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Primary hypothyroidism and quality of life

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Abstract

In the 1970s, treatment with thyroid extract was superseded by levothyroxine, a synthetic L form of tetraiodothyronine. Since then, no major innovation has emerged for the treatment of hypothyroidism. The biochemical definition of subclinical hypothyroidism is a matter of debate. Indiscriminate screening for hypothyroidism has led to overdiagnosis and treatment initiation at lower serum levels of thyroid-stimulating hormone (TSH) than previously. Adverse health effects have been documented in individuals with hypothyroidism or hyperthyroidism, and these adverse effects can affect health-related quality of life (QOL). Levothyroxine substitution improves, but does not always normalize, QOL, especially for individuals with mild hypothyroidism. However, neither studies combining levothyroxine and liothyronine (the synthetic form of tri-iodothyronine) nor the use of desiccated thyroid extract have shown robust improvements in patient satisfaction. Future studies should focus not only on a better understanding of an individual's TSH set point (the innate narrow physiological range of serum concentration of TSH in an individual, before the onset of hypothyroidism) and alternative thyroid hormone combinations and formulations, but also on autoimmunity and comorbidities unrelated to hypothyroidism as drivers of patient dissatisfaction. Attention to the long-term health consequences of hypothyroidism, beyond QOL, and the risks of overtreatment is imperative.

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Author contributions

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Competing interests

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Treatment of hypothyroidism with thyroid extract was replaced by synthetic levothyroxine in the 1970s. A decade later, the development of sensitive thyroid-stimulating hormone (TSH) assays led to a reduction in the average daily dose of levothyroxine, following the demonstration that serum TSH was often suppressed, indicating overtreatment[1]. Patient dissatisfaction with levothyroxine became evident in the 1990s[1]. Evidence from rodent experiments highlighted that levels of tri-iodothyronine (T_3) in tissues could only be reproduced by continuous administration of both liothyronine (the synthetic form of T_3) and levothyroxine[2]. This finding prompted studies to investigate the efficacy of using a combination of levothyroxine and liothyronine. Interpretations of these studies vary[3], and guidelines have struggled to translate the evidence into clear clinical messages[4,5]. In the meantime, indiscriminate screening has led to overdiagnosis of hypothyroidism, and the biochemical threshold for initiating treatment has been lowered[6]. Treatment of hypothyroidism with a combination of liothyronine and levothyroxine has become more widespread and is promoted by some experts and patient advocates[7–10], in the absence of clear evidence of benefit (discussed in this Review). Such treatments might lead to suppression of serum levels of TSH[11], which is concerning as evidence from the past few years points to associations of both raised and suppressed serum levels of TSH with increased mortality[12,13] and dementia[14,15]. As we enter the third decade of the twenty-first century, uncertainty about the optimal treatment of hypothyroidism prevails. Much of the debate is driven by considerations of the response to treatment as measured by quality of life (QOL).

This Review aims to interpret the clinical observations of patient dissatisfaction despite good biochemical management in the context of insights from recent studies into the molecular actions of thyroid hormones[16] and an understanding of the determinants and utility of patient-reported QOL in patients with both overt and subclinical primary hypothyroidism. It differs from many other excellent reviews on hypothyroidism by including authors who have been involved not only in generating the primary laboratory and clinical evidence, which is the subject of this Review Article, but who also represent a range of views as to the aetiology of impaired QOL in primary hypothyroidism.

Definition of hypothyroidism

The diagnosis of primary hypothyroidism depends on an elevated serum level of TSH, reflecting the high sensitivity of the hypothalamic–pituitary axis to changes in circulating levels of thyroid hormones[16]. The earliest stage of hypothyroidism occurs when the circulating level of TSH is elevated while thyroid hormone levels are normal. The initial description of subclinical hypothyroidism stated that it is asymptomatic, but also recognized a second stage of mild hypothyroidism associated with nonspecific symptoms, normal tetraiodothyronine (T_4) levels and increased TSH levels[17]. In overt hypothyroidism, thyroid failure progresses to a low serum level of free T_4, accompanied usually, but not always, by symptoms[18]. The term ‘mild hypothyroidism’ has been largely abandoned in favour of a binary classification of subclinical or overt hypothyroidism. However, in 2015, a call was made to revive this category based on a TSH cut-off of 10 mU per litre[19], although a quarter of the original group of patients with mild hypothyroidism actually had TSH levels below 10 mU per litre[18]. In a 2019 review of 20 surveys from across Europe, 4.7% of the population

had undiagnosed hypothyroidism, which was subclinical in 4.1% of these individuals[20]. This finding reflects the high prevalence of the disease and the poor performance of classic symptoms of hypothyroidism in indicating hypothyroid disease[21].

Free T_4

T_4 that is not bound to protein in the circulation and is therefore available to act on tissues

TSH and thyroid hormone levels are treated as univariate in the standard classification of hypothyroidism; however, a multivariate approach might allow a more accurate diagnosis of euthyroidism[22]. In studies of euthyroid populations without thyroid disease, a reduction in levels of free T_4 and, to a lesser extent, levels of free T_3 show stronger associations with adverse outcomes than reduced levels of TSH[23]. Thus, an elevated TSH level is a valuable test with which to detect primary hypothyroidism but might be less helpful at indicating hypothyroidism within the tissues. Additionally, elevated levels of TSH can be due to causes other than primary hypothyroidism (BOX 1). TSH levels rise with age, so that the upper limit of the reference range might be shifted upwards by 3 mU per litre in those who are 70–89 years old[24]. Not recognizing this fact can lead to overdiagnosis of subclinical hypothyroidism[24,25]. Individuals aged over 55 years with TSH levels in the upper tertile of the normal range live longer than individuals with levels in the middle and lower tertiles, suggesting the need for age-specific reference intervals for TSH[26]. A single measurement of elevated levels of TSH can normalize naturally, especially if TSH levels are below 10 mU per litre, and repeated measurements are required to confirm hypothyroidism[27]. Obesity and smoking are associated with minor elevations in levels of TSH[28], whereas levels of TSH tend to be lower in pregnancy than in non-pregnant women[29]. Additionally, TSH has a diurnal rhythm (amplitude 0.4 mU per litre, with acrophase at 3 am)[30]. However, these factors are unlikely to cause difficulty in making a diagnosis of hypothyroidism.

Acrophase

The time at which a peak in a circadian rhythm occurs

Pathophysiology of hypothyroidism

Thyroid hormone signalling.

The thyroid gland contributes all of the T_4 and approximately 20% of the T_3 in the circulation; the remaining T_3 is produced peripherally, through T_4 deiodination[3]. Although circulating levels of T_3 are critical to systemic thyroid hormone action, there is also substantial physiological control that is tissue-specific[16,31]. In addition, most studies focus on T_3 as the key mediator of thyroid hormone signalling, but a 2021 study indicates that T_4 itself might be able to trigger biological effects that are distinct from those triggered by T_3 (REF.[32]).

Several tissues express type 1 iodothyronine deiodinase (DIO1) and type 2 iodothyronine deiodinase (DIO2), allowing the tissues to convert T_4 to T_3 and return T_3 to the circulation. Studies using rat models revealed that T_3 produced in the liver via DIO1 returns rapidly to the circulation, whereas T_3 produced in the brain, pituitary and brown adipose tissue via DIO2 remains in the tissue much longer and can initiate thyroid hormone signalling locally[33,34]. This is because DIO1 resides in the cellular plasma membrane whereas DIO2 resides in the endoplasmic reticulum, closely associated with the nucleus[35]. Therefore, thyroid hormone signalling in tissues that express DIO2 is defined by the sum of incoming T_3 from the serum (which normally occupies approximately 50% of the thyroid hormone receptors) and T_3 produced intracellularly via deiodination. This additional (intracellular) source of T_3 can elevate thyroid hormone receptor occupancy up to nearly 100%, thereby enhancing thyroid hormone signalling[36]. A unique property of DIO2 is its 'self-destructive' behaviour triggered by T_4, namely, the process of T_4 activation to T_3 ubiquitinates DIO2, tagging it for destruction in the proteasomal system[37]. As a result, during hypothyroidism, the fractional activation of T_4 to T_3 is accelerated, whereas in hyperthyroidism the opposite is seen.

A third deiodinase, DIO3, inactivates both T_4 and T_3, which terminates thyroid hormone action[16]. The prevalent paradigm suggests that local thyroid hormone signalling reflects the balance between the activating and inactivating activities of DIO2 and DIO3, respectively[16,31]. Thus, local control of thyroid hormone signalling is tightly coordinated and the intensity of thyroid hormone signalling can differ among tissues. A key implication of this fact is that optimization of thyroid hormone replacement based on an index, such as serum levels of TSH, that is exclusively secreted by the pituitary gland might be sub-optimal or detrimental for other tissues (such as liver, skeletal muscle, adipose tissue or bone).

Serum levels of TSH as a diagnostic tool.

The medial basal hypothalamus (MBH) and the pituitary gland function as a unit to determine the activity level of the thyroid gland. This unit constantly monitors circulating levels of T_4 and T_3, leading to adjustments in TSH secretion[38]. Whereas T_3 in serum can be detected directly by the MBH and pituitary cells, T_4 in the serum must be converted to T_3 before being detected by the MBH–pituitary unit. Detection of T_4 is possible because the MBH and pituitary gland express the highest level of DIO2 in the brain, converting T_4 to T_3 inside the thyrotrophs and tanycytes that are located near the thyrotropin-releasing hormone (TRH)-secreting neurons[38] (FIG. 1).

Thyrotrophs

Cells in the anterior pituitary gland that secrete TSH

Tanycytes

Specialized ependymal cells lining the walls of the third ventricle

The MBH–pituitary unit is highly sensitive to changes in levels of T_4 and T_3. A small drop in the serum levels of T_4 immediately reduces T_3 signalling in the MBH and pituitary, increasing secretion of TRH and TSH[38]. The reduction in T_3 signalling occurs only because DIO2 is much less sensitive to tagging with ubiquitin in the MBH and pituitary gland than in other tissues, faithfully transducing serum levels of T_4. In other words, the levels of T_3 in the MBH and pituitary are an accurate reflection of serum levels of T_4 (REF.[39]). Although a drop in serum levels of T_3 also stimulates TSH secretion, the homeostatic mechanisms that preserve serum levels of T_3 during hypothyroidism minimize its value as a diagnostic tool. The unique regulation of DIO2 in the MBH–pituitary unit makes serum levels of TSH an excellent index of thyroid activity, and an ideal biochemical marker for diagnosis of primary hypothyroidism. Nonetheless, strictly speaking, TSH levels reflect thyroid hormone signalling in the pituitary. Ideally, the identification of other markers that reflect thyroid hormone signalling in other tissues would provide a much more concise picture of global thyroid status.

TSH levels during levothyroxine treatment.

The advent of synthetic levothyroxine and sensitive TSH immunoassays led to the therapeutic goal of hypothyroidism treatment being switched from clinical to biochemical, that is, the normalization of serum levels of TSH. However, this rationale is flawed because the MBH–pituitary unit adjusts its secretion of TSH in response to changes in the levels of both T_3 and T_4, not T_4 alone.

Typically, the dose of levothyroxine given to patients with hypothyroidism is adjusted with progressive elevation in T_4 levels at intervals of 4–6 weeks. Studies in rats have shown that, as this is happening, T_4 converts to T_3 in the MBH and pituitary via the DIO2 pathway, slowing down TSH secretion[38,39]. T_4 is also converted to T_3 in all peripheral tissues via the DIO1 and DIO2 pathways, elevating serum levels of T_3. However, normalization of T_4 levels does not normalize serum levels of TSH because direct thyroid secretion of T_3 is missing in patients with hypothyroidism and serum levels of T_3 are relatively low when compared with healthy individuals with similar TSH levels. This scenario has been found in rat models as well as in patients treated with levothyroxine. To correct this issue, the physician further increases the dose of levothyroxine. This increased dose slightly elevates serum levels of T_4 to a sufficient degree to normalize T_3 content in the MBH and pituitary gland, which in turn normalizes TSH levels. However, T_4 to T_3 conversion is less efficient in the periphery compared with in the MBH–pituitary unit because T_4 accelerates DIO2 ubiquitination and degradation[39], and DIO1 activity is only fully normalized once T_3 levels are fully restored, which limits the increase in circulating levels of T_3 (REF.[40]). Thus, typically a patient treated with levothyroxine might have normal serum levels of TSH, but with T_4 levels at, or slightly above, the upper limit of the normal range and serum levels of T_3 at, or slightly below, the lower limit of the normal range (FIG. 1).

Studies in patients with hypothyroidism and rat models have shown that, in some tissues, thyroid hormone signalling remains subnormal under the scenario described earlier in this Review (normal TSH, marginally high free T_4, marginally low free T_3)[2,39,41,42]. Some patients seem to be more affected than others, which might reflect polymorphisms in genes

encoding thyroid hormone transporters and DIO2 (REFS[43,44]), or inactivating mutations in the gene that encodes DIO1 (REF.[45]). These compounding factors would exaggerate differences between the MBH–pituitary unit compared with the periphery in their ability to activate T_4 to T_3. Many of these findings were obtained in levothyroxine-treated rat models, which faithfully reproduce a normalization of serum levels of TSH at a high T_4 to T_3 ratio[16].

Generalized versus local tissue hypothyroidism.

Impaired cognition and feeling tired are among the main concerns of symptomatic patients treated with levothyroxine[46,47]. This observation suggests that T_3 content in the brain is not fully restored by levothyroxine monotherapy. Indeed, the brain responds to subtle changes in local thyroid hormone signalling[48], and is unique in that deiodinases play a substantial part in determining thyroid hormone signalling in the brain[49]. DIO2 is expressed in glial cells[50,51] and the paracrine signalling by glial cell-derived T_3 activates neuronal gene expression[52]. It is estimated that more than half of the thyroid hormone receptors in the brain are occupied with T_3 produced in glial cells[34,49]. This scenario sets conditions that maximize the impact of even minor defects in the DIO2 pathway, such as gene polymorphisms. A mouse with glial-specific inactivation of the *Dio2* gene exhibited depression–anxiety behaviour[53], compatible with a localized reduction in thyroid hormone signalling.

Some patients with hypothyroidism carry the Thr92Ala-*DIO2* polymorphism[54], which reduces DIO2 activity by around 20%. These patients have improved clinical response to therapy containing liothyronine in some, but not all, studies[43]. This finding supports the idea of potential hypothyroidism within the brain in patients taking levothyroxine[54]. Indeed, a subsequent study showed that the association between therapy that contains liothyronine and improved clinical outcomes became even stronger when a polymorphism in the thyroid hormone transporter MCT10 was also considered, although the small sample size was a serious limitation[43,55]. The fact that this polymorphism is prevalent (the minor allele frequency varies between 17% and 47%)[43] and that study outcomes are not readily reproducible across different populations is puzzling. Further studies on molecular signalling of thyroid hormone and tissue-specific responses should clarify the relationship between genetic polymorphisms, treatments for hypothyroidism and QOL.

Unmet patient needs in hypothyroidism

The aim of treatment in primary hypothyroidism is defined as levels of TSH within the reference range, without stipulations regarding symptoms[29]. We have highlighted the pathophysiological issues that this goal raises. In practice, some patients receiving conventional levothyroxine treatment do not return to the premorbid state when the TSH level is normalized. For example, more patients taking levothyroxine had impaired QOL scores, as judged by questionnaires, compared with controls not taking levothyroxine in a cross-sectional primary care survey[46]. In addition, treated patients had poorer cognitive function and wellbeing compared with national reference values for these tests[47]. Furthermore, anxiety and depression scores were higher in women with hypothyroidism taking levothyroxine than in those who were not[56]. Online surveys have confirmed such

dissatisfaction and shown that this was worse in those taking levothyroxine alone or combined with liothyronine compared with those taking desiccated thyroid extract (DTE)[57]. However, the differences between these groups were small, and overall between 20% and 60% of patients remained dissatisfied regardless of treatment (FIG. 2).

These studies have inherent biases owing to subjectivity, case ascertainment and response rates, which favour inclusion of those who have symptoms and particular disease-related beliefs. The persistent symptoms reported are often nonspecific (for example, tiredness, depression and ‘brain fog’), but might include feeling cold, hoarseness, dry skin, weight gain and constipation; hypothyroid-like symptoms can overlap with the experiences of the euthyroid population[18].

Such dissatisfaction demands attention given the large number of people with hypothyroidism and the increasing prescription of levothyroxine, particularly for subclinical hypothyroidism[58,59]. There are three possible explanations for this patient dissatisfaction, which are not mutually exclusive. The first possibility is that treatment with levothyroxine alone is physiologically unable to achieve adequate T_3 levels in the tissues, possibly determined by genetic polymorphisms in deiodinases and hormone transporters. Alternatively, the symptoms could be due to an ongoing autoimmune process rather than hypothyroidism[60,61]. The final possibility is that the symptoms these patients are experiencing are unrelated to their thyroid disease. In this regard, similar symptoms have been reported in many other disorders, including Addison disease[62], and any diagnostic labelling can itself be associated with poorer self-rated health than for individuals without a diagnosis[63]. Moreover, persistent unexplained physical symptoms are common in primary care[64]. Given the prevalence of thyroid dysfunction[20], it is inevitable that new cases of hypothyroidism will be discovered coincidentally in such patients. The situation is aggravated by inappropriate treatment of equivocal TSH abnormalities.

Patient expectations for the effect of hypothyroidism therapy are increasing, in some cases driven by poor online information or distorted by healthism[65]; meanwhile, professional certainty over the optimal treatment for hypothyroidism seems to be declining among physicians[5].

Tools for QOL determination

QOL is a complex and challenging concept, though it is commonly used and broadly correlates to an individual’s wellbeing[66]. Health-related QOL (HRQOL) encompasses the parts of QOL that relate to health. HRQOL is multi-dimensional and based on perceptions of health, including physical, social and psychological factors[67]. HRQOL might be unaffected in individuals who have a disease when they are asymptomatic and unaware of it. In this context, it is interesting that in a large population study, hypothyroidism identified by screening during the study was not associated with perceived poor health, whereas individuals who already had the diagnostic label of hypothyroidism reported poor health despite being treated[63]. Researchers have developed techniques that conceptualize and measure the multiple domains of HRQOL[67]. HRQOL is of particular importance when a treatment causes unwanted adverse effects, even while other outcome measures (such

as survival) might be favourable. From the perspective of clinical research, HRQOL is an important metric that complements other measures of treatment efficacy. HRQOL is usually measured by patients' self-rating. The tools can be generic or disease-specific; the latter are more sensitive, while the former allow comparisons across diseases[68]. The choice of HRQOL tool depends on whether it is intended to inform patients and healthcare professionals about the HRQOL benefit of an intervention or to inform policy makers about the relative value of a treatment.

Three often-used, generic HRQOL questionnaires are EQ-5D, SF-36 and WHOQOL, which have been validated and tested for cross-cultural applicability[69–72]. A variety of generic questionnaires have been used in studies of patients with hypothyroidism[73] (TABLE 1). Single-item scores for HRQOL alone are considered insufficient to demonstrate the relative effectiveness of one intervention compared with another because they are subject to bias and often too crude to detect changes in health. The European Network For Health Technology Assessment recommends that HRQOL questionnaires should be completed by the patients themselves[73], given that biases due to the use of proxies have been identified repeatedly[74–76]. Furthermore, they recommend that HRQOL measures must be valid, reliable, responsive and acceptable[77,78].

Responsive

The responsiveness of an instrument determines its ability to detect relevant clinical changes over time

Acceptable

How acceptable an instrument is determines its ease of use by participants

Several disease-specific tools have been developed for thyroid diseases and used in trials of patients with hypothyroidism (TABLE 1). An extensive review of thyroid-related HRQOL tools[68] identified three questionnaires pertaining to hypothyroidism, the Chronic Thyroid Questionnaire[79], the Thyroid Symptom Questionnaire (TSQ)[46] and the Underactive Thyroid-Dependent Quality of Life Questionnaire[80]. However, robust validation was lacking for all three (absence of evaluation by qualitative studies, cognitive interviewing, clinical known-groups comparisons, multitrait analyses, differential item functioning and structural equation modelling[81]). It also became apparent that patients with thyroid conditions and clinicians had different and complementary perspectives on HRQOL[82]. Whereas patients were primarily concerned about the psychosocial impact on their everyday condition, clinicians were focused on disease characteristics (such as physical symptoms and signs of hypothyroidism)[83].

The realization that there was a need for a sensitive and validated HRQOL tool led to the development of Thyroid Patient Related Outcome (ThyPRO)[81,82] for patients with benign thyroid diseases. ThyPRO consists of 13 scales (FIG. 3). Four of these pertain to symptoms associated with goitre, hypothyroidism, hyperthyroidism and eye symptoms. The remaining scales cover mental health symptoms, function and wellbeing, and participation

and functionality in social situations. Clinical validity and the test–retest reliability of the ThyPRO questionnaire were found to be high[82]. Prospective evaluation of responsiveness of ThyPRO in a large cohort of patients with hypothyroidism, hyperthyroidism and non-toxic goitre showed that ThyPRO was responsive to treatment across the range of benign thyroid diseases and performed better than SF-36 (REF.[81]). Psychometric modelling supported the construct validity of ThyPRO; however, some potential problems were identified (the questionnaire was long (85 items) and reported in numerous (13) scales)[84,85]. These potential shortcomings and the fact that ThyPRO is lengthy led to the development of a shorter 39-item version[86], which was found to preserve responsiveness, clinical validity and test–retest reliability. Cross-cultural validity has since been demonstrated for this shorter version[87] and the minimal important change was defined in 2021[88]. ThyPRO has been translated into 19 languages[89]. The short version of ThyPRO[86] seems to be the most appropriate tool for studying HRQOL in patients with hypothyroidism (FIG. 3).

Test–retest reliability

Stability of the scores obtained from the same person on two or more separate occasions

Minimal important change

The smallest change in an outcome that is perceived by an individual patient as important

Effect of treating mild hypothyroidism

Impact of levothyroxine treatment on QOL.

Although patients with mild or subclinical hypothyroidism might have more symptoms (such as tiredness and cognitive issues) compatible with hypothyroidism compared with euthyroid patients[90], there is very limited evidence to support QOL improvements with levothyroxine replacement in these patients. Overall, 11 studies have randomized patients with subclinical hypothyroidism to receive levothyroxine or placebo and reported subjective outcomes[91–100] (TABLE 1). These studies are mostly small and quite heterogeneous, with four studies recruiting mainly older participants (median age >65 years, n = 9,732)[96,99,101], whereas the remaining seven studies recruited younger patients (mean age 50 years, n = 466). Most studies examined more than one subjective outcome and the overall conclusion from meta-analyses is that levothyroxine did not improve symptoms, QOL or cognition[102,103].

Nevertheless, the two largest studies are notable for their differences in design and outcomes[95,101]. The ‘TRUST’ study randomized 737 older people (median age 74 years) recruited largely from primary care databases to receive levothyroxine (median dose 50 μg daily) or placebo for a year[101]. The mean TSH level before treatment was 6.4 mU per litre in the participants randomized to levothyroxine, falling to a mean of 3.6 mU per litre during treatment. Although this study was originally designed to examine vascular endpoints, only three patients died of cardiovascular events, and the primary outcomes became fatigue and QOL, which were measured using ThyPRO. However, because of the recruitment strategy,

patients had QOL scores indicating a low symptom burden at the study commencement and these scores were not improved by a small dose of levothyroxine. Further analysis of participants aged 80 years or older from this study and another trial of similar design with mean baseline TSH values of 6.3–6.4 mU per litre (n = 251 in total) also showed no positive effect of levothyroxine treatment on QOL scores[99]. By contrast, a 2007 study[95] performed a crossover study of 100 younger patients (mean age 54 years), with a median TSH of 5.2 mU per litre on placebo and 0.5 mU per litre while taking 100 μg levothyroxine daily. They found a statistically significant reduction in reported tiredness from 89% to 78% during levothyroxine treatment, however, all other QOL indicators, including SF-36, were not significantly changed. Three of the other studies in younger participants (mean ages ranging from 34 to 58 years) also found statistically significant benefits from levothyroxine treatment[92,98,100], whereas one study showed more anxiety symptoms in the active treatment arm[93].

Although most of the current evidence is derived from these two larger studies[95,101], neither study was perfect in design, and the levothyroxine doses and achieved serum concentrations of TSH were quite different. It is unknown whether treatment of subclinical hypothyroidism in elderly participants who have symptoms of hypothyroidism or whose TSH values at the start of the study are clearly above an age-adjusted reference range might still show some symptomatic benefits. In addition, there is little good-quality evidence to inform management of younger people less than approximately 60 years of age with subclinical hypothyroidism. Based on these studies, clinical guidelines do not recommend treating subclinical hypothyroidism in elderly people unless their serum levels of TSH rise to 10 mU per litre or higher[104,105]. However, the guideline endorsing a cut-off of 20 mU per litre[105] is based on a meta-analysis[103] in which the mean pooled baseline TSH values of patients included in the respective outcome meta-analyses were in the range of 6.4–7.3 mU per litre, with the upper limit of the 95% confidence intervals being 6.9–8.8 mU per litre[106]. By contrast, European and North American guidelines endorse a time-limited trial of levothyroxine therapy in symptomatic younger individuals as clinical experience shows that around 40% of these individuals will experience some subjective improvement[29,104]. Although there are signals of these positive effects in several of the randomized trials in younger participants[92,93,98,100], these findings remain to be confirmed in larger, longer duration trials conducted in this age group.

Effect of treating overt hypothyroidism

Impact of no treatment compared with levothyroxine on QOL.

Signs and symptoms of overt hypothyroidism resolve with initiation of levothyroxine therapy[18]. However, there are few studies examining QOL when patients with hypothyroidism are initiated on levothyroxine therapy and clearly such studies are uncontrolled unless there is a subgroup of untreated patients. A mixed study of 78 patients with overt or subclinical hypothyroidism with a median age of 47 years showed that levothyroxine administration improved 9 of 13 ThyPRO scales and 5 of 8 SF-36 scales, although there were still deficits compared with normative data and only 12 participants had overt hypothyroidism[107] (FIG. 3). In another study in which patients with overt

hypothyroidism were started on a full replacement dose of 1.6 μg/kg levothyroxine versus a 25 μg dose with incremental increases once every 4 weeks for 24 weeks, clinical symptoms and QOL measured using the RAND-36 questionnaire had improved in both groups by 24 weeks[108] (TABLE 2).

However, there are several studies in which participants underwent a reversal of therapy, and levothyroxine was withheld during procedures for diagnosis or treatment of thyroid cancer (TABLE 2). Although these patients developed profound hypothyroidism, it was of relatively abrupt onset and short duration and so the effects on QOL might differ from those occurring with chronic hypothyroidism. For example, in a 2006 study using the SF-36 to assess QOL, withdrawal from levothyroxine led to a decline in all eight domains compared with both withdrawal and recombinant TSH (rTSH) groups at baseline and the rTSH group following rTSH administration[109]. The SF-36 scores were similar to those reported by patients with heart failure and depression, indicating a substantial decrease in QOL. Similar declines in QOL during levothyroxine withdrawal compared with use of rTSH were seen in other studies using a questionnaire designed by the investigators[110] and using the Functional Assessment of Chronic illness Therapy-Fatigue (FACT-F) questionnaire and a visual analogue scale[111]. In another study, FACT-F scores worsened with increased duration of levothyroxine withdrawal[112]. In summary, although these studies do not provide randomized control trials of levothyroxine versus placebo for treatment of overt hypothyroidism, the benefits to QOL of treating overt hypothyroidism are undisputed and can be inferred from these ‘withdrawal’ studies.

During levothyroxine treatment.

Patients with hypothyroidism have impaired QOL compared with populations without hypothyroidism, despite achieving normal levels of TSH (TABLE 2). This was shown in a study in which surveys were sent to patients with hypothyroidism undergoing treatment and age-matched and sex-matched control individuals without hypothyroidism. Worse psychological wellbeing measured using the General Health Questionnaire (GHQ) was found in patients with hypothyroidism compared with control individuals[46]. Another study found impaired wellbeing in treated patients compared with standard reference values[47]. Similarly, in a study of treated patients versus healthy controls, the TSQ, symptom number and tiredness, Beck’s depression inventory, and Well-Being Questionnaire-12 (WBQ-12) were worse in the treated patients[113]. QOL in patients with hypothyroidism might be worse in those with higher BMIs[114]. Two blinded trials that altered the levothyroxine dose in patients receiving monotherapy to achieve different TSH values did not show resultant changes in the QOL of patients with hypo thyroidism[115,116] (TABLE 2). Notably, one of these studies found that participants preferred the dose of levothyroxine that they perceived to be higher, irrespective of the actual dose administered[116].

By contrast, a cross-sectional study showed worse QOL according to the Hypothyroidism Symptom Rating Questionnaire (ThySRQ) for patients whose TSH values were in the upper part of the normal range compared with those whose TSH values were in the lower part of the normal range[113]. Undertreatment of patients, regardless of whether the iatrogenic (undertreated) hypothyroidism is subclinical or overt, resulted in decreased QOL

as measured by the SF-36 questionnaire[117]. However, in another study of patients being treated for hypothyroidism, QOL measured using the RAND 36-Item Health Survey did not differ between euthyroid individuals and those with either iatrogenic, subclinical or overt hypothyroidism[118]. There do not appear to be controlled trials of the effect of levothyroxine formulations on QOL. In one uncontrolled trial of patients taking levothyroxine tablets 30–60 minutes before breakfast who were switched to liquid levothyroxine with breakfast, there was an improvement in the ThyTSQ score[119]. However, given that both the levothyroxine formulation and the levothyroxine timing were changed simultaneously, it is difficult to determine which contributed to the improved TSQ score.

Levothyroxine and liothyronine combination treatment.

Fifteen randomized, controlled trials have examined the effect of levothyroxine and liothyronine combination therapy compared with levothyroxine monotherapy on various parameters (13 of these have been reviewed in a clinical practice guideline for the treatment of hypothyroidism[120])[121,122]. Fourteen trials examined mood or QOL and ten of these 14 trials did not show improvement in these parameters. Two trials showed improvement in multiple measures[123,124], whereas two trials showed improvement in a minority of measures[125,126] (TABLE 2). Several trials showed a placebo effect during the levothyroxine therapy arm, as suggested by the improvement of QOL measurements in both treatment groups despite no change in levothyroxine dose[120,123]. In a 1999 trial[124], the improvement was seen in the Profile of Mood Scores and a Visual-Analogue scale assessing mood and physical symptoms. In a 2009 trial[123], improvement was seen in the SF-36 questionnaire, the Beck's depression inventory, and the SCL 90-R scale. In a 2005 trial[126], there was improvement in the GHQ scores in both groups at 3 months, with significantly more benefit in the combination therapy group, which was not maintained at 12 months. During a further 2009 trial[125], the only improvement in patients receiving combination therapy was a decreased score in the anxiety and/or insomnia subscale of the GHQ-28, without changes in other subscales. By contrast, one substantial study found statistically significant worsening of GHQ-28 scores and increases in anxiety and nausea in the combined levothyroxine and liothyronine group[127]. Taken together, these studies do not suggest a beneficial effect of levothyroxine and liothyronine therapy for most participants.

Despite the lack of clear benefit of combination therapy, a 2021 consensus statement concluded that future trials that addressed some of the shortcomings of the prior trials could potentially be worthwhile[128,129]. The shortcomings identified in these published trials included many small studies with inadequate power, short-duration studies, failure to include patients who remained symptomatic while taking levothyroxine therapy, use of once-daily liothyronine administration and failure to study thyroid-specific patient-reported outcomes. With respect to adequate power, there has yet to be a prospective, adequately powered study of the effect of deiodinase polymorphisms or other genetic variants relevant to thyroid hormone homeostasis on patient response to therapy. Future studies that address these critiques, and potentially utilize a sustained-release liothyronine preparation, are anticipated now that the phase I trial of such a preparation has been completed. The results of a pharmacokinetic study of a sustained release T_3 preparation (polyzincliothyronine)

have been published online[130] and a sustained release T_4 and T_3 combination might be forthcoming.

Desiccated thyroid hormone treatment.

Several surveys and uncontrolled studies suggest that patients prefer DTE treatment to levothyroxine treatment[7,8,57,131], probably based on participant self-selection for unblinded treatments, but only two randomized studies have compared DTE to levothyroxine[122,132]. Using a crossover design, patients received each therapy for 16 weeks, and neurocognitive testing was performed at baseline and at the end of each period[132]. Despite marked biochemical differences characterizing the two therapies (lower free T_4 while taking DTE; higher T_3 with DTE), there were no differences in the primary outcomes, including memory, mood and QOL (TABLE 2). The QOL measures included a modified TSQ and the GHQ-12. There was a preference for DTE in 49% of the participants. A second randomized crossover study of 75 people confirmed no QOL benefit from DTE treatment compared with levothyroxine monotherapy or combined levothyroxine and liothyronine treatment[122].

Effect of overtreatment on QOL.

The thyrotoxic state can be associated with neuropsychiatric symptoms, including euphoria[133]. Large doses of liothyronine have been used in euthyroid patients with depression, with apparently some efficacy[134]. Thyroid hormone ingestion in excess can, at least for some patients, improve HRQOL[135]. The long-term repercussions for morbidity and mortality of such overtreatment, well documented for levothyroxine[12,13], remain unclarified for levothyroxine and liothyronine combination treatment.

Thyrotoxic

A metabolic state characterized by elevated serum levels of tri-iodothyronine

Horizon scanning.

The fact that the commonest cause of hypothyroidism is autoimmune and that its clinical phase is preceded by subclinical disease defined by the presence of autoantibodies[3] suggests potential interventions aimed at arresting or reversing the autoimmune attack. Emerging insights into the regulation of the autoimmune response[136] might lead to therapies other than hormonal substitution, with potentially complete restoration or prevention of impairment of HRQOL. Regenerative medicine might also be able to offer novel solutions to patients with established hypothyroidism of other aetiologies[137].

Conclusions

The appropriate threshold of serum levels of TSH at which to initiate levothyroxine treatment is still debated and has been falling over the past 20 years[6]; meanwhile, hypothyroidism is diagnosed in some individuals who are biochemically euthyroid, many of whom receive thyroid hormone therapy[9]. These trends in diagnosis and treatment are accompanied (and in many cases are driven), by high expectations by patients that their QOL[8] will be improved by thyroid hormone treatment. Against this backdrop, clinicians are

faced with a substantial minority of patients for whom levothyroxine treatment has failed to improve their QOL[49].

The principal use of QOL instruments is in clinical research. Thyroid-specific QOL should be quantified with instruments able to measure relevant patient-related outcomes for hypothyroidism[68]. The most robust of these instruments is the ThyPRO, which has high content validity and test–retest reliability[81,82]. It responds to changes in benign thyroid disease phenotype and has cross-cultural validity; also, a minimally important change for hypothyroid symptoms has been defined[88]. Despite this, large well defined populations are needed to demonstrate statistically significant differences in QOL in relation to medical intervention[128,129].

Content validity

Extent to which the items tested are representative of the entire domain the test seeks to measure

The underlying causes of impaired QOL in patients with hypothyroidism are unclear, but might be classifiable into three broad categories. These are an inability of levothyroxine alone to achieve adequate T_3 levels in the tissues[128], inflammation caused by underlying autoimmunity[138], or other physical[139] and psychosocial co-morbidities[140–142]. An extensive body of evidence, summarized in systematic reviews and a meta-analysis conducted within the past five years, has shown that levo thyroxine and liothyronine combination therapy and DTE treatments were no different to levothyroxine alone in terms of QOL, neurocognitive function and somatic symptoms[120,132]. The latter two hypotheses on the cause of poor QOL have been studied less rigorously.

In line with the multifactorial aetiology of hypothyroidism[143], the aetiology of poor QOL is also most probably multifactorial. Therefore, all the previously described causes of suboptimal QOL need further exploration in well controlled prospective trials including aetiologically better defined (and, ideally, genetically characterized) individuals with hypothyroidism[144]. While investigating a variety of thyroid hormone combinations and formulations[145] and non-pharmacological interventions, we should also be reminded that persistent thyroid dysfunction is a health hazard[5] for individuals with hypothyroidism. Over-zealous treatment is also a health hazard, as the duration of decreased TSH in treated individuals has a greater impact on mortality than duration of elevated levels of TSH[10]. The measurement of serum levels of TSH for diagnosis of primary hypothyroidism is the most reliable diagnostic test and the normal range for TSH at present remains the most appropriate target for patients treated with levothyroxine[13].

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Key points

- Epidemiological data suggest that the prevalence of (typically mild) hypothyroidism is increasing, partly owing to increased screening, which has led to a lower threshold for initiating treatment with levothyroxine.
- Approximately 10–15% of individuals with hypothyroidism treated with levothyroxine experience persistent symptoms and dissatisfaction with therapy (that might or might not be due to their hypothyroidism), which can lead to overtreatment.
- Health-related quality of life (QOL) is a complementary measure to morbidity and mortality; it should be measured with a validated thyroid-specific instrument for patient-related outcomes.
- Poor QOL has been attributed to failure to achieve adequate T_3 levels in tissues, polymorphisms in deiodinase and hormone transporter genes and/or symptoms unrelated to hypothyroidism such as autoimmune disease.
- There is little evidence of durable QOL improvements with levothyroxine and liothyronine combination therapy, or from therapy with desiccated thyroid hormone, from a multitude of randomized controlled trials and meta-analyses.
- Future research should investigate non-thyroidal causes of impaired QOL in patients with hypothyroidism as, at present, overtreatment for hypothyroidism constitutes a greater threat to health than undertreatment.

Box 1 |

Causes of an elevated serum levels of TSH

With normal thyroid hormone levels

- Subclinical hypothyroidism
- During recovery from a non-thyroidal illness
- During recovery from subacute or silent thyroiditis
- Drugs (amiodarone, lithium, metoclopramide, domperidone)
- Assay interference due to heterophile antibodies or macro-TSH
- Mutations in the TSH receptor (partial TSH resistance)
- Addison disease (corrected by glucocorticoid replacement)

With abnormal thyroid hormone levels

- Overt hypothyroidism (low free T_4)
- Thyroid hormone resistance syndrome (elevated free T_4)
- TSH-secreting pituitary adenoma (elevated free T_4)
- Hypothalamic–pituitary disease (low free T_4)

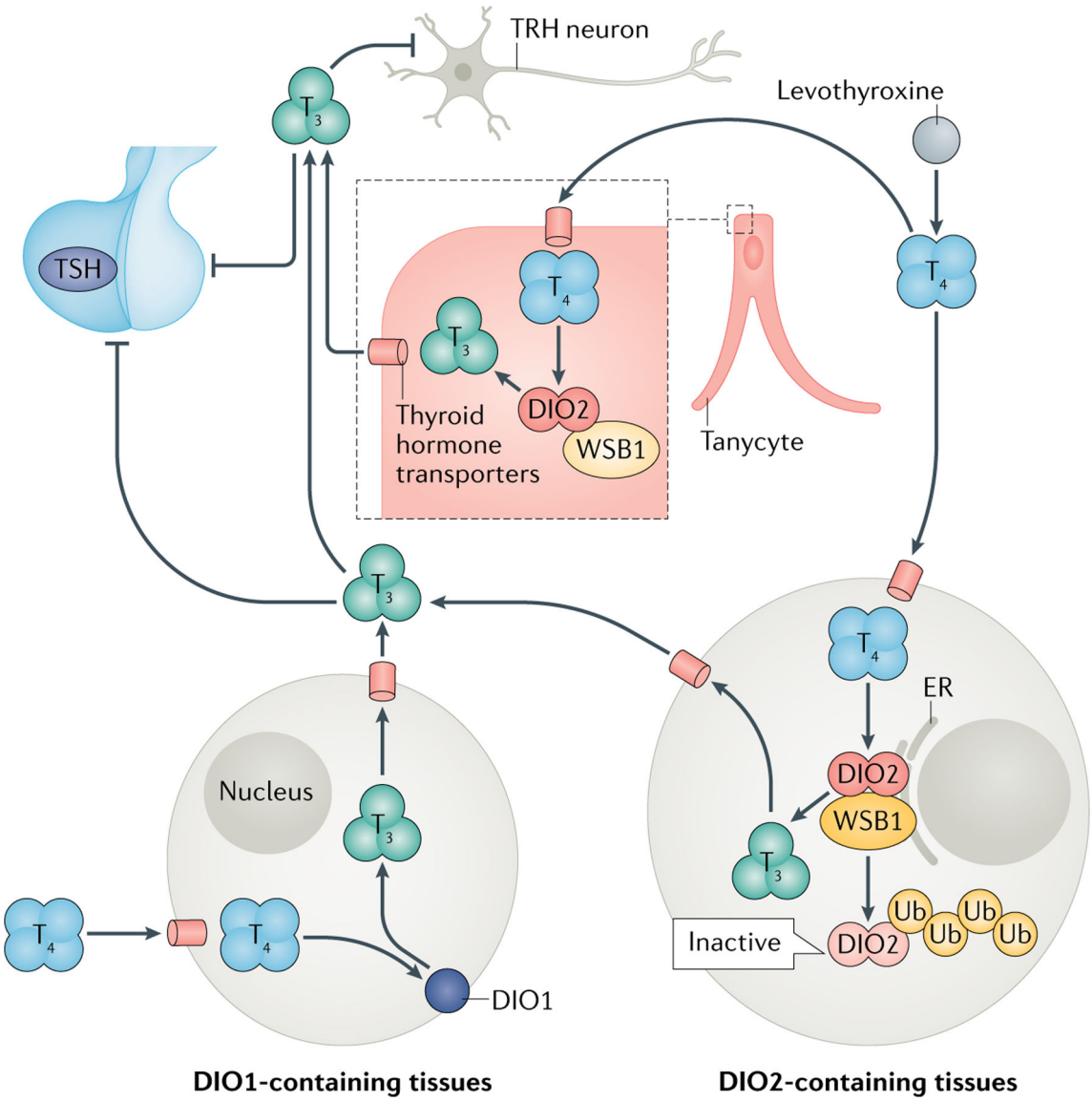

Fig. 1 |. Roles of the DIO1 and DIO2 pathways in the TSH feedback mechanism during treatment with levothyroxine.

Levothyroxine is converted into triiodothyronine (T_3) by the action of type 1 deiodinase (DIO1) and type 2 diodinase (DIO2). T_3 produced in DIO1-expressing tissues (such as the liver) rapidly returns to the circulation, whereas T_3 produced in DIO2-expressing tissues (such as the brain, pituitary and adipose tissue) remains in the tissue longer and stimulates local thyroid hormone signalling. Conversion of levothyroxine or thyroxine (T_4) to T_3 triggers the ubiquitination of DIO2 and its destruction by the proteasome. Serum levels of T_4 are detected by the medial basal hypothalamus (MBH)–pituitary unit. Tanycytes within the MBH express high levels of DIO2, allowing them to convert T_4 into T_3, which then suppresses thyroid-stimulating hormone (TSH) secretion from the thyroid and thyrotropin releasing hormone (TRH) secretion from TRH neurons. ER, endoplasmic reticulum; Ub, ubiquitin. WSB1 is a subunit of ubiquitin ligase. FIGURE 1 adapted with permission from REF.[128], Mary Ann Liebert Inc.

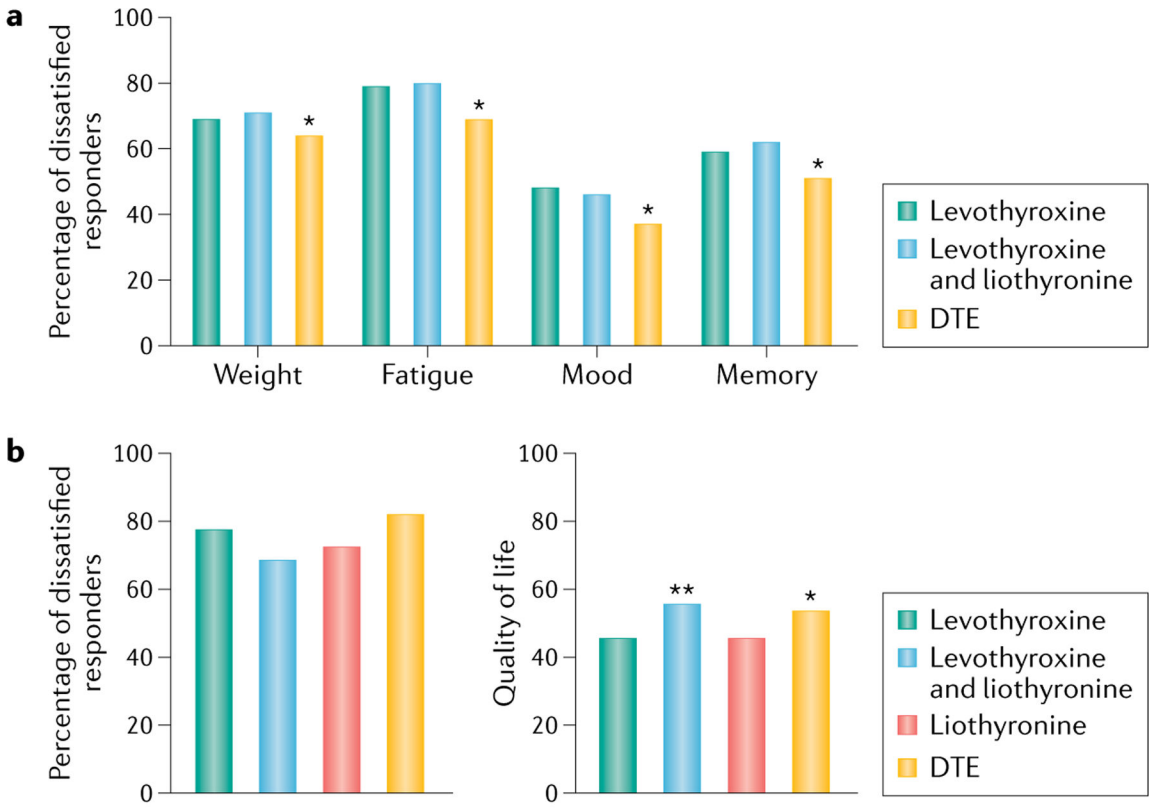

Fig. 2 |. Proportion of dissatisfaction expressed by patients with self-reported hypothyroidism by type of treatment for hypothyroidism.

a | Percentage of dissatisfied responders across four categories: weight, fatigue, mood and memory. Responders received one of three treatments: levothyroxine (n = 6,949); levothyroxine and liothyronine combination therapy (n = 978) or desiccated thyroid extract (DTE) (n = 3,239). An asterisk denotes that the values for DTE were statistically significantly different ($P < 0.05$) to other treatments. **b** | Percentage of dissatisfied responders (left) receiving either levothyroxine (n = 677), levothyroxine and liothyronine combination therapy (n = 124), liothyronine (n = 45) or DTE (n = 123). Quality of life (QOL) scores (right) for the same patient groups. A score of 100 represents the best possible QOL while a score of 0 represents the worst. Asterisks denote statistically significant differences between levothyroxine compared with levothyroxine and liothyronine combination (**P = 0.001), and levothyroxine compared with DTE (*P = 0.010). These graphs show that the differences between different treatments are minor and that a substantial proportion of patients are dissatisfied and have a suboptimal QOL regardless of type of treatment, which suggests that combination treatment with levothyroxine and liothyronine or DTE often fails to restore health-related QOL. Panel **a** is derived from data from Peterson et al.[57]; panel **b** is derived from data from Mitchell et al.[8].

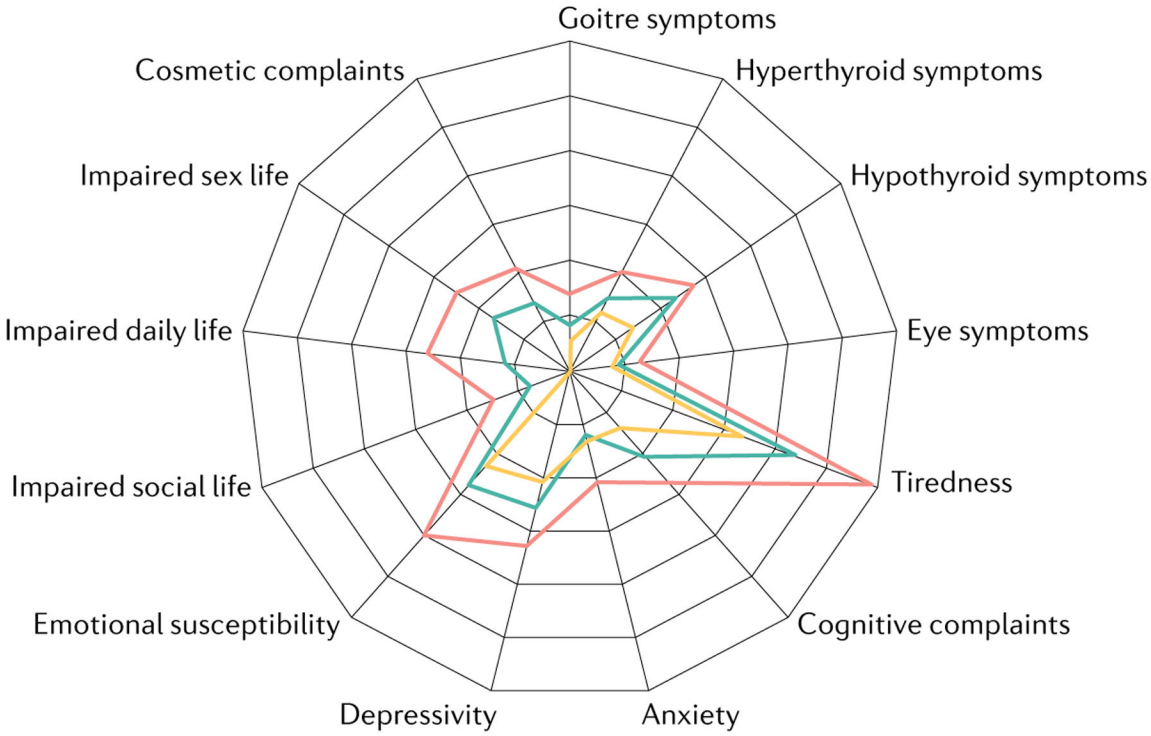

Fig. 3 |. Changes in components of QOL before and after treatment of hypothyroidism.
Radar plot showing patient-related outcome using ThyPRO, at baseline (red) and six months after starting levothyroxine treatment for autoimmune hypothyroidism (green), compared with normative data (yellow). FIGURE 3 is adapted from REF.[107], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Table 1 |

Randomized studies showing altered QOL during treatment of subclinical or mild hypothyroidism

Condition	QOL measure	Type of study	Effect on QOL with levothyroxine compared with placebo	Number of patients (mean age in years)	Ref.
Younger participants [a]					
Levothyroxine versus placebo for 48 weeks	Billewicz & Zulewski Symptom Score	Randomized, double-blind trial	Improved symptom scores on levothyroxine	66 (58)	Meier et al. (2001)[92]
Levothyroxine versus placebo for 26 weeks	Hospital Anxiety and Depression Scale, GHQ30	Randomized, double-blind trial	Worse anxiety on levothyroxine	40 (53)	Kong et al. (2002)[93]
Levothyroxine versus placebo for 52 weeks	BDI, GHQ30, Wechsler Memory Scale-Revised	Randomized, double-blind trial	No change	69 (62)	Jorde et al. (2006)[94]
Levothyroxine and placebo (given in a random order) for 12 weeks	ThyDQoL, SF-36	Randomized blinded crossover trial	Tiredness improved on levothyroxine	100 (54)	Razvi et al. (2007)[95]
Levothyroxine versus placebo for 12 weeks	WMS	Randomized, double-blind trial	Improved memory on levothyroxine	60 (34)	Aghili et al. (2012)[100]
Levothyroxine versus placebo for 6 months	BDI, Zulewski, SF-36	Randomized, double-blind trial	Marginal benefits on SF-36	71 (50)	Reuters et al. (2012)[97]
Levothyroxine versus placebo for 12 weeks	BDI	Randomized, double-blind trial	Somatic symptoms statistically significantly improved by levothyroxine versus placebo	60 (34)	Najafi et al. (2015)[98]
Older participants [a]					
Levothyroxine versus placebo for 40 weeks	CTQ Composite psychometric memory score	Randomized, double-blind trial	Improved memory score on levothyroxine	37 (68)	Jaeschke et al. (1996)[91]
Levothyroxine versus placebo for 52 weeks	Mini-Mental State Examination, cognitive function	Randomized, double-blind trial	No change	94 (74)	Parle et al. (2010)[96]
Levothyroxine versus placebo for 52 weeks	ThyPRO	Randomized, double-blind trial	No change	737 (74)	Stott et al. (2017)[101]
Levothyroxine versus placebo for 52 weeks	ThyPRO, EQ5D	Randomized, double-blind trial	No change	105 (84)	Mooijaart et al. (2019)[99]

BDI, Beck's Depression Inventory; CTQ, Chronic Thyroid Questionnaire; GHQ, General Health Questionnaire; WMS, Wechsler Memory Scale.

[a]Younger participants are defined as having a mean age of 50 years; Older participants are defined as having a median age >65 years.

Table 2 |

Studies showing altered QOL during treatment of overt hypothyroidism[a]

Overt hypothyroidism					Ref.
Condition	**QOL measure**	**Type of study**	**Effect on QOL**	**Number of patients**	
Untreated versus treated with levothyroxine: initiation of levothyroxine	ThyPRO, SF-36	Open label (all untreated to treated)	Improved, based on both ThyPRO and SF-36	78 (15% overt hypothyroidism)	Winther et al. (2016)[107]
Untreated versus treated with levothyroxine: initiation of levothyroxine	Clinical and symptom scores RAND-36	Open label (all untreated to treated), low dose versus full dose initiation	Improved based on RAND-36 in both low and full dose arms	50 (median TSH 48–61 mIU per litre)	Roos et al. (2005)[108]
Untreated versus treated with levothyroxine: withdrawal of levothyroxine	SF-36	Withdrawal compared with rTSH	Decreased QOL with withdrawal	228	Schroeder et al. (2006)[109]
Untreated versus treated with levothyroxine: withdrawal of levothyroxine	Questionnaire designed by investigators	Withdrawal compared with rTSH	Decreased QOL with withdrawal	291	Lee et al. (2010)[110]
Untreated versus treated with levothyroxine: withdrawal of levothyroxine	FACT-F	Withdrawal compared with rTSH	Decreased QOL with withdrawal	74	Taieb et al. (2009)[111]
Untreated versus treated with levothyroxine: withdrawal of levothyroxine	FACT-F	Withdrawal compared with rTSH	Decreased QOL with withdrawal and duration of withdrawal	78	Chow et al. (2006)[112]
Levothyroxine treated versus control populations (matched controls)	GHQ	Cross-sectional euthyroid patients versus matched controls	Decreased QOL in patients	1,922	Saravanan et al. (2002)[46]
Levothyroxine treated versus control populations (reference values)	Symptom checklist-90 RAND-36	Cross-sectional euthyroid patients versus reference values	Decreased QOL in patients	2,509 (141 patients; 2,368 reference individuals)	Wekking et al. (2005)[47]
Levothyroxine treated versus healthy controls	ThySRQ, ThyDQoL HDS, BDI, SF-36, WBQ-12, SCL-90-R	Cross-sectional euthyroid patients versus healthy controls	Decreased QOL in patients using ThySRQ symptom number and tiredness, BDI, WBQ-12	36	Quinque et al. (2013)[113]
Patients receiving levothyroxine to target different TSH goals	GHQ-28, SF-36, TSQ	Randomized, blinded, three-period crossover study	No significant effect	56	Walsh et al. (2006)[115]
Patients receiving levothyroxine to target different TSH goals	SF-36, mood profile of states	Randomized, double-blind trial	No significant effect	138	Samuels et al. (2018)[116]
Patients receiving levothyroxine with different TSH values within the normal range	ThySRQ, ThyDQoL HDS, BDI,SF-36, WBQ-12, SCL-90-R	Cross-sectional	QOL (based on ThySRQ) worse with upper normal TSH values	102	Quinque et al. (2013)[113]
Patients receiving levothyroxine, some with iatrogenic hypothyroidism	SF-36	Cross-sectional	Decreased QOL with undertreatment (both subclinical and overt hypothyroidism)	2,057 (21.5% subclinical, 4.4% overt)	dos Santos Vigario et al. (2013)[117]
Patients receiving levothyroxine, some with iatrogenic hypothyroidism	RAND-36	Cross-sectional	No significant effect	9,491 (10.3% TSH 4–10 mU per litre, 0.7% TSH >10 mU per litre)	Klaver et al. (2013)[118]

Overt hypothyroidism					Ref.
Condition	**QOL measure**	**Type of study**	**Effect on QOL**	**Number of patients**	
Patients taking levothyroxine switched from tablet to liquid levothyroxine	ThyTSQ	Open label	Improved QOL with liquid levothyroxine	418	Guglielmi et al. (2018)[119]
Patients taking levothyroxine switched to levothyroxine versus levothyroxine and liothyronine	SF-36, BDI, SCL-90-R	Randomized blinded, two-period crossover study	Improved with levothyroxine and liothyronine	59	Nygaard et al. (2009)[123]
Patients taking levothyroxine switched to levothyroxine versus levothyroxine and liothyronine	Visual analogue scale	Randomized, non-blinded, two-period crossover study	Improved with levothyroxine and liothyronine	33	Bunevicius et al. (1999)[124]
Patients taking levothyroxine switched to levothyroxine versus levothyroxine and liothyronine	GHQ-12, TSQ, HADS	Randomized, double-blind trial	GHQ-12 caseness (but not GHQ Likert) and HADS improved with levothyroxine and liothyronine at 3 months but not at 12 months	697	Saravanan et al. (2005)[126]
Patients taking levothyroxine switched to levothyroxine versus levothyroxine and liothyronine	GHQ-28	Randomized trial	Reduced anxiety and/or insomnia scores with levothyroxine and liothyronine	71	Valizadeh et al. (2009)[125]
Patients taking levothyroxine switched to levothyroxine and liothyronine	ThyPRO-39	Open label trial	Improved ThyPRO composite score with levothyroxine and liothyronine	23	Michaelsson et al. (2018)[146]
Patients taking levothyroxine, levothyroxine and liothyronine, liothyronine, or DTE	Scale from 0–100	Online survey	Improved QOL associated with levothyroxine and liothyronineor DTE	969	Mitchell et al. (2021)[8]
Patients taking levothyroxine, levothyroxine and liothyronine, liothyronine, or DTE	Scale from 0–10	Online survey	Improved QOL associated with DTE	12,146	Peterson et al. (2018)[57]
Patients taking levothyroxine switched to levothyroxine versus DTE	GHQ-12, TSQ-36, BDI	Randomized, double-blind crossover trial	No statistically significant effect	70	Hoang et al. (2013)[132]
Patients taking levothyroxine switched to levothyroxine monotherapy vs levothyroxine and liothyronine combination vs DTE	TSQ-36, GHQ-12, WMS-IV, BDI	Randomized double-blind crossover trial	No statistically significant effect	75	Shakir et al. (2021)[122]

BDI, Beck's Depression Inventory; DTE, desiccated thyroid extract; FACT-F, Functional Assessment of Chronic illness Therapy-Fatigue; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression questionnaire; SCL, Symptom Check List; ThyDQoL, Underactive Thyroid-Dependent Quality of Life Questionnaire; TSQ, Thyroid Symptom Questionnaire; WBQ, Well-Being Questionnaire; WMS, Wechsler Memory Scale.

[a]Nine randomized controlled trials of combination therapy did not show a benefit of levothyroxine and liothyronine to QOL. One trial did not report QOL parameters[147].