Section A-Research paper

An Overview on Subclinical hypothyroidism (SCH)

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Abstract

Background: Subclinical hypothyroidism (SCH) is biochemically defined as elevated levels of thyroid-stimulating hormone (TSH) with normal levels of free thyroxine (fT4), while controversiesexist on the limits of the TSH reference range. The prevalence of SCH is large and ranges between 3% and 18% in the adult population, with women, elderly persons, and iodine sufficient populations being affected more often. The most common cause of SCH is chronic autoimmune thyroiditis associated with antithyroid peroxidase antibodies (Hashimoto's thyroiditis), Individualswith SCH are often asymptomatic, but clinical manifestations can include non-specific complaintsor symptoms similar to those seen in overt hypothyroidism, such as fatigue, weakness, weight gain,cold intolerance, and constipation. Adverse clinical effects of overt thyroid disorders are well known, and given the multiple actions of thyroid hormones on the heart, the vessels, bones and brain, long-term adverse outcomes could be suspected even in subclinical dysfunction.

Keywords: Subclinical hypothyroidism

Introduction

Subclinical hypothyroidism (SCH) is defined as an increased concentration of thyroid-stimulating hormone (TSH) with a normal circulating level of thyroid hormones (free T3 and T4). SCH, the mildest form of hypothyroidism, lacks the specific signs and symptoms of clinical hypothyroidism **(Daya, et al., 2022).**

The prevalence of SCH is between 4% and 20% in the general population and higher in women than in men and from 11% to 17% in elder populations and progresses to overt hypothyroidism in approximately 2% to 5% of cases annually **(Razvi, et al., 2018).**

The most common cause of SCH is chronic autoimmune thyroiditis associated with antithyroid peroxidase antibodies (Hashimoto's thyroiditis), Individuals with SCH are often asymptomatic, but clinical manifestations can include non-specific complaints or symptoms similar to those seen in overt hypothyroidism, such as fatigue, weakness, weight gain, cold intolerance, and constipation **(Biondi and Cooper,2006).**

Adverse clinical effects of overt thyroid disorders are well known, and given the multiple actions of thyroid hormones on the heart, the vessels, bones and brain, long-term adverse outcomes could be suspected even insubclinical dysfunction. **(Cooper and Biondi,2012).**

Table (1): An overview of the level of evidence on the association between SCH and various clinical conditions. **(Gencer, et al.,2012).**

Strength of association	Benefit of treatment	TSH 4.5–9.9 mIU/l	TSH ≥10 mIU/l
Progression to overt hypothyroidism.	Good	stronger	Effective, especially if TSH ≥10 mU/l
Elevation in serum total cholesterol andLDL.	**Fair**	**Stronger**	**insufficient**
Risk of coronary heart disease.	**insufficient**	**Stronger**	**No evidenceRisk of**
congestive heart failure	**insufficient**	**Stronger**	**No evidenceCardiac**
dysfunction	**insufficient**	**insufficient**	**insufficient Systemic**
symptoms of hypothyroidism	**insufficient**	**insufficient**	**insufficient**
Neuropsychiatric symptoms (e.g.,depression, cognitive dysfunction)	**insufficient**	**insufficient**	**insufficient**
Muscle strength.	**insufficient**	**insufficient**	**insufficient**
Fatigue.	**insufficient**	**insufficient**	**insufficient**
Risk of Treatment Development o SCH.			**14%–21%**

LDL = low-density lipoprotein cholesterol; TSH = thyroid-stimulating hormone

Natural course and progression to overt hyperthyroidism:

Individuals with SCH are at risk for progression to overt thyroid dysfunction with an average yearly progression rate of 2% to 6% and an increased risk in females, individuals with higher levelsof TSH, and in the presence of antithyroid peroxidase antibodies, although those without antithyroid peroxidase antibodies have also a higher risk of progression **(Vanderpump, et al.,1995).**

In contrast, TSH levels normalize in 15% to 65% of those with a single elevated TSH without treatment, overfollow-up periods going from 1 to 6 years, and the likelihood of spontaneous recovery is higher with TSH levels <10 mIU/l. **(Somwaru, et al.,2012).**

TSH levels vary throughout the day and are highest at night, and considerable variations within the same person over months can occur that can be accentuated by sleep deprivation or exercise **(Surks, et al.,2005).**

Serum TSH is known to increase with age, while this increase might not be associated with mortality and might even be associated with longevity as suggested by the Leiden 85+ Study that prospectively followed599 individuals from age 85 years through age 89 years **(Waring, et al.,2012).**

A longitudinal study of patients over the age of 55 years with SCH found an incidence rate of overt hypothyroidism at about 10 cases per 100 patient-years.15 The incidence rate was greater in patients with higher TSH levels, with 1.8 cases per 100 patient-years in patients with TSH 5.0–9.9 mIU/l, ascompared to 19.7 cases per 100 patient-years in those with TSH 10.0–14.9 mIU/l. Interestingly, during the mean follow-up period of 32 months, 37% patients with SCH, in the study, normalisedtheir thyroid function without treatment **(Diez and Iglesias,2004).**

Other reasons for persistent or transient TSH elevation with normal fT4 levels in the absence of thyroid pathologies include the recovery phase after major illness (euthyroid sick syndrome), obesity, adrenal insufficiency, TSH-assay problems (i.e., presence of heterophilic antibodies), medications (i.e., amiodarone, sertraline, lithium, tyrosine-kinase inhibitors, etc.), chronic renal failure, central hypothyroidism, or in rare cases mutations leading to the inactivation of the TSH receptor **(Cooper and Biondi,2012).**

Diagnosis of SCH:

Most patients with SCH don't present with classical symptoms and signs of hypothyroidism.The diagnosis of SCH, which is based on laboratory tests, is usually straight forward; a serum TSH level above the

normal laboratory reference range, alongside a FT4 within the reference range suggests the diagnosis. The degree of SCH is often described as mild (TSH<10 mu/L) or severe (TSH 10 mu/L or more). When interpreting the laboratory results, one must consider various physiological and pathological factors that may affect serum TSH levels. For example, TSH secretion follows a diurnal rhythm with peak levels at night and trough levels during the afternoon; therefore, the TSH result may vary depending upon the timing of the blood test **(Roofbeam, et al., 2010).**

It is also well known that TSH levels progressively increase with age, with some experts suggesting that this phenomenon represents adaption of the hypothalamus- pituitary-thyroid axis to ageing, Furthermore, ethnicity has also been shown to influence serum TSH levels, with higher TSH levels in Caucasians than in Blacks or Hispanics **(Surks and Boucai,2010).**

This is at least partly related to different genetic make-up, as several genetic polymorphisms have been recently shown to be associated with increased serum TSH levels in individuals without thyroid disorders **(Porcu, et al.,2013).**

Finally, it has been shown that the variation in the TSH levels in an individual over time is much narrower than the population- based reference range, suggesting that each individual has a TSH set point. Therefore, a deviation from that set point, despite being within the population based reference range, may be abnormal for the individual **(Andersen, et al.,2012).**

There are several other conditions associated with a raised serum TSH and normal FT4 apart from subclinical hypothyroidism (Table 2). The presence of heterophile or human anti-animal antibodies can interfere with TSH assay showing spuriously elevated level of serum TSH **(Koulouri, et al,.2013).**

Furthermore, recent studies have found that about 1.5% patients showing thyroid function tests consistent with subclinical hypothyroidism actually have circulating macro-TSH, which is a biologically inert large molecular complex of TSH and immunoglobulin **(Hattori, et al.,2015).**

Non-thyroidal illness and thyroiditis (subacute, painless or postpartum) can also lead to transient changes in TSH levels. In addition, TSH may be elevated in a patient with untreated Addison's disease and this returns to normal following treatment with glucocorticoid replacement. Therefore, Addison's disease must be suspected in a patient with non-specific symptoms, with raised TSH, if the symptoms worsen after the initiation of levothyroxine treatment **(Hattori, et al.,2015).**

Resistance to thyroid hormone due to mutations in the thyroid hormone receptor b gene is an autosomal dominant syndrome often associated with raised TSH and variable levels of FT4; however, most patients with this condition will have FT4 above or towards the upper end of the reference range **(Hattori, et al.,2015).**

In patients with subclinical hypothyroidism, testing for thyroid peroxidase antibodies (TPO-Ab) is useful because the presence of TPO-Ab confirms autoimmunity as the aetiology of subclinical hypothyroidism. Furthermore, TPO-Ab positivity also has a prognostic value in predicting progression to overt hypothyroidism **(Madathil, et al.,2015).** .

Does treatment with levothyroxine help?

RCTs suggested an improvement in tiredness with levothyroxine treatment. beside some evidence for beneficial effects of levothyroxine in lipid profile, features in echocardiography and other cardiac imaging, and arterial stiffness **(Table3) (Madathil, et al.,2015).**

A large retrospective observational study of the UK general practice research database has shown that levothyroxine may reduce the risk of fatal and nonfatal coronary heart disease events in younger patients (age 40–70 years) with subclinical hypothyroidism; however, similar beneficial effect was not seen in patients older than 70 years **(Razvi, et al.,2012).**

A large-scale cohort study of the Danish national registries found no evidence of reduction in myocardial infarction, cardiovascular deaths or all-cause mortality with levothyroxine treatment in patients with subclinical hypothyroidism, except all cause mortality was reduced in patients under the age of 65 years **(Andersen, et al.,2015).**

Furthermore, another cohort study of the Danish national registries revealed no benefit nor harm from levothyroxine use in patients with subclinical hypothyroidism and established cardiovascular disease in terms of all-cause mortality, major adverse cardiac events, stroke and all-cause hospital admissions.Finally, a randomised controlled trial in elderly patients (above the age of 65 years) showed no benefit of levothyroxine treatment in subclinical hypothyroidism to improve cognitive function **(Andersen, et al.,2011).**

Table (2): ***Differential diagnosis of SCH: Conditions associated with raised TSH and normal Free T4*** **(Cooper and Biondi,2012).**

Conditions	Characteristic features	Further investigations
Non-thyroidal illness.	*Recent acute illness. (e.g. pneumonia or myocardial infarction).*	*Repeat tests two to three months after recovery from illness.*
Thyroiditis (subacute, painless or postpartum).	*History of recent viral illness and neck tenderness(subacute thyroiditis) Delivery in the past six months (postpartum thyroiditis).*	*Repeat tests after two to three months.*
Addison's disease.	*Fatigue, low blood pressure, postural hypotension, weight loss, skin pigmentation; worsening of symptoms following initiation of levothyroxine.*	*Check 9 a.m. serum cortisol or perform short synacthen test*
Resistance to thyroid hormone (THR b gene mutation).	*Often asymptomatic but may present with symptoms of thyrotoxicosis or hypothyroidism.*	*Check thyroid function tests in first degree relatives; TRH test; mutation screening of the thyroid hormone receptor b gene.*
Non-concordance with levothyroxine Treatment.	*History of intermittently missing levothyroxine dose; raised TSH despite high dose of levothyroxine.*	*Review prescriptions; occasionally thyroxine absorption test.*

Potential risks of levothyroxine treatment:

As in overt hypothyroidism, levothyroxine treatment in SCH is safe provided that thyroid function is monitored regularly and the dose of levothyroxine is adjusted to keep the TSH level withinthe normal reference ranges. However, both over-treatment and under-treatment are common in patients on levothyroxine, and the over-treatment leading to the suppression of TSH can increase the risks of atrial fibrillation and osteoporosis, particularly in elderly patients **(Turner, et al., 2011).**

Table(3): ***Summary of potential long-term consequences associated with SCH, level of evidence and evidence for treatment benefit.***

Consequence	*Highest Evidenc eLevel*	*Evidence for association*	*Evidence for Treatment*
Coronary heartdisease	***Meta-analysis***	***Yes, but only in younger patients; Stronger association in patients with high TSH levels***	***Some evidence for benefit in younger patients***
Heart failure	***Meta-analysis***	***Yes, but only in patients with TSH 10mu/l***	***No***
Cerebrovascular diseases	***Meta-analysis***	***Yes, but only in younger patients ;stronger association in patients with high TSH levels***	***No***
Adverse lipid profile	***Meta-analysis***	***Yes***	***Some evidence***
Type 2 DM and its complications	***Meta-analysis***	***Yes***	***No***
Osteoporotic fractures	***Meta-analysis***	***No***	***Not applicable***
Dementia and impaired cognition	***Meta-analysis***	***No, although possible association in younger patients***	***No***
Impaired neuro psychological function and quality of life	***Cohort studies***	***Uncertain***	***No***

Patients with SCH on levothyroxine are likely to be more prone to overtreatment and associated adverse effects than those with overt hypothyroidism. This is supported by a large retrospective cohort study of the UK-based general practice research database, which showed that as levothyroxine treatment is being started at progressively lower TSH values over the study period (2001– 2009), an increasing proportion of the treated patients had suppressed TSH. **(Taylor, et al.,2014).**

long-term complications of untreated SCH:

Cardiovascular risk and heart failure:

Thyroid hormones are well known to act on the heart and vasculature, and the impact of subclinical thyroid dysfunction on the cardiovascular system has been an important topic of research in recent years. Subclinical hypothyroidism can lead to impaired systolic and diastolic cardiac function as well as vasculardysfunction with increased vascular stiffness and endothelial dysfunction **(Razvi, et al.,2017).**

A pooled analysis of individual participant data has found an increase in heart failure events in individuals with a TSH of 10 mIU/l and higher compared to euthyroid controls with a hazard ratio (HR) 1.86 (95% confidence interval [CI] 1.27–2.72). **(Gencer et al.,2012). (Table 2).**

SCH has also been associated with an increased risk of fatal and non-fatal coronary heart disease (CHD) events **(Rodondi, et al.,2010).**

The increased cardiovascular risk that is primarily observed with TSH levels of 10 mIU/l and above can be explained by several mechanisms. TSH has known effects on the endocrine system, and studies have shown elevated total cholesterol and a higher prevalence of dyslipidaemia in individuals with SCH**(Monzani, et al.,2014).**

A systematic review including 13 heterogeneous studies concluded that thyroxine treatment leads to a reduction in serum total cholesterol and LDL cholesterol in persons with subclinical hypothyroidism, this finding has been confirmed in subsequent randomised controlled trials (RCTs**) (Razvi, et al.,2017).**

Evidence on the association of subclinical hypothyroidism with increased blood pressure is controversial. Ina cross-sectional study, Liu et al. found an increased blood pressure in these individuals **(Liu, et al.,2010).**

An interventional study including 56 women with subclinical hypothyroidism found an elevated systolic and diastolic blood pressure, serum cholesterol and homocysteine levels compared to healthy controls, withnormalization of these factors after 18 months of levothyroxine therapy **(Adrees, et al.,2009).**

Other possible explanations for the increased cardiovascular risk in persons with subclinical hypothyroidism include increased carotid intima-media thickness, hypercoagulability, insulin resistance, oxidative stress, andendothelial dysfunction **(Razvi, et al.,2017).**

A reduction in carotid intima-media thickness and improvement of brachial artery endothelial function following thyroxine replacement in individuals with subclinical hypothyroidism has been shown **(Razvi, et al.,2017).**

In a small RCT, normalization of TSH levels by thyroxine replacement therapy led to an improvement in cardiac function, and recent findings based on retrospective administrative data suggested that thyroxine treatment leads to a reduction in ischemic heart disease in younger individuals, but not in persons aged 70 years or older **(Weaver, et al.,2012).**

Thyroid hormones have known effects on heart rate and cardiac excitability. In contrast to the increased risk of atrial fibrillation in patients with excess thyroid hormones, evidence on this association in individuals with SCH is conflicting, while recent observational data have suggested a protective effect of SCH on the development of atrial fibrillation **(Collet.,2012).**

Cerebrovascular disease

SCH has been shown to be associated with an increased risk of cerebrovascular diseasein younger patients. A recent meta-analysis of 17 observational studies (47,573 adult subjects; 3451 with SCH) found no overall increased risk of all stroke events (HR 1.05; 95% CI 0.91–1.21)or fatal stroke (HR 1.07; 95% CI 0.8–1.42) in individuals with SCH as compared to those with euthyroidism **(Chaker, et al.,2015).**

However, there was a significantly increased risk of fatal stroke in younger patients (under the age of 65 years) with SCH (HR 2.29; 95% CI 1.41–3.74), and a trend for a higher risk with increasing TSH levels **(Chaker, et al.,2015).**

Adverse metabolic parameters:

SCH has been shown to be associated with several adverse metabolic parameters, which may partly explain the increased cardiovascular and cerebrovascular risk in younger patients with SCH. A recent meta-analysis of 16 observational studies (included 41,931 adults; 4526 with SCH) found significantly increased levels of serum total cholesterol, LDL cholesterol and total triglyceride in patients with SCH compared to euthyroid individuals; serum HDL cholesterol levels were similar in the two groups **(Liu, et al.,2014).**

Another meta-analysis showed an association between type 2 diabetes and SCH, witha 1.93-fold (95% CI 1.66–2.24) increased prevalence of SCH in patients with type 2 diabetes as compared to a healthy population **(Han, et al.,2015).**

In addition, this study has suggested that SCH increases the risk of the development of diabetic complications, including diabetic nephropathy (OR 1.74; 95% CI 1.34–2.28), diabetic retinopathy (OR 1.42; 95% CI 1.21–1.67), peripheral vascular disease (OR 1.85; 95% CI 1.35–2.54) and peripheral neuropathy (OR 1.87; 95% CI 1.06–3.28). Finally, patients with SCH have also been shown to have higher plasma homocysteine (a risk factor for atherosclerosis) and insulin resistance (measuredby homeostatic index of insulin resistance; HOMA-IR) as compared to healthy individuals **(Yang, et al.,2015).**

One prospective cohort study found a higher prevalence but not incidence of metabolic syndrome in adults with SCH , while another large cohort study could not find a difference in weight change in these individuals **(Garin, et al.,2014).**

Neuropsychiatric symptoms:

An association between SCH and mood disorders including depression and increased anxiety , as well as a reduced quality of life have been suggested. Treatment failure for depression has been more commonly observed in patients with SCH **(Pae, et al.,2009).**

Impaired cognitive function:

Several studies have examined an association between SCH and impairment incognitive function. A recent meta-analysis of six prospective observational studies (7401 participants, 416 patients with dementia, mean follow-up period 64.6 months) showed no association between SCH and dementia, or decline in cognitive function. In contrast, another meta-analysis has suggested that younger patients (age <75 years) with SCH, particularly those with higher TSH levels, have an increased risk of impaired cognitive function and dementia,34 suggesting more research is required before conclusions can be drawn **(Rieben, et al.,2016).**

Musculoskeletal system and functional capacity:

Persons with SCH more often suffer from weakness and myalgia, and reduced musclestrength has been shown in these individuals **(Reuters, et al.,2009).**

Confirming this hypothesis, beneficial effects of levothyroxine replacement on strength measurements and cardiopulmonary exercise performance have been demonstrated. A possible mechanism for the lower exercise capacity could be higher oxygen requirements during exercise in people with SCH as well as a possible association with anaemia **(Ravanbod, et al.,2013).**

On the other hand, large cohort studies did not find a reduction in functional mobility or functional capacityassessed in elderly individuals with SCH, and persons with only mild elevations of TSH even revealed a slightly better mobility than euthyroid controls **(Virgini, et al.,2014).**

High TSH levels as seen in hypothyroidism have been shown to directly affect bone metabolism through inhibition of osteoclast formation and survival, osteoblast differentiation and expression of collagen type 1 **(Abe, et al.,2003).**

For SCH, an increased risk for hip fractures in men (multivariable-adjusted HR 2.31 [95% CI 1.25–4.27]) but not in women was demonstrated in a prospective cohort study including 3,567 participants with a median follow-up of 13 years **(Lee, et al.,2010).**

In contrast, another prospective study of 25,205 individuals from Norway did not show a significant association with hip or forearm fractures when the results were adjusted for age, BMI and smoking status except in a subgroup of women with TSH >4.0 mIU/l and negative antithyroid peroxidase antibodies, wherethe HR for hip fracture was 1.75 (95% CI 1.24–2.46) **(Svare, et al.,2013).**

SCH and GIT

Other clinical implications the influence of overt hypothyroidism on gastrointestinal mobility with symptoms such as constipation are well known. A recent study demonstrated impaired gastric motility and consecutivesymptoms in premenopausal women with SCH **(Canpolat, et al.,2013).**

Given the suggested associations between SCH and the metabolic syndrome, Chung et al. performed a cross-sectional study and found a dose-dependent relation between TSH levels and non- alcoholic fatty liver diseases in individuals with subclinical and overt hypothyroidism **(Chung, et al.,2012).**

SCH and blood:

To date, there is no strong evidence on the association between SCH and anaemia:persons with SCH had higher mean haemoglobin levels compared to their euthyroidcounterparts in one cohort study, but this finding was not significant **(Bremner, et al.,2012).** …

However, two RCTs have concluded that the addition of levothyroxine in subclinically hypothyroid patientswith iron-deficiency anaemia led to a more pronounced increase in haemoglobin and ferritin than treatmentwith iron salt alone **(Ravanbod, et al.,2013).**

Subclinical hypothyroidism and pregnancy:

For pregnant women, lower trimester-specific TSH reference ranges should be used due to the changes in thyroid physiology during pregnancy **(Wilson, et al.,2012).**

Thyroid hormones are crucial for the normal foetal maturation and brain development, and the foetus relies on placental passage of maternal thyroid hormones during the first trimester of pregnancy due to the immaturity of the foetal thyroid gland and the consecutive inability to produce sufficient thyroid hormones. Foetal consequences of maternal overt hypothyroidism including perinatal morbidity and mortality and neurological impairment are widely known, and SCH has also been associated with adverse outcomes during pregnancy. SCH affects 0.5% to 2.5% of women during reproductive age and can lead to higher rates of placental abruption, pregnancy loss, gestational hypertension, and severe preeclampsia**(Wilson, et al.,2012).**

An increased risk of preterm delivery has been found in subclinically hypothyroid women an might explain some of the neonatal complications seen in neonates born to those mothers, including neonatal respiratory distress and an increased risk of neonatal death **(Benhadi, et al.,2009).**

Summary

In summary, SCH is associated with an increased risk of cardiovascular and cerebrovascular morbidity and mortality, in younger patients and in those with high TSH levels (particularly TSH10 mu/L) . This association is partly explained by adverse lipid and other metabolic parameters, more prevalent in patients with SCH. In contrast, there is no convincing evidence to suggest that subclinical hypothyroidism is associated with an increased risk of impaired cognitive function, osteoporotic fractures, frailty, poor neuropsychological function and reduced quality of life **(Benhadi, et al.,2009).**

Recommendations for screening and treatment:

Due to the lack of large-scale RCTs examining relevant clinical outcomes, current screening and treatment recommendations are principally based on observational data small clinical trials with short follow-up durations and expert opinions. Screening recommendations vary widely across different medical societies and expert groups **(table 4) (Biondi and Cooper,2008).**

Overall, screening of the general population cannot be recommended and should likely be restricted to high- risk individuals including patients with autoimmune disorders, a personal or family history of thyroid disease, or those with potential symptoms **(table 4).**

Also, in asymptomatic pregnant women evidence for universal screening is equivocal, and most professional societies recommend a targeted screening strategy, e.g., in women coming from iodine insufficient areas or in those with morbid obesity, diabetes type 1, a family or personal history of thyroid disease or a history of abortion or preterm delivery **(Lazarus, et al.,2014).**

Due to the lack of evidence from randomised controlled trials to show that levothyroxine treatment can prevent associated cardiovascular and cerebrovascular adverse effects, its management remains controversial. However, in view of the associated longterm cardiovascular morbidity and mortality in patients with subclinical hypothyroidism, particularly in young patients and those with high TSH levels, the current guidelines from the American Thyroid Association/the American Association of Clinical Endocrinologists and the European Thyroid Association recommend treatment of subclinical hypothyroidism with levothyroxine if TSH is 10mu/L **(Lazarus, et al.,2014).** .

Table(4): *Recommendations for screening of subclinical hypothyroidism in asymptomatic adults* **(Blum, et al.,2013).**

Organisation	Screening recommendation
American Thyroid Association, American Association of Clinical Endocrinologists and The Endocrine Society	*Routine examination in all adults, including pregnant women or women wishing to become pregnant, especially if symptoms/signs compatible with thyroid dysfunction*
College of American Pathologists	*Women ≥50 years consulting a physician, all geriatric patients admitted to a hospital and at least every five years*
American Academy of Family Physicians	*Patients ≥60 years*
American College of Obstetrics and Gynecology	*High risk patients (autoimmune disorder, family history for thyroid disease).*
American College of Physicians	*Women >50 years with recent occurrence of symptoms compatible with thyroid disorder*
Royal College of Physicians	*No screening indicated*
U.S. Preventive Services Task Force	*Insufficient evidence for or against screening*
Swiss Society of Endocrinology and Diabetes	*Women, age ≥40 years, unspecific complaints, geriatric patients, patients at high risk: after therapy of overt hyperthyroidism, combined autoimmune syndrome, smokers*

The European guidelines recommend a more cautious approach in treating subclinical hypothyroidism in older patients above the age of 70 years. For persons with moderately elevated TSH concentrations between 4.5–10 mIU/l, TSH levels should be monitored every 6 to 12 months and treatment outside of a clinical trial is currently not recommended **(Helfand,2014).**

A pragmatic algorithm for management of SCH is shown in **Figure 1**. In new patients showing high serum TSH and normal FT4, other potential causes apart from SCH should be considered and excluded **(Table2).**

Thyroid function tests should be repeated in 2 to 3 months, as patients with transient thyroiditis and non-thyroidal illness may show spontaneous normalization of thyroid function **(Helfand,2014).**

In patients with persistent SCH, with TSH 10 mu/L, treatment with levothyroxine should be considered, particularly if the patient is young (<70 years), has symptoms of hypothyroidism and has other cardiovascular risk factors **(Helfand,2014).**

In patients with TSH<10 mu/L and symptoms of hypothyroidism, a trial of levothyroxine for three to six months to assess symptomatic benefit is worthwhile. In asymptomatic patients with TSH<10 mu/L, levothyroxine treatment is not indicated but thyroid function should be monitored annually in presence of TPO-Ab and every three years in absence of TPO-Ab **(Pearce, et al.,2013**

Current guidelines from the Swiss Society of Endocrinology and Diabetes recommend treatment of individuals with SCH according to a risk stratification taking into account a TSH level >10 mIU/l, the presence of goitre, antithyroid antibodies, cardiovascular risk factors or prevalent CHD, smoking, dyslipidaemia, clinical symptoms, ovulatory dysfunction or infertility, and pregnancy. **(Pearce, et al.,2013).**

In pregnant women with TSH levels above the trimester-specific TSH cutoffs and in women with infertility or wishing to become pregnant with TSH values of 2.5 mIU/l or higher, initiation of thyroxine replacement therapy is recommended **(Lazarus, et al.,2014).**

In patients starting levothyroxine, TSH should be checked regularly after initiation of treatment, and then annually, to ensure that TSH suppression does not occur **(Lazarus, et al.,2014).**

There is no evidence to support the use of liothyronine, combination of levothyroxine/liothyronine, or desiccated thyroid extract in subclinical hypothyroidism **(Lazarus, et al.,2014).**

All these recommendations are based on expert opinion in the absence of randomised clinical trials on the treatment effects of SCH on clinical outcomes **(Lazarus, et al.,2014).**

The Swiss guidelines recommend an initial treatment dose of 25 ug daily in persons aged above 50 years or with known CHD; in all other individuals, levothyroxine should be dosed at 50 to 75 μg daily at the

beginning of treatment with the goal of reducing the TSH level into the reference range **(Pearce, et al.,2013).**

The European Thyroid Association recommends similar thyroxine starting doses, with 25–50 ug daily in elderly individuals or those with cardiac disease, and weight-adjusted starting doses of approximately 1.5 μg/kg daily in all other persons **(Lazarus, et al.,2014).**

Before treatment is initiated, a follow-up blood test should be ordered after 3 to 6 months of the initial diagnosis given the high rate of spontaneous normalisation of elevated TSH levels **(Canaris et al.,2000).**

Risks of treatment have been mainly associated with overtreatment, which is reported in 14% to 21% of subclinically hypothyroid individuals on thyroxine replacement therapy **(Flynn, et al.,2010).**

Possible adverse effects from thyroxine include atrial fibrillation, angina pectoris, congestive heart failure, and symptoms associated with excess thyroid hormone such as nervousness and palpitations. Overtreatment can result in a decrease of bone mineral density and an increase in fracture risk **(Flynn, et al.,2010).**

In The future There is a clear need for high quality randomised controlled trials of levothyroxine replacement in subclinical hypothyroidism **(Flynn, et al.,2010).**

***Fig. (1): Subclinical Hypothyroidism Approach* (Amlashi and Tritos ,2016).**