

Approach to Subclinical Thyroid Disease

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Summary:

Subclinical thyroid dysfunction is defined as an abnormal serum thyroid-stimulating hormone level and free thyroxine and triiodothyronine levels within their reference ranges. The prevalence of subclinical hyperthyroidism is about 2 percent. Subclinical hypothyroidism is found in approximately 4 to 8.5 percent of the population. Most national organizations recommend against routine screening of asymptomatic patients, but screening is recommended for high risk populations. The management of subclinical thyroid dysfunction is controversial. There is good evidence that subclinical hypothyroidism is associated with

progression to overt disease. Patients with a serum thyroid-stimulating hormone level greater than 10 mIU/L have a higher incidence of elevated serum low density lipoprotein cholesterol concentrations; however, evidence is lacking for other associations. There is insufficient evidence that treatment of subclinical hypothyroidism is beneficial. A serum thyroid stimulating hormone level of less than 0.1 mIU/L is associated with progression to overt hyperthyroidism, atrial fibrillation, reduced bone mineral density, and cardiac dysfunction. There is little evidence that early treatment alters the clinical course.

(J Bangladesh Coll Phys Surg 2008; 26: 91-96)

Introduction:

Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptom

It is a common clinical problem. Some patients will progress to overt disease, and in some patients, the serum thyroid-stimulating hormone (TSH) concentration will remain stable over time or will spontaneously return to the reference range.^{1,2}

There are many controversial issues regarding screening, evaluation and management.

In 2002, a consensus committee was formed with representatives from the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society. The committee makes recommendations about the controversial issues.³

Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free thyroxine (FT₄) concentration is within its reference range.⁴ The panel defined the reference range of normal serum TSH concentration as 0.45 to 4.5 mIU/L³

Subclinical hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT₄ and triiodothyronine (T₃) concentrations are within their reference ranges.⁴

Epidemiology of Subclinical Thyroid Disease:

The prevalence of subclinical hypothyroidism in the US adult population is about 4% to 8.5% in those without known thyroid disease.^{5,6} The prevalence increases with age, and in women older than 60 years, subclinical hypothyroidism is present in up to 20%.⁶

Subclinical hyperthyroidism is much less common than subclinical hypothyroidism. When the lower limit of TSH is less than 0.4 mIU/L, 3.2% of the population is defined as having subclinical hyperthyroidism.⁵ If patients with known thyroid disease are excluded, the prevalence decreases to 2%. Subclinical hyperthyroid disease is more common in women than men, in blacks than whites, in the elderly, and in patients with low iodine intake.⁷

Screening for Thyroid Disease:

In January 2004, the U.S. Preventive Services Task Force concludes that “the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults.”¹

The 2002 consensus group’s expert panel recommended against population-based screening but recommends “screening asymptomatic person for

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Received: 24 June, 2007

Accepted: 15 April, 2008

thyroid disease should be considered, specially for those older than 60 years or with risk factors such as women with a family history of thyroid disease, prior thyroid dysfunction, symptoms suggestive of hyperthyroidism or hypothyroidism, abnormal thyroid gland on examination, type 1 diabetes, or a personal history of autoimmune disorder.³

The panel found insufficient evidence to recommend for or against screening pregnant women or women planning a pregnancy.³

The American College of Physicians (1998), recommends screening for women older than 50 years who have symptoms consistent with thyroid disease.⁸

Subclinical Hypothyroidism:

Etiology

Hashimoto's thyroiditis, protracted recovery from acute thyroiditis, early hypothalamic disorder, inadequate levothyroxine replacement therapy in a patient with known hypothyroidism.³

Consequences of Untreated Subclinical Hypothyroidism:

Serum lipid levels in subclinical hypothyroidism (SCH) have been reported as either normal⁹ or elevated¹⁰. In the Tromso study, low density lipoprotein – cholesterol (LDL-C) levels were significantly higher.¹⁰ In Suita study, no significant association was observed between sub clinical thyroid dysfunction and lipid metabolism. The Suita study reported that SCH was associated with lower fasting blood glucose (FBG).¹¹

SCH patients have impaired endothelial function, normal / depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort.¹² In two studies, positive association between arterial stiffness & SCH has been reported.^{12, 13} But no significant association between SCH and intima-media thickness (IMT) was observed in Suita study¹¹, which suggests that SCH might not be related to an increased risk of atherosclerosis.

Patient may exhibit the feature of systemic hypothyroid symptoms^{6,14}, neuropsychiatric symptoms^{6,14} and may progress to overt, symptomatic hypothyroidism.¹⁵

Evaluation of Subclinical Hypothyroidism :

The TSH measurement should be repeated along with an FT₄ measurement at a minimum of 2 weeks, but no longer than 3 months, after the initial assessment.

If a high serum TSH concentration is confirmed on repeat testing and serum FT₄ is within the reference range, the patient should be evaluated for signs and symptoms of hypothyroidism, previous treatment for hypothyroidism, thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should be reviewed. Women who are pregnant or hope to become pregnant in the near future deserve special consideration.

Anti-thyroid peroxidase (Anti-TPO) antibodies are to be measured because the presence of anti-TPO antibodies predicts a higher risk of developing overt hypothyroidism (4.3% per year vs 2.6% per year in antibody-negative individuals).¹⁶

Risks of Treating Subclinical Hypothyroidism:

The potential risks of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine.¹⁷

Treatment:

Subclinical Hypothyroidism With Serum TSH of 4.5 to 10 mIU/L.

- Routine levothyroxine treatment is not recommended for patients with TSH levels between 4.5 and 10 mIU/L, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor for improvement or worsening in TSH level.³ Very recently a study showed that patient with subclinical hypothyroidism with TSH > 4 mIU and FT₄ in normal range obtained improvement in their cardiovascular risk factor profile and reduced tiredness after treatment with Levothyroxine.¹⁸ Thyroxine therapy for TSH level between 4.5- 10 mIU/L should be reserved for patients who have goitre, women that are anticipating pregnancy or are pregnant, patient with depression or bipolar disorder or TPO antibody positive. Thyroxine therapy may be considered in patients with symptoms of hypothyroidism who have TSH level between 4.5-10 mIU/L and continued only if there is clear symptomatic benefit.

Subclinical Hypothyroidism With Serum TSH Higher Than 10 mIU/L

Levothyroxine therapy is reasonable. The rate of progression is 5% in comparison with patients with lower levels of TSH.³

Subclinical Hypothyroidism During Pregnancy. A TSH level might be obtained in pregnant women and women who wish to become pregnant if they have a family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, or a personal history of autoimmune disorders. Pregnant women or women of childbearing potential planning to become pregnant who are found to have elevated serum TSH should be treated with levothyroxine to restore the serum TSH concentration to the reference range.³ The requirement for Levothyroxine in treated hypothyroid women frequently increases during pregnancy. Therefore, the serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy.

Subclinical Hypothyroidism in Treated Overt Hypothyroid Individuals.

When the serum TSH is in the upper half of the reference range and levothyroxine-treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase the levothyroxine dosage to bring the serum TSH into the lower portion of the reference range. Minimal TSH elevations may not require dosage adjustment in patients who feel well.

Subclinical Hyperthyroidism

Etiology

It may be transient or persistent

Persistent

- Exogenous
 - Iatrogenic- excessive thyroxine replacement
 - Intentional suppression
 - Surreptitious
- Endogenous
 - Early graves' disease
 - Toxic multi nodular goiter
 - Autonomous functioning nodules

Transient

- De Quervain's thyroiditis
- Postpartum thyroiditis

Differential diagnosis of low TSH

Hyperthyroidism

- Over
- Subclinical

Secondary

- pituitary insufficiency

Euthyroidism

- Physiological (Near end of first trimester)
- Elderly patients

Non thyroidal illness

Interpretation of Thyroid laboratory test

FT4 level	Normal TSH	Increased TSH	Decreased TSH
Normal	Normal, euthyroid sick syndrome.	Subclinical hypothyroidism	Subclinical hyperthyroidism
Increased	Early thyroiditis	Hyperthyroidism (Pituitary adenoma)	Hyperthyroidism (Graves' disease, toxic nodule)
Decreased	Late thyroiditis	Hypothyroidism (Primary thyroid failure)	Hypothyroidism (Primary pituitary failure)

Consequences of Untreated Subclinical Hyperthyroidism:

The potential adverse outcomes would be related to the degree of TSH suppression. Patients with serum TSH levels < 0.1 mIU / L are at higher risk than those patients with TSH levels between 0.1 & 0.45 mIU/L.³

Some studies noted, subclinical hyperthyroid patients have an increase in heart rate¹⁹, increase in the frequency of atrial & ventricular premature beats²⁰ & an increase in left ventricular mass.^{19, 21} However, a recent study noted, sub clinical hyperthyroidism was not associated with left ventricular hypertrophy.²²

Two studies found minimal or no effect on systolic function^{19, 20} and one showed slightly enhanced systolic function²³. Biondi et al.²³ also reported a statistically significant impairment in diastolic function with decreased transmitral blood flow due to slowed left ventricular relaxation, but significant changes were not observed in two other study.^{19, 20} Gussekloo et al.²⁴ found individuals over age 85 years with low serum TSH values had the highest rates of mortality. In contrast, two studies found no increased frequency of coronary artery disease or cardiovascular mortality.^{25, 26}

Bone mineral density is lower at all sites in post menopausal women²⁷, in contrast, in premenopausal women it appears to be normal.²⁸

In one report, the risk of vertebral fracture was elevated 4- fold and hip fracture was elevated 3- fold in women of 65 years of age or older with serum TSH values 0.1 mIU / L or less compared with control.²⁹

Recently, two studies described an increase in typical hyperthyroid symptoms (Palpitation, tremor, heat sensitivity, sweating, and nervousness) in young & middle aged patients with sub clinical hypothyroidism.^{19, 23}

In a community- based study of persons age 65 years & older, there were no significant differences in mood, anxiety or cognition between sub clinical hyperthyroid persons & those who were euthyroid³⁰.

One study showed an increased basal oxygen consumption that decreased to normal after treatment with methimazole.³¹ In another study, patients with sub clinical hyperthyroidism were found to have decreased muscle strength compared with control.³²

The risk of progression of overt hyperthyroidism varies. The etiology plays a role in this regard. Woeber³³ observed that serum TSH values normalized in five of seven patients with Graves' disease and subclinical hyperthyroidism followed for 3-19 months, whereas it remained subnormal in patients with multinodular goiters followed for 11-36 months.

Evaluation of Subclinical Hyperthyroidism :

Individuals With Serum TSH 0.1 to 0.45 mIU/L Not Treated With Levothyroxine. Measurement should be repeated by measuring FT₄ and either total T₃ or FT₃ levels. Repeat testing within 2 weeks is prudent for patient with atrial fibrillation, cardiac disease, or other serious medical conditions. Repeat testing within 3 months is recommended, when these factors are absent.³

If the repeat serum TSH concentration remains higher than 0.1 but lower than 0.45 mIU/L, with normal FT₄ and T₃ concentrations, and the patient has no signs or symptoms of cardiac disease, atrial fibrillation, or other arrhythmias, retesting should occur at 3- to 12-month intervals, until either serum TSH level normalizes or the clinician & patient are confident that the condition is stable.³

Individuals With a Serum TSH Lower Than 0.1 mIU/L. The measurement is repeated along with an

FT₄ and a total T₃ or FT₃ within 4 weeks if the patient has no signs or symptoms of cardiac disease, atrial fibrillation or other arrhythmia but within a shorter interval if signs or symptoms of hyperthyroidism are present.³

The panel recommends further evaluation to establish the etiology of the low serum TSH.³

A radio-active iodine uptake & Thyroid scan can distinguish between destructive thyroiditis & hyperthyroidism due to Graves' disease or nodular Goiter.

Risks of Treatment of Subclinical Hyperthyroidism:

The risks of treatment with antithyroid drugs are potential allergic reactions including agranulocytosis. Radioactive iodine therapy commonly causes hypothyroidism & may cause exacerbation of hyperthyroidism or Graves' eye disease.³⁴

Treatment:

Exogenous Subclinical Hyperthyroidism With TSH 0.1 to 0.45 mIU/L.

The indication of thyroid hormone therapy should be reviewed. Many patients with thyroid cancer & some patients with thyroid nodules required TSH suppression and target TSH level should be reviewed by the treating physician. When prescribed for other causes the dosage of levothyroxine is decreased to allow serum TSH to increase toward the reference range.³

Exogenous Subclinical Hyperthyroidism With TSH Lower Than 0.1 mIU/L.

The indication for thyroid hormone therapy should be reviewed. For patients with thyroid cancer and thyroid nodules, the target serum TSH value should be reviewed by the physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range.³

Endogenous Subclinical Hyperthyroidism (Serum TSH 0.1-0.45 mIU/L)

The panel³ recommends against routine treatment for all patients whose TSH is mildly decreased (0.1-0.45 mIU/L). Because of a possible association with

increased cardiovascular mortality,³⁵ clinicians might consider treatment of elderly individuals and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism, despite the absence of supportive data from intervention trials and no therapy is required for younger patient .

Endogenous Subclinical Hyperthyroidism (Serum TSH Lower Than 0.1 mIU/L)

The panel³ recommends that treatment be considered for subclinical hyperthyroidism (TSH <0.1 mIU/L) due to Graves or nodular thyroid disease. Treatment should be considered for patients who are older than 60 years and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism. Younger individuals with subclinical hyperthyroidism and serum TSH persistently (months) lower than 0.1 mIU/L may be offered therapy or follow-up depending on individual considerations.

Conclusions:

There are many controversies regarding the management of subclinical thyroid disease. Until data of well conceived and executed intervention trials are available, following may be recommended: If TSH > 10 mIU/L, thyroxine therapy is to be given. If TSH 4.5- 10 mIU/L, thyroxine therapy may be given for goitrous patients, women who are pregnant or anticipating pregnancy, or patient with depression or TPO antibody positive. Postmenopausal women or patient older than 60 years or with heart disease or osteoporosis or symptoms of hyperthyroidism should be treated if TSH <0.1 mIU/L and considered for treatment if TSH 0.1 to 0.45 mIU/L. Premenopausal women or patient <60 years, or no heart disease or osteoporosis or symptoms of hyperthyroidism therapy is optional if TSH <0.1 mIU/L and no therapy is required if TSH 0.1 to 4.5 mIU/L

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