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NARRATIVE REVIEW

Differentiation between Clinical and Subclinical Hypothyroidism in Pathophysiology, Symptoms, Diagnosis and Treatment – A Narrative Review

Mustafa M. Albassam, Noor M. Obaid and Yasser Kadhim Hashem Al-Zwaini

College of Pharmacy, Al-Esraa University, Baghdad, Iraq

ABSTRACT

Subclinical hypothyroidism is characterized by an elevation in thyroid-stimulating hormone (TSH) levels, accompanied by normal concentrations of serum free thyroxine (fT4) and free triiodothyronine (fT3). On the other hand, when the fT4 concentration falls below the normal reference range, it is referred to as overt primary hypothyroidism. Due to varying upper limits of normal for TSH, accurate diagnosis and treatment of subclinical hypothyroidism present difficulties in clinical practice. This review article focuses on the differentiation between clinical and subclinical hypothyroidism in pathophysiology, symptoms, diagnosis, and treatment. People with overt hypothyroidism do not exhibit a singular symptom identifying the condition. On the other hand, many people with subclinical hypothyroidism do not display any symptoms. Moreover, the manifestations of hypothyroidism have non-specific symptoms such as mild to moderate weight gain, tiredness, impaired concentration, depressive symptoms, and menstrual irregularities. It is important to note that these symptoms alone are insufficient for the definitive diagnosis of hypothyroidism, necessitating administering a thyroid function test to establish a definite clinical diagnosis. Levothyroxine (LT4) has historically served as the predominant therapeutic intervention for managing hypothyroidism and holds a prominent position as one of the most extensively prescribed pharmaceutical agents globally. The chemical known as LT4 exhibits a slower onset of action and produces effects that are more protracted compared to endogenous thyroid secretions. The administration of LT4 facilitates the conversion of thyroxine (T4) to triiodothyronine (T3) and normalizes TSH levels, thereby replenishing the body's T3 reserves. In treating hypothyroidism, using LT4 alone or in combination with Liothyronine (LT3) could be considered for hypothyroid patients. Nevertheless, evidence suggests that T3 levels may not be restored in patients undergoing LT4 treatment.

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INTRODUCTION

The thyroid gland is an essential endocrine gland located in the lower region of the neck [1], characterised by its distinctive butterfly form. The structure is located anteriorly and laterally to the trachea, positioned inferiorly to the larynx [2]. The thyroid gland is vital to regulating the basal metabolic rate (BMR) [3] and promotes physical and psychological growth [4]. Additionally, it plays a crucial role in the metabolism of calcium. The gland in question comprises two distinct lobes, the right and left, interconnected by an intermediary structure known as the isthmus [5]. Occasionally, an additional lobe known as the pyramidal lobe may extend from the isthmus. The human anatomy features a fibrous or fibromuscular band known as the levator glandulae thyroideae, which extends from the body of the hyoid bone to the isthmus of the thyroid gland [6 7] The two primary thyroid hormones encompass T3, recognised as the more biologically potent type, and T4 [8]. T4 is exclusively secreted from the thyroid gland in response to TSH [9,10], whereas less than 20% of T3 synthesizes within the same gland [8,11,12]; Most T3 forms arise from the enzymatic conversion of T4 catalyzed by the enzyme 5' monodeiodinase in the peripheral tissues [13]. The secretion of TSH by the anterior pituitary gland plays a crucial role in regulating the production of thyroid hormones. These hormones, in turn, are subject to negative feedback control by the circulating levels of free thyroid hormone and extrathyroidal deiodination [8,14].

EPIDEMIOLOGY

The geographical distribution of reported hypothyroidism prevalence exhibits heterogeneity, which can be attributed, in part, to disparities in disease definitions, the inclusion of poorly defined and heterogeneous populations in studies, fluctuations in the sensitivity of historical tests of thyroid function, and variations in iodine intake [14–16]. Subclinical hypothyroidism is essentially a moderate form of thyroid dysfunction, most commonly brought on by autoimmune thyroid disease. The aetiology can be attributed to chronic autoimmune disorders such as atrophic autoimmune thyroiditis or Hashimoto's thyroiditis (HT) or iatrogenic factors such as radioiodine therapy or surgical intervention for hyperthyroidism. These factors collectively contribute to approximately one-third of hypothyroidism cases observed in the general population [17]. The incidence of hypothyroidism tends to be greater among female persons compared to their male counterparts, as well as among older adults and individuals of Caucasian ethnicity [16,18]. Moreover, people with autoimmune disorders, such as diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, and those with additional conditions, including human immunodeficiency virus (HIV) infection, are highly susceptible to developing hypothyroidism [16,19–21].

According to a recent study, clinical hypothyroidism was 3%, whereas subclinical hypothyroidism was at a rate of 7.4% [22–24]. The estimated prevalence of overt hypothyroidism in the general population in Europe ranges from 0.2% to 5.3% [25,26]. A meta-analysis of seven studies conducted in nine European countries yielded an estimated prevalence

rate of roughly 5% for undiagnosed hypothyroidism, encompassing overt and subclinical cases [26]. In the United States (US), it is estimated that the occurrence of both overt and subclinical hypothyroidism is approximately 0.3% and 4.3%, respectively. The prevalence of hypothyroidism appears to be higher in individuals of white ethnicity than in those of black or Hispanic ethnicity [14] Alternatively, a meticulous revaluation of data derived from the National Health and Nutrition Examination Survey (NHANES III) reveals that non-Hispanic black individuals exhibited a 54% reduced susceptibility to hypothyroidism compared to their non-Hispanic white counterparts [27].

Thus, this review article focuses on the differentiation between clinical and subclinical hypothyroidism in pathophysiology, symptoms, diagnosis, and treatment.

PATHOPHYSIOLOGY

Primary hypothyroidism is a disorder characterised by insidious onset, causing notable morbidity. It is accompanied by modest and nonspecific symptoms [28], as well as clinical indicators. The initial biochemical abnormality observed is a rise in serum TSH concentration, while serum fT4 and fT3 concentrations remain within the normal range [29]. This condition is known as subclinical hypothyroidism [30]. Subsequently, there is a decline in serum fT4 concentration, at which point most patients begin experiencing symptoms and derive therapeutic benefits from treatment. This stage is referred to as overt or clinical hypothyroidism [17,23,27]. Subclinical hypothyroidism is characterised by a TSH level exceeding 3.6 mlU/L, although fT3 and fT4 levels remain within the established reference ranges [23,31], while clinical hypothyroidism has a TSH level of more than 3.6 mlU/L, an fT3 level equal to or less than 6.47 pmol/L, and an fT4 level lower than 10.29 pmol/L [23,32]. An elevation in TSH levels serves as the initial indication of primary hypothyroidism. Many individuals exhibit a fT4 level that falls within the established normal range, indicating the presence of compensated or subclinical hypothyroidism [33]. As the disease advances, there is a decrease in the levels of fT4, falling below the established normal range. Despite the low T4 levels, the concentration of T3 remains within the usual range. In due course, the serum concentrations of free and/or total T4 and T3 diminished [8]. Accurate diagnosis of thyroid dysfunction is crucial due to its adverse impact on human health, particularly in pregnant women and individuals with cardiovascular conditions [23]. The issue of iodine shortage persists and is the primary aetiology of thyroid problems, notably hypothyroidism [14,34]. In recent years, the global prevalence of iodine insufficiency mitigates through the widespread use of salt iodization. Consequently, the existing instances of iodine shortage are now predominantly characterized as mild to moderate in severity. Iodine is a crucial substrate required for the biosynthesis of thyroid hormones within the thyroid gland [34]. Most people experience primary hypothyroidism due to thyroid gland dysfunction attributed to chronic HT. Chronic autoimmune thyroiditis is a pathological condition distinguished by diffuse infiltration of lymphocytes, fibrosis, and atrophy of the thyroid parenchyma [35]. In regions where iodine levels are adequate, they represent the prevailing aetiology of pri-

mary hypothyroidism. Circulating autoantibodies targeting thyroglobulin and thyroid peroxidase (TPO) have been observed in nearly all individuals diagnosed with autoimmune hypothyroidism. Most instances of HT first present as subclinical or even euthyroid. The likelihood of transitioning from subclinical to overt hypothyroidism is associated with the degree of rise in TSH, and the presence of thyroid peroxidase antibodies (TPOAb) is nearly ubiquitous (occurring in over 95% of cases) among affected individuals [36–38].

SYMPTOMS

Numerous comprehensive observational studies and meta-analyses have provided evidence indicating that approximately 4-7% of community-based populations in the US and Europe have undiagnosed hypothyroidism [39]. The symptoms associated with hypothyroidism are typically non-specific, exhibiting significant similarities with other medical illnesses and the health implications commonly observed in older individuals. Individuals diagnosed with hypothyroidism commonly exhibit a variety of relatively non-specific symptoms, including but not limited to fatigue, sensitivity to cold temperatures, weight gain, constipation, low mood, cognitive impairment, muscle discomfort, weakness, dry skin, brittle hair, and nails, reduced sexual desire, carpal tunnel syndrome, and dysmenorrhea [40,41]. Specific symptoms are observed in individuals with overt or subclinical hypothyroidism as opposed to those with normal thyroid function. There is a possibility that subclinical hypothyroidism increases the risk of heart failure, coronary artery disease events, and coronary heart disease death. However, it is essential to note that these symptoms could be observed in both hypothyroid and euthyroid populations, and their presence or absence cannot be relied upon as a definitive indicator of thyroid status [42,43]. Consequently, individuals diagnosed with overt hypothyroidism display specific symptoms. However, only a subset of these symptoms, including constipation, dry skin, hair loss, and proximal weakness, are more indicative of thyroid dysfunction. Furthermore, these symptoms are more prevalent in younger individuals, particularly younger men, than older women [14,44–46]. There was no significant difference in hypothyroidism scores between subclinical hypothyroid patients and euthyroid controls. Among individuals with subclinical hypothyroidism, comorbidities significantly influence symptoms such as fatigue, dyspnoea, and wheezing. Conversely, the TSH level did not have any discernible impact on the severity of symptoms. Additionally, younger age was associated with increased psychological distress in the form of fatigue, mood swings, and restlessness. However, higher body mass index (BMI) and smoking are linked to dyspnoea. Hence, individuals diagnosed with subclinical hypothyroidism based on their thyroid function test results do not exhibit a higher frequency of symptoms associated with thyroid disease than those with normal thyroid function [40,41].

The restricted availability of resources poses challenges for doctors in resource-constrained settings when assessing thyroid functions. Consequently, this situation can lead to the under-recognition of hypothyroidism until its signs and symptoms substantially influence an individual's quality of life. One potential strategy for addressing this issue

involves implementing a clinical scoring system that utilizes widely observed symptoms and indications associated with hypothyroidism. A scoring system was established in 1997, utilizing Billewicz's score as a foundation to assess TSH and thyroid hormone levels. The indications and symptoms outlined in Table (1) are utilized and transformed into a practical and straightforward scoring system to screen hypothyroidism [47].

Table 1. The scoring system for Zulewski's

Symptoms	Identified based on	Present	Absent
Diminished sweating	Perspiring in a heated environment or during a season characterised by high temperatures	1	0
Hoarseness	The topic of interest pertains to the distinction between speaking and singing voices	1	0
Paraesthesia	Subjective sensation	1	0
Dry skin	Skin dryness, observed without any apparent cause, necessitates intervention	1	0
Constipation	The frequency of defecation and the utilisation of laxative agents	1	0
Impairment of hearing	The gradual deterioration of auditory function	1	0
Weight increase	Recorded weight increase, tightness of clothes	1	0
Physical signs			
Slow movements	Witness the patient disrobing	1	0
Delayed ankle reflex	The relaxing of the reflex	1	0
Coarse skin	Examination of the hands, forearms, and elbows to assess the presence of roughness and thickening of the skin	1	0
Periorbital puffiness	This action intends to obfuscate the curvature of the malar bone	1	0
Cold Skin	Examine the temperature of the hands in comparison with that of the examiner	1	0
Sum of all symptoms and signs present		12	0

The patient clinically considered hypothyroid if score was ≥ 5, euthyroid if score was < 3, and intermediate if the score was between 3 and 5

DIAGNOSIS

The diagnosis of hypothyroidism severity is determined through biochemical means, specifically by measuring the level of TSH [48,49]. A diagnosis occurs when the TSH level exceeds the reference range established by individuals with normal thyroid function, often ranging from 0.4 to 4 mIU/L [43,50]. Emerging evidence suggests that clinical manifestations of hypothyroidism may exhibit a stronger association with thyroid hormones, specifically fT4 or fT3, rather than TSH [51]. These findings can influence future guidelines and enhance the accuracy of identifying individuals with clinical hypothyroidism [9], as shown in Table (2) thyroid hormones normal range [52]. The diagnosis of overt hypothyroidism is charac-

terized by a significant elevation in TSH levels (>10 mIU/L) and low levels of serum fT4. The process becomes uncomplicated once the patient has presented and completed thyroid function tests. Further investigation is required to diagnose subclinical hypothyroidism when there are slight elevations in TSH levels beyond the established reference range while T4 levels remain within the average range. It is often essential to conduct TSH screening within a span of 1 to 3 months prior to diagnosing hypothyroidism, particularly in instances of subclinical hypothyroidism [53–55].

Table 2. The normal range of thyroid hormones

Test	Normal Range
T4	57.92 - 154.46 nmol/L
T3	1.39 - 3.08 nmol/L
TSH	0.4 to 4 mIU/L
fT4	9 – 20.6 pmol/L
fT3	3.54 – 6.46 pmol/L

Abbreviations: T4 = Thyroxine, T3 = Triiodothyronine, TSH = Thyroid-Stimulating Hormone, fT4 = Free Thyroxine, fT3 = Free Triiodothyronine.

TREATMENT

The treatment history and interventions field has a long-standing and diverse cultural background spanning over two thousand years. In the 6th century, individuals with cognitive impairments in ancient China were administered sheep thyroid as a treatment [56]. The administration of transplanted animal thyroid tissue in 1890 elicited a rapid clinical improvement in a patient suffering from myxoedema [57], In 1891, there were reports of the administration of sheep thyroid injections [56,58]. After a year, the observation showed that the oral administration of freshly obtained sheep thyroid glands was efficacious. In a relatively short period, the medical community acknowledged the potential risks associated with excessive administration of extracts. Consequently, dosage recommendations were established, emphasizing the importance of commencing treatment with a conservative dose and adjusting it incrementally in response to the manifestation of symptoms. The utilization of orally consumed extracts gained significant popularity, leading to the crystallization of T4 by 1914 [57]. In 1927, T4 was synthesized as an acid, limiting oral absorption [56,59]. In 1949, introducing a sodium salt derivative of T4 marked a significant milestone [60]. LT4 is commonly used for thyroid hormone replacement and is recognized as one of the essential medicines by the World Health Organization, necessary for primary healthcare and suppressive therapy. This medication is chemically stable, cost-effective, and exhibits oral bioavailability [8,61]. LT4 has emerged as the prevailing pharmaceutical intervention in the

US [62,63], and the United Kingdom (UK) ranks third in terms of prevalence [63]. The chemical known as LT4 exhibits a slower rate of action. It produces effects of longer duration when compared to the secretion of thyroid hormones naturally produced by the body [64,65]. According to the European Thyroid Association (ETA) criteria, treating more severe types is most common. For individuals presenting with less severe manifestations, the recommended course of action may involve the administration of LT4 in instances where there are many TSH levels ranging from 5 to 10 mIU/L. This approach is considered an optimal method for monitoring and adjusting LT4 dosage [63,66–68], We are discontinuing medical intervention without a discernible clinical improvement—approximately three to four months following the normalization of TSH levels [63,66]. The initial dosage requirements for LT4 therapy can differ significantly depending on the individual's condition. For individuals with mild or subclinical disease, where the therapy requires supplementing their natural thyroid function, initial doses as low as 25-50 μg may be sufficient [69]. However, larger doses ranging from 88-175 μg may be necessary for patients with minimal or no natural thyroid function [70]. According to a recent guideline, the initial treatment in overt hypothyroidism starts when the TSH level exceeds 10 mIU/L [71]. However, it is essential to note that the data supporting this recommendation is considerably less robust in individuals under 65 [63,72]. Clinical trials have also indicated a lack of definitive data about the efficacy of LT4 therapy in individuals with a less severe manifestation (TSH<10 mU/L) of subclinical hypothyroidism in improving lipid status and other cardiovascular risk factors. Moreover, there is a potential increase in the risk of experiencing adverse effects associated with this treatment [73]. The initiation of LT4 medication is necessary in cases of subclinical hypothyroidism (TSH > 4.0 mIU/L) among women who are either planning to conceive or are already pregnant and with TPOAb positive [74,75]. Maintaining normal thyroid function significantly reduces the likelihood of experiencing miscarriage and other difficulties during pregnancy [76,77]. Despite the transition to LT4 monotherapy during the 1970s [78,79], In recent therapeutic guidelines, there has been a renewed focus on the necessity of combination therapy using LT4 + LT3 [14,68,80–83]. The argument posits that incorporating synthetic LT3 alongside conventional LT4 therapy in patients would yield a treatment regimen that aligns more closely with natural physiological processes [84]. The problem at hand has been extensively examined by a significant number of clinical guidelines, which have generally advised against the routine implementation of combination medication. However, it is worth noting that guidelines from the European, UK, and American Thyroid Association (ATA) suggest considering combination therapy as an experimental strategy in certain situations [78,80,85]. Recent studies have demonstrated that the transition from LT4 to LT3 executes without substantial alterations in thyroid-responsive indicators or the manifestation of adverse drug reactions (ADRs) [86]. LT3 utilizes as a therapeutic intervention for treating hypothyroidism since its introduction in 1956 [87]. In an initial investigation, patients with myxoedema were subject to a daily oral dosage of 70 to 105 mcg LT3. This intervention's outcome was restoring clinical euthyroidism within 10-14 days [88]. The indications and symptoms of hypothyroidism exhibited a swift and comprehensive resolution, with no observed adverse or toxic effects. During the initial fortnight of treatment, patients

saw weight loss and maintained a euthyroid state throughout the therapy [68]. Although the prescription of LT3 effectively and promptly restores euthyroidism and normalizes blood TSH levels in individuals with hypothyroidism, there is no justification for using LT3 as the only treatment for hypothyroid patients. The administration of LT3 at dosages ranging from 30-45 mcg/day is necessary to attain clinical and biochemical euthyroidism. However, this dosage level temporarily elevates serum T3 levels, surpassing the established reference range within 2-3 hours after intake. It is important to note that this acute increase in T3 levels does not immediately impact thyroid-responsive parameters or result in adverse cardiovascular effects. The guidelines established by the American Association of Clinical Endocrinology (AACE), ATA, the British Thyroid Association (BTA), and the National Institute for Health and Care Excellence (NICE) do not endorse the use of LT3 therapy as a treatment for hypothyroidism [68,89–91].

CONCLUSION

It was found that using the new scoring system for assessing signs and symptoms of hypothyroidism, with thyroid function testing, offers significant advantages in the individual evaluation of thyroid failure and the ongoing monitoring of treatment.

The assessment of therapeutic serum TSH levels is considered the monitoring indicator with the highest sensitivity and specificity to adjust LT4 dosage. The decline in concentration typically commences within a few hours, while returning to a normal state usually takes two to six weeks. Monitoring TSH and T4 levels at six-week intervals is recommended until a euthyroid state is attained. A high TSH level is indicative of inadequate replacement therapy.

Most individuals receiving treatment for hypothyroidism experience favourable levels of overall well-being. The administration of lifelong LT4 therapy should generally be limited to cases of clinically evident hypothyroidism. In subclinical hypothyroidism, where the TSH levels exceed 10 mIU/L, therapy is warranted. In cases of milder subclinical hypothyroidism, adopting a watchful waiting approach may be a prudent course of action to observe if spontaneous normalisation occurs. Nevertheless, individuals with cardiovascular risk factors who exhibit subclinical hypothyroidism could benefit from administering LT4 medication. The consideration of withholding LT4 may be supported in cases of mild severity when there is a lack of clinical improvement or uncertainty regarding the diagnosis, but ongoing monitoring is necessary.

The presence of persistent fatigue and/or weight gain symptoms in individuals with normal thyroid function test results does not necessitate administering an alternate thyroid medication. The underlying cause may be alternative diagnoses, lifestyle factors, or significant life events. The most suitable approach for individuals who have not experienced any improvement from LT4 treatment is to conduct a trial involving combination therapy with LT4 and LT3. It suggests that a reduction of 25 mcg/day in LT4 dosage, accompanied by the

addition of 2.5-7.5 mcg of LT3 once or twice daily, can serve as a suitable initial approach, given that serum TSH levels fall within the normal range.

LT3, as a standalone treatment for hypothyroidism, has become less common in contemporary medical practice. The recommended dosage for achieving clinical euthyroidism and normalising blood TSH levels is 30-45 mcg/day. It is important to note that these doses can result in serum T3 levels exceeding the normal reference range's upper limit for several hours.

ABBREVIATIONS

TSH Thyroid-stimulating hormone fT4

Free thyroxine

fT3 Triiodothyronine

LT4 Levothyroxine T4

Thyroxine

LT3 Liothyronine

BMR Basal metabolic rate HT

Hashimoto's thyroiditis

HIV Human immunodeficiency virus US

United States

NHANES III National Health and Nutrition Examination Survey TPO

Thyroid peroxidase

TPOAb Thyroid peroxidase antibodies

BMI Body mass index

UK United Kingdom

ETA European Thyroid Association

ATA American Thyroid Association

ADRs adverse drug reactions

AACE American Association of Clinical Endocrinology BTA

British Thyroid Association

NICE National Institute for Health and Care Excellence

DECLARATIONS

1. All authors contributed equally to the paper, with tasks divided collaboratively, including research and writing. Each author shares equal responsibility for the con- tent and conclusions.
2. Conflict of interest

   The authors declares no conflict of interest

3. Ethical Approval

   (Institutional ethical approvals and informed consent)

   This research does not conflict with our university's ethical standards, nor with any known ethical criteria.

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