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Clinical Practice Recommendations for Assessment and Management of Hypothyroidism

Saud Alsifri[1], Nasser Aljuhani[2], Ahmed Aljedai[3], Tariq Nasser[4], Fahad Alsabaan[5], Hajer Almudaiheem[3], Ashraf Amir[6], Ebtissam Baissa[7], Nadia Ghannam[8], Mohammed Aldawish[9], Afaf Alshammari[4], Emad R. Issak[10*]

[1]Alhada Armed Forces Hospital, Taif, Saudi Arabia
[2]East Jeddah Hospital, Jeddah, Saudi Arabia
[3]Ministry of Health, Riyadh, Saudi Arabia
[4]Ministry of National Guards Hospital, Jeddah, Saudi Arabia
[5]Security Forces Hospital, Riyadh, Saudi Arabia
[6]International Medical Center, Jeddah, Saudi Arabia
[7]Alrawdaha General Hospital, Dammam, Saudi Arabia
[8]First Clinics, Jeddah, Saudi Arabia
[9]Prince Sultan Military Hospital, Riyadh, Saudi Arabia
[10]Aslam Center, Cairo, Egypt
Email: *dr.emad.r.h.issak@gmail.com

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Abstract

Hypothyroidism is a common disorder, potentially severe, often clinically ignored, easily diagnosed by laboratory tests, and highly treatable. It may cause chronic illnesses if left untreated. Saudi Society of Endocrinology and Metabolism (SSEM) assembled a panel of twelve endocrinologists with experience in thyroid diseases in adults and children and made up a task force. An initial concept proposal that included types of hypothyroidism, population, scope, and prevalence in Saudi Arabia was obtained. The proposal was divided into several topics discussed in February 2022. The panel approved that the consensus will include all types of hypothyroidism in Saudi Arabia, screening, diagnosis, management, and special population. A literature review was carried out. Most of the latest international guidelines were screened in Europe and USA. The literature search was completed in March 2022. They drafted a report that was distributed to the entire panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on April 2022. Subsequently, the panel reviewed and discussed the supporting rationale of

the revised recommendations. This article presents these practical recommendations.

Keywords

Hypothyroidism, Screening, Diagnosis, Management

1. Introduction

Hypothyroidism is a common disorder, potentially severe, often clinically ignored, easily diagnosed by laboratory tests, and highly treatable. It may cause chronic illnesses if left untreated. Most patients are oblivious to their condition as the symptoms of hypothyroidism are non-specific. It may be primary hypothyroidism due to damage in the thyroid gland or central due to pituitary gland disorder. It can affect many special populations, such as neonates, children, adults, pregnant women, and older people. Also, it can be subclinical hypothyroidism (mild or no symptoms) or overt hypothyroidism (clinically symptomatic) [1]. In Saudi Arabia, the prevalence of hypothyroidism ranged from 18.7% to 25.5%. Females represented 57.5% to 86.3% of cases [2] [3]. At the same time, congenital hypothyroidism among the Saudi population varied from 1:2666 to 1:4208 live births [4].

Saudi Society of Endocrinology and Metabolism (SSEM) assembled a panel of experts to develop a **consensus** that includes the screening, diagnosis, and management of different types of hypothyroidism in different populations.

2. Methods of Consensus Development

Twelve endocrinologists from the SSEM with more than 15 years' experience in thyroid diseases in adults and children made up a task force. An initial concept proposal that included types of hypothyroidism, population, scope, and prevalence in Saudi Arabia was obtained. The proposal was divided into several topics discussed in a hybrid physical and virtual meeting held on the 26th of February, 2022. The meeting panel approved that the consensus will include all types of hypothyroidism in Saudi Arabia (primary, central & subclinical), screening, diagnosis, management, and special population, and finally, among the entire Saudi population (nonpregnant and pregnant adults, childhood and adolescence and neonates).

Afterward, Expert writers searched the literature based on their search strategies, and they determined their databases. Most of the last updated government-sponsored guidelines were screened in the United States, Canada, and the United Kingdom. These included American Thyroid Association (ATA), Canadian Task Force on Preventive Health Care (CTFPHC), Choosing Wisely Canada, National Institute for Health and Care Excellence (NICE), British Thyroid Association (BTA), and European Thyroid Association (ETA). No attempt was

made to grade the rationale or recommendations. The literature search was completed in March 2022.

Draft reports written by the experts were then distributed electronically to the entire expert panel. Approval of the recommendations required consensus, defined as a majority approval. The recommendations were revised to accommodate any differences of opinion until a consensus was reached. Recommendations were finally formulated on April 2022. Subsequently, the panel reviewed and discussed the supporting rationale of the revised recommendations. Despite differences between the guidelines and the available drugs, the panel tried its best to develop a consensus statement to be valid worldwide.

3. Screening/Detection of Hyothiroidsim

3.1. Asymptomatic Hypothyroidism

Population-based screening has the potential for overdiagnosis, long-term monitoring, the need for follow-up testing, and consuming resources. The rationale is insufficient, and the benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults cannot be determined [5].

Recommendation 1: Population-based screening is **not recommended** for thyroid disease in asymptomatic nonpregnant adults.

3.2. Subjects for Screening

The American Thyroid Association and the American Association of Clinical Endocrinologists advise people over 60, those at higher risk for hypothyroidism, and expectant mothers to be screened for the condition [6]. The US Preventive Services Task Force identified several risk factors for hypothyroidism, including previous hyperthyroidism (which may have been caused by ablation therapy leading to iatrogenic thyroid dysfunction), female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goitre, and external-beam radiation in the head and neck region [1] [2].

Recommendation 2: Screen for hypothyroidism should be considered in patients older than 60 years, women older than 50 years.

Recommendation 3: Screen only those individuals (adults and children) with clinical risk factors for hypothyroidism.

Recommendation 4: High-risk patients for hypothyroidism are identified as patients with goiter, a history of autoimmune disease, previous radioactive iodine therapy and/or head and neck irradiation, Family history of thyroid disease, previous or current use of medications that may impair thyroid function, if there is a clinical suspicion of thyroid disease, type 1 diabetes, new-onset atrial fibrillation, or depression or unexplained anxiety.

3.3. Children

Out of a worldwide birth population of approximately 130 million infants annually, it is estimated that 37 million infants (29 percent) are screened, and ap-

proximately 12,000 infants with hypothyroidism are detected annually. Early detection and treatment of congenital hypothyroidism through screening prevents neurodevelopmental disability and optimizes developmental outcomes [7] [8].

TSH level elevation is widely noticed in obese patients, yet it is more likely to be one of the obesity sequels and commonly false hypothyroidism. Thyroid function test should only be performed in other healthy children only if they have short stature and diminished velocity relative to the puberty stage [9] [10] [11] [12].

Recommendation 5: Screening of all Saudi newborns is recommended with particular emphasis on those at risk of congenital hypothyroidism as preterm neonates; low birth weight and very low-birth-weight neonates; ill and preterm newborns admitted to neonatal intensive care units; and multiple births (particularly same-sex twins).

Recommendation 6: Avoid routinely measuring thyroid function and/or insulin levels in children with obesity.

3.4. Pregnant Women

The results of observational studies suggest that assessment of thyroid function only in women at high risk for thyroid or other autoimmune diseases (targeted screening) will miss up to one-third of women with subclinical or overt hypothyroidism (TSH > 3.5 mU/L) [13]. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, recommended that patients who are planning pregnancy, including assisted reproduction, should be screened. At the same time, that universal screening is not recommended [13] [14] [15].

Recommendation 7: Screen for thyroid dysfunction in **all** asymptomatic pregnant women in the first trimester.

Recommendation 8: Screen for thyroid dysfunction in **all** women who are **planning for pregnancy**.

3.5. Screening Tests

Expert panels have agreed upon screening the general population using TSH only. The ATA recommends screening in all adults above 35 years and every five years after that. The AACE recommends routine TSH level testing in older patients (ages not specified), especially women. The American Academy of Family Physicians suggests routine screening in asymptomatic patients older than age 60 years, and the American College of Physicians recommends case finding in women older than 50 years [16] [17] [18] [19].

Recommendation 9: Order TSH only for **all** patients, and if abnormal, TSH measurement should be repeated along with additional evaluation or treatment depending on the findings:

If the TSH is above the reference range, measure free T4 in the same sample.

If the TSH is below the reference range, measure free T4 and free T3 in the same sample.

Serum concentrations of Anti-Thyroid Peroxidase Antibodies (TPO-Ab) are increased in more than 90% of patients, as almost all of them have autoimmune thyroiditis [20].

Recommendation 10: Do not routinely test for TPO-Ab.

The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend measuring TSH in any high-risk people for hypothyroidism (e.g., personal history of type 1 diabetes or other autoimmune diseases, family history of thyroid disease, history of neck radiation to the thyroid, history of thyroid surgery) [7].

Recommendation 11: Order TSH at initial screening for **some** patients recommended for screening.

Recommendation 12: Order TSH, T4, and anti-TPO at initial screening for **some** patients recommended for screening if thyroiditis is suspected.

Routine screening is required for all neonates to detect primary hypothyroidism. An increase in TSH concentration can last up to 24 h following birth. Thus, it is best to measure a sample taken at least 48 h after delivery to avoid false positive results. Newborn babies should be screened for congenital hypothyroidism by measurement of bloodspot TSH using a sample collected within 2 - 8 days after birth as part of a national screening program. All hypothyroid neonates should be treated as early as possible.

Recommendation 13: For newborn screening, it is recommended to use a primary TSH/backup T4 method TSH. The sample is to be collected within 2 - 8 days after birth.

3.6. Screening Interval

Due to these problems, many qualified experts advise repeating thyroid function tests if the results are above or below a stated reference interval for confirmation of persistent dysfunction (for instance, over 3- to 6-month intervals in asymptomatic individuals), before making a diagnosis or thinking about any treatment options, unless the serum TSH level is higher than 10.0 or lower than 0.1 mU/L. In four to six weeks, the patient should have another evaluation and check their serum TSH levels. The patient will need another TSH measurement in six weeks if the TSH remains over the reference range [21] [22] [23].

Recommendation 14: Do not repeat thyroid function tests if TSH is normal except for diabetes patients.

Recommendation 15: Repeat thyroid function tests if TSH is abnormal in asymptomatic persons. The optimal screening interval for thyroid dysfunction is 4 - 8 weeks.

Recommendation 16: Repeating the tests for thyroid dysfunction if symptoms worsen or new symptoms develop but not sooner than **six** weeks from the most recent test.

4. Diagnosis of Hypothyroidism

In populations who have been screened, the accuracy of hypothyroidism diagnosis based on clinical findings is quite low. In a case-control study, 30% of newly hypothyroid patients reported symptoms, whereas 17% of controls with normal thyroid function reported the same nonspecific symptoms. Clinical diagnosis errors and inaccuracies of hypothyroidism may be connected to other medical and non-medical diseases with comparable symptoms [24].

Recommendation 17: Generally, hypothyroidism diagnoses rely on thyroid function tests because of the lack of specificity of the typical clinical manifestations.

4.1. Primary Hypothyroidism

Hypothyroidism is diagnosed when there is a subnormal serum free T4, either primary, where serum TSH is elevated, or central, where serum TSH is normal or low. There is controversy about the upper limit of normal serum TSH. The majority of laboratories have been using 4.5 to 5.0 mU/L values. The National Academy of Clinical Biochemistry recommended that the upper limit of normal euthyroid is 2.5 mU/L because 95% of euthyroid volunteers had serum levels within this limit when screened [25] [26] [27] [28].

The upper limit of TSH values may elevate with age, as seen in the NHANES (National Health and Nutrition Examination Survey) III population. If the TSH upper level stays at 4.5 mU/L, 74% of the TSH values of elderly patients older than or equal to 80 years without TPO-Ab positive values would be above this level. According to a reanalysis of the NHANES III TSH distribution curves in TPO-Ab negative individuals between 50 - 59 years, TSH upper levels would correspond to 4.2 mU/L, between 60 - 69 years, to 4.7 mU/L, between 70 - 79 years, to 5.6 mU/L, and in subjects over age 80, to 6.3 mU/L [29].

Previous literature showed that positive results of TPO-Ab tests had a significant association with hypothyroidism. Elevated TPO-Abs titers in subclinical hypothyroid patients signify progression prediction to overt hypothyroidism. Many societies and clinical Endocrinologists support TPO-Abs measuring in patients with subclinical hypothyroidism because TPO-Abs were positive in patients with a high risk of developing hypothyroidism [30] [31] [32].

Recommendation 18: Laboratory findings in **primary hypothyroidism** include a decrease in serum free thyroxine (FT4) and an increase in serum thyroid stimulating hormone (TSH).

Recommendation 19: An elevated serum TSH in **primary hypothyroidism** is above the normal reference range's upper limit, typically 4 - 5 mU/L and 2.5 - 3 mU/L in healthy individuals without thyroid disease.

Recommendation 20: Serum TSH distribution shifts towards higher values with age > 70 or obesity: 6 - 8 mU/L in healthy octogenarians (between 80 and 89 years old), 4.6 mU/L in persons older than 70 - 80 years, and up to 7.5 mU/L in class 3 obesity.

Recommendation 21: Measure TPO-Abs in:

- Adults with TSH levels above the reference range but do not repeat TPO Abs testing in primary and subclinical hypothyroidism.
- Children and young people with TSH levels above the reference range, with possible repeat TPO Abs testing at the time of transition to adult services.

4.2. Secondary Hypothyroidism

Weight gain and intolerance to cold complaints are the most common. Symptoms of concomitant hormone deficiencies, such as hypogonadism could mask the clinical manifestations of central hypothyroidism. Thus, laboratory testing is crucial for those patients. Central hypothyroidism is diagnosed with a decline in serum free T4, despite a low or normal TSH in the same laboratory testing [33] [34] [35] [36].

Hypothalamus or pituitary disorders cause thyroid hormone deficiency, defined as central hypothyroidism, resulting in normal or low TSH levels with decreased free T3 and T4. One study showed that in central hypothyroidism, free T4 was low normal in 18% of adult patients, where the rest were below normal levels, while the majority had normal levels of TSH. Normal levels of TSH are due to its normal immunoactivity, yet its biological activity is diminished. Measurement of T3 levels is rarely necessary for the diagnosis of central hypothyroidism. This recommendation is based on ETA Guidelines on the Diagnosis and Management of Central Hypothyroidism [19] [37] [38] [39] [40].

Recommendation 22: The diagnosis of central hypothyroidism is based on clinical manifestations and thyroid function tests.

Recommendation 23: Laboratory findings in **secondary (central) hypothyroidism** as normal or low level of TSH in the presence of decreased serum free T4.

Recommendation 24: Measure serum TSH and free T4 if pituitary or hypothalamic disease is suspected (e.g., a young woman with amenorrhea and fatigue).

Recommendation 25: Measure free T4 if the patient has convincing symptoms of hypothyroidism despite a normal TSH result.

Recommendation 26: It is not helpful to measure T3 in most patients with suspected central hypothyroidism. Although, it may aid when the diagnosis of central hypothyroidism is uncertain.

4.3. Diagnosis during Pregnancy

High TSH and low free T4 characterize overt hypothyroidism. Two factors donate to this result: hypothyroid women with no ovulation and newly diagnosed or undertreated hypothyroidism. Spontaneous abortion in the first trimester is observed in this type of pregnancy [41] [42] [43]. Concerning reported studies, representing the guidelines published by the American Thyroid Association or the American Endocrine Society suggested the following TSH reference range: first trimester, 0.1 to 2.5 mU/L; second trimester, 0.2 to 3.0 mU/L; third trimes-

ter, 0.3 to 3.0 - 3.5 mU/L [44] [45] [46] [47] [48].

Trimester-specific reference range of thyroid function might vary a lot. It affects the accurate diagnosis, causing delays or undertreated conditions. Guidelines released by the American Thyroid Association for the Diagnosis and Management of Thyroid Disease in 2017 recommended that trimester-specific thyroid function reference ranges were crucial in various laboratories and regions to detect and control pregnancy thyroid disorder more appropriately [49].

There has been a strong debate about the importance of hypothyroidism, represented by high TSH and hypothyroxinaemia (low FT4), as the more prognostic of events in pregnancy. This hypothesis found support by Dutch studies, which showed an association between euthyroid hypothyroxinaemia and delayed cognitive development at different ages. Total T4 assay is preferred to free T4, especially in the last part of pregnancy. American Thyroid Association, European Thyroid Association, and Endocrine Society guidelines state that TT4 elevates 1.5 times pre-pregnant levels after week 16 of pregnancy [50]-[55].

Recommendation 27: Overt hypothyroidism is defined as an elevated TSH concentration in conjunction with a decreased free T4 concentration which is population and trimester specific.

Recommendation 28: If there is a generalized trimester-specific reference range, it will be as follows: 0.1 - 2.5 mU/L for the first trimester, 0.2 - 3.0 mU/L for the second trimester, and 0.3 - 3.0 mU/L for the third trimester.

Recommendation 29: When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice.

Recommendation 30: When evaluating thyroid tests during pregnancy, we typically measure TSH and free T4.

Recommendation 31: Measurement of total T4 may be superior to free T4.

4.4. Congenital Hypothyroidism

High TSH and low free T4 results on serum testing indicate primary hypothyroidism. Treatment is indicated, starting as soon as possible. High TSH and normal free T4 or total T4 results on serum testing indicate subclinical hypothyroidism. Treatment should be initiated if the TSH is highly elevated (e.g., >20 mU/L). If the serum FT4 is low and TSH is low, normal, or slightly elevated, the diagnosis of central congenital hypothyroidism should be deemed. In most countries, there are newborn screening programs, and infants with congenital hypothyroidism are diagnosed after detection by screening tests. The diagnosis should be endorsed by finding an elevated serum TSH and low T4 or free T4 level. Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin, may help spot the underlying causes [56] [57] [58].

Recommendation 32: The diagnosis of hypothyroidism can be confirmed or excluded by the results of serum tests of thyroid function.

Recommendation 33: If the diagnosis of hypothyroidism is confirmed, other studies (such as thyroid radionuclide uptake and scan, ultrasonography, serum

thyroglobulin, tests for thyroid autoantibodies, or urinary iodine excretion) may be performed to identify the cause.

Recommendation 34: In congenital hypothyroidism: High TSH and low free T4 confirm the diagnosis of primary hypothyroidism; High TSH and normal free T4 or total T4 defines subclinical hypothyroidism; and Low or normal TSH, low free T4 suggests the possibility of central hypothyroidism.

5. Management of Hypothyroidism

5.1. Managing Primary Hypothyroidism

5.1.1. Levothyroxine Replacement Therapy

Levothyroxine (LT4) is the cornerstone for the treatment of hypothyroidism. Oral LT4 has a prolonged serum half-life that allows daily administration and results in the remission of the signs and symptoms in most patients. Thyroid hormone action is crucial for growth and is critical in adults' function regulation and organ system metabolism. LT4 is converted peripherally into its active metabolite T3 [59] [60] [61] [62].

Recommendation 35: Levothyroxine is the standard replacement therapy for correcting primary hypothyroidism in adults, children, and young people. That is because of its long-term efficacy, safety profile, ease of administration, and low cost.

5.1.2. New Formulation of Levothyroxine Therapy

Most patients use LT4 tablets. One study reported that the pharmacokinetic characteristics of the gel capsule were the same as tablets in healthy individuals. The gel capsule or liquid is an option for patients with suspected poor absorption of the standard solid tablet, especially in the presence of atrophic gastritis. It may also be better absorbed after bariatric surgery [63].

Recommendation 36: Using levothyroxine (LT4) dissolved in glycerin and supplied in gelatin capsules or liquid formulation has no advantage over tablets. The soft gel capsule/liquid may be an option for patients with suspected poor absorption of the standard solid tablet. Also, it may be an option with the concomitant use of proton pump inhibitors or coffee. It may also be an option after bariatric surgery. Increasing the dose of levothyroxine tablet with monitoring of TSH is a less costly option than new formulations.

5.1.3. Switching between Formulations or From Brand to Generic

The bioequivalence of different LT4 formulations is controversial. Alteration in the LT4 content of brand-name and generic names guided many professionals to prefer a particular formulation. In 1997, a study of two generic formulations and two brand names of LT4, using US Food and Drug Administration (FDA)-recommended methodology to determine bioequivalence, stated that the four preparations were equivalent. Nevertheless, some experts considered the methodology used to determine bioequivalence in the study imperfect since endogenous T4 concentrations were not considered [64] [65] [66].

Due to the narrow therapeutic index of LT4, FDA has stipulated that LT4 formulations maintain 95% - 105% of their stated potency, amended from a prior requirement of 90% - 110%, during their shelf life. Moreover, FDA has required that all LT4 products be reassessed as if they were new drugs. America Thyroid Association advises maintenance of a specific formulation of LT4. Switches between LT4 products could potentially cause alterations in the administered dose and should largely be avoided for that reason [59] [67].

Recommendation 37: We recommend that patients remain on the same formulation used of levothyroxine.

Recommendation 38: It is acceptable to take either a generic or a brand-name formulation. Switching levothyroxine formulations (from brand to generics or different brands from different countries) has to be made cautiously and then re-evaluate the serum TSH until it is at a steady state.

5.1.4. Dosing and Administration

Starting dose based on the serum level of TSH, with a full replacement dose (1.6 μg/kg), is required when the serum TSH is significantly elevated, and lower doses (e.g., 25 - 50 μg) are required in mild hypothyroidism. T4 requirements relate better with lean body mass than total body weight. In one study, the average full replacement dose after thyroidectomy was 1.76 mcg/kg body weight for body mass index (BMI) < 25 kg/m^2, 1.47 mcg/kg for BMI 25 to 29 kg/m^2, 1.42 mcg/kg for BMI 30 to 34 kg/m^2, 1.27 mcg/kg for BMI 35 to 39 kg/m^2, and 1.28 mcg/kg for BMI over 40 kg/m^2. Patients who can wait an entire hour before eating breakfast are few. The closeness to food intake, instead of any time of day, is more critical. A meta-analysis showed no significant difference in the effectiveness of morning dosing compared to bedtime dosing based on TSH level assay [7] [68] [69] [70].

Some studies showed that TSH levels were lower and constant in the case of fasting administration of LT4 than with the non-fasting administration (e.g., mean serum TSH 1.06 ± 1.23, 2.93 ± 3.29, and 2.19 ± 2.66 mU/L if administered one hour before breakfast, with breakfast, or two hours after the last meal at bedtime, respectively) [71] [72].

Recommendation 39: For adults < 65 years old: start levothyroxine at 1.6 mcg/kg body weight per day (rounded to the nearest 25 mcg) with no history of cardiovascular disease.

Recommendation 40: Dosing should be adjusted based on actual body weight and ideal body weight.

Recommendation 41: Regarding administration concerning meals, we recommend that levothyroxine be consistently taken either 1 hour before breakfast or at bedtime after ≥3 hours of the evening meal for optimal, consistent absorption.

5.1.5. Target Therapy

The aim is to maintain serum TSH levels within the normal range (0.5 to 5.0 mU/L). Nevertheless, there is an age-related variation where higher TSH con-

centrations were measured in elderly patients. Amongst patients with goiter, nearly 50 percent will experience a decrease in goiter size, which delays the fall in TSH secretion. The appropriate upper limit of normal for serum TSH is controversial. The serum TSH is the parameter used to adjust the LT4 dose, with the target TSH typically being 0.5 to 3.5 or 4 mU/L [7] [73] [74] [75].

Recommendation 42: The goals of therapy for levothyroxine therapy are normalization of serum TSH, resolution of symptoms and avoidance of overtreatment.

Recommendation 43: We recommend maintaining TSH levels within the normal reference range when treating primary hypothyroidism with levothyroxine. Target normal range is 0.5 to 4.0 mU/L.

5.1.6. Monitoring and Assessing Adequacy of Therapy

In agreement with the most recent guidelines published by the ATA, "TSH is the most dependable marker of competence of replacement treatment, and a level within the reference range (0.4 - 4.0 mU/L) is to be the therapeutic target." As recommended by NICE guidelines for treating hypothyroidism, they agreed that TSH levels could take up to 6 months to return to the reference range if they have been very high or have been high for a long time. They agreed that healthcare professionals should consider this when adjusting doses to avoid large dose increases that could cause thyrotoxicosis. They made different recommendations for children under two years because of the impact of poorly treated hypothyroidism [7] [76].

Recommendation 44: TSH is the recommended marker for adequacy of levothyroxine therapy. Do not use Free T4 or T3, or clinical symptoms to monitor and adjust levothyroxine therapy.

Recommendation 45: For adults, measure TSH every 3 months until the level be stabilized (Two similar measurements within the reference range three months apart), and then once a year.

For children aged 2 years and over and young people, measure Free T4 and TSH every 6 - 12 weeks until the TSH level be stabilized (Two similar measurements within the reference range three months apart), then every 4 - 6 months until after puberty, then once a year.

For children aged between 28 days and 2 years, measure Free T4 and TSH every 4 - 8 weeks until the TSH level be stabilized (Two similar measurements within the reference range two months apart), then every 2 - 3 months during the first year of life, and every 3 - 4 months during the second year of life.

5.1.7. Factors Affecting Dose Required, Concomitant Medications, Concomitant GIT Condition

Levothyroxine dosing is affected by body weight. Studies have shown that patients demonstrated an alteration in levothyroxine requirement after weight loss bariatric surgery. Up-titration of the levothyroxine dose when there is weight gain is a recommendation of the Guidelines on the Diagnosis and Management of Central Hypothyroidism [35] [77] [78].

Carbamazepine, phenobarbital, rifampin, and phenytoin can increase the levels of the LT4 glucuronidation enzyme. Goldberg *et al.* mentioned an example, "the concurrent administration of rifampin and LT4 was correlated to a significantly higher area under the plasma T4 concentration-time curve" [79] [80] [81].

In a prospective study, the cure of *H. pylori* was linked with serum TSH levels reduction from 30.5 to 4.2 mU/L in nonresponsive patients to high doses of LT4. Moreover, eradication of *H. pylori* and starting omeprazole were correlated with low and high TSH values, respectively. Furthermore, in patients who took LT4 therapy, the degree of their LT4 requirement was associated with the existence or nonexistence of serum parietal cell antibodies. Celiac disease is likewise more common in patients with underlying Autoimmune thyroid disease. Two retrospective studies recorded higher LT4 needs in patients with celiac disease compared with unaffected hypothyroid patients [82] [83] [84] [85].

Recommendation 46: Levothyroxine doses should be increased if weight gain/loss is increased or decreased by more than 10% of body weight.

Recommendation 47: Measure TSH levels when medications such as phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline are initiated as high doses may be required.

Recommendation 48: Evaluation of gastrointestinal disorders such as H. pylori-related gastritis, atrophic gastritis, or celiac disease should be considered, as levothyroxine dose requirements are much higher than expected. If such disorders are detected and effectively treated, re-evaluation of TSH and levothyroxine dosage is recommended.

5.1.8. Failure of Therapy

Patients with gastritis have higher requirements for LT4. A study showed that the LT4 dose was higher in patients with parietal cell antibodies. The same consequence can be seen in celiac disease patients [83] [84].

In patients with elevated TSH, it should be established that LT4 is taken daily with water on an empty stomach, before breakfast for an hour, and any medicines that affect T4 absorption should be taken several hours after the LT4 dose. Poor compliance is the most popular explanation for high LT4 dose requirements. Patients will admit to occasionally forgetting their tablets. Nevertheless, it is hard to determine how often "occasionally" happens. Clinicians can check adherence by direct patient reports, clinical improvement, or pharmacy refills. A study also suggests checking for proper storage of LT4 tablets (e.g., moisture, light protection, and temperature) [86] [87] [88].

Dose adjustment of LT4 is regularly required regardless of the initial dose estimate. This happens because of many factors, including limitations in the dose calculations, inter-patient differences, drug absorption, or concurrent diseases or medications [59].

The half-life of levothyroxine is nearly one week. If needed, reexamining thyroid condition by measuring TSH levels and free thyroxine levels are required after six weeks of treatment. If the TSH is not at the preferred goal, the LT4 dose

can be modified. In a systematic review that included nine randomized trials, one trial stated the advantageous effects of combination therapy on feelings, quality of life, and psychological functioning compared to LT4 therapy alone. The following meta-analysis of 11 randomized trials included 1216 patients revealed that there was no advantage of combined therapy [68] [89] [90].

Recommendation 49: If TSH elevation persists, adherence to therapy, proper administration regarding food, other co-medications, or diseases should be checked.

Recommendation 50: If symptoms persist, adjust the levothyroxine dose to achieve optimal well-being without reaching thyrotoxicosis.

Recommendation 51: If symptoms persist despite a normal serum TSH level, we recommend measuring free T4 with TSH in patients with hypothyroidism symptoms to exclude other causes.

Furthermore, acknowledgment of the patient's symptoms and evaluation for alternative causes are recommended in such cases. Future research into whether there are specific subgroups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged.

5.1.9. Special Treatment Situations: (Target)

Coronary heart disease: The thyroid hormone raises myocardial oxygen requirement, correlated to a small risk of arrhythmias, angina, or myocardial infarction in older patients. A total of 1961 reports are the most prominent and finest study of the impacts of starting thyroid hormone on chest pain in patients with hypothyroidism. Among 1503 hypothyroid patients, fifty-five patients had angina before the replacement therapy. Through therapy, 21 improved, 25 had no difference, and 9 had more angina. While thirty-five patients experienced new angina during treatment, 6 in the first month, 6 in the first year, and 23 after one year. Hence, angina may improve with LT4 treatment, and it does not often first appear during LT4 replacement therapy [91] [92].

Recommendation 52: For patients with cardiovascular disease: start levothyroxine at a dosage of 12.5 - 25 mcg/day with *slow titration* over 4 - 6 weeks based on symptoms and serum TSH levels.

Elderly patients: Patients older than 60, with concomitant cardiovascular problems, or patients with a history of coronary heart disease should start treatment with 25 to 50 mcg LT4. The dose can be raised by 12 to 25 mcg/day every three to six weeks to achieve complete replacement, as determined by a normal serum TSH. However, if the increase in dose results in cardiac symptoms, in this case, less than a full replacement can be accepted. It is crucial to note that there is an age-related turn towards higher TSH concentrations in older patients, with an upper limit of normal of nearly 7.5 mU/L in 80 years old [93].

Recommendation 53: Patients over 65 - 70 years should start levothyroxine at lower doses (25 - 50 mcg/day) with titration based on TSH level for adults with a history of cardiovascular disease.

Infants and children: Delays in diagnosis and treatment of hypothyroidism

in infants lead to neurocognitive impairment. However, the intelligence quotient (IQ) and neurologic development may endure after diagnosis if the infant has suboptimal treatment throughout the first two to three years of life, a time when the thyroid hormone is crucial for normal brain development. Hence, proper initial therapy and follow-up are vital to ensure optimum dosing of thyroid hormone, with monitoring and dose adjustments and support for the family to promote close obedience to treatment. The quick normalization of thyroid hormone levels (In the first two weeks after therapy initiation) and the maintenance of somewhat higher FT4 concentrations during the first year of life results in a better outcome. The regular monitoring of TSH and FT4 levels is needed for this reason and also to avoid the incidence of prolonged phases of supraphysiological thyroid hormone levels [94]-[100].

Recommendation 54: Levothyroxine should be initiated once a newborn has a positive screening, even before the result of a confirmatory test. In cases where screening tests are borderline, a treatment decision can be postponed until the results of the confirmatory tests return.

Recommendation 55: Tailoring the dose based on the severity of initial TSH and T4 deficit may be the most reasonable approach. In mild cases: a dose of 8 to 10 mcg/kg/day is recommended. Higher doses may be required for infants with severe congenital hypothyroidism. (12.5 to 15 mcg/kg/day).

Recommendation 56: A Dosing regimen based on age:

- Full-term newborn: a dose of 10 - 15 mcg/kg/day
- Preterm newborn: a dose of 10 - 15 mcg/kg/day, though in milder cases, often characterized by delayed TSH elevation, a starting dose of 8 to 12 mcg/kg/day
- Age 1 to 3 years - 4 to 6 mcg/kg body weight
- Age 3 to 10 years - 3 to 5 mcg/kg
- Age 10 to 16 years - 2 to 4 mcg/kg

OR

Dosing regimen is based on body surface area calculated at 100 kg/m^2/day

Recommendation 57: The aim of therapy in **infants** is to maintain the serum TSH in the mid-to-upper half of the pediatric reference range and the serum thyrotropin in the mid-to-lower half of the pediatric reference range. The target should be to normalize serum thyroxine approximately 2 - 4 weeks after initiation of therapy. Once the proper dose is identified, surveillance testing with a serum TSH and FT4 should be performed every 1 - 2 months during the first year of life with decreasing frequency as the child ages.

The aim of therapy in **children** is to normalize their biochemical parameters and reverse the signs and symptoms of hypothyroidism.

Pregnancy: In ongoing pregnancies, hypothyroidism has been associated with a high risk of various complications. These complications include placental abruption, preeclampsia, gestational hypertension, preterm labor, increased chance of cesarean section, postpartum hemorrhage, and neuropsychological and cognitive impairment in the newborn child. About 14 studies calculated the population-based pregnancy-specific reference ranges for TSH. Korevaar *et al.* showed

that in nearly 90% of all studies, the upper limit for TSH was above 2.5 mU/L. ATA 2017 guidelines suggested determining pregnancy-specific and lab-specific reference ranges for TSH. For hypothyroid pregnant women, serum TSH levels should be assessed every 3 - 4 weeks during the first half of pregnancy and every 6 - 10 weeks afterward. The LT4 dose should be modified to keep the serum TSH below 2.5 mU/L. TSH and free T4 levels should be measured 3 - 4 weeks after every dosage adjustment [101]-[110].

Preconception counseling is essential in this regard. Studies have reported that nearly 30 percent of women taking LT4 have a TSH level > 4 mU/L when they show up for their first prenatal visit. In such women, serum TSH of (4.5 - 10) compared with <2.5 mU/L is a forecaster of miscarriage (95% CI 1.03 - 3.14). Nearly 50% - 85% of women with preexisting hypothyroidism require high LT4 doses during pregnancy. Another study showed that 17% of women with preconception TSH values < 1.2 mU/L needed a dose increase during the following pregnancy, compared with 50% of women with preconception TSH levels between 1.2 and 2.4 mU/L [111]-[116].

Recommendation 58: Treatment of women with overt hypothyroidism with levothyroxine replacement therapy is recommended. The dosing should be titrated to achieve a target TSH serum level.

Recommendation 59: TSH target in pregnancy is in the lower half of **the trimester-specific reference** range. If not possible, target TSH levels are below 2.5 mU/L.

Recommendation 60: Serial TSH levels should be assessed every 4 - 6 weeks during the first half of pregnancy for dosing adjustment of levothyroxine to maintain TSH levels within the target range. During the second half of pregnancy, TSH should also be reassessed.

Recommendation 61: In women on levothyroxine who are planning pregnancy, TSH level should be evaluated preconception, and doses adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.

Recommendation 62: For women already on levothyroxine therapy, increase the total daily dose by approximately 25% - 30%.

Estrogen therapy

Recommendation 63: Reassessment of TSH serum level after 4 - 8 weeks if estrogen therapy is initiated or discontinued, as it may alter the levothyroxine requirement. Interval is 6 to 12 weeks after starting estrogen therapy.

Hospitalized patients:

Recommendation 64: For patients who are on levothyroxine therapy and unable to take enteral levothyroxine, It can be given intravenously until enteral absorption improves. The dose should be approximately 70% - 80% of the patient's oral dose.

Also, it may be given via nasogastric tube using extemporaneous preparation or rectal route using a hospital-prepared levothyroxine suppository.

Poorly compliant patients: The efficacy of a single weekly dose was assessed in a crossover trial that included 12 patients. On administration of a single

weekly dose, the mean TSH concentration was higher than when the usual daily dose (6.6 versus 3.9 mU/L), but the elevated value normalized one day after the next weekly dose. No difference has been observed in symptoms between daily and weekly dosing [117].

Recommendation 65: For patients who do not respond to efforts to improve adherence to daily oral levothyroxine, a total weekly oral administration (7 times the daily dose) may be given.

Levothyroxine allergy: Most patients on LT4 therapy tolerate the medication without unfavorable adverse effects because LT4 is identical to the hormone released in the body. Nevertheless, few patients recognize adverse reactions from the treatment, including headaches, tachycardia, anxiety, and other nonspecific symptoms. A reasonable attempt in such cases would be to lower the LT4 dose and increase it slowly. One report of symptoms recorded symptoms resolution when the concurrent iron deficiency was corrected. Highlighting that the correct acknowledgment of the reason for symptoms is challenging. Allergy to the dye in the tablet may infrequently occur and can be resolved using 50 mg, dye-free tablets. An allergy report presented a rash that appeared in a patient taking an LT4 formulation made in Korea and having tartrazine yellow no. 4 and red no. 3 was bypassed by giving the patient a different LT4 product. If problems continue, refer the patient to an allergist to rule out other causes [118] [119] [120].

Recommendation 66: For patients with apparent allergy to levothyroxine, changing the dose, formulation, and brands, by treating concomitant iron-deficiency anemia or an allergist consultation could be reasonable approaches.

5.1.10. Combination T4 and T3 Therapy

There is no sufficient rationale to support its benefits over T4 monotherapy, uncertain safety profile, and multiple daily dosing [121].

Recommendation 67: We do not suggest the routine use of combined T4 and T3 therapy to treat primary hypothyroidism.

5.2. Managing Subclinical Hypothyroidism (Definition, Management, Follow-Up)

5.2.1. Candidates for Treatment

Data discussing the pros and cons of LT4 treatment in patients with serum TSH levels (4.5 - 10 mU/L) is scarce. Treatment in patients with lower serum TSH concentrations may improve nonspecific symptoms of hypothyroidism, such as lethargy and constipation, and may diminish the goiter size if present. This recommendation was made by the NICE panel based on their experience. Some experts recommend that the existence of cardiovascular-disease risk factors may endorse treatment [122] [123].

Recommendation 68: When discussing whether or not to start treatment for subclinical hypothyroidism, consider features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous radioactive iodine treatment or thyroid surgery, or raised levels of thyroid autoantibodies.

Adults: Even though nearly all experts suggest the treatment of patients with serum TSH levels > 10 mU/L, the routine treatment of asymptomatic patients with TSH levels of (4.5 - 10 mU/L) stays debatable. This recommendation is in harmony with the suggestions of a clinical consensus group including representatives from the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) also with the European Thyroid Association guidelines [7] [99] [100] [124] [125] [126] [127].

It was raised that dependence on serum TSH levels to make decisions about treatment is common in clinical practice, which may be problematic. Other factors, including patients' symptoms, are to affect their demand for therapy. The committee saw that a trial period of 6 months of therapy would be suitable for symptomatic patients with TSH lesser than ten mlU/L. Based on their previous experience, the committee decided that therapy was less likely to have a benefit but that the risk-benefit ratio was most beneficial for adults under the age of 65. The committee stated that adults over 65 were less likely to experience symptoms improvement and the harm potential from suppressing TSH is high. The committee approved that the trial of LT4 therapy should be stopped if symptoms continue with TSH levels within the reference range, as this may be due to reasons other than hypothyroidism[76] [128].

Recommendation 69: Consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mU/litre or higher on 2 separate occasions 3 months apart.

Recommendation 70: Consider a 6-month trial of levothyroxine for adults under 65 with a TSH above the reference range but lower than 10 mU/litre on 2 separate occasions 3 months apart, and symptoms of hypothyroidism.

Recommendation 71: If symptoms do not improve after starting levothyroxine, re-measure TSH. If the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment.

Recommendation 72: Follow-up and monitoring as patients with primary hypothyroidism

Pregnant: Evaluation of antibody status is essential because women with subclinical hypothyroidism and positive TPO-Ab manage to have the greatest risk of adverse pregnancy consequences, and adverse outcomes happen at a lesser TSH than in women without TPO-Ab. The ATA systematic review (ATA guidelines on thyroid disease during pregnancy) stated that the risk of pregnancy-specific complications was clear in TPO-positive women with TSH > 2.5 mU/L but was not steadily clear in TPO-negative women until TSH values surpassed 5 - 10 mU/L. In some studies, treatment of TPO-Ab-positive pregnant women with normal thyroid function with LT4 improved abortion rates. Nevertheless, in a meta-analysis that included 3 studies of LT4 treatment initiation in the first trimester of pregnancy, there was no effect of LT4 on miscarriage. However, a significant reduction in the preterm labor rate was observed. A prospective study

included 115 euthyroid patients showed that TPO-Ab patients. Half were randomly allocated to LT4 (median dose 50 mcg daily), and half did not receive treatment; a comparison was made with 869 euthyroid, TPO-Ab-negative patients. Mean baseline TSH was higher in the TPO-Ab positive women and significantly higher during the pregnancy in the untreated TPO-Ab positive women than in the LT4-treated, TPO-Ab positive women [108] [129]-[134].

Recommendation 73: Pregnant women with TSH concentrations > 2.5 mU/L should be evaluated for TPO-Ab status.

Recommendation 74: Initiate low dose of levothyroxine treatment in a pregnant patient with subclinical hypothyroidism. A dose of only 50 mcg/day is typically required for effective treatment of subclinical hypothyroid women.

Children: Most pediatric patients with subclinical hypothyroidism will not progress to overt hypothyroidism, and no significant risk appears with no treatment. In a gigantic, retrospective study that included 121,052 pediatric patients aged from 6 months to 16 years of age, 73.6% of participants with a TSH (5.5 - 10 mU/L). Their TSH returned to normal on five years of follow-up. In participants with a TSH > 10 mU/L, 40% normalized their TSH levels, 33.1% of their TSH values declined, and no more than 25% maintained or increased their TSH level. Besides the lack of Rationale reflecting a high risk of progression, no short-term or long-term complications accompanying untreated pediatric subclinical hypothyroidism, no adverse effect on growth, and no rise in cardiovascular risk or cognitive problems [135]-[142].

Recommendation 75: Treatment is generally not recommended when the TSH is 5 - 10 mU/L.

And

Levothyroxine replacement may be reasonable for patients with TSH > 10 mU/L with signs and symptoms consistent with primary thyroid disease and/or risk factors associated with progression,

Or

- For patients above 2 years

1) TSH level of ≥20 mU/L.

2) TSH level between 10 and 20 mU/L on 2 separate occasions 3 months apart.

3) TSH level between 5 and 10 mU/L on 2 separate occasions 3 months apart, and thyroid dysgenesis, or signs or symptoms of thyroid dysfunction.

- For children aged between 28 days and 2 years who have a TSH level ≥ 10 mU/L. This recommendation is based on NICE guideline [50].

Recommendation 76: Start levothyroxine lower doses (e.g., 25 - 50 mcg) if the patient has subclinical hypothyroidism.

Recommendation 77: Follow-up and monitoring as patients with primary hypothyroidism.

5.2.2. Monitoring for Untreated Patients

Recommendation 78: Follow up **untreated**/stopped adult patients with subclinical hypothyroidism by measuring TSH and free T4 once a year if they have features

suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, or once every 2 to 3 years if they have no features suggesting underlying thyroid disease.

Recommendation 79: Follow up untreated children over 2 years old and adolescents' patients with subclinical hypothyroidism < 10 mU/L by measuring TSH and free T4 every 3 to 6 months if they have features suggesting underlying thyroid disease, such as thyroid dysgenesis (an underdeveloped thyroid gland) or raised levels of thyroid autoantibodies, or every 6 to 12 months if they have no features suggesting underlying thyroid disease.

Recommendation 80: Follow up untreated children less than 2 years old and adolescents' patients with subclinical hypothyroidism < 10 mU/L, by measuring TSH and free T4 every 1 to 3 months.

5.2.3. Monitoring after Stopping Treatment

Recommendation 81: Follow up with adults' patients with subclinical hypothyroidism who stopped treatment, by measuring TSH and free T4 once a year if they have features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies, or once every 2 to 3 years if they have no features suggesting underlying thyroid disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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