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# Subclinical hypothyroidism

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Subclinical hypothyroidism is a common condition associated with a raised thyroid stimulating hormone and a normal serum free thyroxine affecting about 10% of females over age 55 years. The most common cause is autoimmune thyroid disease and 2.5% of patients with subclinical hypothyroidism progress to clinically overt hypothyroidism each year. The rate of progression is higher in patients with anti-thyroid peroxidase antibodies and higher thyroid stimulating hormone levels. Only a small proportion of patients with subclinical hypothyroidism have symptoms and although there is some debate in the literature about which patients should be treated, the National Institute for Health and Care Excellence clinical knowledge summaries give clear recommendations. There is an increased risk of cardiovascular disease in patients with subclinical hypothyroidism it is uncertain whether treatment with levothyroxine reduces this risk. When deciding whether to treat subclinical hypothyroidism consider the patient's age, symptoms, presence of anti-thyroid peroxidase antibodies, thyroid stimulating hormone levels and risk factors such as cardiovascular disease.

## The GP curriculum and subclinical hypothyroidism

Clinical module 3.17 Care of people with metabolic problems states that a GP should be able to:

- Demonstrate an understanding of how common endocrine or metabolic disorders such as diabetes mellitus, thyroid or reproductive disorders can present
- Biomechanical tests can be diagnostic and often necessary for monitoring metabolic and endocrine diseases so it is important for GPs to know which tests are useful in a primary care setting and how to interpret these tests and understand their limitations

## Definition

Subclinical hypothyroidism (SCH) is defined by an elevated thyroid stimulating hormone (TSH) but normal serum free thyroxine (T4) and triiodothyronine (T3) concentration. Clinical symptoms are usually absent but in patients with TSH above 10 mIU/L symptoms are more often present (NICE, 2018; Peeters, 2017).

## Epidemiology

SCH is common with a prevalence of approximately 3-8%. Prevalence typically increases with age and it is more common in women (Fatourechi, 2009, Lowth, 2014, McCarthy et al., 2016). For male and female patients in their sixties the prevalence is similar with a combined prevalence of 10% (Fatourechi, 2009). Antithyroid antibodies are detected in approximately 80% of patients with SCH (Fatourechi, 2009).

## **Aetiology**

The most common cause is autoimmune thyroid disease however previous radioiodine therapy, thyroid surgery and external radiation therapy can also result in SCH (Fatourech, 2009).

## **Subclinical hypothyroidism and association with other diseases**

### **Cardiovascular disease**

There is a known link between cardiovascular disease (CVD) and subclinical hypothyroidism (Fatourech, 2009, Rodondi et al., 2010, Tseng et al., 2012, Adamarczuk-Janczyszyn et al., 2016, Tng, 2016, Carbotta et al., 2017, Delitala et al., 2017, Redford et al., 2017). A meta-analysis of individual participant data from 11 prospective cohort studies with 55,000 participants demonstrated that the risk of fatal and nonfatal events of coronary heart disease increased with higher TSH levels, particularly those greater than 10 mIU/L (Rodondi et al., 2010). Another cohort study of 115,746 participants demonstrated that adult Taiwanese patients with SCH had an increased risk for all-cause mortality and CVD death (Tseng et al., 2012). Multiple observational studies have demonstrated a significant association between SCH and CVD however data is lacking from randomised control trials for the treatment of SCH with levothyroxine and the effect on the long term clinical outcomes of cardiovascular disease (Peeters, 2017).

### **Dyslipidaemia**

There have been other studies which have looked specifically at the relationship between increased TSH and dyslipidaemia (Biondi et al., 2008). One study compared obese women aged 50 to 70 years: 100 women with SCH, 45 with overt hypothyroidism and 42 with normal TSH levels (Adamarczuk-Janczyszyn et al., 2016). Total cholesterol, low-density lipoprotein (LDL)-cholesterol and triglyceride concentrations were higher in the SCH group compared with controls and these decreased after treatment with levothyroxine. Furthermore both systolic and diastolic blood pressure decreased significantly after treatment. Other studies also support the benefit of improving lipid profiles in patients with SCH treated with levothyroxine (Zhao et al., 2016). Another study found that in SCH female patients with positive thyroid peroxidase antibodies (TPOAb), their total cholesterol, LDL cholesterol and triglycerides were significantly raised (Srivastava et al., 2017).

### **Nonalcoholic fatty liver disease**

One study demonstrated that in patients with significant SCH (TSH levels greater than 10 mIU/L) and those with mild SCH (TSH 4.2 – 10mIU/L) with dyslipidaemia, who received thyroxine replacement, experienced decreases in the prevalence of non-alcoholic fatty liver disease (NAFLD) and serum ALT levels. This suggests that in SCH patients with NAFLD, appropriate treatment with levothyroxine may improve their NAFLD (Liu et al., 2017).

## Clinical features

For patients diagnosed with SCH symptoms are usually milder than patients with overt hypothyroidism and tend to increase in both number and severity with increasing levels of TSH (Peeters, 2017). Elderly patients are reported to have fewer symptoms than younger patients. A summary of the symptoms and signs observed in SCH is outlined below (Box 1). The key features of the clinical assessment of a patient with suspected SCH are summarised in Box 2.

### Box 1 and 2

## Clinical management

### Investigations

Request thyroid function tests, which include thyroid stimulating hormone (TSH normal range 0.20 – 4.00 mIU/L) and free thyroxine (FT4 normal range 10.0 – 20.0 pmol/L). Suspect SCH if the TSH is elevated above the normal range and FT4 is in the normal range.

The National Institute for Health and Care Excellence (NICE) clinical knowledge summary (CKS) guidelines advise repeating TSH and FT4 approximately 3-6 months after the initial result to exclude transient causes of raised TSH (NICE, 2018). NICE also recommend checking TPOAb if autoimmune thyroid disease is suspected. The European Thyroid Association (ETA) guideline on the management of subclinical hypothyroidism considers TPOAb to be the most sensitive serological test for thyroid autoimmunity in SCH (Pearce, 2013). ETA recommend that patients with a raised serum TSH and FT4 within the reference range should have repeat TSH, FT4 and TPOAb after a 2 to 3 month interval. Repeat testing of TPOAb is not recommended and does not enhance the monitoring of patients with SCH. Neck ultrasound scan (USS) is not routinely recommended.

### When to treat with levothyroxine?

Many patients with SCH do not need treatment. NICE treatment recommendations are based on the TSH result and characteristics of the patients and are summarised in box 3.

### Box 3

### Levothyroxine initiation and titration

For most people 50-100 micrograms of levothyroxine once daily is an appropriate starting dose. This should be adjusted in increments of 25-50 micrograms every 3-4 weeks according to clinical response. The usual maintenance dose is 100-200 micrograms once daily. For people aged over 50 years and people with cardiac disease or severe hypothyroidism the recommendation is 25 micrograms once daily, adjusted in increments of 25 micrograms every 4 weeks according to clinical response. After initiation or a change in levothyroxine dose TSH should be checked within 6-8 weeks (Chakera et al., 2012). Clinicians should aim for an appropriate dose of levothyroxine to maintain a stable TSH level in the lower half of the reference

range (0.4 – 2.5 mIU/L). Once this is achieved check TSH at 4-6 months and annually thereafter. Advise patients to take levothyroxine at least 30 minutes before breakfast, caffeine-containing liquids such as tea or coffee and any other drugs. The NICE CKS guidelines outline contraindications and cautions, adverse effects and drug interactions which can be located easily online (NICE, 2018). Box 4 outlines when to refer or discuss a patient with SCH.

#### Box 4

### Prognosis

Without treatment 37% of people with SCH may revert spontaneously back to normal (LeFevre, 2015). Approximately 2-5% of people with SCH develop overt hypothyroidism and this is more likely with higher levels of TSH (greater than 10 mIU/L) and positive thyroid autoantibodies (LeFevre, 2015). The annual rate of progression for patients with both anti-thyroid antibodies and raised TSH is 4% and for raised TSH alone 2-4%. In patients with anti-thyroid antibodies alone 1-3% progress to overt hypothyroidism (Cooper et al., 2012).

#### Case Study 1.

A Caucasian female in her sixties with a 10-month history of abdominal bloating worse after eating wheat but without any change in bowel habit, dysphagia or vomiting presents at a routine appointment. Weight is unchanged and abdominal examination is normal. Blood tests (full blood count, thyroid function tests, Ca125, coeliac screen) and an urgent ultrasound scan of the abdomen and pelvis are requested.

The blood tests are normal expect for abnormal thyroid function tests. The ultrasound shows gallstones and fatty liver changes but is otherwise normal. The patient subsequently has a laparoscopic cholecystectomy.

The thyroid function tests reveal a TSH of 19.4 mIU/L (0.20 – 4.00) and a T4 of 11.0 pmol/L (10.0 – 20.0). At follow up the patient reports a two-year history of low energy, tiredness, feeling the cold and low libido. Her weight has remained stable with a normal bowel habit and a menopause at age 50. There is a family history of laryngeal cancer affecting her mother who also takes levothyroxine following a partial thyroidectomy. There is no family history of any autoimmune disease.

On examination blood pressure is 198/96 mmHg, pulse is regular at 73 beats per minute and BMI 29.1 kg/m<sup>2</sup>. Visual acuity, fundoscopy and neck examination are normal with no goitre or cervical lymphadenopathy.

Amlodipine is prescribed for blood pressure. Repeat thyroid function tests, including thyroid peroxidase antibodies, urea and electrolytes, liver function tests, full lipid profile and haemoglobin A1c are requested.

Results reveal a TSH of 33 mIU/L (0.20 – 4.00), a T4 of 10.4 pmol/L (10.0 – 20.0) and thyroid peroxidase antibodies of 582 iu/mL(<100). The total

cholesterol was 5.7 mmol/L with normal urea and electrolytes and liver function tests.

Levothyroxine 25 micrograms once a day is started. Amlodipine is further increased to 10mg once a day as the follow blood pressure is 148/74 mmHg. Her QRISK2 cardiovascular disease 10-year risk score is calculated to be 8.97% and a statin is not therefore indicated.

Cholesterol levels may be elevated in hypothyroidism and decrease with Levothyroxine treatment; coexistent hypothyroidism and statin therapy may increase the risk of myopathy and rhabdomyolysis.

Six weeks after initial treatment the TSH has reduced to **13.1** mIU/L and the T4 to 12.7 pmol/L. The dose of levothyroxine is increased to 50 micrograms daily and repeat thyroid function tests planned 6 weeks later. Her repeat blood pressure was 126/74 mmHg and Amlodipine 10mg daily is continued.

#### Key points

- Subclinical hypothyroidism (SCH) is a common condition
- SCH is defined as a raised TSH and normal T4 and T3, clinical symptoms are usually absent but in patients with TSH above 10 mIU/L symptoms are more often present
- Symptomatic patients are more likely to have significantly elevated TSH and positive thyroid peroxidase antibodies
- The associated risks of SCH include cardiovascular disease (CVD), dyslipidaemia and non-alcoholic fatty liver disease
- The associated risks may improve with Levothyroxine treatment of SCH although there is uncertainty about the long-term outcomes of CVD
- NICE recommend treatment of SCH in patients with a TSH greater than 10 mIU/L under age 70 years
- In patients under age 65 years with symptoms suggestive of hypothyroidism and a TSH between 4-10 mIU/L, consider a trial of levothyroxine

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Box 1. Symptoms of subclinical hypothyroidism
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- |   |
|---|
| <ul style="list-style-type: none"><li>• Fatigue</li><li>• Muscle weakness</li><li>• Weight gain</li><li>• Cold intolerance</li><li>• Constipation</li><li>• Depression, impaired concentration, memory</li><li>• Menstrual irregularities</li><li>• Dry skin, reduced body and scalp hair</li></ul> |
|---|



## Box 2. Clinical assessment of the patient

### History

- Ask about the common symptoms listed in box 1
- Family history of thyroid or autoimmune disease.
- Personal history of autoimmune disease.
- Radiotherapy to the head and neck
- Radioiodine treatment or previous surgery for hyperthyroidism
- Iodine deficiency
- Drug use (e.g. Amiodarone/Lithium)

### Examination

- Height, weight and BMI
- Blood pressure
- Pulse rate
- Examine the thyroid gland, looking for any obvious goitre
- Cervical lymph node examination

## Box 3. Summary of NICE Recommendations for management of SCH

### **If TSH is greater than 10 mIU/L and FT4 is normal**

- Start treatment (even if asymptomatic) with levothyroxine if aged 70 years or younger
- In older people (especially over 80 years) monitor the patient and generally avoid hormonal treatment

### **If TSH is between 4 and 10 mIU/L and FT4 is normal**

- In people aged less than 65 years with symptoms suggestive of hypothyroidism consider a trial of levothyroxine and assess response at 3-4 months
- If there is no improvement in symptoms stop the levothyroxine

### **Follow up of people with SCH who are started on levothyroxine**

- Reassess symptoms, if improvement, lifelong treatment may be considered
- If symptoms have not improved or they have had adverse effects, stop levothyroxine after a 3-6 month trial
- Once a stable TSH has been reached, in the lower half of the reference range (0.4-2.5 mIU/L), TSH should be measured at least annually
- If lipids were elevated at initial assessment, recheck to see if they have improved or whether they need treatment for this

### **Follow up of people with SCH who are NOT started on levothyroxine**

- If TSH has normalised without treatment, no further testing is needed if the person is asymptomatic, has negative autoantibodies and does not have a goitre
- If TSH remains elevated, arrange TFTs every 6 months for the first 2 years

then annually

- Arrange annual TFTs in people with SCH who are thyroid peroxidase antibody (TPOAb) positive or have a goitre
- Arrange repeat TFTs every 3 years in people with SCH who are TPOAb negative
- If lipids were elevated at initial assessment recheck these to see if a person needs treatment for this
- 

Source: NICE, 2018

#### Box 4. NICE recommendations on when to refer patients with SCH

- Suspected subacute thyroiditis (de Quervains' thyroiditis) – painful swelling of the thyroid gland thought to be caused by a viral infection
- Goitre
- If malignancy is suspected refer via two-week wait criteria
- If there is an associated endocrine disorder such as Addison's disease (do not start thyroid replacement as this can precipitate an adrenal crisis)
- Adverse effect from levothyroxine
- Are female and planning a pregnancy
- Pre-existing cardiac disease
- Atypical thyroid function tests
- Have an uncommon cause of hypothyroidism e.g. drug induced (amiodarone)
- Persistently raised TSH despite adequate treatment

Source: NICE, 2018