



REVIEW

# Diagnosis and Management of Hypothyroidism in Gulf Cooperation Council (GCC) Countries

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## ABSTRACT

Hypothyroidism is one of the most common chronic endocrine conditions. However, as symptoms of hypothyroidism are non-specific, up to 60% of those with thyroid dysfunction are unaware of their condition. Left untreated, hypothyroidism may contribute to other chronic health conditions. In the Arabian Gulf

States, hypothyroidism is thought to be common, but is underdiagnosed, and management approaches vary. An advisory board of leading Saudi endocrinologists and policy advisers was convened to discuss and formulate recommendations for the diagnosis and management of hypothyroidism in Saudi Arabia based on their clinical expertise. The final document was shared with leading endocrinologists from the other Gulf Cooperation Council (GCC) and a consensus report was generated and summarized in this article. While there is no consensus

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regarding population screening of hypothyroidism, current recommendations suggest screening patients with risk factors, including those with a history of head or neck irradiation, a family history of thyroid disease or pharmacological treatment that may affect thyroid function. Evidence from a cross-sectional study in Saudi Arabia suggests screening the elderly (> 60 years), at least in the primary care setting. In Saudi Arabia, the incidence of congenital hypothyroidism is approximately 1 in every 3450 newborns. Saudi nationwide population prevalence data are lacking, but a single-centre study estimated that the prevalence of subclinical hypothyroidism in the primary care setting was 10%. Prevalence rates were higher in other cross-sectional studies exclusively in women (13–35%). The recommendations included in this article aim to streamline the diagnosis and clinical management of hypothyroidism in the GCC, especially in the primary care setting, with the intention of improving treatment outcomes. Further study on the incidence, prevalence and risk factors for, and clinical features of, hypothyroidism in the GCC countries is required.

**Keywords:** Hypothyroidism; L-thyroxine; Saudi Arabia; Subclinical hypothyroidism

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### Key Summary Points

Hypothyroidism is a common but under-recognised and under-diagnosed condition in the Gulf Cooperation Council (GCC) Countries.

A group of Saudi and GCC endocrinologists and policy advisers developed a set of diagnosis and treatment guidelines based on expert opinion and local and international clinical evidence.

Cross-sectional studies reported a higher incidence of hypothyroidism among older women, pregnant women and in patients with comorbidities (sleep apnoea, diabetes).

Screening is suggested for patients with clinical signs/symptoms or risk factors for thyroid disease and in special patient groups (e.g. pregnant women).

Once diagnosis is confirmed, levothyroxine treatment is usually appropriate.

## INTRODUCTION

It is estimated that thyroid diseases affect 200 million people worldwide [1], with up to 60% of those with thyroid dysfunction unaware of their condition [2]. The most common cause of thyroid dysfunction is iodine deficiency and an estimated 2 billion individuals have insufficient iodine intake [3]. In countries with routine iodine supplementation, however, autoimmune thyroid disorders are the most common causes of thyroid disorders [4].

Hypothyroidism is caused by insufficient production of thyroid hormones by the thyroid gland, resulting in diminished metabolic action at the target tissue [5]. Left untreated, hypothyroidism can contribute to other chronic health conditions, such as dyslipidaemia, hypertension, cognitive impairment, infertility and neuromuscular dysfunction [6].

Hypothyroidism affects other endocrine functions including male fertility and semen quality and testicular function [7, 8]. Hypothyroidism is commonly seen in outpatient clinics and causes a range of metabolic and body dysfunctions; however, patients seldom exhibit clear symptoms. Indeed, thyroid dysfunction is frequently subclinical [9].

The prevalence of overt hypothyroidism in the general population varies between 0.2% and 5.3% in Western countries [10], and estimates for the prevalence of subclinical hypothyroidism (SH) range between 1% and 10% of the population according to epidemiological data reported from across the globe [11–13]. While there have been no national studies to determine the population-wide prevalence of hypothyroidism in Saudi Arabia, a similar prevalence of SH (10%) was reported among 340 adults attending a primary care centre in a cross-sectional study in Riyadh [14]. No overt hypothyroidism was reported, likely due to the study exclusion criteria: no history of thyroid disease, not taking thyroid medication and consultation at clinic not related to thyroid illness [14].

There is evidence that hypothyroidism remains an underdiagnosed condition in Saudi Arabia and other Gulf states: for example, a single-centre cross-sectional study of 199 female Saudi adults reported that 5.5% of participants had undiagnosed hypothyroidism [15]. Furthermore, thyroid conditions and iodine deficiency are risk factors for thyroid cancer [16], which poses a significant health care burden for Saudi Arabia [17]. There are also currently no Saudi-specific guidelines for the diagnosis and management of hypothyroidism published in the academic literature. For these reasons, a group of leading Saudi endocrinologists and policy advisors convened more than once in Jeddah and Riyadh, Saudi Arabia, during the period March 2018–January 2019 to discuss and formulate recommendations on the diagnosis and management of hypothyroidism in Saudi Arabia based on their clinical experience and currently available clinical evidence specific to Saudi Arabia. In addition, the members communicated by email and telephone on specific issues related to these recommendations and consensus. All members of the advisory board are authors of this

review, which summarises recommendations from their panel discussion for the screening, diagnosis and management of hypothyroidism in the general population as well as in special populations. Furthermore, the occurrence and types of hypothyroidism in Saudi Arabia are discussed. The final document was shared and accepted by leading endocrinologists from the GCC countries. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## CLINICAL PRESENTATION

The clinical signs and symptoms of hypothyroidism may be broad and non-specific and vary from patient to patient. Common symptoms include fatigue, menstrual irregularities and lack of concentration, while other symptoms associated with hypothyroidism may include cold intolerance, constipation and hair loss, among others [5, 18]. The number of these symptoms a patient has reflects the degree of thyroid dysfunction [19].

The clinical signs of hypothyroidism may include (but are not limited to) oedema, weight gain, goitre, cognitive impairment and delayed relaxation phase of deep tendon reflexes. Laboratory results may show elevated C-reactive protein, hyperprolactinaemia, hyponatraemia, increased creatine kinase, increased low-density lipoprotein (LDL) cholesterol, increased triglycerides, normocytic anaemia and proteinuria [20]. Possible electrocardiography findings include bradycardia, low voltage and flattened T-waves [5]. Clinical presentation of severe hypothyroidism can be confused with septic shock, with clinical signs including pericardial effusion, pleural effusion, haemodynamic instability and coma [18].

## SCREENING AND DIAGNOSIS

There is no current consensus regarding population screening for hypothyroidism. The American Thyroid Association (ATA) recommends screening all adults from 35 years of age

and every 5 years thereafter [20]; the American Association of Clinical Endocrinologists (AACE) and the American Academy of Family Physicians recommend routine thyroid-stimulating hormone (TSH) measurements in older patients [21, 22]. Conversely, the Royal College of Physicians of London, the US Preventative Services Task Force and a consensus panel of the ATA, AACE and the Endocrine Society do not recommend routine screening for thyroid disease in healthy adults [23–25]. The current clinical practice guidelines for hypothyroidism in the USA recommend screening all adult patients who visit primary care clinics for signs and symptoms of hypothyroidism, including weight gain, dry skin, constipation, sleepiness, depression, anaemia, fatigability, cold intolerance, sleep apnoea, overweight/obesity and irregular menses/infertility (Fig. 1) [26]. Patients who have four or more of these symptoms should undergo screening for hypothyroidism by measurement of plasma TSH levels. Screening of asymptomatic patients should be considered every 5 years in all adults aged > 35 years and those with risk factors, such as a history of head or neck irradiation, family history of thyroid disease or pharmacological treatment with drugs known to affect thyroid function (Fig. 1) [26].

Special patient groups may warrant screening regardless of symptom history; these include pregnant women and those with infertility, psychiatric patients (especially those with a history of depression), patients with hyperlipidaemia and children with short stature (Fig. 1).

The best laboratory assessment of thyroid function in the outpatient setting is the serum TSH test [27]. If TSH levels are elevated, serum free thyroxine ( $T_4$ ) should be tested. Overt primary hypothyroidism is diagnosed if TSH levels are elevated and serum free  $T_4$  levels are low. Subclinical hypothyroidism (SH) is diagnosed if a patient has elevated serum TSH levels (generally > 4.0 milli-international units of biological activity per litre of serum [mIU/l]) with a normal serum free  $T_4$  level [28]. In general, TSH screening should be repeated 1–3 months before a diagnosis of hypothyroidism is rendered in cases of subclinical hypothyroidism. A

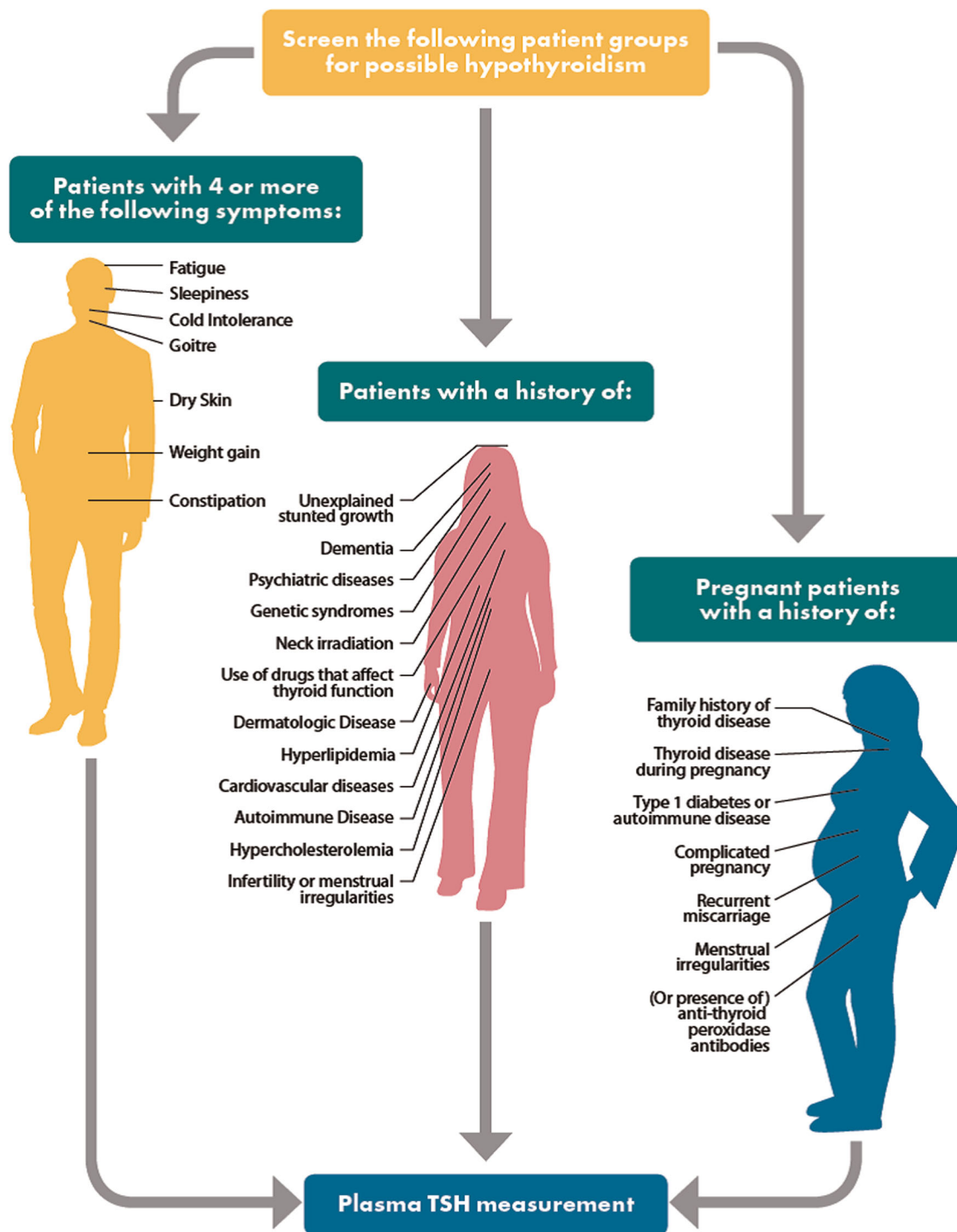
low serum free  $T_4$  level with a low serum TSH level is consistent with secondary hypothyroidism and requires further investigation of hypothalamic-pituitary insufficiency [26]. A clearly low serum  $T_4$  level with an inappropriately normal or even slightly but disproportionately elevated TSH should also suggest central hypothyroidism and should be further investigated. In these situations, measurement of serum TSH alone is not enough to diagnose hypothyroidism. Therefore, when the clinical setting suggests central hypothyroidism, serum  $T_4$  or FT $_4$  should be measured and further investigations might be warranted [29].

Newborn screening for congenital hypothyroidism (CH) is crucial for disease detection; however, diagnosis is complex as many factors affect the levels of  $T_4$  and TSH, including infant birth weight, prematurity and age at specimen collection. The New York State Newborn Screening programme screens all infants for  $T_4$  levels, and those with a result in the lowest 10% are then screened for TSH. Infants with low  $T_4$  and elevated TSH are referred for follow-up diagnostic testing [30].

## MANAGEMENT OF HYPOTHYROIDISM

Currently, the treatment of choice for hypothyroidism is levothyroxine sodium due to its efficacy, favourable safety profile, ease of administration, good intestinal absorption, long serum half-life and cost-effectiveness [31]. Synthetic levothyroxine sodium is indicated for replacement of thyroid hormones in primary, secondary or tertiary congenital or acquired hypothyroidism. Levothyroxine acts as an endogenous thyroxine once absorbed and undergoes deiodination to the biologically active triiodothyronine ( $T_3$ ) [32].

Although the majority of patients with hypothyroidism respond to levothyroxine treatment, some individuals experience persistent symptoms despite adequate serum thyroxine correction. The combined use of levothyroxine and liothyronine, a synthetic form of  $T_3$ , has been investigated in patients who have persistent symptoms of



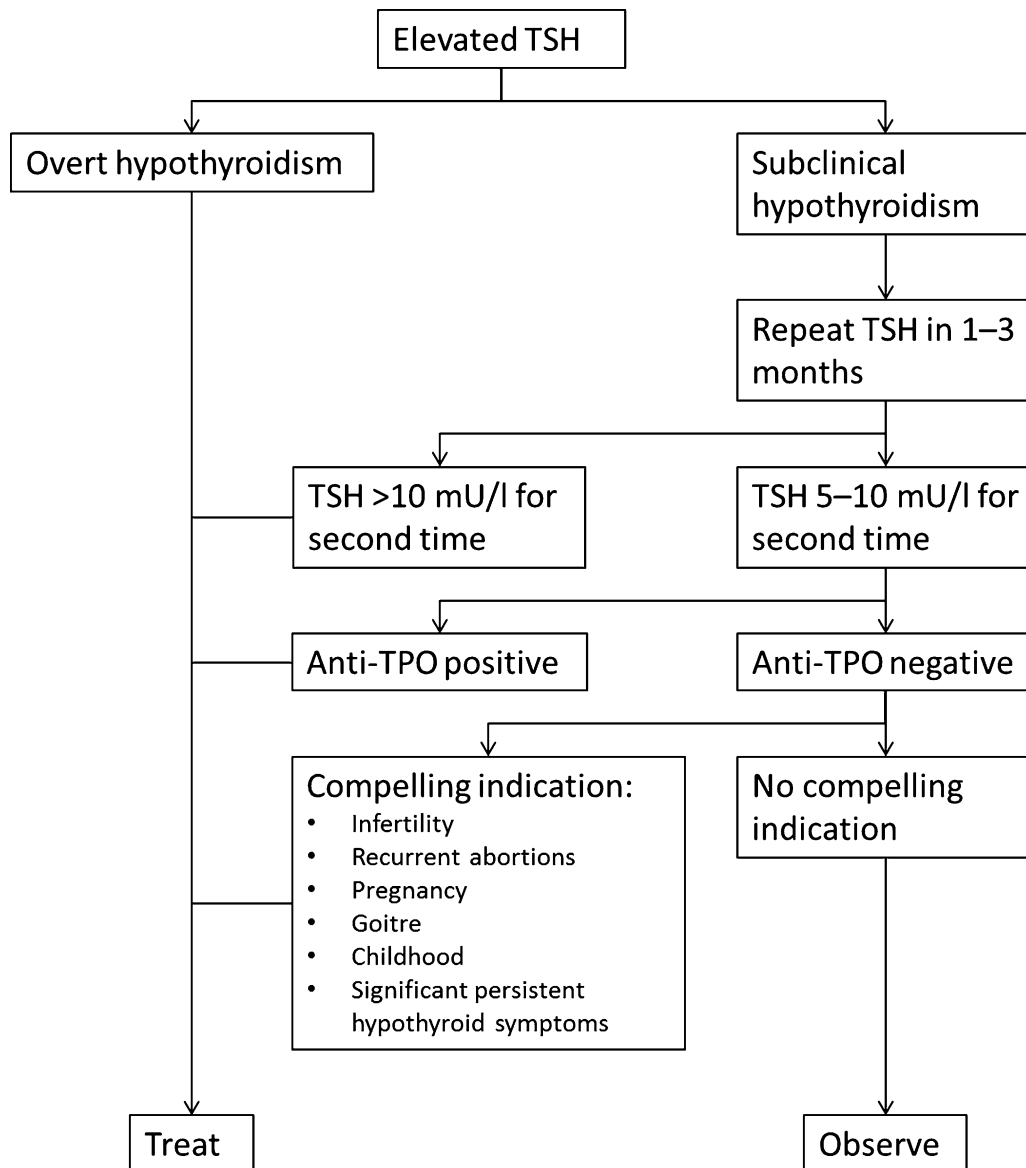
**Fig. 1** Screening recommendations for hypothyroidism. *TSH* thyroid-stimulating hormone. Reproduced with permission from Springer Healthcare (©2018) [34]

hypothyroidism with levothyroxine monotherapy; however, there is inconsistent evidence of

the superiority of combination therapy over monotherapy with levothyroxine [31, 33].

Patients with elevated TSH levels are classified into two groups according to their symptoms and free T<sub>4</sub> level, subclinical and overt hypothyroidism; for patients diagnosed with overt hypothyroidism, thyroid replacement therapy with levothyroxine is indicated. In patients with subclinical hypothyroidism (SH), TSH levels should be tested in 1–3 months; if TSH levels are > 10 mIU/l at both tests, levothyroxine may be initiated. Otherwise,

thyroid peroxidase (TPO) antibody levels should be assessed in these patients. If the patient is TPO antibody-positive, levothyroxine may be initiated if TSH levels are above normal but < 10 mIU/l. In patients with elevated TSH levels on two occasions (above the upper limit of normal range but < 10 mIU/l) who are negative for TPO antibodies, levothyroxine should be considered if the patient is a child, a



**Fig. 2** Management algorithm for patients with hypothyroidism. *TPO* thyroid peroxidase, *TSH* thyroid-stimulating hormone. Reproduced with permission from Springer Healthcare (©2018) [34]

pregnant woman or has infertility or goitre (Fig. 2) [34].

### Dosing Schedule of Levothyroxine

Levothyroxine has been marketed traditionally as a tablet (levothyroxine sodium). However, in recent years two novel formulations, a soft gel and a liquid formulation, have been marketed in some but not all countries [35]. Levothyroxine should be administered in the morning [36] and on an empty stomach, preferably 1 h before a meal, to improve thyroid hormone levels [37]. For children and adults who may not be able to take tablets, it may be dissolved in a small amount of water. Known medications that may interfere with the absorption or metabolism of levothyroxine and lead to changes in the required dose include iron, calcium, proton pump inhibitors, antacids, oestrogen, bile acid sequestrants and anticonvulsants, among others [32, 38]. Some of these drugs interfere with absorption of levothyroxine from the gastrointestinal tract (e.g. calcium, iron, bile acid sequestrants) and some interfere with the metabolism or plasma transport of levothyroxine (e.g. oestrogen, anticonvulsants) [39, 40]. Administration of those agents that interfere with levothyroxine absorption should be separated by at least 4 h from administration of levothyroxine. TSH levels should be measured 6–8 weeks after initiation of treatment and the levothyroxine dose adjusted if necessary [41].

For newly diagnosed, healthy, young or middle-aged patients (< 65 years of age) who have no comorbidities or cardiovascular risk factors, the full levothyroxine dose may be appropriate from the beginning of treatment [31]. For patients with significant morbidities, cardiovascular disease (CVD) or multiple CVD risk factors, 25–50% of the calculated dose should be used initially and the dose should be gradually increased to the full dose over the next few weeks [32, 42].

### Safety and Tolerability of Levothyroxine

The adverse effects of levothyroxine are characteristic of hyperthyroidism, i.e. due to

therapeutic overdose, and may include weight loss, fever, excessive sweating, nervousness, hyperactivity, tremors, muscle weakness/spasm, dyspnoea, menstrual irregularities, hair loss, rash, diarrhoea, vomiting and various cardiovascular manifestations (e.g. arrhythmias, tachycardia, increased pulse rate, elevated blood pressure, heart failure, angina, myocardial infarction) [32]. In particular, therapeutic overdosing in patients with underlying CVD and/or elderly patients may precipitate cardiac adverse reactions [32]. Likewise, there is an increased risk of osteoporosis, especially in post-menopausal women, with supraphysiological levothyroxine doses [32].

At physiological replacement doses, the risk of osteoporosis or cardiac complications does not seem to differ between patients receiving levothyroxine and euthyroid individuals. A systematic review found that replacement levothyroxine was not associated with long-term adverse effects, such as osteoporosis [43]. This was supported by results from a cohort study that found that levothyroxine was not associated with impaired bone mineral density or reduced bone strength in treated patients when compared with controls [44].

### Management of Special Patient Groups

Elderly, pregnant and paediatric patients require special attention in the treatment of hypothyroidism (Table 1). Elderly individuals may have TSH levels that are slightly above the normal range [45] and should not be automatically treated if TSH is elevated. It is recommended to first investigate for signs and symptoms suggestive of hypothyroidism, associated CVD or multiple risk factors for CVD, and whether TPO antibodies are present, and consider levothyroxine therapy if these signs or symptoms are identified. In elderly patients and those with comorbidities, especially ischaemic heart disease, a period of observation and reassessment is recommended [31]. These patients should start on a low dose of 25–50 µg/day and an increase of 25 µg every 2 weeks (Table 1) [34].

**Table 1** Management of hypothyroidism in special patient groups [34]

Patient group	Clinical characteristics	Pharmacological management
Adults	Newly diagnosed, good overall health, < 65 years of age, no comorbidities and no CVD risk factors	Full levothyroxine starting dose: 1.6 µg/kg body weight
Elderly	Normal or slightly above normal TSH levels, signs and symptoms suggestive of hypothyroidism, CVD or multiple risk factors for CVD, and/or positive TPO antibodies	Consider levothyroxine at starting dose of 25–50 µg/day, raised by 25 µg every 1–2 weeks until full dose is reached
	Normal or slightly above normal TSH levels, no signs and symptoms of hypothyroidism	A period of observation and reassessment is recommended
Pregnant women	OH, where TSH concentration above trimester-specific reference intervals with a decreased free T <sub>4</sub> , should be treated. SH, where TSH concentration above trimester-specific reference intervals with normal free T <sub>4</sub> might be considered for treatment with L-thyroxine, especially those with anti-TPO Abs (see text)	Initiate levothyroxine and titrate the dose to maintain TSH within trimester-specific range Serum thyrotropin levels assessed every 4 weeks during first half of pregnancy and every 4–6 weeks in the second half of pregnancy to allow dose adjustment
	Trimester-specific TSH range: 0.1–2.5 mIU/l (first trimester) 0.2–3.0 mIU/l (second trimester); and 0.3–3.0 mIU/l (third trimester)	
	Women with SH, who were not initially treated	Monitor for progression to OH with serum TSH and free T <sub>4</sub> tests approximately every 4 weeks until 16–20 weeks gestation and at least once from 26–32 weeks
Paediatric patients	Diagnosis of CH	Initiate levothyroxine according to patient age: Neonate to 6 months: 10–15 µg/kg/day 6–12 months: 8–10 µg/kg/day 1–2 years: 6–8 µg/kg/day >2 years: 5–6 µg/kg/day

CH congenital hypothyroidism, CVD cardiovascular disease, OH overt hypothyroidism, TPO thyroid peroxidase antibody, SH subclinical hypothyroidism, TSH thyroid stimulating hormone

In pregnant women if treated, TSH levels should be in the lower half of the trimester-specific range if known for the population or < 2.5 mIU/l if the trimester-specific range is not available [46]. When levothyroxine is initiated, free T<sub>4</sub> levels should be maintained in the upper third of the normal range. Women with

hypothyroidism who become pregnant may need increased doses of levothyroxine. In the later stages of pregnancy, TSH levels may start to rise because of an increased demand for thyroxine. This elevation and increased demand can be significant, leading to an increase in TSH of up to 25% from baseline. In



pregnant women with hypothyroidism who are on levothyroxine replacement therapy, it is recommended to repeat TSH measurements every 4 weeks until TSH levels stabilise and every trimester thereafter [46].

For young children with CH, the following levothyroxine replacement dosing is recommended: for neonates to 6 months 10–15 µg/kg; for 6 months to 1 year 8–10 µg/kg; for 1–2 years 6–8 µg/kg; for > 2 years 5–6 µg/kg (Table 1) [31, 34].

Individuals with Down syndrome (DS) are at an increased risk of developing thyroid disease, primarily autoimmune, with a lifetime prevalence ranging from 13% to 63% [47]. Congenital hypothyroidism is 28 times more common among infants with DS than in the general population [47].

## HYPOTHYROIDISM IN SAUDI ARABIA

This section describes the types of hypothyroidism causing the most concern in Saudi Arabia and GCC countries.

### Congenital Hypothyroidism

The main cause of CH is insufficient production of thyroid hormone in newborns, which can lead to failure to grow and mental retardation [48]. CH is classified into two types: (1) thyroid dysgenesis, in which defective thyroid gland development leads to athyreosis, thyroid ectopy and hypoplasia [49], and (2) thyroid dyshormonogenesis, which is a defect in thyroid hormone synthesis [50].

The estimated incidence of CH was 1 in 3450 (0.03%) live births in Saudi Arabia from 1988 to 1995 [51, 52]. This is comparable with other countries in the Middle East-North Africa region. In a pilot screening programme for CH in Oman, 36,000 infants were screened and the estimated prevalence of CH was 1:2200 (0.05%) from 1995 to 2000 [53]. In a pilot cord blood screening study of 35,067 newborns in Iran from 1998 to 2002, the estimated prevalence of CH was 1:1403, with a positive correlation

between disease and parental consanguinity [54].

In a comprehensive mutation screening of Saudi patients with CH using next generation sequencing, the overall mutation rate was 52.7%. The most frequent genetic defects in thyroid dyshormonogenesis and dysgenesis were *TG* and *TSHR* mutations, respectively. The proportion of patients with *TSHR* mutations was 10.9% [48], which was significantly higher than that previously reported in Chinese patients (1.6%) [55]. Furthermore, *TSHR* mutations in Saudi patients were biallelic, whereas all *TSHR* mutations in Chinese patients were monoallelic, which may not cause symptomatic CH [55].

The mutation spectrum in Saudi patients with CH is narrow and specific, and mainly concentrated in the *TG* and *TSHR* gene loci, which may reflect the consanguineous nature of the disease. Other gene mutations include *TPO*, *DUOX2*, *SLC26A4*, *TSHB*, *TSHR*, *NKX2-1*, *PAX8*, *CDCA8* and *HOXB3* [48].

There may be regional differences in the prevalence of CH in Saudi Arabia. A retrospective study found that the prevalence of CH among children born in the Arar Central Hospital in Arar City, a Northern Borders Province in Saudi Arabia, was 2.6 per 10,000 (0.03%) between 2008 and 2014 [56]. In contrast, the prevalence of CH in Najran, a southern province of Saudi Arabia, was reported to be 1 per 1400 (0.07%) between 1990 and 1995 [57]. Of note, the time period of screening was different for the two regions, which may affect the comparability of CH prevalence in these two Saudi Arabian studies.

Given the high prevalence of CH in Saudi Arabia, newborn screening has been suggested in the Middle East and North Africa as a preventative health measure [58].

### Subclinical Hypothyroidism

The estimated prevalence of SH in adults in the primary care setting in Saudi Arabia is 10.3% [14].

In cross-sectional studies in Saudi Arabia that included only women, the prevalence of SH was

high again, being 35% in a study exclusively in those aged > 50 years [59] and 14.9% (data available only as an abstract) [60] and 13% (95% CI 9.8–16.8%) [61] in studies in pregnant women. The study of 257 women aged > 50 years (mean age  $55.8 \pm 7.2$  years) was conducted at the King Abdulaziz University outpatient clinic in Jeddah and defined SH as a TSH level of > 4.2 mIU/l and normal levels of free  $T_4$  (12–22 pmol/l) and free  $T_3$  (0.27–7.1 pmol/l) [59]. Fatigability was the most common symptom (20%), followed by constipation (16%), infertility (12%), cold intolerance (7%) and weight gain (4%). This high SH prevalence was likely due to environmental or genetic factors, although verification in further studies is required. The fully published study in pregnant women used slightly different criteria for SH: in this multicentre, cross-sectional study conducted in Riyadh [61], the 2011 ATA criteria for SH were used (TSH 2.5–10 mIU/l and trimester-specific normal range of  $T_4$  [62]). This study also found that pregnant women were three times more likely to be diagnosed with SH if they were screened randomly compared with screening based on their physician's judgement [61]. As previously mentioned, screening for SH is warranted in pregnant women.

The prevalence of SH was investigated in Saudi Arabian patients with obstructive sleep apnoea (OSA) in a cross-sectional study of patients referred to a sleep disorder centre [63]. SH was defined as a serum TSH level of > 5.0 mIU/ml with serum  $T_3$  level within normal levels. Newly diagnosed SH was found in more of the 271 subjects diagnosed with OSA (11.1%) than in the 76 subjects without a diagnosis of OSA (4%). Although authors concluded that routine thyroid function testing in OSA patients was probably not warranted unless signs and symptoms were present [63], sleep apnoea itself is considered to be one of the clinical signs of hypothyroidism, at least according to US guidelines [26].

As expected, the prevalence of SH in Saudi Arabia may be explained in part by the role of iodine intake in the development of hypothyroidism. In one Saudi Arabian study, TSH levels were high in 13.3% of patients who did not use iodised salt in their diet compared with 8.9% in

those who used iodised salt [14]. Another study of patients with thyroid diseases attending clinics at three hospitals in Makkah ( $n = 391$ ) found that iodine deficiency and poor nutrition were significantly more common in women ( $n = 142$ ) with hypothyroidism than men ( $n = 54$ ) with hypothyroidism [64].

Other clinical characteristics of hypothyroidism and comorbidities differing between women and men in the Makkah study included a greater incidence of autoimmune thyroiditis (Hashimoto thyroiditis, Graves' disease), congenital hypothyroidism, thyroid malignancy, psychiatric disorders and diabetes mellitus among male than female patients and a lower incidence of iodine deficiency, goitre, poor nutrition and benign thyroid cancer [64]. Further study of the clinical characteristics of patients with hypothyroidism and risk factors for hypothyroidism in Saudi Arabia is required.

Patient age may also be a contributing factor to SH, as in one study TSH levels were higher in elderly patients [14]. Therefore, thyroid screening in primary care settings among adults, particularly those aged > 60 years, may be warranted for early detection of SH [14].

### Consequences of Hypothyroidism

There is insufficient evidence to support hypothyroidism as a causative factor in clinical heart disease; however, mild thyroid gland failure and elevated TSH levels may be associated with cardiovascular disease [65]. A study of 1149 elderly women from Rotterdam, The Netherlands, showed that SH was associated with an increased risk of atherosclerotic vascular disease and myocardial infarction [11].

In a cross-sectional study of the prevalence of thyroid disease in Colorado, USA, significantly elevated LDL cholesterol was observed in patients with SH [66]. Furthermore, a longitudinal follow-up study showed that patients with symptomatic improvement of hypothyroidism had improved left ventricular contractility and cardiorespiratory exercise capacity and reported increased energy and decreased skin dryness and constipation [65].

In a primary care study of Saudi patients with SH, there was a non-significant trend of increasing blood pressure and hyperlipidaemia in patients with high TSH levels [14].

A study of 111 Saudi women with heart failure found that 33.3% had hypothyroidism and 14.4% had SH. There was a significant negative correlation between TSH levels and ejection fraction, indicating a close association between hypothyroidism and heart failure in this population [67].

Thyroid disorders are also associated with an increased prevalence of anaemia and iron deficiency. In a study of non-pregnant Saudi women, the prevalence of anaemia was significantly higher in participants with thyroid abnormalities (44%) compared with euthyroid participants (14.3%,  $p = 0.00002$ ) [68].

An association between diabetes and thyroid disorders has also been postulated, as both diseases are caused by endocrine dysfunction and both insulin and thyroid hormones contribute to body metabolism; disruption in either hormone can impair the function of the other [69]. In a case-control study of 100 Saudi patients with type 2 diabetes at King Abdulaziz University Hospital, thyroid autoimmunity was detected in 10% of patients with diabetes versus 5% of controls ( $p = 0.05$ ), and thyroid dysfunction was detected in 16% of patients with diabetes versus 7% of controls ( $p = 0.03$ ) [70]. A subsequent study of patients with type 2 diabetes at a Golestan Hospital Diabetes Clinic in Ahvaz, Iran, showed high levels of TPO antibodies in 33.9% of patients and high levels of anti-thyroglobulin antibodies in 32.7% [71]. Therefore, due to the relationship between thyroid dysfunction and diabetes, patients with type 2 diabetes should undergo annual screening of serum TSH levels.

## CONCLUSIONS

Hypothyroidism is a common and often underdiagnosed disease in the GCC countries. The prevalence of hypothyroidism varies with age, sex and comorbidities such as diabetes and OSA.

There is no consensus regarding routine screening for hypothyroidism in the general adult population. Symptoms are non-specific, but the presence of multiple characteristic symptoms should raise the possibility of hypothyroidism. High-risk groups (e.g. individuals with a family history, goitre, positive for anti-TPO antibodies) and individuals who would be most affected by the disease (e.g. infants and children, pregnant women, patients with hypercholesterolaemia) should be screened for hypothyroidism. The diagnosis of SH should be substantiated by repeating the TSH test in 1–3 months, measuring anti-TPO antibodies and assessing risks and benefits of initiating levothyroxine replacement therapy.

Overt hypothyroidism should be treated with appropriate doses of levothyroxine. Dose selection and adjustments should take into consideration the severity of hypothyroidism, the patient's age and the presence of comorbidities.

The panel recommends maintaining a high index of suspicion for the diagnosis of hypothyroidism, especially in the high-risk groups such as children, pregnant women, patients with multiple symptoms and patients with a family history of hypothyroidism. The diagnosis should be based on biochemical evaluation and TSH measurement is the primary diagnostic test for hypothyroidism in the vast majority of cases. For patients with SH, the decision to treat or observe should be based on laboratory findings such as significant and persistent elevation of TSH and/or the presence of hypothyroid symptoms, in accordance with established recommendations [28]. Levothyroxine remains the primary therapy for all types of hypothyroidism targeting the appropriate TSH level for the patient being treated.

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