deNovo Medica

Leader in digital CPD for Southern African healthcare professionals

Earn 3 free CEUs

Endocrine

Clinical issues in optimising thyroid treatment

Dr Salman Razvi
Endocrinologist
Newcastle University
United Kingdom

Click here – you need to watch the video in order to complete the CPD questionnaire.

Introduction

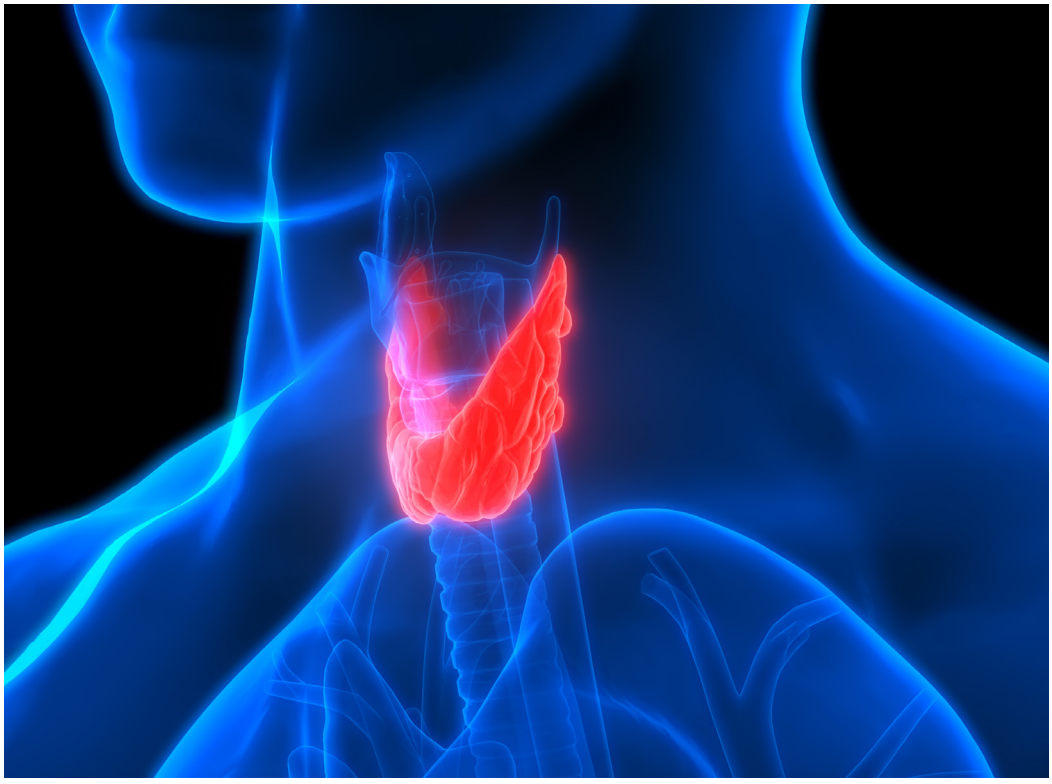
Thyroid disease is a common clinical problem encountered by all healthcare practitioners. Despite adequate treatment, some patients with hypothyroidism remain symptomatic, prompting many health professionals to question the treatments used and the recommended treatment targets. In addition, frustrated patients often turn to alternative medical supplements when their symptoms fail to improve on prescribed treatment.[1]

Evidence-based guidance on the many clinical aspects of managing patients with hypothyroidism are considered in this best practice review, informing general patterns of care that will enhance the management of patients suffering from this disorder.

LEARNING OBJECTIVES

You will learn:

- About the symptoms associated with hypothyroidism
- How to make an accurate diagnosis of hypothyroidism and assess severity of disease
- Evidence-based treatment recommendations for overt and subclinical hypothyroidism
- Factors that may interfere with thyroid function and L-thyroxine treatment.



This report was made possible by an unrestricted educational grant from Merck. *The content of the report is independent of the sponsor.*

MERCK

Symptoms of hypothyroidism

There is no single symptom or cluster of symptoms diagnostic of thyroid disease

Fatigue is one of the biggest reasons for a patient consulting a general practitioner. It is also the commonest symptom of hypothyroidism, prompting the checking of thyroid function.

Other symptoms attributable to hypothyroidism were studied in the Colorado Thyroid Disease Prevalence Study,[2] in which the percentage of euthyroid subjects compared with those with an elevated thyroid-stimulating hormone (TSH), or thyrotropin, level who reported each symptom was assessed (Figure 1). Of the associated symptoms, those more strongly associated with hypothyroidism were drier skin, poorer memory, slower thinking, weaker muscles, more muscle cramps, feeling colder and a deep voice.

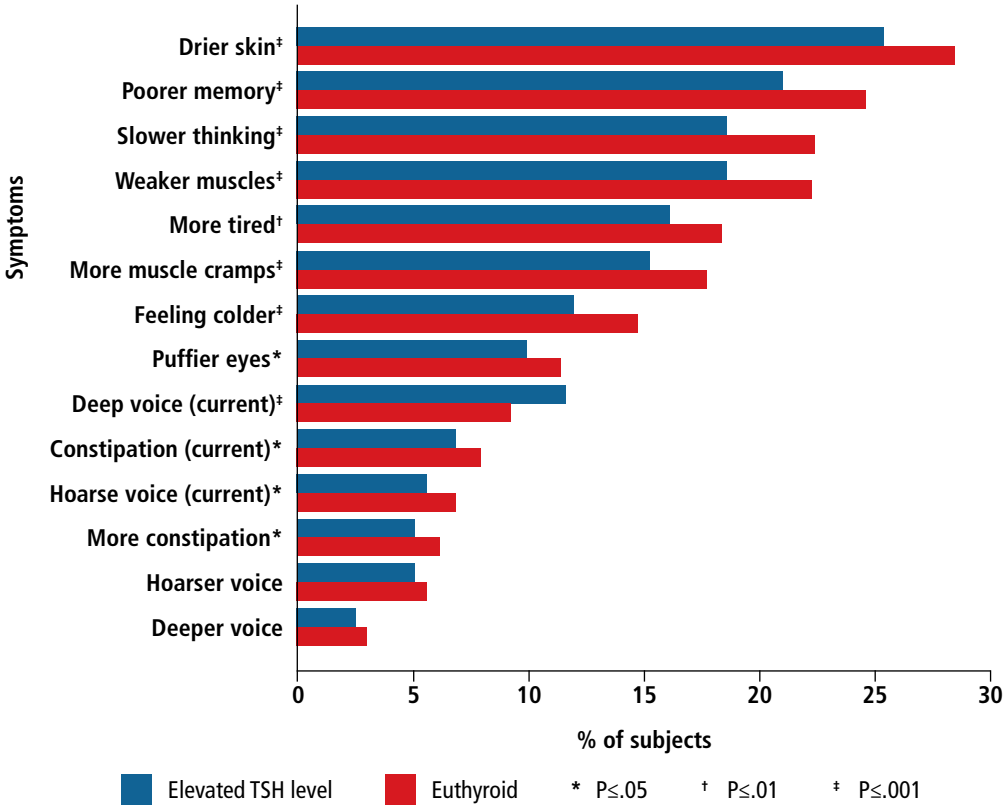


Figure 1. Symptoms and signs of hypothyroidism[2]

However, these and other minor symptoms also occur in people who have normal thyroid function. For example, when it comes to feeling more tired, the difference between people who have a normal TSH and those who have an elevated TSH is modest, indicating that just feeling tired by itself does not necessarily indicate that a patient has hypothyroidism. Symptoms arising from poor lifestyle are often attributed to thyroid disease.

There is no single symptom or cluster of symptoms diagnostic of thyroid disease; symptoms are non-specific, often with several other potential sources. This presents a challenge to both clinicians and patients looking for the source of these symptoms and their resolution.

Making an accurate diagnosis

Testing and interpreting TSH levels

TSH levels are a good marker of thyroid hormone levels. Figure 2 illustrates the relationship between the thyroid hormone, thyroxine (T4), and TSH incorporating physiological and statistical principles. The relationship is such that when free T4 levels change by a factor of 2 (either double or halve), TSH levels will change 100-fold, suggesting that the change in TSH levels will be large even when there are only small changes in T4 levels.[3]

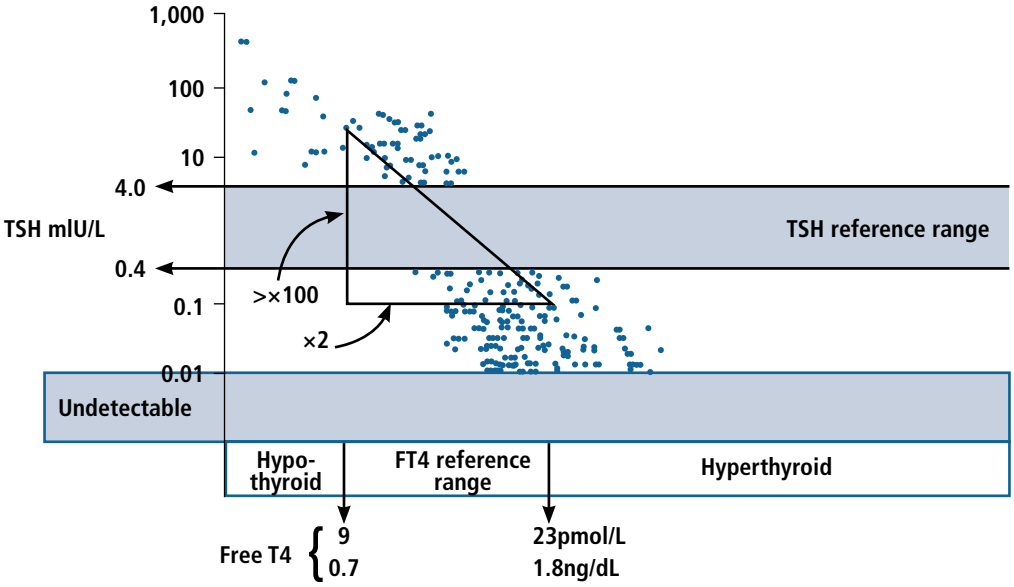


Figure 2. Log-linear relationship between TSH and T4[3]

In a young healthy adult with overt hypothyroidism, L-thyroxine can be initiated at full replacement doses based on body weight (1.6µg/kg/day)

Reference ranges for TSH levels (0.45-4.12mIU/l) have been derived from the National Health and Nutrition Examination Survey (NHANES) III study. Dr Razvi elaborates: "This reference range … is not based on symptoms and is not based on progression, but just on pure mathematics…" with the assumption, however, that the 2.5% of people with TSH <0.45mIU/l and the 2.5% of people with TSH >4.12mIU/l are abnormal. This is a statistical assumption that may not be relevant to the specific patient.[4,5]

Determining the severity of primary hypothyroidism

Thyroid hormone levels are used to determine the severity of primary hypothyroidism. Early in the course of progression, TSH levels increase abruptly while free T3 (triiodothyronine) and T4 levels generally remain normal. It is usually at this point that patients are diagnosed with subclinical hypothyroidism (Figure 3), despite not knowing what the normal T4 levels should be for that person. T4 levels decline much later than TSH levels, if they do at all, and T3 levels tend to be the last indicator of change.

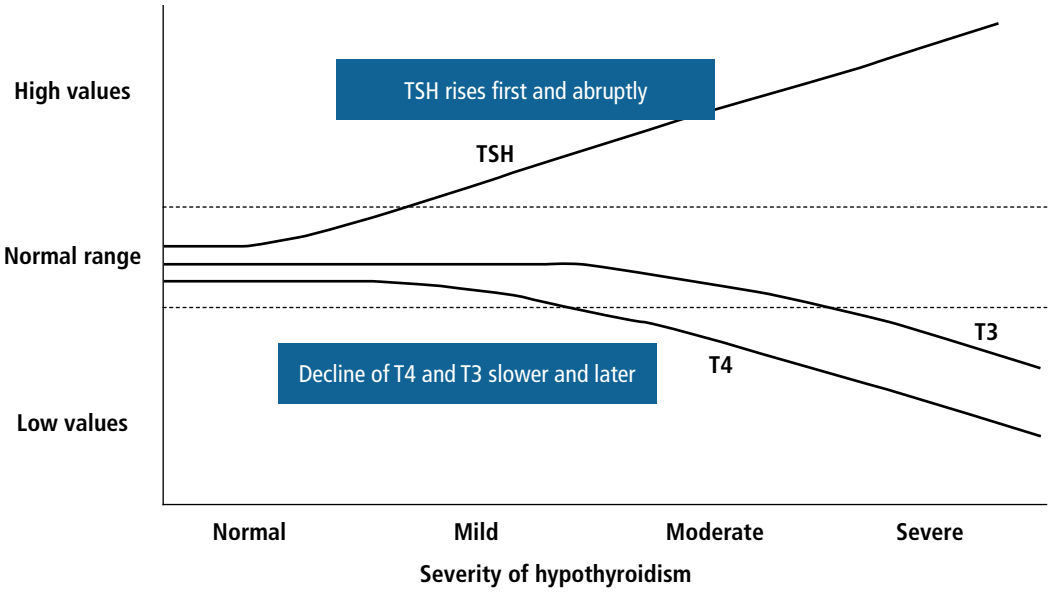


Figure 3. Severity of primary hypothyroidism as determined by thyroid hormone levels

Treating overt hypothyroidism

The 2015 Society for Endocrinology, Metabolism and Diabetes of South Africa, and Association of Endocrinologists of South Africa (SEMDSA/ACE-SA) guideline for the management of hypothyroidism in adults provides a useful treatment algorithm based on TSH measurement (Figure 4).[1]

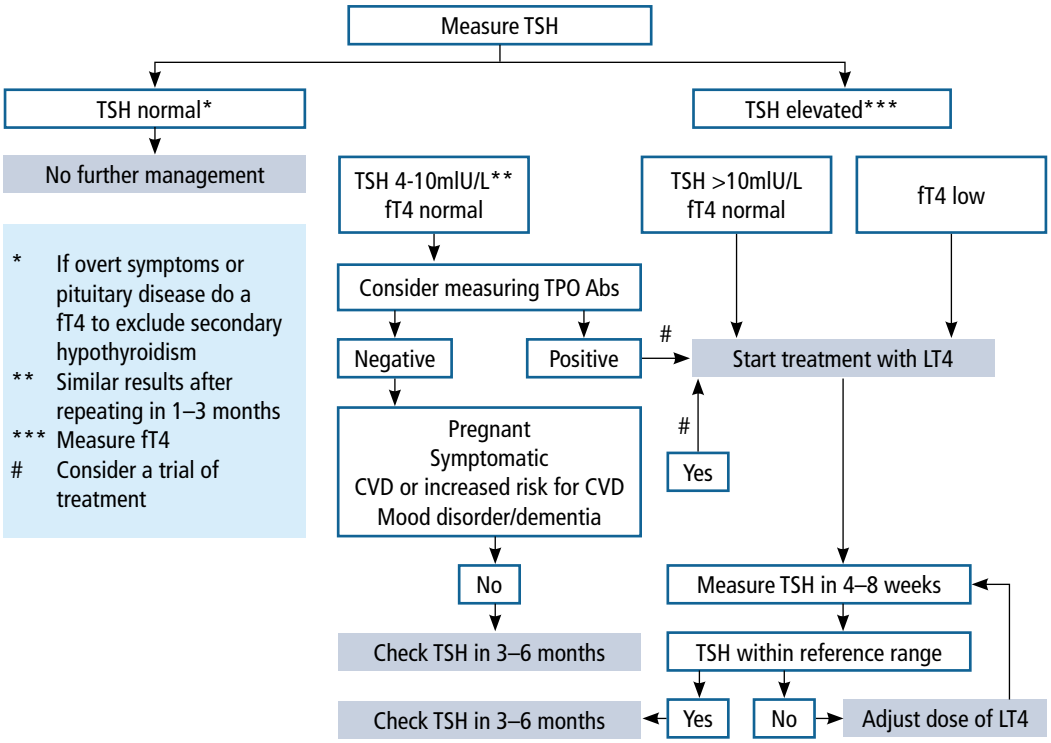


Figure 4. Algorithm for the management of a patient with hypothyroidism[1]

Dr Razvi cautions that slow L-thyroxine titration is particularly important in the patient older than 80 years

In a young healthy adult with overt hypothyroidism (high TSH and low free T4 levels), levothyroxine (L-thyroxine or LT4) can be initiated at full replacement doses based on body weight (1.6µg/kg/day). In older people with overt hypothyroidism and without evidence of coronary heart disease, it is preferable to initiate L-thyroxine at lower doses (50µg/day) and then gradually titrate upwards to full replacement doses (Table 1).

Dr Razvi cautions that slow L-thyroxine titration is particularly important in the patient older than 80 years. "You don't necessarily want to increase the metabolic rate and increase the oxygen requirements for their heart, particularly if they have a coronary artery lesion sitting there." In the patient with established coronary artery disease, it is better to treat that first before initiating thyroxine. If that is not possible for any reason, initiate L-thyroxine at very low doses (12.5µg/day) and up-titrate very, very slowly to reduce the risk of precipitating a myocardial infarction.

In the case of pregnancy and overt hypothyroidism, it is best to initiate full replacement doses as soon as possible, and titrate to the trimester-specific reference range. This is because the foetal thyroid gland does not begin to function until 10-12 weeks into pregnancy, and the foetus relies completely on the mother's thyroid hormone levels.

Table 1. L-thyroxine dosing recommendations

When initiating therapy in young healthy adults with overt hypothyroidism, begin treatment with full replacement doses (1.6µg/kg/day)
When initiating therapy in patients older than 60 years with overt hypothyroidism, without evidence of coronary heart disease, an L-thyroxine dose of 50µg/day should be considered
Evidence suggests that if you want to keep TSH at the lowest level for the intended dose, it is probably best to take L-thyroxine at least half an hour prior to breakfast.

Treatment failure on L-thyroxine

How common is abnormal thyroid function in the patient already using L-thyroxine? In a Birmingham study half of the patients using L-thyroxine had abnormal thyroid function tests (TFTs). Similarly, abnormal TFTs in patients using L-thyroxine were seen in the Colorado study[2] (40%) and NHANES III[4] (55%). There are several reasons why either low or high TSH levels while on treatment are so common among patients.

Drugs and food interfere with L-thyroxine levels[5]

Many food products, drugs and supplements affect absorption, metabolism and clearance of L-thyroxine. Dietary factors that reduce absorption of L-thyroxine include ingestion with a meal, grapefruit juice or Espresso coffee, as well as a diet high in fibre or soya products. The list of drug-drug interactions is very long and Dr Razvi highlights some examples of commonly used agents that affect absorption of L-thyroxine (Table 2).

Consider… taking L-thyroxine at a different time prior to increasing the dose or using a different formulation

Table 2. Common drugs and supplements affecting absorption of L-thyroxine

• Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
• Sucralfate
• Cation exchange resins (kayexalate)
• Oral bisphosphonates
• Proton pump inhibitors (PPIs)
• Raloxifine
• Multivitamins – particularly those containing iron or calcium
• Ferrous sulphate
• Phosphate binders (sevelamer, aluminium hydroxide)
• Calcium salts (carbonate, citrate, acetate)
• Chromium picolinate
• Charcoal
• Orlistat
• Ciprofloxacin
• H2 receptor antagonists.

Concomitant disease and thyroid function

Several concomitant diseases (and their treatment) may compromise thyroid function. Coeliac disease and pernicious anaemia reduce absorption of L-thyroxine. Amiodarone has massive amounts of iodine, approximately 500-fold more than the recommended daily intake, which completely compromises thyroid function. Much like amiodarone, lithium can cause both hypo- and hyperthyroidism.

If investigation into the reasons for abnormal TFTs despite treatment with L-thyroxine does not provide adequate answers, consider taking L-thyroxine at a different time prior to increasing the dose or using a different formulation.

Risks of over- and under-treatment

To date there are no randomised controlled trials investigating the risks of over- and under-treatment of thyroid disease, with current best evidence based on observational data. From a study in Scotland, those with low or high TSH levels while on L-thyroxine treatment had a higher risk of cardiovascular events and

arrhythmias. Those with low TSH levels had a higher risk of fractures.[6] Other observational data suggest that in populations where more thyroxine is being prescribed, there is also a higher risk of atrial fibrillation.[7]

Subclinical hypothyroidism

Consequences of not treating subclinical hypothyroidism

The potential risks of failing to detect thyroid disease early include progression to overt hypothyroidism, which is more likely in the patient with high TSH levels. Patients who test positive for thyroid peroxidase antibodies (TPOAbs) are 3-4 times more likely to progress to overt hypothyroidism than those who test negative. Younger patients may have an increased risk of heart disease, particularly if there are pre-existing cardiovascular risk factors such hypertension, diabetes and previous myocardial infarction, among others. While particularly the case with younger individuals, this is relevant to all those with suboptimal thyroid function; untreated non-specific symptoms impair quality of life (Table 3).

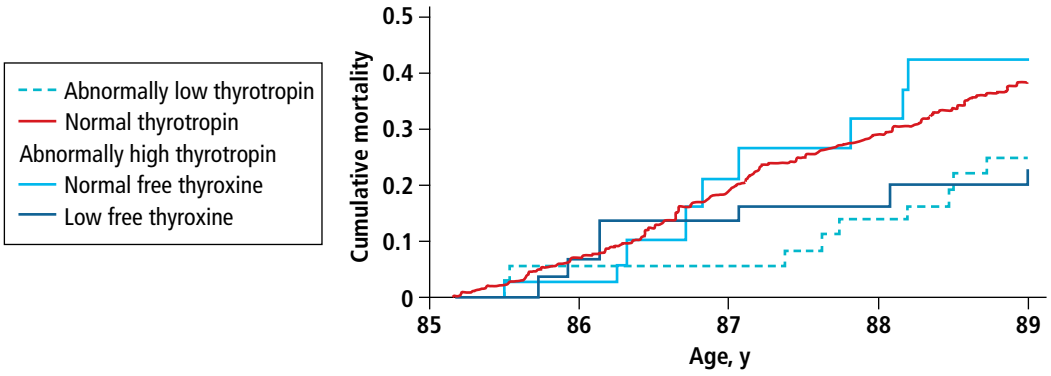
Younger patients may have an increased risk of heart disease, particularly if there are pre-existing cardiovascular risk factors

Table 3. (Potential) Risks of not detecting thyroid disease early

Progression to overt hypothyroidism
• Higher baseline TSH
• Positive TPOAb status
Cardiovascular disease
• Younger individuals
• With existing cardiovascular risk factors
Impaired quality of life due to symptoms
• Younger individuals

Age and TSH levels

The prevalence of subclinical hypothyroidism increases with age, as TSH levels rise with age. Of interest, a study from the Netherlands showed that 85-year-olds with slightly elevated TSH levels survived longer than those with a TSH that was normal (Figure 5).[5,8] Treatment with L-thyroxine for mildly raised TSH levels in those aged 60 years and older did not improve symptoms or quality of life over 12 months in those participating in the randomised controlled TRUST trial.[9]



Abnormally low thyrotropin	19	18	15	13	11
Normal thyrotropin	472	441	385	335	287
Abnormally high thyrotropin					
Normal free thyroxine	30	28	26	25	23
Low free thyroxine	37	36	35	32	28

Plasma thyrotropin levels below 0.3mIU/L were considered to be abnormally low; levels above 4.8mIU/L were considered to be abnormally high. Plasma free thyroxine levels below 1.01ng/dL (13pmol/L) were considered to be abnormally low; levels between 1.01 and 1.79ng/dL (13 and 23pmol/L) were considered to be normal.

Figure 5. Mortality in 85-year-old adults based on TSH at baseline[7]

The 2013 European Thyroid Association (ETA) guidelines suggest taking the patient's age, TSH levels and symptoms into account; and then, if the patient is older than 70 years and TSH is <10mIU/l, just observe and repeat thyroid function tests in six months (Figure 6).[9,10] If TSH is >10mIU/l, then consider treatment if there are symptoms. Treat if the patient is younger than 70 years and the TSH is >10mIU/l, but also if TSH is <10mIU/l and they have symptoms.

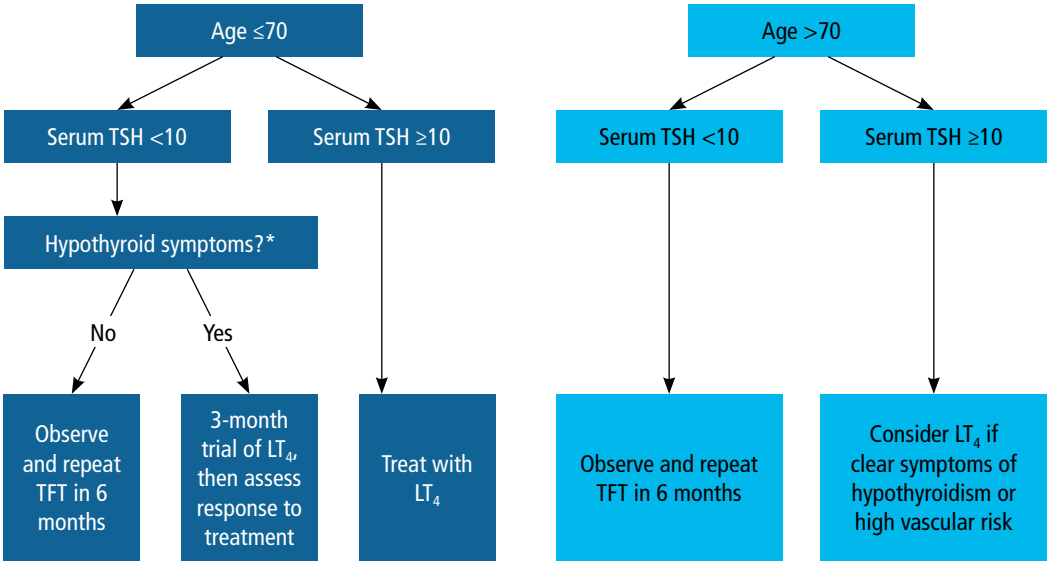


Figure 6. ETA guidelines for L-thyroxine therapy in older patients[10]

The prevalence of subclinical hypothyroidism increases with age, as TSH levels rise with age

Pregnancy and hypothyroidism

Currently, L-thyroxine therapy is usually only prescribed for TPOAb-positive pregnant women with a TSH greater than the trimester-specific reference range. The 2017 guidelines of the American Thyroid Association (ATA) have a broader approach to the management of subclinical hypothyroidism in pregnancy (Table 4), with a strong recommendation for treatment of TPOAb-negative pregnant women if TSH is >10mIU/l.[11]

Table 4. ATA approach to subclinical hypothyroidism in pregnancy[11]

• LT4 therapy is recommended for: – TPOAb-positive women with a TSH level greater than the pregnancy-specific reference range. Strong recommendation, moderate-quality evidence. – TPOAb-negative women with a TSH level >10.0mIU/l. Strong recommendation, low-quality evidence.
• LT4 therapy may be considered for: – TPOAb-positive women with TSH level >2.5mIU/l and below the upper limit of the pregnancy-specific reference range. Weak recommendation, moderate-quality evidence. – TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and <10.0mIU/l. Weak recommendation, low-quality evidence.
• LT4 therapy is not recommended for: – TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range or <4.0mIU/l if unavailable).

This CPD accredited programme was compiled for *deNovo Medica* by
Julia Aalbers
B.Sc (Hons) Pharmacology

So, who should be treated?

- TSH >10mIU/l (all ages)
- Aged <70 years with high cardiovascular risk
- Aged <70 years with symptoms (TSH >4.0mIU/l)
- Pregnant women with TSH >4.0mIU/l and TPOAb-positive
- Women who are infertile (TSH >4.0mIU/l)
- Women who have had recurrent miscarriages (TSH >4.0mIU/l)

KEY LEARNINGS

- Clinical examination and history are as important as biochemistry in determining the extent of thyroid disease
- Measuring levels of TSH is the most reliable screening test for thyroid dysfunction
- Treatment can be affected by several factors and should be tailored to the individual patient.

References

Click on reference to access the scientific article

1. Dave JA, Klisiewicz A, Bayat J, *et al*. SEMDSA/ACE-SA Guideline for the management of hypothyroidism in adults. *JEMDSA* 2015; **20**(2): 18-26.
2. Canaris GJ, Manowitz NR, Mayor G, *et al*. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med* 2000; **160**(4): 526-534.
3. Fish LH, Schwarz HL, Cavanaugh MD, *et al*. Replacement dose, metabolism and bioavailability of levothyroxine in the treatment of hypothyroidism. *N Engl J Med* 1987; **316**: 764-70.
4. Hollowell JG, Staehling NW, Flanders WD, *et al*. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002; **87**(2): 489-499.
5. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: Implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2007; **92**(12): 4575-4582.
6. Flynn RW, Bonellie SR, Jung RT, *et al*. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab* 2010; **95**(1): 186-193.
7. Razvi S, Bhana S, Mrabeti S. Challenges in interpreting thyroid stimulating hormone results in the diagnosis of thyroid dysfunction. *J Thyroid Res* 2019; **3**: 1-8.
8. Gussekloo J, van Exel E, de Craen AJ, *et al*. Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 2004; **292**(21): 2591-2599.
9. Stott DJ, Rodondi N, Kearney PM, *et al*. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017; **376**: 2534-2544.
10. Pearce SH, Brabant G, Duntas LH, *et al*. 2013 ETA Guideline: Management of subclinical hypothyroidism. *Eur Thyroid J* 2013; **2**(4): 215-228.
11. Alexander EK, Pearce EN, Brent GA, *et al*. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017; **27**(3): 315-389.

Published by
© 2020 deNovo Medica
Reg: 2012/216456/07
70 Arlington Street, Everglen, Cape Town, 7550
Tel: (021) 976 0485 | info@denovomedica.com