**Subclinical thyroid disease**

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**Introduction:**
Subclinical thyroid disease is defined as normal free T4 and T3 levels with TSH levels persistently outside the reference range. Abnormal TSH levels on a single test require confirmation on repeat testing as values return to the reference range in more than 50% cases.

*Subclinical hypothyroidism* is present in around 4% of the population, with prevalence 2-3x higher in women and increasing with age to around 14% at > 80 years of age. The majority of cases are due to autoimmune thyroiditis. Progression to overt hypothyroidism is very slow – around 25% at 20 years with a raised TSH alone. It is more rapid if thyroid autoantibodies are also detectable (around 50% at 20 years) and if the initial TSH is higher. Many cross sectional studies suggest an excess of symptoms in populations with subclinical hypothyroidism such as dry skin, cold intolerance and mental slowness, but these symptoms are common in the population and sampling bias may have distorted the results in many studies. There appears to be a higher LDL, impaired endothelial and cardiac function in subclinical hypothyroidism and a long-term excess risk of cardiovascular disease. There also appears to be impaired neuropsychological development in children born to subclinically hypothyroid mothers and possibly an increased risk of obstetric complications. To date, randomised controlled trials of treatment of subclinical hypothyroidism have been small (n < 100) and here have been no long-term studies of improvements in cardiovascular outcome. It is important also define any risks of thyroxine treatment in large populations – for example subclinical hypothyroidism has been associated with increased longevity in the very elderly – before routine screening and treatment can be recommended. Currently treatment with thyroxine is recommended in pregnancy and a trial of treatment can be considered in symptomatic patients.

*Subclinical hyperthyroidism* is 1.5x more common in women and affects around 1/5th of the number with subclinical hypothyroidism – around 1% > 60 yrs and 3% at > 80 years – of these 75% have a low but not fully suppressed TSH. The commonest cause for persistently suppressed TSH is nodular thyroid disease (especially in the elderly). The risk of progression to overt thyrotoxicosis is low if the TSH is low but not suppressed, and around 2-5% per year if the TSH is suppressed. Low TSH levels appear to be associated with an increased risk of atrial fibrillation and meta-analyses suggest an increased cardiovascular mortality and risk of fracture due to osteoporosis. Despite this, no large scale trials of treatment have been conducted to determine if this improves overall outcome and to determine which treatment (e.g. radioiodine or thionamides) is best. Treatment is frequently recommended in the elderly and those at high cardiovascular risk.

**Key learning points:**
- Need to distinguish transient, self-resolving or secondary dysfunction from primary subclinical disease
- Subclinical thyroid disease is very common in the population
- Progression to overt disease is slow – only test every 6-12 months unless high risk.
- Uncertainty about related symptoms.
- Long-term risks if untreated: subclinical hypothyroidism probably increases the risk of cardiovascular disease and reduced neuropsychological outcome in pregnancy for the foetus. Subclinical hyperthyroidism is more convincingly associated with increased cardiovascular mortality and probably also atrial fibrillation and osteoporotic fracture.
- Studies of the risks versus benefits for treatment are limited, with no long-term outcome data.
- Critical appraisal of the literature is required before recommending treatment.
- Current recommendations are not fully evidence based. Treatment of subclinical hypothyroidism is recommended in pregnancy and of subclinical hyperthyroidism in patients at high cardiovascular risk.
Controversies in the field:
- Association of symptoms (e.g. mental slowness) with subclinical hypothyroidism
- Long-term benefits and risks of treatment of subclinical disease.
- Indications/justification for screening for subclinical disease, e.g. in pregnancy

Future developments:
- Large, well-designed population based studies of screening and treatment of subclinical disease.
- Genetic basis for individual variation in risks associated with subclinical disease and benefits of treatment.
- Identification of markers of increased risk associated with subclinical disease
- Benefits of screening and treatment of subclinical hypothyroidism in pregnancy

Key summary:
Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.