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REVIEW

Hypothyroidism in Context: Where We've Been and Where We're Going

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ABSTRACT

Hypothyroidism affects up to 5% of the general population, with a further estimated 5% being undiagnosed. Over 99% of affected patients suffer from primary hypothyroidism. Worldwide, environmental iodine deficiency is the most common cause of all thyroid disorders, including hypothyroidism, but in areas of iodine sufficiency, Hashimoto's disease (chronic autoimmune thyroiditis) is the most common cause of thyroid failure. Hypothyroidism is diagnosed biochemically, being overt primary hypothyroidism defined as serum thyroid-stimulating hormone (TSH) concentrations above and thyroxine concentrations below the normal reference range. Symptoms of hypothyroidism are non-specific and include mild to moderate weight gain, fatigue, poor concentration, depression, and menstrual irregularities, while the consequences of untreated or under-treated hypothyroidism include cardiovascular disease and increased mortality. Levothyroxine has long been the main tool for treating hypothyroidism and is one of the world's most widely prescribed medicines. In adults with overt hypothyroidism, levothyroxine is usually prescribed at a starting dose of 1.6 μg/kg/day, which is then titrated to achieve optimal TSH levels (0.4–4.0 mIU/L), according to the therapeutic target. We here summarise the history of levothyroxine and discuss future issues regarding the optimal treatment of hypothyroidism. Because nearly one-third of patients with treated hypothyroidism still exhibit symptoms, it is important that levothyroxine is used more appropriately to achieve maximum benefit for patients. In order to ensure this, further research should include more accurate assessments of the true prevalence of hypothyroidism in the community, optimisation of the levothyroxine substitution dose, proper duration of treatment, and identification of patients who may benefit from combination therapy with levothyroxine plus levotriiodothyronine.
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PLAIN LANGUAGE SUMMARY

Hypothyroidism is one of the most common diseases worldwide, and levothyroxine is the usual medication prescribed to manage it. Hypothyroidism occurs when the thyroid gland, located in the neck, does not produce enough thyroid hormone for the body's requirements. This can result in heart disease, infertility, and poor brain development in children. People with hypothyroidism may have changes in body weight, and feel tired, weak or unhappy, all of which can reduce their quality of life. In underdeveloped parts of the world, the main reason why people develop hypothyroidism is that they not getting enough iodine from food. Thus, many countries try to increase iodine intake by adding iodine to salt. In areas of the world where people ingest enough iodine, the most common cause of hypothyroidism is Hashimoto's disease. This is an autoimmune disease in which the person's immune system produces cells and antibodies that attack the thyroid gland. Most people with hypothyroidism will need to take levothyroxine for a long time, perhaps even for the rest of their lives. Levothyroxine replaces the person's levels of thyroid hormone and makes them feel better, but the dose often needs to be adjusted for the best effect. In addition, many people with hypothyroidism do not know they have it. Research is ongoing to ensure that more people with hypothyroidism are diagnosed and are given effective treatment, and to work out the best way to use levothyroxine so that patients get the best results.

INTRODUCTION

Hypothyroidism is a chronic disease associated with deficiency in the thyroid hormones, thyroxine (T4) and triiodothyronine (T3) [1, 2]. The consequences of untreated or inadequately treated hypothyroidism include infertility, cardiovascular disease, and neurological and musculoskeletal symptoms [3–5]. Environmental iodine deficiency is the most common cause of thyroid disorders, including hypothyroidism, worldwide [6], while in areas of iodine sufficiency, the most common cause of primary hypothyroidism is autoimmune thyroiditis (Hashimoto's disease) [2, 6, 7].

The full implications of hypothyroidism in the population are not completely appreciated or defined. Hypothyroidism affects up to 5% of the population according to European prevalence estimates [8–11], while as many as 5% of the population may have undiagnosed thyroid failure [9]. Of patients who are treated, up to one-third are not receiving adequate treatment [12, 13]. The economic impact of undiagnosed, untreated or undertreated hypothyroidism is therefore not inconsequential, especially with regard to costs associated with maternal and congenital hypothyroidism [14, 15], or with hypothyroid patients having comorbid conditions such as diabetes mellitus [16]. Hypothyroidism is also associated with decreased quality of life [1, 12, 17–19], increased number of sick leave days [20], and even increased mortality [21].

Levothyroxine is the mainstay of treatment for hypothyroidism, and is one of the World Health Organization's essential medicines required for basic health care [22]. Here, we review the background of hypothyroidism, including aetiology, prevalence, and symptoms, with a focus on the use of levothyroxine in the management of hypothyroidism. In particular, we review advances to date and unresolved issues in the treatment of hypothyroidism.

METHODS

A search of the literature was conducted using PubMed and general search terms such as primary hypothyroidism, levothyroxine, aetiology, economic impact, quality of life and treatment guidelines. Potential articles of interest were identified by title and abstract, and citation lists of articles of interest were used to identify additional literature. This article is based on previously conducted studies and does

not contain any studies with animals performed by any of the authors. Some of the cited studies include analyses, or studies with human participants, performed by the authors and completed prior to the initiation of this manuscript.

HYPOTHYROIDISM IN CONTEXT

Causes of Hypothyroidism

As described earlier, hypothyroidism is characterised by deficiency in the T4 and T3 hormones [1, 2]. T4 is the main hormone produced by the thyroid gland, which only produces a small amount of T3. Only 20% or less of T3 in peripheral tissue originates in the thyroid gland [23, 24]; the rest is derived from the enzymatic conversion of T4 to T3 within the target tissues [2]. Failure of the thyroid to produce T4 and T3 stimulates the pituitary to increase production of a thyroid-stimulating hormone (TSH) through a negative feedback mechanism [2].

In over 99% of cases, hypothyroidism is caused by a failure of the thyroid gland to produce thyroid hormones (primary hypothyroidism) [2, 25]. The remaining 5% of patients have hypothyroidism from other causes, including secondary hypothyroidism, caused by underproduction of TSH by the pituitary gland, tertiary hypothyroidism, caused by deficiency of thyrotropin-releasing hormone, and peripheral (extra-thyroidal) hypothyroidism [2, 3]. Central hypothyroidism, which includes both secondary and tertiary hypothyroidism, and peripheral hypothyroidism account for less than $< 1\%$ of cases [3, 26].

A large population study in Denmark reported that the most common subtype (present in 84.4% of patients) was spontaneous (presumably autoimmune) hypothyroidism, followed by post-partum (4.7%) and amiodarone-induced hypothyroidism(4.0%). Less common causes were subacute thyroiditis (1.8%), previous radiation or surgery (1.8%) to the thyroid gland, congenital hypothyroidism (1.6%) and lithium-associated (1.6%) thyroid failure [7]. Nowadays, iatrogenic causes have become more frequent due to various immunotherapies.

Prevalence and Incidence

The reported prevalence of hypothyroidism varies geographically, in part due to differences in disease definitions, poorly defined and diverse populations studied, variability in the sensitivity of measures of thyroid function used in the past, and iodine intake [27]. In Europe, the estimated prevalence of overt (i.e. symptomatic) hypothyroidism in the general population is 0.2–5.3% [8–11, 28]. Across nine European countries, the prevalence of undiagnosed hypothyroidism, including both overt and subclinical hypothyroidism, has been estimated at approximately 5% in a meta-analysis of seven studies [9]; the same meta-analysis calculated the incidence rate at 226.2 (222.26–230.17) per 100,000 per year. Similarly, the prevalence of overt and subclinical hypothyroidism in the US has been estimated at 0.3% and 4.3%, respectively [29].

Primary hypothyroidism is up to 8–9 times more common in women than in men, and the prevalence increases with age, with a peak incidence between the ages of 30 and 50 years [2, 30]. In the US, hypothyroidism affects an estimated 4% of women aged 18–24 years and 21% of women older than 74 years [27]; respective values in men are 3% and 16% [27]. A UK survey determined that approximately 7.5% of women and 2.8% of men have elevated serum levels of TSH [10], while a Danish population study found that the lifetime risk of overt hypothyroidism was 4.1% in women and 1.3% in men [7].

Hypothyroidism also appears to be more prevalent in white people than in black or Hispanic people [29–32].

Impact of Iodine

Worldwide, environmental iodine deficiency is the most common cause of thyroid disorders, including hypothyroidism [6]. Iodine is an essential component of thyroid hormones, but is also thought to make the thyroid gland more antigenic [2, 3, 33]. Despite the implementation of iodine supplementation programmes (e.g. salt iodization), iodine intake remains

suboptimal in large parts of Europe, Africa and Asia [34], while it can affect specific subpopulations in developed countries, such as pregnant women in some areas of Italy, the US and UK [3, 33–36]. Socioeconomic factors may play a role in the lack of adherence to iodine supplementation programmes. A recently published Italian study showed that poverty and lack of access to public health services were barriers to the use of iodized salt and maternal iodine supplements among poor or immigrant women [37]. Iodine intake and hypothyroidism demonstrate a "U-shaped" relationship: hypothyroidism prevalence decreases in populations with mild iodine deficiency as compared to those with severe deficiency, while autoimmune hypothyroidism increases in prevalence as population iodine intake increases to sufficiency or excess [3].

Autoimmune Hypothyroidism

In areas of iodine sufficiency, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease) [2, 6]. Hashimoto's disease is characterised by diffuse infiltration of the thyroid by lymphocytes and the presence of thyroid auto-antibodies, such as anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin antibodies (TgAb) [2, 38]. One study found that the prevalence of overt hypothyroidism was strongly correlated with the presence of the former, with no hypothyroid individuals having positive TgAb in the absence of positive TPOAb [29]. Thyroid antibody positivity is almost universal (> 95%) among patients with overt hypothyroidism [39] and present in ~ 50% with subclinical hypothyroidism [40], while 10–20% of the background population have thyroid antibodies [41].

While this disease entity is often named Hashimoto's hypothyroidism, all cases in the original study by Hashimoto had large goitres [42]. Therefore, autoimmune hypothyroidism is often referred to as Ord's hypothyroidism in those with small thyroid glands, and Hashimoto's disease in those with goitres [43]. However, this distinction is not clear-cut since thyroid size in hypothyroidism shows a normal distribution, with cases of thyroid atrophy or goitre representing extremes within this distribution [43].

The prevalence of autoimmune thyroiditis is increased in populations with high dietary iodine, as well as in severely iodine-deficient populations, likely as a result of prolonged thyroid adaptation to iodine intake in both cases [2, 3, 44, 45]. Other environmental factors that have been implicated in autoimmune thyroiditis are deficiencies in vitamin D [46] and selenium [47], whereas moderate alcohol consumption has been found to reduce the risk [48]. Immune changes during pregnancy can also provoke the onset of autoimmune hypothyroidism, which occurs at a rate of 92.3 per 100,000 women per year according to a nationwide Danish study [49].

Primary hypothyroidism can also be caused by damage to, or destruction of, the thyroid gland caused by treatment or conditions, such as thyroidectomy, radioactive iodine therapy for Graves' disease or nodular goitre, radiotherapy for head and neck cancer, or toxic exposure to some chemicals or drugs [2, 3]. Drugs that may cause hypothyroidism include amiodarone, interleukin-2, kinase inhibitors, and lithium [50]. Rarely, primary hypothyroidism may be congenital, caused by failed embryologic development of the thyroid gland (thyroid dysgenesis) or inherited defects of the genes responsible for the thyroid hormone synthesis (thyroid dyshormonogenesys) [3, 7].

Burden of Hypothyroidism

The economic impact of undiagnosed/untreated hypothyroidism may be significant, especially with regard to costs associated with maternal and congenital hypothyroidism [14, 15], or with hypothyroid patients having comorbid conditions such as diabetes mellitus [16].

Hypothyroidism is also associated with decreased quality of life, most likely related to symptoms such as changes in body weight, fatigue, weakness and depression [1, 12, 17–19]. Physicians and patients themselves rate fatigue

and emotional susceptibility as being particularly relevant to the impact of hypothyroidism [51].

Hypothyroidism is implicated in many other diseases, involving most organs of the body, but is most extensively studied in terms of cardiovascular disease. Specifically, hypothyroidism is associated with reduced cardiovascular contractility, and its association with coronary artery disease has long been recognised [3]. Hypothyroidism also contributes to infertility [3, 4], and can cause reversible dementia, as well as neurosensory, musculoskeletal and gastrointestinal symptoms [3]. A considerable number of untreated patients with either overt or subclinical hypothyroidism show evidence of asymptomatic small fibre sensory neuropathy [5].

Diagnosis of Hypothyroidism

Hypothyroidism has a varied clinical presentation and non-specific symptoms, including weight gain, fatigue, poor concentration, depression, diffuse muscle pain, menstrual irregularities, and constipation [4], with no particular symptom definitively predicting the presence of hypothyroidism [52]. Furthermore, symptoms generally become apparent by the time (and even long-term after) circulating thyroxine levels have decreased [53]. As a result, patients with overt hypothyroidism exhibit a greater number of symptoms [27], but only some of them, such as constipation, dry skin, hair loss and proximal weakness, are more characteristic of thyroid failure [4]. While not definitive, use of symptoms to diagnose hypothyroidism is more successful in some population groups than in others. Symptoms more accurately predict overt hypothyroidism in men than in women [54], and in younger than older people, particularly in younger men compared with older women [55].

The diagnosis of hypothyroidism is therefore entirely based on repeated biochemical findings [3, 4, 26, 53, 55, 56].

An imbalance between reactive oxygen species and the anti-oxidant defence system, leading to an increased oxidative stress, has been described in humans and in animal models of hypothyroidism [57]. The pro-oxidant environment induced by hypothyroidism could promote the atherosclerotic processes frequently described in this condition. In an experimental model of hypothyroidism, the total nitric oxide synthase (NOS) activity increased and significant changes in the mRNA and protein expression of all three NOS isoforms were observed [58]. However, serum assays of pro-oxidant and anti-oxidant species are currently not included in the diagnostic work-up of hypothyroid patients.

Overt primary hypothyroidism is defined as serum TSH concentrations above, and free thyroxine concentrations below, the normal reference range [3, 53]. It is also important to note that reference ranges are a subject of ongoing debate and differ with the assay used, as well as by patient age, sex, and ethnic origin [3]. The upper limit of the TSH reference range generally increases with age in adults [3]. Furthermore, individuals have their own TSH reference range, which effectively covers only 25% of the reference range for the entire population [59].

LEVOTHYROXINE

Thyroid hormone replacement therapy with levothyroxine, the exogenous form of T4, has been the “gold standard” for the treatment of primary hypothyroidism for more than 60 years [60]. The first use of thyroid hormone to treat hypothyroidism was documented in the 1890s, when an ovine thyroid gland was grafted into a patient with myxoedema (severe hypothyroidism) [61]. Subsequently, sheep thyroid extract was injected into two patients with myxoedema [61, 62], with both showing an improvement in their condition. Extraction of the vital ingredient, thyroxine, followed in 1914, with its structure finally established a decade later [63, 64]. Synthetic formulations of thyroxine have been available for use since the 1950s. However, desiccated animal thyroid gland remained the mainstay of therapy until the 1970s [63, 64].

Thyroxine occurs naturally as a racemic mixture of levo (sodium L-thyroxine) and

dextro forms [64]. Levothyroxine was introduced in 1962 with the realization that the levo form was better absorbed and had greater physiological activity compared with the dextro form [63, 64]. In the 1970s, it was also noted that administration of both LT4 and LT3 was not required for successful treatment of hypothyroidism [65]. Because the T3 preparations have a short biological half-life, the treatment approach transitioned to LT4 monotherapy, such that today almost all patients with hypothyroidism receive once-daily synthetic thyroxine preparations [4].

Levothyroxine is available as tablets and soft-gel caps, intravenously, and, more recently, in liquid formulations (Table 1) [60, 65]. The liquid formulations demonstrate improved absorption when ingested with food, and have been developed with the aim of improving adherence [1, 65].

Because levothyroxine is classified as a narrow therapeutic index medication, indicating that small differences in dose or blood concentration may lead to therapeutic failure or adverse drug reactions [66], the American Association of Clinical Endocrinologists, American Thyroid Association (ATA) and the Endocrine Society recommended the consistent use of a single preparation of brand-name levothyroxine over generic preparations, which can vary in potency (Table 1) [2, 60, 63, 67, 68].

Levothyroxine is among the most widely prescribed medications in the world, and is one of the two most frequently prescribed medications in the US [60, 69, 70]. It is considered by the World Health Organization as an essential medicine for basic health care [22].

THE USE OF LEVOTHYROXINE TO TREAT HYPOTHYROIDISM

Upon diagnosis of hypothyroidism, lifelong treatment with levothyroxine is often initiated [4, 53, 67, 68, 71–73], except in cases where hypothyroidism is caused by transient forms of thyroiditis or by drugs which can be discontinued [50].

The starting dose of levothyroxine depends on patient age, the presence of co-existing cardiac disease, and the aetiology and the severity of the patient's biochemical hypothyroidism [2]. The levothyroxine dose is titrated until TSH levels are normalised [53, 71, 73] at between 0.4 and 4.0 mIU/L [68]. Healthy adult patients diagnosed with overt hypothyroidism aged less than 50 years usually receive the full replacement dose of levothyroxine (1.6 μg/kg/day) orally, while those with coronary artery disease or aged 50–60 years receive a lower starting dose (25–50 μg once daily) [71]. In pregnancy, dose adjustment of levothyroxine should aim to achieve TSH in the lower half of the trimester-specific range, when available, or below 2.5 mIU/L [74]. In subclinical hypothyroidism, doses around 50–75 μg may be sufficient for normalising the serum TSH.

Due to the long half-life of levothyroxine (1 week), TSH should be measured 4–6 weeks after initiation of therapy or dosage change. Thereafter, patients with stable normal serum TSH levels should be monitored every 12 months [67, 71, 73].

The goal of levothyroxine treatment is to reduce symptoms and prevent long-term complications [2, 53, 68, 71, 72]. Generally, disease control is easily accomplished, with full recovery upon adequate replacement of thyroid hormones [2]. Over a period of years, levothyroxine replacement dose may require adjustment as the disease progresses or if the patient develops other conditions that affect thyroid hormone metabolism [2]. Other factors that can lead to, or necessitate, an adjustment in levothyroxine dose include a lack of medication adherence, use of concomitant medications or dietary supplements such as calcium or iron, and changes in body mass and dietary habits [60].

UNRESOLVED ISSUES IN HYPOTHYROIDISM MANAGEMENT

Despite the switch to levothyroxine monotherapy in the 1970s [65], the need for combination therapy with levothyroxine + LT3 has been recently readdressed in several clinical guidelines [13, 75, 76]. More than a third of patients remain inadequately treated despite

levothyroxine therapy, with evidently elevated TSH levels and/or persistent symptoms [12, 13]. Even when TSH levels are controlled on levothyroxine, about 5–10% of treated hypothyroid patients have persistent symptoms for various reasons [76], including differences in individual set-points, coexistence of other autoimmune diseases, and failure to appropriately convert T4 to T3 with a low T3/T4 ratio, on levothyroxine monotherapy.

It has been argued that, in such patients, the addition of synthetic LT3 to standard LT4 therapy would create a more natural treatment plan [13]. The majority of Clinical Guidelines have addressed this issue and recommend against the routine use of combination therapy, but European, UK and ATA guidelines recommend combination therapy as an individual experimental approach, but only in some circumstances [13, 65, 68, 76]. The 2012 European Thyroid Association guidelines only recommend combination therapy as an experimental approach in patients with ongoing symptoms despite good adherence to LT4 therapy, and a serum TSH within the normal reference range for longer than 6 months [76]. The Italian Society of Endocrinology and the Italian Thyroid Association endorsed this instance in a 2016 paper [77]. Prior to commencing combined therapy, other autoimmune conditions (e.g. type 1 diabetes mellitus, autoimmune B12 deficiency, adrenal insufficiency, coeliac disease) must be ruled out and, if symptoms do not improve after 3 months, the patient should be shifted back to T4 monotherapy [76].

Another matter of debate is the treatment of subclinical hypothyroidism with levothyroxine. While there is consensus on the need to treat subclinical hypothyroidism with levothyroxine in pregnant women and in those contemplating pregnancy, in order to decrease the risk of pregnancy complications and effects on infant cognitive development, treatment of non-pregnant adults remains controversial [78]. Subclinical hypothyroidism is considered a sign of early thyroid failure [3, 79–81] and is defined as serum TSH concentrations above the reference range associated with a normal concentrations of free thyroxine. However, there is debate about which upper reference range of serum TSH should be used as a threshold for treatment [3, 80, 81]. It is believed that treatment of subclinical hypothyroidism with levothyroxine may prevent progression to overt hypothyroidism, as well as reduce the occurrence of coronary artery disease and improve neuropsychiatric and musculoskeletal symptoms associated with hypothyroidism

Table 1 Available formulations of levothyroxine

Product	Manufacturer	Initial AB, subsequent AB	AB rating
Tablets			
Unithroid	Stevens	BX	AB1, AB2, AB3
Synthroid	Abbvie	BX	AB1, AB2
Levoxyl	King	BX	AB1, AB3
Levo-T	Alara	BX	AB1, AB2, AB3
LT4	Mylan	BX	AB1, AB2, AB3, AB4
Soft-gel caps			
Tirosint	IBSA	None	None
Intravenous			
LT4	Fera pharm	AP	
LT4	Fresenius	AP	
LT4	Par sterile	AP	
Liquid			
Tirosint-SOL	IBSA		

AB rating indicates interchangeability across formulations where AB1 = therapeutic equivalence with Unithroid; AB2 = therapeutic equivalence with Synthroid; AB3 = therapeutic equivalence with Levoxyl; AB4 = therapeutic equivalence with Levothroid (ThyroTabs); and BX = data are insufficient to determine therapeutic equivalence and therefore presumed non-equivalent. *AP rating* also indicates clear in vivo and/or in vitro evidence of equivalence for aqueous solutions

[82, 83]. However, these benefits must be balanced against the risk of cardiovascular, neuropsychiatric and musculoskeletal side effects associated with the administration not only of excess levothyroxine but also of a normal substitution dose [82]. Indeed, there is evidence to suggest that, at least in very old patients, subclinical hypothyroidism may confer a longevity benefit over euthyroidism, with patients with lower levels of circulating T4 living longer [84]. Since there is currently a lack of data regarding the benefits/risks of treatment of subclinical hypothyroidism [80, 81, 83, 85], the decision on whether or not to treat should be individualised [79, 80].

Further studies are clearly warranted in the areas of subclinical hypothyroidism and regarding the use of levothyroxine monotherapy versus combination therapy with LT3. The rates of underdiagnosis and undertreatment of hypothyroidism and the issue of iodine insufficiency must also be addressed. However, lifelong treatment with levothyroxine has successfully treated many people with hypothyroidism over the last 60 years, and will continue to benefit many others in the future.

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