Subclinical Thyroid Disease

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Thyroid disease is common and may present to a wide range of doctors. With the advent of serum thyrotropin (TSH) radioimmunoassay in the 1970s, the entity of mildly elevated TSH and normal serum thyroid hormones levels was recognised, the introduction of the second and third generation sensitive TSH in the 1980s identified the entity of subclinical hyperthyroidism in which serum TSH is suppressed and serum thyroxine T4 and triiodothyronine T3 levels are normal\(^{(1)}\). Controversy centers on whether early treatment or close follow-up is warranted in apparently healthy persons in whom the only indication of a thyroid disorder is an abnormal test result. We will summarise the existing epidemiological and clinical data on subclinical hyperthyroidism and hypothyroidism and discuss the rationale of management.

**SUBCLINICAL HYPERTHYROIDISM**

Subclinical hyperthyroidism is defined as a persistently suppressed serum TSH with normal thyroxine and triiodothyronine in patients who do not have symptoms. Subclinical hyperthyroidism can be caused by the same thyroid disorders that result in clinical hyperthyroidism. Suppressed TSH levels may occasionally result from non-thyroidal causes (Table I \(^{(2,3)}\)). The most common cause of subclinical hyperthyroidism is excessive thyroid hormone therapy.

Survey\(^{(4)}\) and 12% in the Framingham study\(^{(5)}\). More recently, the Colorado Thyroid Disease Prevalence Study involving 25,862 subjects showed a prevalence of 2.1%\(^{(6)}\). Joseph et al studied a representative population of 17,353 people aged 12 and above and found that the prevalence of subclinical hyperthyroidism was only 0.7%\(^{(7)}\).

The precise pathophysiology and natural history of subclinical hyperthyroidism are unknown. In the Whickham Survey where 2,779 subjects were followed up for 20 years, the incidence of hyperthyroidism in the surviving women was 3.9% and the calculated incidence rate was only 0.8/1,000/year\(^{(8)}\). The initial TSH level also appears to influence outcome. Subclinical hyperthyroid subjects with initial suppressed but detectable TSH levels tend to return to normal on follow-up while those with undetectable TSH remained unchanged with a small risk of progression to frank hyperthyroidism\(^{(9)}\). The rate of progression to overt hyperthyroidism has been estimated to be 5% per year with subjects with autonomous thyroid adenoma and nodular goiter\(^{(10)}\). Therefore, the likelihood of progression of subclinical hyperthyroidism to overt hyperthyroidism is small.

**CLINICAL IMPLICATIONS**

Increasingly, it is recognised that subclinical hyperthyroidism is not merely a biochemical abnormality dissociated from the clinical manifestations and sequelae of thyrotoxicosis. In fact, clinical features of thyrotoxicosis can be identified in subclinical hyperthyroidism albeit of insufficient severity to cause major symptoms. The clinical significance of subclinical hyperthyroidism thus relates to three risk factors: (1) progression to overt hyperthyroidism, (2) cardiac effects, and (3) skeletal effects.

**CARDIAC EFFECTS**

The data on cardiac effects of subclinical hyperthyroidism come largely from studies of patients on L-T4 suppressive therapy. A study on 20 patients receiving oral L-T4 to suppress TSH secretion for a period of one to nine years showed a number of significant effects.
cardiovascular changes: 1) increased heart rate, 2) increased incidence of atrial arrhythmia such as atrial premature beats, 3) increased left ventricular mass, left ventricular posterior wall and interventricular septal thickness, and 4) enhanced left ventricular systolic function\(^{(11)}\). Some of these effects such as heart rate, arrhythmia, cardiac wall thickness can be reduced with addition of β-blocker which result in amelioration of symptoms such as palpitations, nervousness, tremor, heat intolerance and sweating\(^{(12)}\). These findings show that many patients taking L-T4 at suppressive doses complain of symptoms similar to those present in hyperthyroid patients, which, even if of minor importance, contribute to their poor quality of life. The beneficial effect of β-blockade was further confirmed in a study by Fazio et al\(^{(13)}\) which also found that there was significant prolongation of isovolumic relaxation time, suggestive of impaired diastolic function. This was significantly reduced by β-blockade. Long-term thyrotropin suppressive therapy with levothyroxine also adversely affect cardiac reserve and exercise capacity. Biondi et al found that the maximal exercise capacity was markedly impaired in all patients, with significant reduction in peak workload and exercise duration. The left ventricular ejection fraction fell markedly during exercise, due to changes in the end-systolic left ventricular volume\(^{(14)}\). Therefore, long term L-T4 therapy can cause subtle cardiac abnormalities that can be potentially harmful. Attempts at tailoring TSH suppressive dosage showed beneficial effect in individuals on titration dose. These patients had improvement in thyrotoxic scores, echocardiographic parameters and maximal exercise workload\(^{(15)}\).

These concerns over adverse cardiac effects can be extrapolated to subclinical hyperthyroidism. Patients with endogenous subclinical hyperthyroidism were more symptomatic with higher Symptom Rating Scale scores with higher prevalence of palpitations, nervousness, tremor, heat intolerance, and sweating. Similar to the situation in suppressive L-T4 therapy, there was significant increase in the average heart rate, prevalence of atrial premature beats, mean interventricular septum and left ventricular posterior wall thickness and left ventricular mass. The left ventricular systolic function was significantly higher in the patients and the isovolumic relaxation time was also significantly prolonged in the patients\(^{(16)}\). Another well-known complication of thyrotoxicosis is atrial fibrillation. Subclinical hyperthyroidism is a risk factor for the development of atrial fibrillation. The strongest evidence emerged from the Framingham Study\(^{(17)}\) in which a cohort of 2,007 persons aged 60 years and above was followed up for 10 years. The cumulative incidence of atrial fibrillation over this period was 28% and relative risk of atrial fibrillation in those with low serum thyrotropin was 3.1. Auer et al also reported a fivefold increased in risk of developing atrial fibrillation in subjects with subclinical hyperthyroidism\(^{(18)}\).

### Skeletal Effects

Most data on skeletal effects of subclinical hyperthyroidism are derived from small, retrospective and non-randomised studies. It has been shown thus far that endogenous subclinical hyperthyroidism in the premenopausal period is not associated with increased bone metabolism\(^{(19)}\) or a decrease in BMD in the lumbar spine, femoral neck or mid shaft of radius. The situation during the postmenopausal period is more controversial. Foldes et al found significant decrease in the BMD of the lumbar spine, femoral neck and mid-shaft of radius in postmenopausal women\(^{(20)}\). Kung et al showed reduction in BMD affecting both cortical and trabecular bones in postmenopausal women taking long term suppressive therapy\(^{(21)}\). In contrast, Grant et al showed no significant changes in BMD in another study involving postmenopausal patients\(^{(22)}\). A meta-analysis done by Uzzan et al found that thyroid hormone therapy has no effect on bone mass in premenopausal women except in the spine where thyroid hormone had a paradoxical beneficial effect but had a significant detrimental effect at all sites (including spine and femur neck) in postmenopausal women\(^{(23)}\). With respect to fracture risk, Bauer et al follow-up 686 women above 65 years of age for a mean of 3.7 years. The authors found a three fold increase in risk of hip fracture among women with low TSH compared to those with normal TSH even after adjustment for age, previous hyperthyroidism, self-rated health, and current use of estrogen. The risk of new vertebral fracture was also threefold higher with the adjusted relative hazard ratio at 4.5. This prospective study showed that those with TSH levels of 0.1mIU/l or less have a significantly increased risk of new vertebral and vertebral fractures\(^{(24)}\).

### Treatment

From the results presented above, it can be seen that patients with subclinical hyperthyroidism of exogenous or endogenous origins, are symptomatic. The occurrence of cardiovascular abnormalities in subclinical hyperthyroidism emphasises that subclinical hyperthyroidism should be considered as a mild form of tissue thyrotoxicosis. Parle et al found an increased in mortality from all causes and from circulatory disease in patients with subclinical hyperthyroidism after following a cohort of 1,209 subjects for 10 years\(^{(25)}\). Sgarbi et al studied the effect of early antithyroid therapy for endogenous subclinical hyperthyroidism\(^{(26)}\).
In this study, significant reduction in the heart size was observed six months after treatment with methimazole, accompanied by a significant reduction in the symptomatic score after reaching the euthyroid state. Euthyroid state was related to an improvement of clinical, laboratory, and cardiac parameters. It suggests that early subclinical hyperthyroidism should be considered. In contrast, Yonem et al found no favourable effects of antithyroid treatment on BMD, heart rate and arrhythmia incidence in a young group of patients during a six-month period although there was partial symptomatic relief(27). Faber et al demonstrated that RAI treatment of postmenopausal women with nodular goitre and subclinical hyperthyroidism results in normalisation of TSH levels. Bone mass at both the spine and the hip remains unchanged for at least two years at a time when a decline of about 1-2% per year in bone mass is expected in normal euthyroid women. In contrast, untreated postmenopausal women with nodular goitre and subclinical hyperthyroidism demonstrated continued decline in bone mass of approximately 2% per year(28). This effect had been shown by Mudde et al in 1994 after normalising the subclinical hyperthyroidism with methimazole(29).

Treatment of subclinical hyperthyroidism remains controversial, particularly with regard to young and middle-aged people. Young and middle aged patients with untreated subclinical hyperthyroidism are at risk of untoward events:
1. Impaired quality of life.
2. Adverse cardiac effect.
3. Cardiovascular risks, related to onset of overt thyrotoxicosis in heart previously exposed to prolonged periods of subclinical hyperthyroidism.
4. Skeletal diseases as in decrease bone mineral in postmenopausal women and increased risk of fracture.

The prognostic significance of increase in left ventricular mass in patients with subclinical hyperthyroidism remains unknown because of lack of epidemiology studies of cardiovascular risk in these patients. However increased left ventricular mass, not necessarily above the hypertrophic threshold, has been found to be associated with increased risk of sudden death in subjects 45 years of age or older(30).

The American Association of Clinical Endocrinology had recommended treatment in patients with symptoms of hyperthyroidism, atrial fibrillation, or unexplained weight loss and also women with osteopenia(31). However, Biondi et al and Sgarbi et al suggested early treatment of persistent endogenous subclinical hyperthyroidism not only in older but also young and middle-age patients to improve their quality of life and avoid the consequences of long-term exposure of cardiovascular system to small increase in the thyroid hormone. The treatment options include antithyroid drugs or radioactive iodine and surgery. Samuels had proposed that it may be prudent to initiate a trial of antithyroid drug therapy prior to decisions about definitive therapy(32).

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is the term used to describe patients with normal thyroxine and raised thyroid stimulating hormone concentration who do not have symptoms(33). The findings of slightly elevated TSH and normal thyroid hormone levels do not necessarily imply the presence of subclinical hypothyroidism. Several medications and conditions are known to cause an elevation in TSH. Some drugs such as sulfonylureas, lithium, amiodarone, ethionamide, phenylbutazone, aminogluthethimide, and iodine can interfere with thyroid hormone production or release and secondarily result in a slight elevation of TSH. In addition, dopamine antagonist such as metoclopramide and domperidone may cause exaggerated TSH response to TRH stimulation by altering the inhibitory effect of dopamine on TSH secretion. Furosemide has also been shown to increase levels of TSH, especially in recovering critically ill patients. Other conditions that causes elevated TSH include thyroid hormone resistance, thyroid hormone secreting tumors (both should be associated with high free thyroxine level), psychiatric illness, adrenal insufficiency, renal failure, hyperprolactinemia and systemic illness(34).

PREVALENCE AND NATURAL HISTORY

Large population studies have suggested that the prevalence of subclinical hypothyroidism is much higher in women than men and increases with age. In the Whickham survey, TSH levels above 6mIU/l were approximately three times more common in females (7.5%) than in males (2.8%) and occurred more frequently in females over 45 years of age. TSH levels also showed a progressive increase with age in women but not in men(35). The prevalence of subclinical hypothyroidism varies from 4.3-9%. The local prevalence is estimated at 6.5% in a study on 75 subjects admitted to a geriatric ward in a restructured hospital(36).

There is also a strong association between positive antithyroid antibodies and elevated TSH. Generally the prevalence of elevated TSH levels parallels that of antibody positivity(37). A high prevalence of antibodies was found in a UK study where antibodies were present in 81% of those with TSH concentration over 10 mU/l, 46% of those with TSH over 5 mU/l and less than or equal to 10 mU/l and only in 5.7% of those whose TSH concentration was less than...
0.5 mU/l\(^{(9)}\). Interestingly, the NHANES III survey found a significant association between anti-thyroid peroxidase antibody with hypo- or hyperthyroidism but not thyroglobulin antibody\(^{(7)}\).

After 20 years of follow-up of subjects in the Whickham Survey, the risk of overt hypothyroidism was found to be 4.3% per year in women with elevated TSH and antithyroid antibodies at baseline. This is a 38 times increased risk over normal women. Moreover, an isolated elevation in TSH or presence of antithyroid antibodies alone at baseline also conferred an increased risk of overt hypothyroidism (2.6% per year and 2.1% per year respectively)\(^{(8)}\). Progression to hypothyroidism was noted to be more common in those with initial TSH value greater than 10 mU/l and in those with positive anti-thyroid antibodies\(^{(9)}\). Huber et al found that basal TSH, thyroid reserve (increase in T3 after TRH stimulation) and the presence of antithyroid peroxidase antibody with hypo- or hyperthyroidism was more common in those with initial TSH value greater than 10 mU/l and in those with positive anti-thyroid antibodies\(^{(9)}\). Huber et al. found that basal TSH, thyroid reserve (increase in T3 after TRH stimulation) and the presence of antithyroid peroxidase antibody are important prognostic factors for the development of overt hypothyroidism. Interestingly, antibodies against thyroglobulin did not have a predictive value\(^{(10)}\).

**CLINICAL IMPLICATIONS**

The possible advantages of treating subclinical hypothyroidism generally include, firstly, preventing the progression to overt hypothyroidism. Secondly, thyroxine therapy may improve the serum lipid profile and thereby potentially decrease the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities\(^{(36)}\).

**EFFECTS ON SERUM LIPID LEVELS**

The relationship between mild thyroid failure and reversible elevation in serum lipid levels has been widely investigated, but the findings remain controversial. Several cross-sectional studies suggest that serum cholesterol concentrations are elevated in individuals with mild thyroid failure when compared with euthyroid controls\(^{(37,38)}\). In other similar studies, however, the observed differences between euthyroid and mild hypothyroid individuals have not been significant\(^{(39,40)}\). The Colorado study which screened 25,862 subjects found that mean total cholesterol and low density lipoprotein cholesterol progressively increased with increasing serum TSH levels\(^{(8)}\). A reanalysis by Tanis et al. in 1996 found that subclinical hypothyroidism was two to three times more frequent in people with elevated total plasma cholesterol. Thyroid substitution therapy restoring the TSH levels to normal decreased total cholesterol by 0.2 to 0.4 mmol/l\(^{(41)}\) and mean LDL cholesterol by 0.26mmol/l and increased in HDL cholesterol by 0.08 mmol/l\(^{(41,42)}\) while triglycerides, and apolipoprotein AI levels remained unchanged\(^{(43)}\). In another study, total cholesterol and LDL cholesterol levels decreased only in pretreatment TSH values greater than 10 mU/l\(^{(44)}\). The decrease in total cholesterol and LDL levels with pretreatment TSH values greater than 40 mU/l was greater than in those levels between 10 and 40 mU/l\(^{(41)}\).

**CARDIAC EFFECTS**

Cardiac changes are evident in subclinical hypothyroidism. These include impairment of left ventricular diastolic function at rest (affecting the relaxation of the left ventricle and hence ventricular filling), reduced LV systolic function, prolongation of pre-ejection time and lastly, impaired intrinsic myocardial contractility\(^{(46-49)}\). There is evidence that these abnormalities improve with L-T4 treatment, demonstrating that adequate thyroid replacement improves cardiac output accompanied by substantial decrease in systemic vascular resistance, a reversal of diastolic dysfunction, and importantly an improvement in left ventricular ejection fraction during exercise\(^{(46-48,50)}\). It has been demonstrated in the Rotterdam Study that subclinical hypothyroidism is a strong indicator risk for atherosclerosis and myocardial infarction\(^{(51)}\). Inadequately treated hypothyroidism has also been demonstrated to have angiographic evidence of coronary atherosclerosis progression\(^{(52)}\). Impairment of endothelium-dependent vasodilatation, a harbinger of atherosclerosis, has also been detected in patients with subclinical hypothyroidism\(^{(53)}\) which can be reversed by levothyroxine supplementation\(^{(54)}\). In view of clear structural and biological cardiovascular risks associated with the presence of subclinical hypothyroidism, treatment of this condition would be expected to provide protection against the development of cardiovascular disease, although there have been no long term outcome studies published to date.

**SOMATIC AND NEUROMUSCULAR EFFECTS**

Patients with subclinical hypothyroidism can have subtle clinical manifestations and non-specific symptomatology such as dry skin, cold intolerance, constipation, and easy fatigability\(^{(55)}\). In addition, patients with muscular symptoms have mitochondrial oxidative dysfunction with significant lactate increment during exercise\(^{(56)}\). Misiunas et al. also demonstrated the presence of subclinical polyneuropathy of probable axonal origin in patients with subclinical hypothyroidism\(^{(57)}\). Subclinical hypothyroid subjects reported significantly more total symptoms than euthyroid individual in the Colarado study\(^{(58)}\) and these symptoms do improve with
L-T4 therapy. The greatest improvement seen is of patients with baseline TSH of >12 mU/l (49). Kong et al observed no improvement in symptoms score after trial of thyrone for six months in patients with TSH level between 5 and 10 mU/l(50). Prospective studies suggest that patients with mild thyroid failure have a higher prevalence of somatic symptoms, mood disorders, cognitive dysfunction, and atypical responses to standard psychiatric therapeutic interventions(50). The lifetime frequency of depression is significantly higher in patients with subclinical hypothyroidism compared with patients with normal thyroid function, suggesting that subclinical hypothyroidism lowers the threshold for depression(53).

TREATMENT
To date, there is still no consensus regarding the treatment of subclinical hypothyroidism. Evidence seems to indicate that subclinical hypothyroidism represent the mildest form of thyroid hormone deficiency and may be associated with adverse consequences. Some authors have taken the approach of treating patients with subclinical hypothyroidism with view to overall symptomatic improvement, lowering effect of lipoprotein fractions and prevention of progression of cardiac abnormalities(53,54,55,60-62). Others take a more cautious approach(36,59,63-65). Most agree that patients with serum TSH greater 10mU/l should be treated with thyroxine. The AACE has recommended treatment in patients with TSH levels between 5 and 10 mU/l in conjunction with a goitre or positive anti-thyroid peroxidase antibodies or both and also in the presence of symptoms. If the patients are antibody negative and TSH levels are between 5 and 10 mU/l, then an annual check of serum TSH is recommended, with commencement of T4 once the serum TSH rises above 10 mU/l.

The goal of the therapy is to maintain TSH levels within the normal biological range and usually a small dose of levothyroxine is sufficient. Special caution should be exercised in patients with ischemic heart disease. In these cases, a more conservative approach to starting therapy is indicated to prevent dysrhythmias, worsening angina, or even precipitation of myocardial infarction.

REFERENCES