor	*TSH (<0.1 mU/L)*	*TSH (0.1-0.5 mU/L)*
Age >65 yrs	Yes	Consider treating
Age <65 with comorbidities		
Heart disease	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Osteoporosis	Yes	No
Age <65, asymptomatic	Consider treating	No
Toxic nodular goiter	Consider treating	Consider treating

In patients at low risk for complications of hyperthyroidism (young individuals, pre-menopausal women) if the serum TSH value is < 0.1 mU/ml, treatment is undertaken only if the patient has symptoms suggestive of hyperthyroidism, confirmed osteoporosis, cardiovascular disease and a thyroid radionuclide scan showing a toxic nodular goiter. If these features are not present or if the TSH is between 0.1 to 0.5 mU/ml, observation alone is appropriate. TSH, free T4, and T3 must be measured every six months.

During the assessment if patients are found to be osteoporotic or have atrial fibrillation, appropriate treatment with bisphosphonates, calcium and anticoagulation has to be initiated.

Treatment options

The treatment options for patients with subclinical hyperthyroidism are the same as those for overt hyperthyroidism and depend upon the underlying etiology. Beta-adrenergic antagonist drugs are useful to control symptoms of adrenergic over activity such as palpitations and tremor.

Most patients with thyroiditis require no treatment since thyroid dysfunction is transient and rarely severe. However, thyroid tests should be monitored until normalization.

For patients who need treatment, radioactive iodine is the preferred mode of therapy, especially for patients with toxic solitary or multinodular goiters. A 12 month course of anti-thyroid drugs can be considered if the etiology is likely due to Graves' because of high remission rates (9).

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