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A New Formulation of Levothyroxine with Tightened Specification

Springer Healthcare Education

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Foreword

The Modern and Future Management of Hypothyroidism

Hypothyroidism presents a unique challenge in many ways, both to patients with the condition and to healthcare systems that care for them. For example, it is one of the most common non-communicable diseases.[1] While the prevalence of hypothyroidism increases with age, many people worldwide develop the condition at a younger age, including women of childbearing potential.[2] Levothyroxine (LT4), the gold standard for the pharmacologic management of hypothyroidism, appears regularly within the top few most prescribed medications in any given country.[3]

However, these statistics alone do not give the full picture of the burden of hypothyroidism. Unmet medical needs persist in its management. For decades, physicians have understood the principle of adjusting the dose of LT4 based on the circulating level of thyrotropin.[4,5] Nevertheless, careful optimisation of the LT4 dose does not resolve symptoms of hypothyroidism and fully correct the associated dysregulation of cardiovascular factors in a substantial minority of patients.[6] We have strong evidence that hypothyroidism reduces the chances of a woman conceiving a child, and even if she does so, it reduces the chances of a successful pregnancy outcome.[2]

Two complementary strategies are available for addressing the burden of hypothyroidism: refining the existing LT4 treatment and seeking additional treatments for those for whom this will not be enough. The development of novel formulations of LT4, with tightened specifications for dosing accuracy, stability and bioequivalence between dosage strengths, will help to address the current management of hypothyroidism.[7,8] In the future, new thinking, new data and new clinical trials are breathing life into research on the role of triiodothyronine (liothyronine, LT3) in thyroid care.

This book combines a distinguished panel of international expert physicians and clinical researchers to explore these important issues. Professor Leonidas H Duntas lays out the therapeutic rationale for developing a new LT4 with tightened specification for the modern era of hypothyroidism management, and Professor George J Kahaly describes in detail the pharmacokinetics of a modern LT4 preparation. Professors Salman Razvi and Gabriela Brenta review its potential for the management of hypothyroidism, including overt and (always controversial) subclinical presentations. Professors Zhongyan Shan and Kris G Poppe summarise the latest research on the adverse impact of hypothyroidism on fertility and pregnancy outcomes. Drs Ulrike Gottwald-Hostalek and Yorki Tayrouz summarise the implications for safety and tolerability of a modern, re-engineered LT4 preparation. Finally, Professor Antonio C Bianco reviews the current and (and increasingly bright) future prospects for administration of LT3 alongside optimised LT4 in the management of selected patients with hypothyroidism, a field that has long been paralysed by the negative results of inappropriately designed clinical trials.[9,10]

We believe that our book brings together the latest thinking and research on the key aspects of hypothyroidism and its modern management. We hope you find it of interest and useful in your clinical practice.

Gabriela Brenta
Dr. Cesar Milstein Hospital, Buenos Aires, Argentina

Ulrike Gottwald-Hostalek
Merck Healthcare KGaA, Darmstadt, Germany

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Contents

Chapter 1

Designing a New Levothyroxine with Tightened Specification for the Modern Era of Management of Hypothyroidism

Leonidas H Duntas
Evgenidion Hospital, Unit of Endocrinology, Metabolism and Diabetes, University of Athens, Athens, Greece

The mainstay of the pharmacologic management of hypothyroidism is thyroid hormone replacement with levothyroxine (LT4), usually for life. Feedback systems within the hypothalamic-pituitary-thyroid axis are organised in such a way that even minor alterations in the administered dosage of LT4 can cause significant changes in the rate of secretion of thyrotropin, the main hormone which regulates the activity of the thyroid gland. LT4 has, therefore, been described as a "narrow therapeutic index drug". A new formulation (NF) with tightened specification has been engineered in collaboration with regulatory authorities to provide a more accurate and reproducible dose of LT4 throughout the patient's treatment, compared with earlier formulations of LT4. Switching to NF from an older formulation of LT4, therefore, helps to maintain strict control of the level of exposure of the patient

to administered LT4 during long-term treatment, which is crucial for maintaining a stable euthyroid state.

Introduction

Hypothyroidism arises when the secretion of thyroid hormones from the thyroid gland (thyroxine [T4] and triiodothyronine) is insufficient to meet the body's needs. The severity of hypothyroidism is defined according to thyroid hormone status, as described later in this chapter. Briefly, current guidelines for the management of hypothyroidism recommend that all patients with overt hypothyroidism and a proportion of patients with subclinical hypothyroidism require thyroid hormone replacement with levothyroxine (LT4), a pharmacological formulation of T4.[1–3] Treatment is usually for life, particularly concerning a patient with overt hypothyroidism, with periodic dosage adjustment to retain thyroid hormone levels within range.[4]

LT4 is described as a "narrow therapeutic index" drug in that even small variations in the administered dose of LT4 can induce clinically significant disturbances of systemic thyroid function.[5] The need for long-term accuracy, reproducibility and stability of the LT4 dosage during long-term treatment has led regulatory authorities and pharmaceutical companies to refine existing formulations of LT4.[6,7] This chapter describes the therapeutic rationale for the development of a new formulation (NF), which has been designed to meet these needs.

Why do we need an updated formulation of LT4 to manage hypothyroidism?

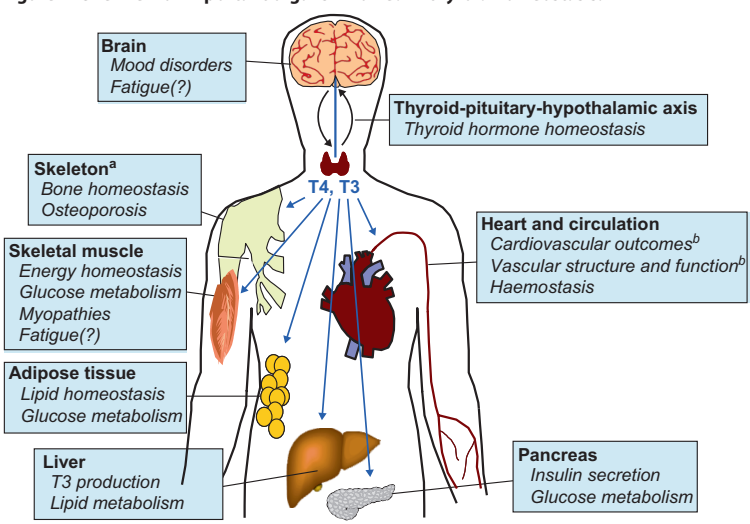
Overview of the regulation of thyroid homeostasis

Multiple feedback loops regulate the activity of the thyroid gland.[8] Briefly, thyrotropin-releasing hormone is released from the hypothalamus to act on the pituitary gland to increase the secretion of thyrotropin

(thyroid-stimulating hormone [TSH]). An increased circulating level of TSH then acts on the thyroid gland to increase the secretion of thyroid hormones (about 80% of which is T4, with the remainder being triiodothyronine [T3]). The resulting change in the level of thyroid hormones in the peripheral tissues impacts the function of every system in the body (Figure 1).[9] Specific deiodinases within these tissues deactivate thyroid hormones.

An increase in the thyroid hormone level also feeds back to the pituitary to reduce the secretion of TSH (and vice versa, with a lower thyroid hormone level increasing the secretion of TSH). In this way, a balance is achieved between the demand for and the secretion of thyroid hormones. Notably, the relationship between thyroid hormone secretion and TSH secretion is not linear: a given change in the level of thyroid hormones causes an increase in TSH secretion that is up to about 100-fold larger.[10] This has significant consequences for the management of hypothyroidism. Firstly, this is why TSH is used as the main clinical biomarker for assessing thyroid function, as it is more practical to measure relatively large changes in the TSH level, compared with much smaller changes in

Figure 1 Overview of important organs involved in thyroid homeostasis.



T3: triiodothyronine. T4: thyroxine. Adapted from reference 9 according to the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

the levels of thyroid hormones themselves, in the routine clinical practice setting (see also Chapters 3 and 4 of this book for information on the clinical management of hypothyroidism). Second, the nature of this feedback mechanism underpins the status of LT4 as a narrow therapeutic index drug. The large level of amplification involved in this circuit means that large and potentially clinically significant changes in the TSH level may arise following even tiny adjustments in the dosage of LT4. For a patient with hypothyroidism, such a scenario would tend to mitigate against the achievement of stable thyroid function during long-term treatment.[11]

LT4 as the mainstay of thyroid hormone replacement

T3 is the active form of thyroid hormone; T4 is converted to T3 in peripheral tissues by deiodinases.[12] The T3 then activates intracellular thyroid hormone receptors, which translocate to the nucleus to influence the transcription of multiple genes, especially those involved in metabolism and energy homeostasis. LT4 is preferred to preparations of T3 for therapeutic use mainly due to their respective pharmacokinetics. The plasma half-life of T4 is measured in days, compared with hours for T3; accordingly, LT4 is suitable for convenient, once-daily oral dosing with little change in circulating T4 levels during the dosing interval.[13] Chapter 8 of this book summarises the latest prospects for the therapeutic combination of T3 with NF for patients with hypothyroidism.

An increasingly challenging regulatory environment

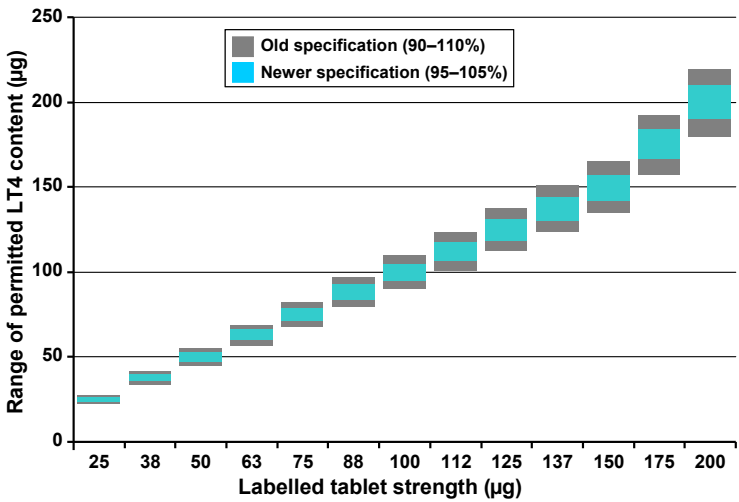
Regulatory authorities began to revise their guidance for the pharmaceutical industry on the pharmaceutical properties required for LT4 tablets from about the beginning of the second decade of this century.[6] These changes related to the accuracy of dosing and also to stricter standards for bioequivalence with a reference LT4 product to ensure more consistent absorption of T4 following ingestion of an LT4 tablet:

Accuracy and stability: The United States Pharmacopeia and National Formulary changed their guidance from "*Levothyroxine sodium tablets contain not less than 90.0 percent and not more than 110.0 percent*

of the labeled amount of levothyroxine sodium" to "*Levothyroxine sodium tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of levothyroxine sodium*".[14] An expert in the field noted at this time that the previous criteria of 90–110% potentially "*could result in differences in levothyroxine content approaching 20% from refill to refill*".[15] Other countries followed suit in subsequent years with requirements for actual vs. stated dosages tightened to 90–105% in the UK[16] and 95–105% in France, for example,[17] among others. Importantly, these criteria apply to the entire lifetime of a given batch of LT4; the French guidance, for example, states explicitly that the shelf life must be reduced if necessary to meet the standard.

Figure 2 illustrates the practical consequences of these new specifications regarding the actual range of amounts of LT4 that can be delivered via the new and old formulations. Note that the old specifications allowed considerable overlap between the actual content of adjacent tablet strengths if these were relatively closely spaced. In practice, this limited the number of dosage strengths that could be offered. The overlap

Figure 2 Ranges of permitted tablet content of levothyroxine (LT4) under newer and older specifications for manufacture of levothyroxine tablets.



Boxes represent ranges of permitted tablet LT4 content as shown for each tablet strength. See the text for a description of the relevant specifications.

is effectively removed according to the new criteria. As a result, tablets of NF containing LT4 in 13 distinct strengths (25–200 μg) shown in Figure 2 have been developed, providing enhanced flexibility and precision during initial dose titration and periodic adjustments in countries where these are available.

Bioequivalence: Establishing formal bioequivalence between two preparations of the same drug should ensure a minimum change in biological effect when switching a patient from one formulation to the other. Bioequivalence is assessed by comparing standard pharmacokinetic parameters between the two preparations, especially the area under the drug concentration-time curve (AUC), which is the principal measure of overall exposure to the drug. For most drugs, the upper and lower 90% confidence intervals for the geometric mean ratio of the AUC values for the two formulations must lie between 0.8 and 1.25 (often cited as 80–125).[18] Once again, the European criteria for new LT4 preparations are stricter, with a permitted range of 90–111.11% for the geometric mean ratio, consistent with its status as a narrow therapeutic index drug.[19] In the United States of America (USA), a narrow therapeutic index drug such as LT4 must meet *both* the standard 80–125% criteria and additional criteria derived from a calculation based on the within-subject variability of absorption of the drug.[20]

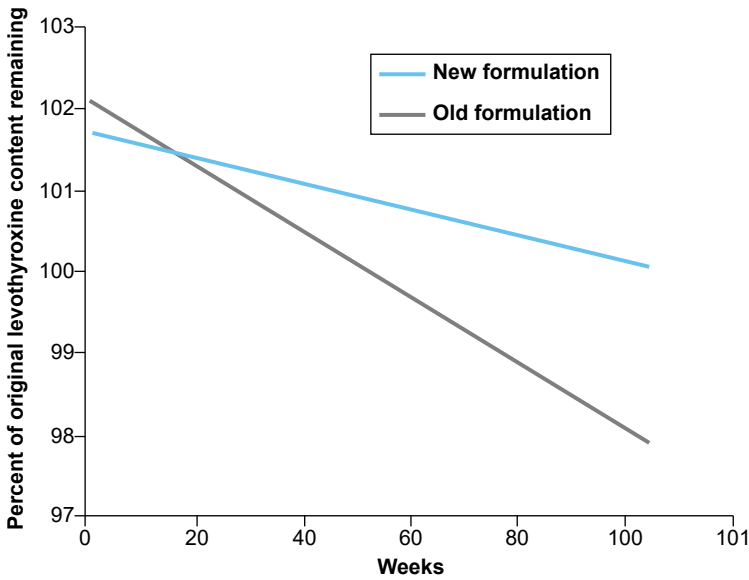
Development and properties of T4 new formulation

Historically, most pharmaceutical preparations have included a small amount of lactose as an excipient,[21] as the physical properties of lactose are well suited for constructing tablets containing low doses of an active ingredient.[21] The concentration of lactose used in medicinal formulations is normally too low to cause problems for the great majority of patients, even for people who are intolerant to lactose.[22,23] For example, a randomised trial in a population with confirmed lactose intolerance due to lactase deficiency showed that ingestion of a tablet containing 400 mg

lactose did not cause gastrointestinal side effects.[24] Nevertheless, case reports of gastrointestinal symptoms apparently associated with lactose-containing tablets have been published.[23] The NF tablet no longer contains lactose, as this has been replaced with mannitol and citric acid, which are other common and safe pharmaceutical excipients. Thus, NF is suitable for use for almost all patients with hypothyroidism, irrespective of their tolerance to lactose, and physicians can reassure their patients concerning this point.[6]

The inclusion of lactose also causes an additional problem associated with a spontaneous chemical reaction that occurrs slowly over time between lactose and LT4. In fact, the product of this reaction, levothyroxine-2-ketolactose, represents the main degradation product found, which emphasises the extent of the benefit of removing lactose in terms of the stability of the tablet. The shelf life of NF is 3 years in all climate zones, having been improved from 24 to 36 months in some hotter areas. All dosage strengths of the NF tablet meet the criteria for accurate dosing

Figure 3 Stability of the levothyroxine content of new formulation vs. old formulations.



Ten batches each were analysed.
Source: Merck healthcare KGaA, Darmstadt, Germany (data on file).

(described above) throughout this period. Figure 3 shows the improved stability of the active LT4 content of NF versus the older formulation.

Absorption of the NF

NF meets the strict bioequivalence criteria applicable to narrow therapeutic index drugs. Moreover, dose equivalence has been established between different tablet strengths so that different NF tablets can be combined to achieve a precise dosage, which can be useful when titrating the LT4 dose. Moreover, the specificity and quality of NF tablets renders the continuous use of these tablets imperative and makes even more strict the recommendation to avoid interchanging with generic or non-NF compounds. The studies underpinning these findings are described in detail in the following chapter.[25]

Summary and conclusions

The improvements made during the development of NF (summarised together in Table 1) have the potential to add precision and convenience during the initiation and maintenance of treatment for hypothyroidism

Table 1 Summary of improvements made during the development of a new formulation of T4 (NF) in comparison with the older formulation.

Attribute	Description
Lactose	No longer used in NF tablets
Dosage accuracy	Meets the specification of 95–105% of labelled tablet content at all dosage strengths
Stability	Shelf life of NF is 3 years in all climate zones (meets the above specification throughout this time)
Clinical	Meets enhanced European regulatory specifications relevant to narrow therapeutic index drugs for bioequivalence with the old formulation[a] Dose proportionality between tablet strengths facilitates combining different strengths to achieve precise dosing[a]
Tablets	Availability of up to 11 different tablet strengths from 25 µg to 200 g (as per the older formulation) facilitates switching and precise titration of the levothyroxine dose[b] Two additional strengths of NF are planned

Discussed in greater detail in Chapters [a]2 and [b]4.

for both the patient and their physician. Each can be confident that moving to the next tablet strength will indeed provide the promised incremental increase in the LT4 dose, and that prescribing the next treatment period will not incur significant variations between batches, irrespective of how long the tablets have resided on the pharmacy shelf. Finally, the availability of closely spaced dosage strengths and the ability to mix them to achieve a desired total dosage provide a new level of flexibility and precision for the prescribing physician.

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Chapter 2

Metabolism and Pharmacokinetics of LT4 New Formulation with a Tightened Specification

George J Kahaly
Department of Medicine, Johannes Gutenberg University (JGU) Medical Center, Mainz, Germany

The pharmacokinetic profile of levothyroxine (LT4) delivered by a new formulation (NF) with a tightened specification was evaluated in two randomised trials in healthy volunteers. The first trial demonstrated formal bioequivalence between NF and the older LT4 formulation, according to the exacting standards required by updated regulatory guidance for narrow therapeutic index drugs such as LT4. The second trial demonstrated dose equivalence between different dosage strengths of NF. The interchangeability of different NF tablet strengths is essential for its clinical use, as the overall daily dose of LT4 administered during initial titration and maintenance therapy is sometimes made up of combinations of different tablet strengths. The pharmacokinetic properties of NF with tightened specification have facilitated switching from the older formulation and support a flexible, individualised approach to establishing the precise level of thyroid hormone replacement for a patient with hypothyroidism.

Introduction

Orally administered thyroid hormone replacement with levothyroxine (LT4) is the mainstay of pharmacologic management of hypothyroidism.[1,2] In practice, the dose of LT4 is titrated cautiously until the serum level of thyrotropin (thyroid-stimulating hormone [TSH]) lies within a predefined reference range specifically, between the 2.5th and 97.5th percentiles of TSH from a healthy population without known thyroid disease, which equates roughly to 0.4–4.5 mIU/L.[3] LT4 is a "narrow therapeutic index" drug, and small changes in the dosage have the potential to cause a clinically significant level of disturbance of thyroid function. Accordingly, the physician must have confidence in the accuracy and reproducibility of LT4 dosing when managing a patient with a new diagnosis of hypothyroidism or conducting periodic adjustments of therapy, as thyroid function drifts over time.

This chapter summarises the metabolism and pharmacokinetics of LT4. LT4 new formulation (NF) is an updated formulation of LT4 with a tightened specification, engineered for more accurate and reproducible delivery of LT4 over time (see Chapter 1 of this book for more details).[4–6] This chapter also explores the pharmacokinetic profile of LT4 delivered via NF in detail, and considers some important practical considerations relating to the therapeutic use of NF and other LT4 preparations.

Overview of the metabolism of levothyroxine

LT4 derived from NF is identical to the physiological thyroxine (T4) produced by the thyroid gland and once ingested into the bloodstream is accordingly metabolised in the same way. Table 1 provides an overview of the metabolism of LT4.[7–10] Approximately four-fifths of an oral dose of LT4 is absorbed, assuming it has been taken on an empty stomach as directed (see below), with the upper small intestine being the most important site for absorption. There is some evidence that absorption of LT4 is reduced in elderly patients. Absorption is relatively rapid, with maximum

Table 1 Overview of key elements of the absorption and metabolism of orally administered levothyroxine.

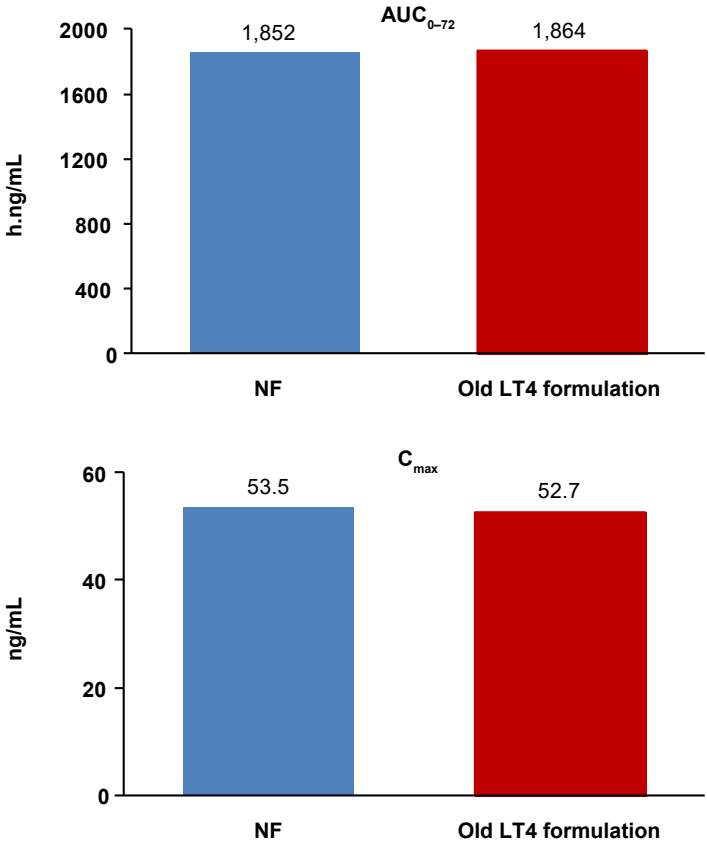
Absorption	• About 70–80% of an oral dose of LT4 is absorbed • At least half of the dose is absorbed from the upper small intestine (ileum and jejunum) • Absorption appears to be slightly lower in elderly patients (>70 years) • Maximum plasma concentrations are achieved in 2–3 hours
Distribution	• Distributed extensively in the body (volume of distribution = 11–15 L)
Metabolism	• The plasma half-life of T4 is about 7 days • T4 is converted to T3 (the biologically active form) by deiodinases D1 and D2 in target tissues for thyroid hormones • Inactivation is principally via deiodinases D1 and D3, especially in the liver and kidney, resulting ultimately in conversion to diiodothyronine or reverse triiodothyronine
Excretion	• Primarily via the kidneys (decreases with age) • About 20% of T4 is excreted unchanged in the faeces • T4 is also excreted in bile after hepatic conjugation to glucuronic and sulphuric acids

Compiled from information presented in references 7–10.

plasma concentrations achieved within about 2–3 hours. The volume of distribution of T4 is high, equating roughly to the total extracellular space of the body (up to 15 L). Almost all T4 in the circulation (>99.9%) is bound to plasma proteins, principally thyroxine-binding globulin (which binds about 80% of total T4), transthyretin, thyroxine-binding prealbumin and albumin; this buffers the level of T4 and helps to maintain it at a constant level.[11] A long plasma elimination half-life of T4 of about 1 week is consistent with the high volume of distribution of T4 and its high level of protein binding.[11,12]

Deiodinases in peripheral tissues are the most important site of the metabolism of T4. Firstly, T3 is the active thyroid hormone. T4 (whether from the thyroid gland or after ingestion of LT4) is converted to metabolically active T3 in target tissues by deiodinase types D1 and D2.[13,14] Deiodinase D3 (mostly, with some contribution from D1) converts T4 to a reverse T3 (a metabolically inactive form) directly without forming T3; reverse T3 is then converted to another inactive molecule, diiodothyronine. D3 and D1 also inactivate T3, converting it directly to diiodothyronine in this case. Multiple other thyroid hormone metabolites also exist, and many are believed to have physiological roles, although this is incompletely understood at present.[15]

Figure 1 Mean baseline-adjusted principal parameters from a randomised comparison of the pharmacokinetics of LT4 new formulation (NF) and an older formulation of LT4.



Data are based on measurement of total thyroxine. Drawn from data presented in reference 4.

Most of the metabolites of thyroid hormones are excreted via the urine, with a lower excretion rate at older ages. About one-fifth of a dose of LT4 is excreted via the faeces. T4 is known to enter the bile, which likely contributes to the latter route of elimination.

Clinical evaluation of the pharmacokinetics of LT4 NF with a tightened specification

Bioequivalence compared with an earlier formulation

An open-label, randomised, 2-period crossover study compared the pharmacokinetic properties of NF with an older formulation of LT4 in a total of 216 healthy volunteers (Table 2).[4] 216 participants received a single dose of NF or the older formulation (all received a total dose of 600 μg of LT4, made up of three 200 μg tablets, taken with water following an overnight fast). The co-primary outcomes of the study were the area under the plasma concentration-time curve for LT4 over a period of 72 hours post-administration ($AUC_{0–72}$) and the maximum plasma concentration of T4 (C_{max}), each adjusted for the baseline value. Safety outcomes were secondary endpoints.

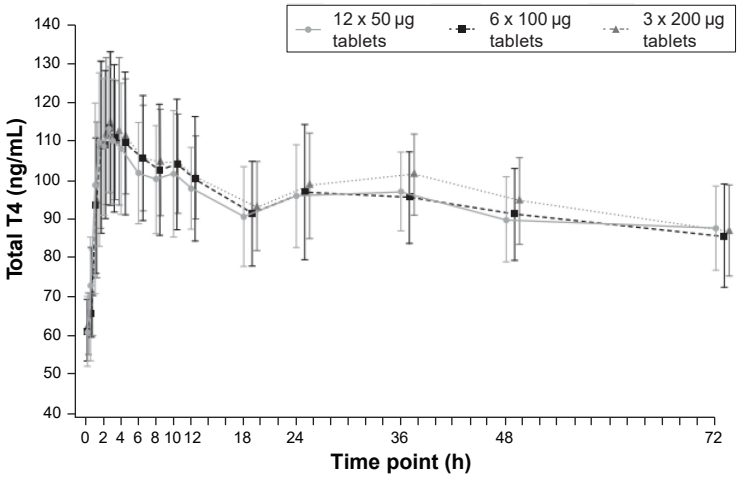
Mean plasma concentrations of total T4 over time were essentially identical between NF and the older LT4 formulation (Figure 2). Consistent

Table 2 Patients and methods of the randomised pharmacokinetic evaluations of LT4 new formulation (NF).

	Bioequivalence study	Dosage form proportionality study
Trial registration	EUDRACT No. 2013-000274-29	EUDRACT No. 2013-000274-33
Design	Open-label, randomised, single-dose, 2-period, 2-sequence crossover study	Open-label, randomised, 6-period, 3-sequence crossover study
Study treatments	Comparison of NF and the older LT4 formulation that it replaced, each at a dose of LT4 600 μg	Comparison of 3 administrations of NF 600 μg made using different tablet strengths (12 x 50 μg, 6 x 100 μg, 3 x 200 μg)
Main outcome	Formal evaluation of bioequivalence between formulations (for $AUC_{0–72}$ and C_{max})	Demonstration of interchangeability of different NF tablet strengths
Study population	216 healthy volunteers Mean age: 35 (9) years Male/female: 59%/41% Mean BMI: 23.5 (2.2) kg/m^2	42 healthy volunteers Mean age: 35 (10) years Male/female: 45%/55% BMI: 23.0 (2.1) kg/m^2

Means (SD) except where stated. $AUC_{0–72}$: area under the T4 plasma concentration-time curve over 72 hours following oral administration of LT4. BMI: body mass index. C_{max}: maximal plasma concentration of T4 following oral administration of LT4. LT4: levothyroxine.
Abstracted from data presented in reference 4.

Figure 2 Mean plasma concentrations of total T4 over time following administration of a single dose of 600 µg of LT4 new formulation (NF) made up of 50 µg, 100 µg or 200 µg tablets to healthy volunteers.



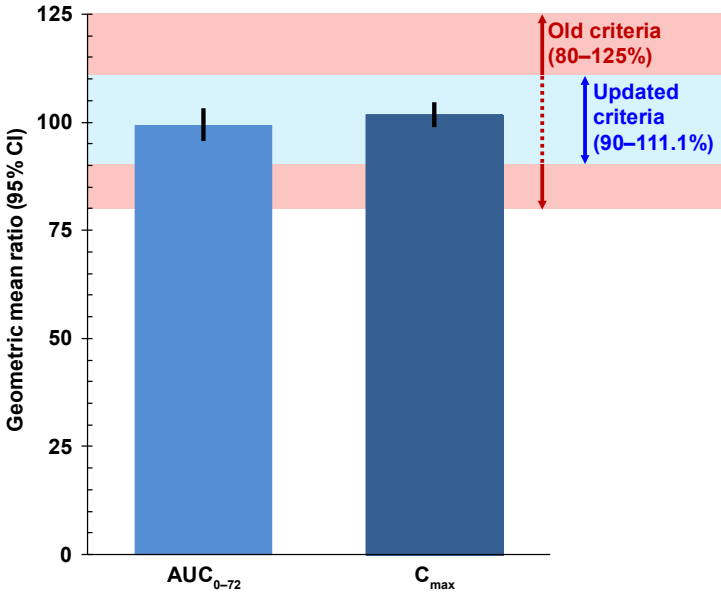
Reproduced with permission from reference 4.

with these observations, the geometric mean ratio for both AUC_{0-72} (99.3 [90% CI 95.6 to 103.2]) and C_{max} 101.7 (98.8 to 104.6]) fell well within both the older (80–125%) and updated (90–111.1%) criteria for the formal evaluation of bioequivalence (Figure 3). We can conclude, therefore, that these newer and older formulations of LT4 are bioequivalent.

Dose equivalence of different tablet strengths

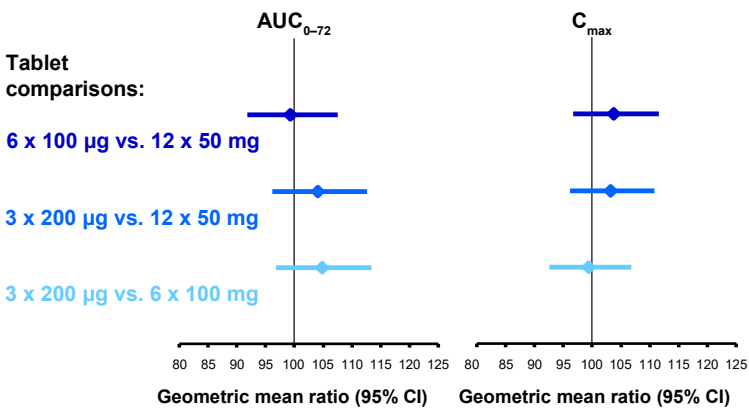
A second randomised, pharmacokinetic study was performed in 42 healthy volunteers (Table 2). For this study, participants received a single dose of NF made up of either 12 x 50 µg tablets, 6 x 100 µg tablets or 3 x 200 µg tablets during each treatment period of a 3-period crossover study. For this analysis, the 95% CI for geometric mean ratios of AUC_{0-72} and C_{max} were required to lie within the standard bioequivalence interval of 80–125% in order to establish dose form proportionality. This was achieved comfortably for all three comparisons (Figure 4). Accordingly, dose proportionality was established between different tablet strengths of NF.

Figure 3 Formal quantification of bioequivalence between LT4 new formulation (NF) and an older formulation of LT4.



Drawn from data presented in reference 4.

Figure 4 Formal demonstration of dosage form proportionality for three tablet strengths of LT4 new formulation (NF).



Drawn from data presented in reference 4.

Factors affecting the absorption of levothyroxine

Food strongly affects the absorption of LT4. The European labelling for NF (and other LT4 tablets) specifies that the dose should be taken after an overnight fast and half an hour before breakfast with half a glass of water. In addition to this general rule, other specific substances have been reported to reduce the absorption of LT4. Some commonly encountered examples of these are shown in Table 3.[16–20] Foods that can reduce LT4 absorption include fibre and soya. Numerous drugs that have been reported to exert a similar effect include iron supplements, calcium or iodine, antacids, and proton pump inhibitors (PPI). The effect of antacids and PPI on the absorption of LT4 appears to be associated with an increase in the pH of the contents of the stomach. General advice is to avoid these combinations of treatments where possible, or if this is impracticable, to separate taking them by at least 4 hours.[20] Concomitant conditions, including some malabsorptive bowel conditions (including certain bariatric surgery procedures associated with generally reduced intestinal absorption),[19] can also decrease LT4 absorption. Other drugs, conditions and demographic factors can alter thyroid homeostasis by

Table 3 Substances and concomitant conditions that have been reported to decrease the absorption of levothyroxine.

Foods	Soya protein Coffee Tea Milk Dietary fibre
Drugs	Antacids (especially those containing aluminium) Calcium supplements Iron supplements Iodide supplements Proton pump inhibitors Phosphate binders
Concomitant conditions	Coeliac disease/lactose intolerance Inflammatory bowel disease Atrophic gastritis *Helicobacter pylori* (*H. pylori*) infection Some bariatric surgery procedures

Compiled from information presented in references 16–20.

either affecting the secretion of TSH or by interfering with a TSH test, and these are reviewed elsewhere.[16]

Sub-optimal adherence to LT4 therapy is another potential cause of lower than expected T4 levels in a patient who has been prescribed LT4. Recent observational studies have reported low adherence rates to LT4 (measured in various ways) of 27% (Pakistan),[21] 28% (Belgium),[22] 39% (Oman)[23] and 67% (Saudi Arabia).[24] Non-compliance with the interval between taking LT4 and ingesting food, or with the need to avoid foods and substances that interfere with LT4 absorption, is also common.[22,25] The LT4 absorption test, where levels of thyroid hormones are followed for a period of hours following a supervised high dose of LT4, can be useful for identifying patients with genuine malabsorption of LT4.[26] Alternative LT4 formulations or injectable LT4 preparations can be an option for the small number of patients with true LT4 malabsorption that is severe enough to preclude the use of LT4 tablets.[27–29]

Summary and conclusions

The long plasma half-life of LT4 (about seven times the dosing interval for once-daily administration) is ideal for establishing a precise and maintained level of thyroid hormone replacement throughout the day. Recent improvements in the design of LT4 tablets with a tightened specification offer greater accuracy in the content of LT4 in each tablet and a longer shelf life. In turn, these innovations have the potential to deliver more precise and reproducible dosing, whether during titration of an initial period of LT4 therapy or during long-term maintenance therapy. It is important, however, to ensure that patients take their LT4 tablets as directed and avoid ingesting food or other substances that interfere with LT4 absorption immediately after taking LT4.

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Chapter 3

Diagnosis and Management of Hypothyroidism: the Role of Modern Formulations of Levothyroxine

Salman Razvi
Institute of Genetic Medicine, University of Newcastle, Newcastle-upon-Tyne, United Kingdom

Hypothyroidism, characterised by low free serum thyroxine (fT4) and elevated thyrotropin (thyroid-stimulating hormone [TSH]), is a highly prevalent condition that is often not managed adequately. Restoring TSH to its reference range with levothyroxine (LT4) resolves the common symptoms and dyslipidaemia associated with hypothyroidism for most patients, which otherwise has the potential to impair long-term clinical outcomes. A number of factors can affect the reliability of the TSH test for identifying genuine thyroid dysfunction, requiring care when interpreting the test result, especially for patients with mild elevations of TSH. Thyroid dysfunction is associated increasingly with cardiovascular diseases, and it may be possible to set reference ranges for TSH and fT4 to minimise the risk of cardiovascular events and associated mortality in the future. The development of

novel formulations of LT4 with tightened specification, with better dosing accuracy, well defined bioavailability and enhanced stability, has the potential to improve the ability of physicians to optimise thyroid homeostasis in patients with hypothyroidism.

Introduction

Hypothyroidism is a common condition accompanied by troubling symptoms that can seriously diminish a patient's quality of life. The purpose of this chapter is to summarise the current clinical and therapeutic landscape of hypothyroidism, with special reference to the pharmacodynamics of levothyroxine (LT4), the diagnosis and management of overt hypothyroidism (the following chapter describes the management of subclinical hypothyroidism), and the role of modern formulations of LT4.

Prevalence of hypothyroidism

The prevalence of hypothyroidism varies between countries and regions, but an expert review concluded that hypothyroidism affects up to about 5% of the populations of countries in Europe.[1] A survey in the north-east of England in 2016 reported a prevalence of hypothyroidism of 4.6%.[2] Additionally, it is believed that a further 5% or so of the population may have undiagnosed hypothyroidism.[1,3] The number of people with hypothyroidism is increasing in developed countries; for example, the prevalence of treated hypothyroidism in the United Kingdom (UK) increased from 2.3% in 2005 to 3.5% in 2014, with a further increase to 4.3% projected for the year 2025.[4] In addition, this study showed that the prevalence of hypothyroidism can vary widely within an individual country, as shown by an analysis of national clinical data from the UK. The prevalence of treated hypothyroidism was 1.4% in London, but 6.3% in the Western Isles of Scotland. Being female, White/Caucasian or obese appeared to predict a higher risk of having treated hypothyroidism.[4]

The impact of hypothyroidism on healthcare budgets is substantial. In the study from the UK described above, 2.9 million people are expected to have treated hypothyroidism by 2025.[4] Hormone replacement therapy with LT4 is the cornerstone of the pharmacological management of hypothyroidism.[5–7] LT4 was one of the three most commonly prescribed medications in the United States of America (USA) between 2008 and 2018,[8] with a similarly high level of use in other countries.[9]

Diagnosis of hypothyroidism

The diagnosis of hypothyroidism is based on the circulating level of thyrotropin (thyroid-stimulating hormone [TSH]). Chapter 1 of this book described the regulation of thyroid hormone secretion and their inactivation, and a concise description only will be included here. Briefly, an increased level of TSH stimulates the thyroid to secrete more thyroid hormones (about 80% thyroxine [T4], with the remainder being triiodothyronine [T3]).

Reference ranges have been defined for serum TSH to describe a "normal range" of this hormone, i.e. between the 2.5th and 97.5th centiles of TSH measured in healthy populations without (known) thyroid dysfunction. These normal ranges vary between regions and assays, and guidelines for the management of hypothyroidism provide guidance on which reference range to use if one from a local reference population has not been established.[7] In general, reference ranges for serum TSH are approximately 0.4–4.5 mU/L. If the secretion of thyroid hormones is deficient, TSH secretion will increase in an attempt to correct this. Accordingly, hypothyroidism is characterised by levels of TSH that are above the reference range. Measurement of free T4 (fT4) distinguishes people with overt hypothyroidism (elevated TSH and fT4 below its own reference range) and subclinical hypothyroidism (elevated TSH with normal fT4); only overt hypothyroidism will be discussed further here.[6–8,10]

Common symptoms of hypothyroidism include fatigue, lethargy, dry skin, feeling cold, weight gain, constipation, muscle aches/cramps, dry/

brittle hair, thinning eyebrows, low mood and changes in the larynx that deepen and coarsen the voice, among others.[10–13] These symptoms are non-specific in nature, occur frequently in the absence of hypothyroidism, can be induced by conditions other than hypothyroidism and are generally not found more frequently in populations with versus without hypothyroidism.[14–16] While the presence of these symptoms might prompt a TSH test, they are of limited value in the formal diagnosis of hypothyroidism. A case control study measured the prevalence of 33 symptoms associated with hypothyroidism and found that only 13 were over-represented in patients with diagnosed hypothyroidism, relative to controls, and that none of the symptoms could be used reliably to diagnose hypothyroidism.[17] Another study in 140 patients with a diagnosis of autoimmune hypothyroidism found that a score derived from 13 symptoms of hypothyroidism predicted the presence of the condition in younger, but not older, patients.[18]

Management of hypothyroidism

What the guidelines say: role of LT4 in the management of hypothyroidism

Current guidelines support intervention with LT4 in all non-pregnant adults with overt hypothyroidism (Chapter 6 discusses the management of hypothyroidism during pregnancy).[6–8] The goals of treatment are to normalise TSH, while improving the levels of other thyroid hormones, and to suppress symptoms of hypothyroidism. Care must be taken to avoid iatrogenic thyrotoxicosis due to over-treatment with LT4. There is no support in most management guidelines at this time for the use of T3 preparations (alone or in combination with T4; see Chapter 8 for a summary of the latest research in this area), or for the use of thyroid extracts. The US guideline notes that there could be a theoretical basis for targeting the lower part of the TSH reference range for hypothyroid patients with persistent symptoms such as obesity, psychological symptoms or dyslipidaemia; however, attempts to achieve this in practice have not led to convincing improvements in these symptoms.[7] One randomised

trial found that manipulating TSH levels within and around the reference range had no significant impact on food intake, energy expenditure, weight or body composition.[19] The patients (masked to treatment) were on average unable to identify which dose was the highest, but there was a significant preference for the dose they *believed* was the highest, suggesting a general concern over the potential for under-treatment.

LT4 is administered once daily, usually 30 minutes before breakfast (ingestion of food reduces the absorption of LT4). However, other regimens such as weekly administration can be considered for patients with problems adhering to a daily regimen, for example.[20] A suitable starting dose of LT4 is selected based on the patient's age, weight and medical history. For example, the UK guideline recommends a starting dose of 1.6 μg/kg for an otherwise healthy adult with primary hypothyroidism, titrated in steps of 25 μg or 50 μg every 3–4 weeks until TSH is in range.[16] Maintenance doses of LT4 lie typically in the range of 100–200 μg/day. Caution is required when managing patients with a history of cardiovascular disease: a lower starting dose of 25–50 μg (age <50 years) or 25 μg (aged >50 years) is appropriate here.

Most patients with hypothyroidism are managed routinely and successfully within the primary care setting. A consultation with a specialist endocrinologist should be considered where hypothyroidism is severe, secondary (central) hypothyroidism is suspected (due to a disorder in the hypothalamus or pituitary), structural alteration of the thyroid is present (e.g. goitre, nodules), Addison's disease (or another significant endocrine condition) is present, or the patient is female and planning a family.

Pharmacodynamics of thyroxine/ levothyroxine

Thyroid hormones, and thus LT4, influence the function of almost every organ system and physiological process in the body. A brief summary of some of the main actions of thyroid hormones on key biological systems and important disease states is given below. As naturally occurring thyroxine and exogenously applied LT4 are identical in chemical terms,

their effects on these physiological systems and on the pathophysiology of disease states are considered together here.

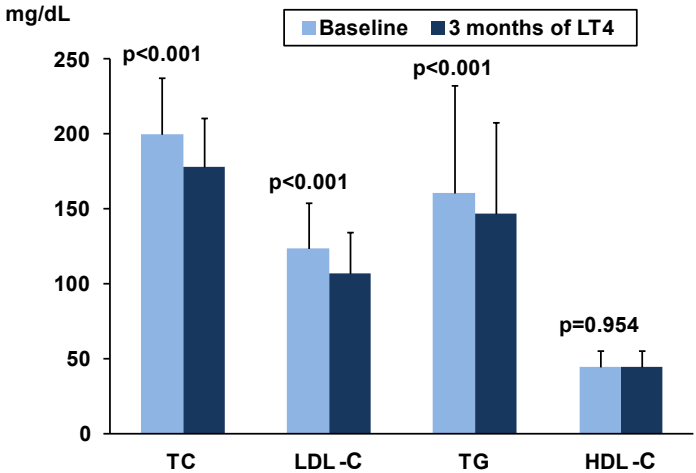
The liver

Lipid profiles: The liver is a major site of metabolism of thyroid hormones, including the conversion of T4 to T3, sufficient to influence the overall level of thyroid homeostasis.[21,22] T3 acts via its intracellular receptors to influence the transcription of thousands of genes, including those involved in regulating lipid and carbohydrate metabolism.[22] Genes affected include those expected to increase cholesterol levels (e.g. increased cholesterol synthesis) and to reduce cholesterol levels (e.g. increased activity of cholesteryl ester transfer protein and increased synthesis and deployment of low-density lipoprotein [LDL]-cholesterol receptors).[22] Consistent with these observations, a Mendelian randomisation study showed that people with a genetic predisposition to higher levels of TSH had higher total cholesterol and LDL-cholesterol.[23] Overall, hypothyroid states are associated with dyslipidaemia characterised by increased total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides, and reduced high-density lipoprotein (HDL)-cholesterol.[22,24] The severity of dyslipidaemia is proportional to the degree of elevation of TSH, although the relationship extends down to within the TSH reference range.[24]

Correction of hypothyroidism with LT4 usually improves the lipid profile, as shown by observational studies and meta-analyses.[25–27] Figure 1 summarises data from an observational study in previously untreated patients with hypothyroidism and an indication for LT4 treatment: 3 months of LT4 reduced TSH from to 47.5 to 2.2 mIU/L and improved the lipid profile, with significant reductions in total cholesterol, LDL-cholesterol and triglycerides.[27]

Non-alcoholic fatty liver disease (NAFLD): Some systematic reviews have associated hypothyroidism with increased progression of NAFLD,[28,29] although this was not a universal conclusion of such analyses.[30] A meta-analysis of 18 mainly cross-sectional studies reported an increased risk associated with hypothyroidism of fibrosis of the liver, an important contributor to the progression of NAFLD and non-alcoholic

Figure 1 Improvement in the lipid profile after correction of hypothyroidism with levothyroxine (LT4) from an observational study of 72 people with hypothyroidism.



The duration of treatment was 3 months. To convert lipid values to mmol/L, multiply by 0.02584 (cholesterol) or 0.01186 (TG). TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.
Drawn from data presented in reference 27.

steatohepatitis.[31] LT4 has been shown to reduce intrahepatic lipids in euthyroid patients with non-alcoholic fatty liver disease and type 2 diabetes, although there is at present no indication for this use of LT4.[32] Research on the possible use of thyroid β-receptor agonists for managing NAFLD is very promising, with a phase 3 trial of resmetirom showing improvement in liver fibrosis by at least one stage compared to placebo.[33]

Skeletal muscle

Glucose metabolism: Thyroid hormones affect glucose metabolism in multiple ways, including alteration of the rate of gluconeogenesis and glycogen synthesis/degradation (in the liver), the rate of absorption of glucose (from the gut), insulin secretion (pancreas), and glucose disposal and utilisation (skeletal muscle).[34] The main overall consequence of the hypothyroid state for glucose metabolism is reduced insulin-mediated glucose disposal in muscle, associated in part with impaired translocation and deployment of the GLUT4 glucose transporter.[34] As a

result, hypothyroidism represents an insulin-resistant state that increases the risk of prediabetes or type 2 diabetes compared with euthyroid controls.[35–38] Again, restoration of a euthyroid state with LT4 treatment improves glucose homeostasis,[34] although not all studies have demonstrated an improvement in insulin resistance with LT4 therapy.[27]

Metabolic rate: Decreased thyroid hormones decrease the metabolic rate in muscle (and vice versa).[39] Given that skeletal muscle accounts for about 40% of overall body weight,[40] this is enough to influence the whole-body metabolic rate.

Muscle health: Thyroid hormones are involved in the repair of muscle fibres, and dysfunction of these systems may contribute to the pathogenesis of certain myopathies.[39,41] Changes in thyroid hormone levels affect the differentiation of muscle cells into fast or slow fibres (higher T3 favours fast-twitch fibres[42]), to the repair or replacement of damaged muscle fibres.[39,43]

Body weight

Thyroid hormones exert complex actions on thermogenesis, the balance of lipogenesis and lipolysis, and on the proliferation of adipocytes.[44] Clinical hypothyroidism is associated with a relatively modest increase in body weight of about 5 kg or less, depending on the severity[45]; for example, in the 3-month study described above, mean body weight was reduced from 73.5 kg to 68.3 kg during LT4 treatment.[27] Increased salt and water retention and reduced metabolic rate alter the balance between energy intake and expenditure (see above).[45] Elucidating the relationships between thyroid function and obesity status has been difficult, as increased body weight itself increases TSH modestly.[46]

Psychological function

Depression is a recognised symptom of hypothyroidism, although longitudinal studies in patients with overt (as opposed to subclinical)

depression are lacking as these patients are rarely left untreated.[13,47] The effect of LT4 on mood and affect has been variable in patients with a diagnosis of hypothyroidism,[48–53] as with other thyroid-related symptoms. Depression itself is common and may not be related to coincidental finding of hypothyroidism. The US guideline for the management of hypothyroidism stresses the need for referral to a mental health practitioner if LT4 treatment does not resolve problems with depression for a patient with hypothyroidism.[7] Some studies have suggested that administration of T3 may enhance the effects of antidepressant drugs of different classes,[54–56] although no data are available for LT4 in this regard.

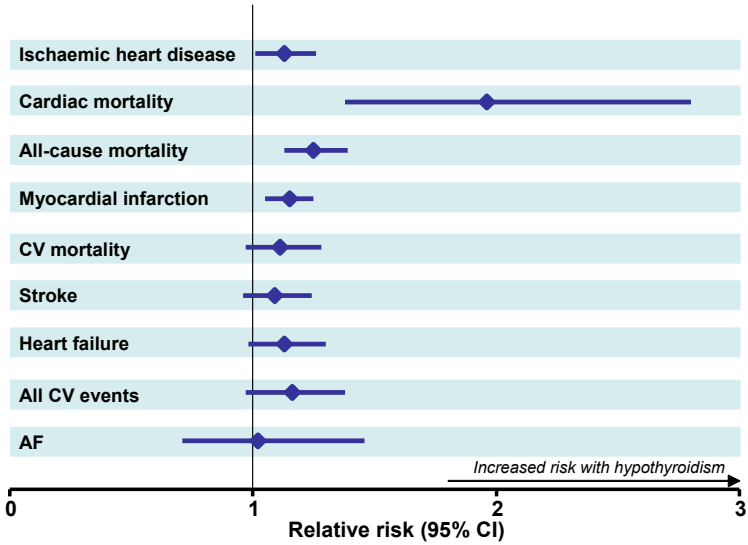
The kidney

Hypothyroidism decreases renal function, and patients with chronic kidney disease have a higher prevalence of hypothyroidism compared with euthyroid populations.[57] The presence of an abnormal thyroid test increased the risk of mortality of a population of patients on dialysis in a systematic review (hazard ratio 2.40 [95% CI 1.47 to 3.93]) for those with versus without low T4.[58] Administration of LT4 has been shown to reduce the rate of progression of renal dysfunction in patients with chronic kidney disease of various aetiologies in a systematic review.[59] Renal benefits arising from the administration of LT4 have also been shown in patients with subclinical hypothyroidism, which is the subject of the next chapter.[60,61]

The heart

A meta-analysis of 55 studies found a significant association between hypothyroidism (any severity) and an increased risk of ischaemic heart disease, myocardial infarction (MI), cardiac mortality and all-cause mortality (Figure 2).[62] An increased risk of cardiac mortality was evident when the analysis was restricted to patients with a history of cardiovascular disease in this analysis (relative risk 2.22 [95% CI 1.28 to 3.83]). Another study demonstrated a higher burden of thrombosis associated with hypothyroidism in patients with non-ST elevation acute coronary syndromes.[63] Hypothyroidism therefore appears to be a risk factor for

Figure 2 Impact of hypothyroidism on cardiovascular and mortality outcomes from a meta-analysis.

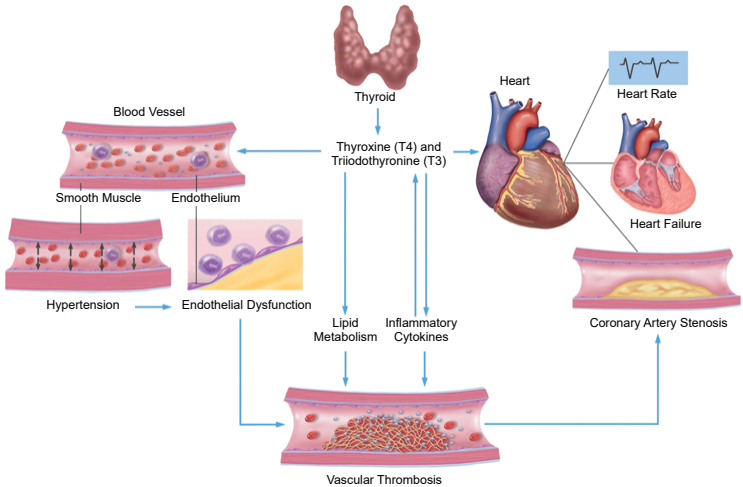


AF: atrial fibrillation; CV: cardiovascular. Drawn from data presented in reference 62.

adverse cardiovascular outcomes. This situation may arise from hypothyroidism-associated dyslipidaemia (see above), systemic inflammation and oxidative stress, exacerbated by defects in endothelial function, increases in blood pressure and cardiac diastolic dysfunction (Figure 3).[64,65] Tumour suppressor p53 is activated during an evolving MI and enhances myocardial cell loss; thyroid hormones suppress this pathway, with a net effect consistent with stimulation of cell growth, increased angiogenesis and metabolic adaptation.[65]

Even mild perturbations of thyroid function can increase the risk of adverse cardiovascular outcomes.[66] A meta-analysis showed that the relationship between fT4 and adverse cardiovascular outcomes is J-shaped, with the lowest risk of a primary composite of coronary heart disease (CHD), stroke, heart failure or death occurring between the 20th and 40th percentiles for fT4.[67] Similarly, the nadir of cardiovascular risk and mortality occurred between the 60th and 80th percentiles of TSH. The risks of adverse cardiovascular outcomes or death increased with increasing fT4 or decreasing TSH, emphasising the importance of

Figure 3 Thyroid hormones and cardiovascular disease.



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avoiding over-treatment of hypothyroidism with LT4. An earlier meta-analysis found no significant association between cardiovascular outcomes and variations in TSH within the normal range, however.[68]

Low T3 levels may be associated with adverse cardiovascular outcomes, especially in patients with pre-existing CHD, which requires further study.[69–71] The adverse influence of cardiovascular disease on thyroid hormone levels, and for potential benefit from intervention with thyroid hormone replacement, is an active area of research.[72,73]

There appears to be a strong association between hypothyroidism and heart failure (HF). Patients with overt hypothyroidism are at increased risk of HF.[74] Increased fibrosis of the heart in the setting of hypothyroidism may contribute to adverse cardiac remodelling in HF.[31] Also, thyroid dysfunction (hypothyroid or hyperthyroid) appears to be associated with increased circulating levels of natriuretic peptides, a marker of the severity of HF.[75] Finally, a history of hypothyroidism also appears to increase the risk of developing atrial fibrillation after cardiac surgery.[76]

In general, hypothyroidism appears to exacerbate pre-existing cardiac problems and increases cardiovascular risk. Patients with hypothyroidism

and cardiovascular disease should be managed with LT4, starting at a low dose (see above).[5–7] A number of studies have demonstrated improved cardiovascular outcomes with LT4 (reviewed elsewhere[71]), although the evidence is conflicting. However, the evidence for improved cardiovascular outcomes with LT4 treatment is based almost entirely on the management of subclinical hypothyroidism; the guideline-driven management of overt hypothyroidism, the subject of the current chapter, requires intervention with LT4, which effectively precludes the conduct of placebo-controlled trials in this population.

Inflammation

People with hypothyroidism demonstrate increased levels of systemic pro-inflammatory markers and associated increased levels of oxidative stress, compared with euthyroid controls.[77,78] In a randomised trial in 165 people with recently diagnosed and untreated Hashimoto's thyroiditis, 6 months of treatment with LT4 reduced the release of tumour necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 from immune cells, and reduced the circulating level of C-reactive protein (CRP), compared with placebo.[79] A recent (2021) systematic review of 93 studies also found that hypothyroidism was associated with increased systemic levels of inflammation/oxidative stress (CRP and malondialdehyde), and that these were reduced by LT4 treatment, with larger effects on overt hypothyroidism compared with milder forms of hypothyroidism.[80]

Haemostasis

Low levels of thyroid hormones are associated with a hypocoagulable state, with increased fibrinolysis, and increased risk of clinically significant bleeding events.[81] Low levels of von Willebrand factor and clotting factor VIII are typical findings.[82,83] Most case reports of bleeding in hypothyroid patients involve mucocutaneous bleeds, which are often minor but may be severe.[82] Cross-sectional and longitudinal data indicated a significant association between hypothyroidism or hyperthyroidism and anaemia in a patient-level meta-analysis.[84]

Advantages and limitations of TSH as a biomarker for the hypothyroidism

Why do we use TSH as a biomarker for thyroid function?

Thyroid hormones act on the peripheral tissues (see above) and also feed back to cells in the pituitary and hypothalamus to inhibit TSH secretion. In this way, a high level of thyroid hormones in the blood reduces TSH secretion and prevents over-production of thyroid hormones; conversely, if the level of thyroid hormones is too low, the secretion of TSH – and ultimately of thyroid hormones – increases. Importantly, this feedback loop includes an amplification of the TSH response, such that a reduction by half of the level of T4 secretion by the thyroid induces a change in TSH secretion that is up to 100-fold larger.[85] These large changes in TSH are more practical to measure in the routine clinical setting, compared with the much smaller associated changes in T4 or T3, particularly when disturbances of thyroid function are relatively subtle.[86] A corollary here is that even relatively small changes in the level of thyroid hormones during treatment with LT4 can cause a significant disturbance of TSH; the therapeutic implications of this are discussed in a later section.

Limitations of TSH as a biomarker for thyroid function

A wide range of drugs, foods and supplements can interfere with the TSH result (Figure 4).[14,85,87,88] This can occur due to:

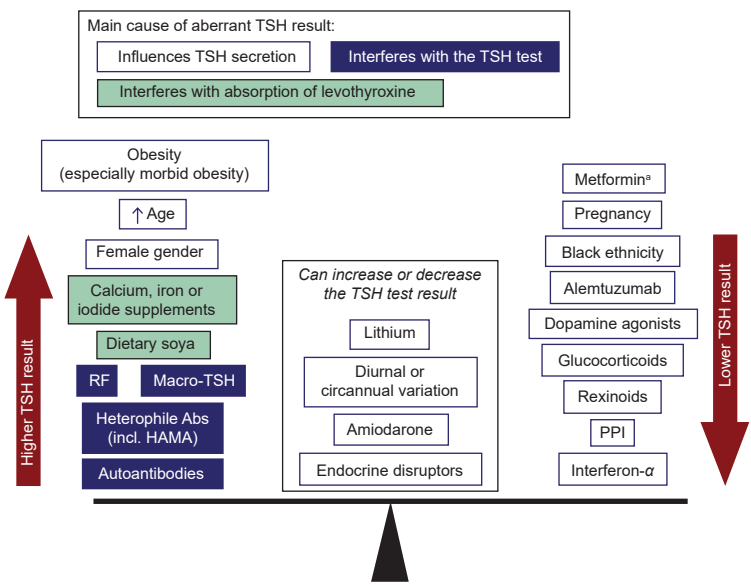
- **Reduced absorption of administered LT4:** e.g. calcium, iron or iodine supplements.
- **Modulation of TSH secretion:** e.g. metformin, alemtuzumab, dopamine agonists, rexinoids, interferons, proton pump inhibitors, lithium, amiodarone, endocrine disruptors, pregnancy, severe obesity, older age, pregnancy and certain ethnicities.
- **Interference with the mechanics of the TSH test itself:** e.g. autoantibodies to TSH, heterophilic antibodies to the mouse antibodies used in some TSH tests, Rhesus factor or macro-TSH

(TSH in a complex with IgG antibodies, which some TSH tests recognise more effectively than others).

Obesity status may be especially important here, as TSH levels rise in line with body mass index (BMI).[46] Conversely, marked weight loss, such as following bariatric surgery, has been shown to reduce TSH or increase fT4, depending on the type of surgery.[89–90] Glucagon-like peptide 1 (GLP-1) receptor agonists usually induce clinically significant weight loss, and this has also been shown to reduce the TSH level.[91] Also, a network meta-analysis showed that bariatric surgery was associated with a fall in serum TSH and a reduced requirement for LT4, such that hypothyroidism resolved in some patients with milder forms of the condition.[92]

In addition, levels of the different thyroid hormones and associated components of the hypothalamus-pituitary-thyroid axis reach a balance that is set differently for each individual and which usually varies little

Figure 4 Drugs, foods, supplements and other substances that can interfere with the result of a thyroid function test.



over time.[93–95] Accordingly, a different "set point" for thyroid homeostasis could potentially explain why, for a given individual, some thyroid hormones may be comfortably within their reference ranges while others remain outside them, and may be entirely appropriate for that individual.

TSH follows a pattern of circadian variation, with the lowest value arising around the middle of the day, and to an extent that may vary according to age and ethnicity.[96–98] A seasonal variation in TSH level has also been reported, with a lower value in the summer, although this is less certain.[14,99] Finally, the reference population used to construct the reference ranges for thyroid function for a TSH test may be more or less relevant to a particular individual in a particular location. Variations in the way that the data on thyroid homeostasis in the reference population are handled can also influence the final reference range cited for the test, with implications for individuals with TSH near the cut-off point of the range.[100]

Thus, some ambiguity surrounds the upper cut-off for a TSH reference range. This is of clinical importance, as even minor variations in the TSH cut-off values result in measurable differences in the number of people being treated for hypothyroidism.[101] All other clinical findings and biomarkers for a given patient should be considered, rather than treating the patient for hypothyroidism solely on the basis of a TSH result that is modestly above its reference range.[102] In particular, strategies to achieve weight loss may be an appropriate initial strategy for a patient with obesity and mildly elevated TSH,[91] and higher cut-offs for TSH can be used to initiate LT4 treatment in elderly patients, without ill effects.[103–106] More accurate diagnosis of thyroid dysfunction, and considerable cost savings, could result from using reference ranges adjusted for gender, seasonality, age and the time of day the blood for the test is drawn.[14] Setting reference ranges for thyroid hormones that minimise the long-term risk of adverse cardiovascular events and mortality provides another strategy for improving clinical outcomes in people with hypothyroidism.[67]

Patients with persistent symptoms of hypothyroidism despite having TSH in range

As many as one in four patients with hypothyroidism who have TSH restored to the normal range by LT4 treatment report persistent or new symptoms reminiscent of hypothyroidism.[107] Fatigue is reported most commonly in this setting. Conducting a thorough examination is vital, not only to ensure that thyroid hormones are well controlled, but to seek evidence of other physical or somatic conditions that may explain the persistent symptoms.[15] This approach will lead to resolution of the problem for most patients.

Recently, the Patient Health Questionnaire-15 was used to gather data from 3,516 patients with hypothyroidism to explore the importance of the somatic symptom disorder, somatisation, which was defined as the appearance of physical symptoms that arise from psychological distress.[108] Almost three-fifths (59%) of the population were categorised as having "probable somatic symptom disorder", associated particularly with patients who were younger, female, had additional comorbidities, demonstrated low mood, depression or anxiety, and did not feel that their thyroid treatment was controlling their symptoms well, among other factors. This study may highlight a psychological mechanism which may explain, in part, why patients are often ready to attribute symptoms that impair their general well-being to thyroid medication, rather than to other potential causes.

Physicians managing patients with hypothyroidism often concentrate on blood test results rather than patients' reports of symptoms, and tend to attribute persistent symptoms to probable non-adherence with treatment.[109] It is also important to remember that patients in this situation will often self-medicate, including the use of various T3 preparations, based on information sourced from social media or the internet that is often of poor quality.[110,111] Dissatisfaction with treatment for thyroid dysfunction is associated strongly with patients' lack of confidence and trust in healthcare professionals.[112] Achieving better education of patients by physicians on their thyroid dysfunction and its treatment is an important component of managing this population.[109,113]

Making the most of modern formulations of levothyroxine

Small variations in TSH, even occurring within the current reference range for TSH, can exert measurable adverse effects on health and well-being.[114] Accordingly, where intervention with LT4 is needed, careful titration of the dose to optimise thyroid homeostasis is required. However, between about one-third and one-half of patients with hypothyroidism were under- or over-treated with LT4 according to one study.[115] This issue is compounded by the need of some patients to start on doses of LT4 of 25 μg or 50 μg, including those with very low body weight or cardiovascular disease.[5–7] The development of newer formulations of LT4 with better chemical stability and more accurate actual LT4 content has improved the prospects for precise dosing with LT4 in this situation (see Chapters 1 and 2 of this book for more details).[116–117] Briefly, the improved accuracy of dosing has allowed closer spacing between tablet strengths; for example, a patient starting on a low dose of T4 with tightened specification can now be titrated from 25 μg through 38 μg, 50 μg, 63 μg, 75 μg, 88 μg and 100 μg, with a further five dosage strengths available between 100 μg and 200 μg.[117] This means that almost all patients can receive a precise dose of LT4 via prescription of a single tablet, which helps to maintain good adherence to treatment. In the unlikely event that a combination of two tablets is needed to construct a desired LT4 dosage, bioequivalence studies have established that this can be done using this preparation without loss of precision of dosing.[116,118]

Conclusions

The level of thyroid hormones influences the function of virtually every system in the body. Hypothyroidism, characterised by low fT4 and elevated TSH, is a highly prevalent condition that is often not managed adequately. Restoring TSH to its reference range resolves the common symptoms of hypothyroidism for most patients, including dyslipidaemia,

which otherwise has the potential to impair long-term clinical outcomes. A substantial minority continue to report these symptoms, however, and careful examination is needed to identify other potential causes of these. It is important to remember that a number of factors can affect the reliability of the TSH test for identifying genuine thyroid dysfunction. Careful consideration of all aspects of the patient's wellbeing is therefore essential when managing hypothyroidism rather than relying solely on the TSH result, especially for patients with mild elevations of TSH or obesity. Emerging evidence has associated thyroid dysfunction with different manifestations of cardiovascular disease and it may be possible to set reference ranges for TSH and fT4 to minimise the risk of cardiovascular events and associated mortality in the future. The development of novel formulations of LT4, with better dosing accuracy, well defined bioavailability and enhanced stability, has improved the ability of physicians to titrate the dose of LT4 carefully in order to optimise thyroid homeostasis.

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Chapter 4

Modern Levothyroxine Preparations and the Management of Subclinical Hypothyroidism

Gabriela Brenta
Dr. Cesar Milstein Hospital, Buenos Aires, Argentina

Subclinical hypothyroidism (SCH) is diagnosed when thyrotropin (thyroid-stimulating hormone [TSH]) is elevated but free thyroxine level is normal. Most people with SCH present without symptoms of hypothyroidism, and most evidence for the benefit of intervention with levothyroxine (LT4) has been from studies in younger patients and those with TSH >10 mIU/L. Evidence from meta-analyses suggests that LT4 treatment may improve cardiovascular outcomes in this population, although again, benefit appears to be limited to younger patients. Maintenance doses of LT4 used in patients with SCH are usually low, even where pre-existing cardiovascular disease is absent. The use of modern LT4 preparations, with multiple dosage steps between 25 mg and 100 mg tablet strengths, helps to provide flexibility and precision in the management of SCH.

Introduction

There is a strong consensus that intervention with levothyroxine (LT4) is required for the management of all people with overt hypothyroidism, as described in the previous chapter.[1] The situation regarding subclinical hypothyroidism (SCH) is more nuanced, and debate and controversy have continued for decades on whether to treat some or all of these patients or whether SCH even exists as an independent clinical entity.[2] This chapter summarises the natural history of SCH and the current thinking on which patients might benefit from active treatment with LT4. We also consider the potential for benefit using modern LT4 preparations for this population.

The previous chapter of this book describes the main clinical features and presentation of hypothyroidism in general, along with the pharmacodynamics of thyroxine (T4) and LT4. This chapter focuses specifically on non-pregnant adults with SCH. The following chapter discusses the management of hypothyroidism (overt and subclinical) during pregnancy.

Diagnosis, clinical features and prognosis of subclinical hypothyroidism

Diagnosis

The aetiology of SCH is the same as that for overt hypothyroidism. SCH may be diagnosed when the level of thyrotropin (thyroid-stimulating hormone [TSH]) is above its reference range, but the level of free T4 (fT4) is normal, confirmed using two tests conducted 2–3 months apart.[3,4] European guidelines for the management of SCH (2013)[4] stratify patients with SCH according to the level of TSH in order to distinguish patients with "mildly elevated" TSH (4–10 mIU/L) from those with "more severely" elevated TSH (≥10 mIU/L), following a precedent set by a guideline from the United States of America (USA) published in 2004.[5] Diseases of the hypothalamus or pituitary, and non-thyroidal

conditions that can affect TSH levels (see below) must be excluded before a confident diagnosis of SCH can be made. It is also helpful to measure anti-thyroid peroxidase antibodies (TPOAb) in these patients to confirm or exclude the presence of autoimmune thyroiditis as an underlying aetiology of thyroid dysfunction and to support subsequent clinical decision-making.

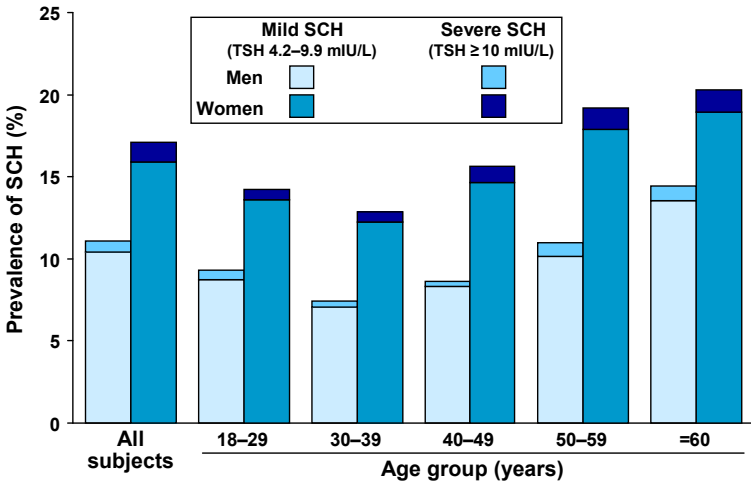
Symptoms of hypothyroidism (e.g. tiredness, lethargy, slow thinking, muscle discomfort, weight gain) are generally of little use for diagnosing hypothyroidism, as they occur with similar frequency in populations with and without hypothyroidism. This challenging situation is compounded for SCH, as the majority of patients with this condition do not present with symptoms[6] and may be diagnosed serendipitously during regular health checks or on presentation with other conditions such as diabetes.

Prevalence

The prevalence of SCH has been described as about 5–15% in Western countries.[3,7] This implies a substantial burden of disease, given that 10% of the adult population represents currently (2021) about 65 million, 27 million and 34 million individuals in Europe, the USA, and Central and South America, respectively.[8] SCH is found more commonly in women versus men and in older versus younger subjects, especially above the age of 60 years; for example, Figure 1 shows the prevalence of SCH according to age and gender from a recent (2023) large, iodine-replete population in China.[9] The overall prevalence of SCH (11.1% in men and 17.1% in women) was more than 10-fold higher than the prevalence of overt hypothyroidism (0.6% in men and 1.2% in women) in this study.

Hypothyroidism is frequently undiagnosed, according to studies conducted in the USA and in Europe, which suggest that 7% of populations were unaware of meeting biochemical criteria for hypothyroidism.[10] Moreover, about four in five of these cases were consistent with a diagnosis of SCH, suggestive of the presence of a large burden of undiagnosed SCH in the community.[10] There is currently no support for mass population screening to detect cases of SCH in influential management

Figure 1 Prevalence of subclinical hypothyroidism according to gender and age from a large (N=78,428) population-based survey in China.



TSH: thyrotropin (thyroid stimulating hormone). TSH 4.2 mIU/L was the upper limit of the normal reference range for the population studied. Drawn from data presented in reference 9.

guidelines, though some authors have called for screening of specific at-risk populations.

Clinical course

SCH may progress to overt hypothyroidism, or up to about half of populations with SCH may revert spontaneously to euthyroidism, over time.[11,12] For example, a study from Japan showed that the risk of developing overt hypothyroidism among elderly people with SCH was 7.0% versus 1.6% for euthyroid control subjects during an average of 4.2 years of follow-up (adjusted odds ratio 4.56, p=0.009).[13] Progression to overt hypothyroidism and regression to euthyroidism was associated significantly with increasing and decreasing TSH at baseline, respectively, in this study. A prospective, longitudinal study of 82 women with SCH from Switzerland found that the 10-year incidence of overt hypothyroidism rose steeply as TSH at baseline increased, from 0% at TSH 4–6 mIU/L, to 43% at TSH 6–12 mIU/L, to 77% at baseline TSH >12 mIU/L (p<0.001 for the trend).[14] An analysis from the US Cardiovascular Health Study

found a 7.1-fold increase in the risk of conversion of SCH to overt hypothyroidism for subjects with TSH 10–20 mIU/L versus 4.5–6.9 mIU/L at baseline.[12] In addition, subjects in this study were 84–88% less likely to revert to euthyroidism at baseline TSH levels of 7.0–9.9 mIU/L or 10–20 mIU/L, each versus 4.5–6.9 mIU/L. The incidence rates of overt hypothyroidism in a Spanish population with SCH were 1.76/100 patient-years for baseline TSH 5.0–9.9 mIU/L, 19.67/100 patient-years for baseline TSH 10.0–14.9 mIU/L and 73.47/100 patient-years for baseline TSH 15.0–19.9 mIU/L.[15]

The presence of TPOAb is also a strong predictor of future overt hypothyroidism. The 10-year incidence of overt hypothyroidism in the prospective study, described above, was 59% (TPOAb+) versus 23% (TPOAb–).[14] Other studies confirmed TPOAb+ status (and/or other thyroid autoantibodies) as a powerful risk factor for progression from SCH to overt hypothyroidism, or for reduced rate of regression from SCH to euthyroidism.[12,14,16]

Challenges in the diagnosis of subclinical hypothyroidism

The clinical relevance of relatively minor elevations in TSH may be questionable in some cases. For example, natural seasonal variations in the TSH level (where TSH is higher in the winter versus summer in the northern hemisphere and fT4 remains fairly constant[17]) are not considered when comparing the TSH level of a patient with the reference range, and this has been described as a potential source of misdiagnosis of SCH, with subsequent over-treatment.[18] The natural tendency of TSH to increase with increasing age may also lead to a misdiagnosis of TSH in an older patient, and expert opinion in this area favours the use of age-adjusted reference ranges and/or toleration of a higher TSH level in older patients.[19] Similarly, severe obesity increases the TSH level,[20] therefore weight loss may be the most effective strategy to achieve normalisation of thyroid function in such patients.[21] Finally, numerous foods, drugs and environmental factors can alter the outcome of a TSH test, and these are described in more detail in Chapter 3 of this book.[19]

Management of subclinical hypothyroidism

Principal therapeutic effects of levothyroxine

Symptoms and thyroid homeostasis

A systematic review showed that LT4 reduces TSH and increases fT4 and free triiodothyronine (fT3) in people with SCH, as it does in people with overt hypothyroidism (see Chapter 3).[22] SCH presents without symptoms in a high proportion of people with SCH and is diagnosed on the basis of elevation of TSH, as described above. One randomised trial reported reduced tiredness in people with SCH who received LT4, without effects on other symptoms of hypothyroidism.[23] Other studies have shown LT4 has little effect on symptoms of SCH or on measures of quality of life in this population, especially where TSH was <10 mIU/L.[24–27]

The Thyroid Hormone Replacement for Subclinical Hypothyroidism (TRUST) study randomly assigned 737 elderly subjects (aged ≥65 years) with SCH to treatment with LT4 (dose guided by the TSH level) or placebo for 1 year.[28] Mean TSH was within the reference range only for the LT4 group after treatment (3.63 mIU/L vs. 5.48 mIU/L for placebo). There was no change in the co-primary endpoints of scores relating to hypothyroid symptoms or tiredness evaluated using a thyroid-specific quality-of-life instrument. A pooled analysis of TRUST with another clinical trial of LT4 in elderly patients with SCH also found no benefit from intervention.[29] The Study of Optimal Replacement of Thyroxine in the Elderly (SORTED1) study showed that elderly patients with SCH could be managed using a higher upper limit for TSH compared with the usual reference range used (8 mIU/L vs. 4 mIU/L).[30–32] The more relaxed approach to TSH management did not lead to any excess of symptoms, meaningful differences in quality-of-life scores, or in the rate of other adverse events.

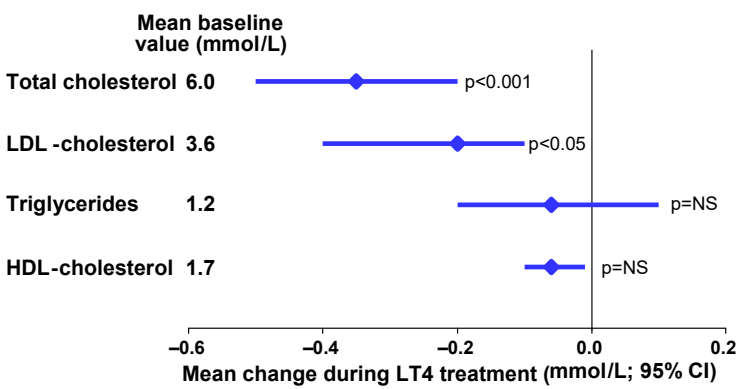
Cardiovascular risk factors

Cardiovascular risk factors often increase in people with SCH, including those with TSH <10 mIU/L.[33–38] A recent (2024) systematic review/meta-analysis showed that LT4 treatment induces a small but potentially

clinically significant reduction in blood pressure in people with SCH of about –4/–2 mmHg.[39] However, blood pressure reductions were generally more apparent in subjects with higher initial TSH or pre-existing hypertension in this analysis. In addition, some[40] but not all[41] meta-analyses in this area describe a reduction in blood pressure with LT4. Another meta-analysis showed that SCH was associated with a 32% increase in the risk of incident hypertension, with all of this excess risk apparent in younger subjects (<65 years).[42]

Hypothyroidism, including SCH, is associated with a more adverse lipid profile.[43] A number of reports, including randomised controlled trials and meta-analyses, have demonstrated improvements in the lipid profile following administration of LT4 to people with SCH.[23,41,44–50] Figure 2 shows the effects of LT4 on the lipid profile from a randomised, placebo-controlled crossover evaluation of LT4 100 μg/day in 100 LT4-naïve patients with SCH and relatively mild elevation of TSH (median baseline TSH 5.3 mIU/L).[23] The LT4 treatment reduced median TSH to 0.5 mIU/L, with a significant ($p<0.001$) mean treatment effect versus placebo of –5.6 mIU/L (95% CI –7.2 to –4.1 mIU/L). This was accompanied by significant reductions in total and LDL-cholesterol, with no significant effect on triglycerides or HDL-cholesterol in this study. Thyroid hormone replacement with LT4 may also enhance the efficacy

Figure 2 Changes in lipid parameters during treatment with levothyroxine (LT4) in a randomised crossover study in 100 subjects with subclinical hypothyroidism.



NS: not statistically significant. Drawn from data presented in reference 23.

of lipid-modifying drugs.[51,52] LT4 treatment also lowers levels of atherogenic remnant lipoprotein levels in women with SCH.[53] In practice, levels of lipids or blood pressure may not be normalised completely by LT4 treatment in many patients,[50] and these individuals should be monitored carefully and their cardiovascular risk managed according to appropriate guidelines.[54]

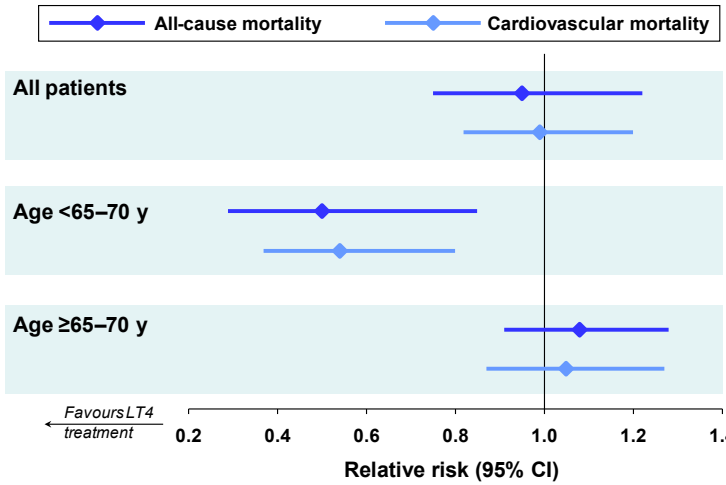
SCH is associated significantly with abdominal obesity and some definitions of metabolic syndrome (which includes high waist circumference).[37,55,56] A systematic review reported that one year of treatment with LT4 did not reduce body mass index in people with SCH.[26]

Cardiovascular outcomes

Reviews and most meta-analyses in this area have associated SCH with an increased risk of adverse cardiovascular and/or mortality outcomes, especially in patients with pre-existing coronary artery disease or heart failure.[57–64] Meta-analyses found no excess cardiovascular risk associated with high TSH in elderly populations, however.[59,62,63] The presence of anti-thyroid antibodies does not increase the risk of adverse cardiovascular outcomes associated with SCH.[65] The risks of venous thromboembolism[66] or atrial fibrillation[67] are also increased in the setting of SCH.

A meta-analysis of nine studies evaluated the effects of LT4 on mortality outcomes with and without stratification of patients by age at baseline.[68] There was no signal for an effect on mortality in the overall population, or in elderly patients, although there were significant reductions with LT4 in both cardiovascular and all-cause mortality in younger patients (Figure 3). An analysis of data within the United Kingdom National Health Service produced a similar result, with a protective effect of LT4 against adverse cardiovascular or mortality outcomes in younger, but not in older, patients with SCH.[69] There was also no effect of LT4 on cardiovascular event rates in the randomised TRUST study, conducted in elderly patients with SCH, although this trial lacked the statistical power to evaluate this definitively.[28] A retrospective analysis from a population of patients with diabetic nephropathy (which itself confers a high level of cardiovascular risk) and SCH showed that treatment with LT4 reduced the risk of acute coronary syndromes and stroke (but not peripheral

Figure 3 Effects of levothyroxine (LT4) on all-cause and cardiovascular mortality outcomes in patients with subclinical hypothyroidism in a meta-analysis.



Drawn from data presented in reference 68.

vascular disease events).[70] Another retrospective study of patients treated in the primary care sector in Sweden showed that LT4 reduced the risk of mortality in women with atrial fibrillation, although this study did not distinguish between patients with SCH or overt hypothyroidism.[71] Other retrospective studies did not suggest a significant effect of LT4 on cardiovascular or mortality outcomes in patients with or without pre-existing coronary heart disease.[72]

SCH has been associated with impaired myocardial function.[73,74] A meta-analysis published in 2022 concluded that there is insufficient evidence to support improved outcomes from intervention with LT4 in patients with SCH and heart failure.[75] However, another meta-analysis, also published in 2022, found that treatment with LT4 improved aspects of cardiac systolic and diastolic dysfunction associated with SCH.[76]

The mechanism by which LT4 treatment may improve vascular function is unclear and may involve decreased progression of atherosclerosis (measured via carotid intima-media thickness),[47,77] improved endothelial function,[23,78] reduced inflammation and oxidative stress,[79,80] or reduced arterial stiffness.[81] It is unknown whether these occur in addition to (or

associated with) the improvements in classical cardiovascular risk factors, described above. One study showed that the improvements in lipids and endothelial function were driven mainly by increases in fT4.[23]

Renal outcomes

SCH was associated with an increased risk of renal failure and with lower average values of estimated glomerular filtration rate in an observational study of older adults (68% females) at elevated cardiovascular risk.[82] Randomised trials have suggested that treatment with LT4 may reduce albuminuria in patients with SCH.[83,84]

Type 2 diabetes and other insulin-resistant states

Thyroid dysfunction is associated with the development of insulin resistance.[85] Populations with type 2 diabetes are enriched with SCH, and those with versus without SCH have a higher risk of diabetes complications. Accordingly, the Latin American Thyroid Society recommends screening of people with type 2 diabetes or metabolic syndrome for thyroid dysfunction, including SCH.[86] No randomised trials in this area are available.

Current guidelines

Current guidelines for the management of SCH recommend thyroid hormone replacement with LT4 if TSH is >10 mIU/L, irrespective of the presence or absence of symptoms reminiscent of hypothyroidism, consistent with the increased risk of conversion to overt hypothyroidism, as described above.[4] The presence of diffuse or nodular goitre, or a history of partial thyroidectomy, is also an indication for use of LT4 in patients with SCH. If TSH <10 mIU/L, a trial of LT4 treatment can be considered for a patient aged <65 years who has symptoms of hypothyroidism; LT4 should be withdrawn after 2–3 months if symptomatic benefit is not observed. It is recommended to avoid use of LT4 wherever possible for elderly patients with TSH <10 mIU/L. There is no clinical justification for the use of LT4 as an attempt to reduce body weight in a patient with SCH and TSH <10 mIU/L. The European guideline for the management

of SCH is now more than ten years old. However, a recent expert review concluded that clinical evidence that has appeared since then has largely continued to support the recommendations made in the guideline.[7]

The phenomenon and management of SCH continue to attract debate and controversy. A consensus review from 2019 considered that intervention with LT4 would be inappropriate for "almost all" people with SCH, possible exceptions being young adults (≤30 years), those with TSH ≥20 IU/L, those with severe symptoms consistent with hypothyroidism or women attempting to become pregnant.[2] Other experts have pointed out that this recommendation was mainly based on observations in older subjects (who may have had a naturally occurring increase in TSH, as described above), with little data available from younger patients (the article calls for more research on younger people with SCH).[87] Some other recent expert opinions published after the 2019 report reached similar conclusions,[88] or echoed the guideline position favouring intervention with LT4 where TSH is ≥10 IU/L, as described above.[27] A joint statement issued in 2019 from two expert societies, the Society for Endocrinology and British Thyroid Association, considered that the 2019 report relied excessively on evidence from elderly patients or from small-scale trials and was insufficiently evidence-based to support such a major alteration to the standard of care for managing SCH.[89]

Impact of modern preparations of levothyroxine

SCH is widely regarded as a relatively mild form of hypothyroidism. Accordingly, initial doses of LT4 are usually low even in patients without pre-existing cardiovascular disease. For example, the median on-trial, titrated dose of LT4 in the randomised TRUST study was 50 μg, which was sufficient to reduce median TSH from 6.4 mIU/L at baseline to 3.6 mIU/L at 12 months.[28] A randomised trial that involved administration of a fixed dose of LT4 100 μg to people with SCH resulted in a reduction in median TSH from 5.3 mIU/L at baseline to a relatively low on-trial median TSH value of 0.5 mIU/L.[23] Accordingly, the titration of LT4 for a person with SCH is likely to start from a low value, and should increase in small steps until TSH is within range. Modern LT4 preparations, with multiple dosage steps between 25 μg and 100 μg, provide

flexibility in LT4 dosing, with a high probability of being able to set an effective well- tolerated dose based on intake of one tablet per day. This approach also minimises the risk of over-treatment with LT4 and signs of iatrogenic thyrotoxicosis, which has been reported in the setting of SCH.[90] LT4 administered at an appropriate dose to people with SCH also has no adverse effects on bone metabolism.[91,92]

Conclusions

Most patients with SCH do not present with symptoms of hypothyroidism. Most of the reported benefits associated with treatment of SCH with LT4 have been observed in patients with TSH >10 mIU/L. Conversely, the evidence for benefit from intervention with LT4 for people with more mild elevation of TSH (<10 mIU/L) or in older subjects is limited. Epidemiological evidence has suggested a significant association of SCH with adverse cardiovascular outcomes, and meta-analytic evidence has suggested improved cardiovascular outcomes associated with LT4 treatment. Several possible therapeutic mechanisms have been proposed to account for this effect, including improvements in blood pressure and lipids, reductions in systemic inflammation and oxidative stress, slowing of the progression of atherosclerosis, and improvements in endothelial function and arterial stiffness. Several studies have shown that improvements in cardiovascular outcomes appear to be restricted to younger patients with SCH, however. Maintenance doses of LT4 used in patients with SCH are usually low, even where pre-existing cardiovascular disease is absent. The use of modern LT4 preparations, with multiple dosage steps between 25 μg and 100 μg tablet strengths, helps to provide flexibility and precision in the management of SCH.

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Chapter 5

Modern Precision Management of Hypothyroidism in Pregnancy

Kris G Poppe
Endocrine Service, University Hospital CHU Saint Pierre,
Free University of Brussels (ULB), Brussels, Belgium

The production of thyroid hormones increases in the first trimester of pregnancy to support the developing foetus, which can prompt a new diagnosis of (subclinical) hypothyroidism or exacerbate existing thyroid dysfunction. The presence of hypothyroidism, including the subclinical form, is associated with a range of adverse pregnancy outcomes. The majority of meta-analyses in this area have shown that thyroid hormone replacement with levothyroxine (LT4) may reduce the risk of some of these adverse outcomes, including pregnancy loss, preterm birth and preeclampsia. Most pregnant women with hypothyroidism will receive daily doses of LT4 in the range of 25–100 mg/day. The use of modern formulations of LT4, with a tightened specification featuring better accuracy of dosing and closer-spaced dosage intervals, can add useful precision to the titration of LT4 at these relatively low doses to maintain thyroid-stimulating hormone within pregnancy-specific reference ranges.

Introduction

Primary hypothyroidism is up to about 10-fold more common in women than in men. Although its prevalence rises steeply in women older than 50 years of age, many younger women present with this condition. For example, cross-sectional data from a nationally representative cohort of women in the United States of America (USA) found that 3.1% of women of potentially childbearing age had biochemical evidence of hypothyroidism.[1] It is inevitable, therefore, that hypothyroidism and pregnancy will often coincide. This chapter explores the prevalence, characteristics and management of hypothyroidism in naturally occurring pregnancy, including the potential role of modern preparations of levothyroxine (LT4) in managing this population. The following chapter of this book deals with the management of fertility in people with hypothyroidism.

Diagnosing hypothyroidism in pregnancy

Thyroid homeostasis during pregnancy

Pregnancy places a significant stress on thyroid homeostasis. The developing foetus does not begin to synthesise thyroid hormones (TH) until the second trimester and is dependent entirely on maternally synthesised TH until this time. In addition, a proportion of the triiodothyronine (T3) passing through the placenta is degraded there by local deiodinase (type 3) enzymes. Adaptive changes in maternal metabolism counteract these potential reductions of TH. For example, the production of human chorionic gonadotrophin (hCG) by the mother increases rapidly from 1–2 weeks post-conception to a peak around the end of the first trimester; hCG has agonist activity at the thyroid-stimulating hormone (TSH) receptor, which increases the secretion of TH while decreasing TSH secretion by the pituitary.[2] In addition, higher levels of oestrogen during pregnancy drive increased circulating levels of TH-binding proteins, which increases the total levels of TH in the circulation.[3]

Overall, about half of the variability in thyroid function during pregnancy is determined genetically. Thyroid autoimmunity (TAI) is the best described contributor to the other half as it impairs the stimulation of TH production by hCG and may contribute to observations that the presence of anti-thyroid antibodies may exacerbate the adverse impact of hypothyroidism on pregnancy outcomes (described below).[4] Parity, smoking status, age, body mass index, iron, endocrine disruptors and ethnicity are all additional candidates for contributing to variability in thyroid function during pregnancy.

Pregnancy-specific reference ranges for thyroid hormones

The changes to thyroid homeostasis during pregnancy have important implications for the diagnosis of thyroid dysfunction at this time. In particular, the use of trimester-specific reference ranges for TSH and free T4 (fT4) would help to increase the accuracy of diagnoses of hypothyroidism in pregnant women.[5] Current (2017) guidelines from the USA for the management of hypothyroidism during pregnancy provide strong support for the use of trimester- and population-specific reference ranges, where available.[6] Where they are not available, it is suggested to use an upper limit of 4 mIU/L rather than the usual 4.5 mIU/L for the first trimester (as TSH falls by about 0.5 mIU/L on average during this period). Draft guidance from the United Kingdom (UK) Royal College of Gynaecologists (RCOG) on the management of thyroid disorders during pregnancy,[7] as well as a guideline from the European Thyroid Association (ETA) on the management of subclinical hypothyroidism (SCH) during pregnancy and in children,[8] provide similar recommendations.

A large individual patient data meta-analysis of cohort studies worldwide has provided additional guidance on the selection of subjects for the definition of trimester-specific reference ranges that are relevant to local populations.[9] Much of the variation in methodology between individual studies (especially with regard to differences in inclusion/exclusion criteria) exerted only a minor influence on the calculated reference range, generally supporting their clinical validity. However, the inclusion

of participants with anti-thyroid peroxidase antibodies (TPOAb) in some studies was found to have increased the upper limit of the TSH reference range by 0.65 mIU/L in the first trimester and by 0.45 mIU/L in the second trimester, with a potentially profound impact on the use of these reference ranges for diagnosing hypothyroidism in pregnancy.

Scale of the problem of hypothyroidism in pregnancy

High prevalence

Hypothyroidism has been described as the second most common endocrine condition affecting women of childbearing potential (after diabetes). The prevalence of hypothyroidism among pregnant women is comparable to that found in the general population at a comparable age. For example, some studies that involved the application of thyroid function tests to substantial populations of pregnant women revealed that the proportions with SCH/overt hypothyroidism (OH) were 8.9%/0.5% (Turkey, 2014–2015),[10] 5.5%/0.92% (India, 2018–2020),[11] 15.6%/8% (Ethiopia, 2022–2023),[12] 3.6%/0.5% (Spain, 2010–2011),[13] 0.07%/6.45% (Saudi Arabia, 2012–2018),[14] 1.35/11.90 (Iran, based on a meta-analysis of local studies)[15] or 17.1% (all hypothyroidism, Lebanon, 2014–2015).[16] Another study from India found a prevalence of hypothyroidism of 14.4–15.1% (of which an undefined majority was SCH) over the three trimesters, with a much higher prevalence of 32–44% if American Thyroid Association (ATA)-recommended trimester specific cut-offs were used.[17]

Reviews in this area tend to cite prevalence values in pregnant women of up to 1% for OH and up to 10% for SCH.[7] The studies cited above show that prevalence of thyroid dysfunction in pregnancy is highly variable and may be notably higher than these values among some populations. Applying even relatively conservative estimates of the prevalence of OH (0.5%) and SCH (5%) to the 3.88 million completed pregnancies recorded for the European Union (EU) in 2022[18] results in an estimate

of 1,940 pregnancies affected by OH and 194,000 pregnancies affected by SCH in that year alone. It should be noted that the prevalence values quoted here are as reported in the individual studies, with or without using trimester-specific TSH ranges, as described above.

Increased risk of adverse pregnancy outcomes

The scale of the clinical literature in the field of thyroid dysfunction in pregnancy is vast, and Table 1 shows the results of systematic reviews and meta-analyses in this area published within approximately the last five years (2019 onwards).[19–31] It is clear that hypothyroidism is associated with an increased risk of adverse pregnancy outcomes, including pregnancy loss, preterm birth, gestational diabetes, anaemia, preeclampsia or other hypertensive disorders of pregnancy and anthropometric, neurocognitive or developmental issues in the offspring.

The adverse impacts of hypothyroidism on pregnancies shown in Table 1 confirm and extend the results of earlier analyses omitted here and reviewed elsewhere.[32] It is well known that OH poses an unacceptable risk of adverse pregnancy outcomes;[33–36] all women with this condition should receive treatment with LT4 whether pregnant or not. However, the studies shown in Table 1 confirm that SCH and TAI (alone or, especially, together) also increased the risk of adverse pregnancy outcomes. Indeed, the presence of TAI also increased the risk of gestational diabetes in euthyroid women.[37] One earlier meta-analysis (2016) suggested that hypothyroidism increased the risk of preterm birth in Caucasian but not Asian women, while TAI was a predictive factor irrespective of ethnicity.[38]

Table 1 Recent systematic reviews and meta-analyses that evaluated the impact of (subclinical) hypothyroidism and TAI on pregnancy outcomes.

Ref	Type of outcome
Pregnancy loss	
[19]	SCH increased the risk of preterm birth vs. euthyroidism (OR 1.29 [1.01 to 1.64]); OR for 1 SD increase in TSH was 1.04 (1.00 to 1.09); TAI also increased the risk of preterm birth (OR 1.33 [1.15 to 1.56])
[20]	TAI associated with recurrent pregnancy loss (OR 1.94 [1.43 to 2.64]); no significant association for SCH alone
[21]	TAI increased the risk of preterm birth among women with recurrent pregnancy loss (RR 1.46 [1.20 to 1.78])
[22]	Trend to higher rates of preterm abortion (OR 2.0 [0.8 to 5.2]) or preterm birth (OR 2.6 [0.9 to 7.3]) when TSH was >10 mIU/L vs. <6 mIU/L; no association between these outcomes and TSH >6 mIU/L vs. <6 mIU/L; no association between TAI and pregnancy loss
Gestational diabetes mellitus (GDM)	
[23]	SCH increased risk of GDM vs. euthyroidism (OR 1.33 [1.041 to 1.72]); however, no increased risk in the absence of TAI or in the 1st trimester irrespective of TAI status
[24]	Women with TSH >4 mIU/L had increased risk of GDM irrespective of TAI (OR 1.60 [1.33 to 1.93); women with TSH <4 mIU/L had increased GDM risk only in the presence of TAI
[25]	Increased GDM risk with OH (OR 1.80 [1.73 to 1.86]), SCH (OR 1.54 [1.03 to 2.30]) or TAI (OR 1.49 [1.07 to 2.07])
[26]	Increased GDM risk with SCH + TAI (OR 3.22 [1.72 to 6.03])
Hypertensive disorder of pregnancy (HDP)	
[27]	SCH increased the risk of HDP vs. euthyroidism (OR 1.54 [1.21 to 1.96]), but only if the upper TSH reference range cut-off was >3 IU/mL
[28]	SCH increased risk of preeclampsia (OR 1.53 [1.09 to 2.15]); no relationship between preeclampsia risk and anti-TPOAb
Effects in offspring born to mothers with (subclinical) hypothyroidism	
[29]	Maternal SCH increased the risk of small for gestational age (OR 1.24 [1.04 to 1.48]) and was associated with lower mean birth weight (mean difference –38 g vs. euthyroid mothers); on average, each increase of 1 SD in maternal TSH predicted a reduction in birth weight of 6 g
[30]	Maternal hypothyroidism associated with increased risk in offspring of ADHD (OR 1.14 [1.03 to 1.26]), autism spectrum disorder (OR 1.41 [1.05 to 1.90]) and epilepsy (OR 1.21 [1.06 to 1.39])
Other pregnancy complications	
[31]	Increased risk of gestational anaemia associated with maternal OH (OR 3.74 [1.95 to 7.15]) or TAI (OR 1.97 [1.19 to 3.26]); no significant risk associated with SCH

Restricted to systematic reviews and meta-analyses published from 2019 onwards for brevity. ADHD: attention-deficit hyperactivity disorder; OH: overt hypothyroidism; OR: odds ratio; SCH: subclinical hypothyroidism; TAI: thyroid autoimmunity; TSH: thyroid-stimulating hormone; TPOAb: anti-thyroid peroxidise antibody. Ranges shown in parentheses are 95% confidence intervals.

Place of levothyroxine in the management of hypothyroidism in pregnancy

Summary of guideline recommendations

Management guidelines for thyroid dysfunction emphasise the need to treat women with OH with LT4, irrespective of their pregnancy status or other risk factors (Table 2).[6–8,39] Interestingly, this has not been tested by a randomised clinical trial, but the association between OH and adverse pregnancy outcomes is considered to be sufficiently strong to preclude randomisation of these women to a control or placebo group for ethical reasons.[6]

Guidance for the management of SCH is more nuanced and depends to some extent on TAI status (Table 2). Guidance from the European Thyroid Association (ETA) favours intervention with LT4 for women with SCH, either planning or during pregnancy. While the overall goal is to maintain TSH within its trimester-specific reference range, TSH should ideally be controlled to <2.5 mIU/L at the point of conception. Women already taking LT4 before pregnancy can have their dosage reduced to the preconception dose after delivery. A woman with a diagnosis of SCH during pregnancy with TSH <5 mIU/L and no thyroid immunity can stop LT4 after the pregnancy, with routine monitoring of thyroid function to follow.

The US guideline recommends use of LT4 where TSH is above the trimester-specific reference range, especially if TAI is present. The case for using LT4 becomes stronger as the TSH level increases, with lower TSH cut-offs for women with TPOAb. This guideline also suggests consideration of LT4 for euthyroid women with TAI who have a history of pregnancy loss. Guidance from the RCOG is generally similar, but without support for the use of LT4 in euthyroid women, even if they are TPOAb+.[7]

All of the guidelines warn that the LT4 requirement may increase by 25–50% during pregnancy, as discussed above. ETA and ATA guidelines also make it clear that TH replacement therapy is based firmly on the use of LT4, with no support for prescribing T3, with or without LT4.

Table 2 Main recommendations from European and US guidelines on the use of LT4 to manage hypothyroidism in pregnant women, or women planning a pregnancy.

ETA recommendations (2014)	ATA recommendations (2017)	RCOG recommendations (2023)
Recommends LT4 for women with newly diagnosed SCH to control TSH to within its trimester-specific reference range or <2.5 mIU/L After SCH (above trimester-specific reference range and if not available >2.5 mIU/L) **Recommends** LT4 to maintain TSH <2.5 mIU/L in women planning pregnancy, especially those who are TPOAb+	**Recommends** LT4 for TPOAb+ women where TSH is above the trimester-specific reference range[a] **Recommends** LT4 for TPOAb– women where TSH is >10 mIU/L[a] **Consider** LT4 for TPOAb+ women where TSH is between 2.5 mIU/L and the top of the trimester-specific reference range **Consider** LT4 for TPOAb– women where TSH is between the top of the trimester-specific reference range and 10 mIU/L **Do not use** LT4 for TPOAb– women where TSH is within the trimester-specific reference range[a]	**Recommends** LT4 where TSH is >10 mIU/L **Consider** LT4 where TSH is between the upper limit of the reference range and 10 mIU/L **Do not use** LT4 for euthyroid TPOAb+ women **Consider** starting LT4 before conception, especially if TPOAb+

[a]Strong recommendation. Recommendations are abbreviated and paraphrased for clarity; see the full guidelines. RCOG: Royal College of Obstetrics and Gynaecology; SCH: subclinical hypothyroidism; TSH: thyroid-stimulating hormone; TPOAb: anti-thyroid peroxidise antibody. Compiled from information presented in refs 6–8.

Expert opinion published in 2020 advocated changes to the US guideline for the management of hypothyroidism in pregnancy published in 2017, with recommendations that LT4 treatment should be required for women without TAI who are diagnosed with SCH in the first trimester, but not in the second or third trimesters.[40]

Evidence base

Systematic reviews and meta-analyses

Table 3 summarises the results of meta-analyses of the effects of LT4 on pregnancy outcomes in women with hypothyroidism.[41–53]

A meta-analysis that included data from 7,342 pregnancies complicated by SCH showed LT4 treatment during pregnancy reduced the risks of miscarriage and neonatal death, although there was no significant effect on other perinatal or neonatal outcomes.[41] In other meta-analyses of studies in populations with SCH, LT4 reduced rates of premature birth, miscarriage, postpartum haemorrhage and low birth weight[42] and rates of pregnancy loss,[43] including in patients with or without TAI.[44] In another meta-analysis, LT4 reduced rates of pregnancy loss and preterm delivery in patients with SCH or TAI.[45] This analysis also demonstrated a reduced risk of gestational diabetes or gestational hypertension (but not preeclampsia) with LT4.[45] Another meta-analysis (7,955 pregnancies exposed to TSH >4.0 mIU/L) also showed that LT4 treatment (versus no treatment) reduced the risk of miscarriage, preterm birth and gestational hypertension, irrespective of TPOAb status.[46] A recent meta-analysis of studies that focussed specifically on patients with recurrent pregnancy loss found that LT4 reduced the rates of premature delivery, miscarriages, premature rupture of membranes and foetal growth restriction in TPOAb+ women and increased the live birth rate and reduced the miscarriage rate in women with SCH.[47]

Not all meta-analyses reported significant benefits on pregnancy outcomes associated with LT4 treatment in populations with SCH, however.[48,49] Also, meta-analyses were consistent in not reporting a benefit for LT4 treatment in euthyroid women (or mixed populations of women who were euthyroid or who had SCH) with TAI.[50–53] Interestingly, one of these

Table 3 Overview of meta-analyses that evaluated the effect of TH replacement with LT4 treatment on pregnancy outcomes.

Ref/ year[a]	Population studied	Main findings
[41] 2021	SCH	LT4 decreased risk of pregnancy loss (RR 0.79 [0.67 to 0.93]), neonatal death (RR 0.35 [0.17 to 0.72]) and foetal macrosomia (RR 0.32 [0.19 to 0.56]); no significant effect on a range of other perinatal or neonatal outcomes and no change in aspects of neurodevelopment of offspring up to age 5 years
[42] 2022	Hypothyroidism	LT4 decreased risk of preterm birth (OR 0.42 [0.30 to 0.58]), abortion (OR 0.34 [0.23 to 0.52]), postpartum haemorrhage (OR 0.40 [0.22 to 0.74]) and low birth weight (OR 0.08 [0.01 to 0.51])
[43] 2019	SCH	LT4 reduced risk of pregnancy loss (OR 0.78 [0.66 to 0.9]) and increased live birth rates (OR 2.72 [1.44 to 5.11]); SCH patients treated with LT4 still had higher odds ratio for preterm labour vs. euthyroid women (OR 1.82 [1.14 to 2.91])
[44] 2019	SCH ± TAI	LT4 reduced risk of pregnancy loss (RR 0.56 [0.42 to 0.75]) and preterm births (RR 0.68 [0.51 to 0.91]) in women with SCH and/or TAI, reduced risk of pregnancy loss (RR 0.43 [0.26 to 0.72]) but not preterm birth in women with SCH, and reduced risk of pregnancy loss (RR 0.63 [0.45 to 0.89]) and preterm birth (RR 0.68 [0.48 to 0.98]) in women with TAI
[45] 2017	SCH or TAI	LT4 increased rates of delivery, clinical pregnancy and fertilisation rates; LT4 reduced rates of miscarriage, gestational diabetes and gestational hypertension; no effect on preeclampsia; fewer preterm deliveries, birth weights <2500 g, deaths and congenital malformations in the LT4 group
[46] 2021	SCH	LT4 reduced risk of pregnancy loss (OR 0.55 [0.43 to 0.71]), preterm birth (OR 0.63 [0.41 to 0.98]) and gestational hypertension (OR 0.78 [0.63 to 0.97])
[47] 2023	SCH + TPOAb + recurrent pregnancy loss	Women with recurrent pregnancy loss and TPOAb+: LT4 decreased risk of premature delivery (RR 0.48 [0.32 to 0.72]), miscarriage (RR 0.59 [0.44 to 0.79]), premature rupture of membranes (RR 0.44 [0.29 to 0.66]) and foetal growth restriction (RR 0.33 [0.12 to 0.89]) Women with recurrent pregnancy loss and SCH: LT4 increased live birth rate (RR 1.20 [1.01 to 1.42]) and reduced miscarriage rate (RR 0.65 [0.44 to 0.97])
[48] 2022	SCH	No significant effect of LT4 on pregnancy outcomes, including preterm delivery, miscarriage, gestational hypertension, preeclampsia, gestational diabetes
[49] 2018	SCH	No significant effect of LT4 on pregnancy outcomes, including miscarriage, gestational hypertension, preeclampsia, preterm delivery, mode of delivery, neonatal intensive care unit admission, birth weight, gestational age at delivery, childhood IQ and neurodevelopmental scores

Ref/ year[a]	Population studied	Main findings
[50] 2021	TAI ± SCH	No significant effect of LT4 on pregnancy rate, miscarriages, preterm delivery or live births
[51] 2020	Euthyroid + TAI	No effect of LT4 on pregnancy outcomes overall; however, miscarriage rate decreased in women who received individualised LT4 doses (RR 0.62 [0.41 to 0.93]), with no difference among women with fixed LT4 dosages Women who initiated LT4 treatment in early pregnancy had a lower preterm birth rate (RR 0.54 [0.31 to 0.92]) vs. no treatment or placebo No effect in women who initiated treatment before conception
[52] 2020	TAI without OH	No effect of LT4 on live birth or miscarriage rates
[53] 2022	Euthyroid + TAI	LT4 reduced preterm birth (OR 0.60 [0.4 to 0.9]); this was driven by a significant effect on observational studies, with no effect in randomised trials

[a]Publication year. SCH: subclinical hypothyroidism. OH: overt hypothyroidism. Odds ratios (OR) or relative risks (RR) are shown with 95% confidence intervals in parentheses. ORs and RRs were against control groups specified in individual analyses.

analyses reported a reduced miscarriage rate in women who received individualised LT4 doses, while no such effect was seen in women who received fixed doses of LT4.[51]

Randomised trials

Additional recent data from randomised trials are also available. A study in 1,768 women showed that intervention with LT4 decreased the risk of pregnancy loss in women with a history of recurrent pregnancy loss if they had either TPOAb or SCH.[54] There was no effect of LT4 on birth rates in women without a history of pregnancy loss. Other randomised trials did not report a reduction in the rate of pregnancy loss in euthyroid women with a history of recurrent pregnancy loss[55] or with TPOAb before conception.[55,56] However, a further randomised trial in 131 women with autoimmune thyroid dysfunction (TPOAb+ but free of OH) found that treatment with LT4 reduced the risk of preterm delivery/miscarriage versus no treatment (relative risk 0.30 [0.1 to 0.85]); the preterm delivery rate was similar to that in a control group of TPOAb– women.[57] These findings add further context to the recommendations in guidelines relating to these populations (Table 2).

Meta-analyses have associated hypothyroidism in pregnancy with adverse developmental effects in offspring (described above). However, recent data from follow-up of children born to pregnancies studied in two randomised trials of LT4 in pregnant women did not detect significant effects of LT4 versus no treatment or placebo on neurocognitive development during the early years of life.[58–59]

Real-world studies

An analysis of 1,013 LT4-exposed pregnancies found that first trimester TSH >2.5 mIU/mL was associated with a higher risk of miscarriage versus lower TSH levels within the first trimester-specific reference range (0.2–2.5 mIU/L).[60] Stratification of the population by TSH level showed that this effect became significant for TSH 4.51–10 mIU/L (odds ratio [OR] 1.80 [1.03 to 3.14]), with a higher risk associated with TSH >10 mIU/L (OR 3.95 [1.87 to 8.37]). These data emphasise the need to control TSH during LT4 treatment to within the pregnancy-specific

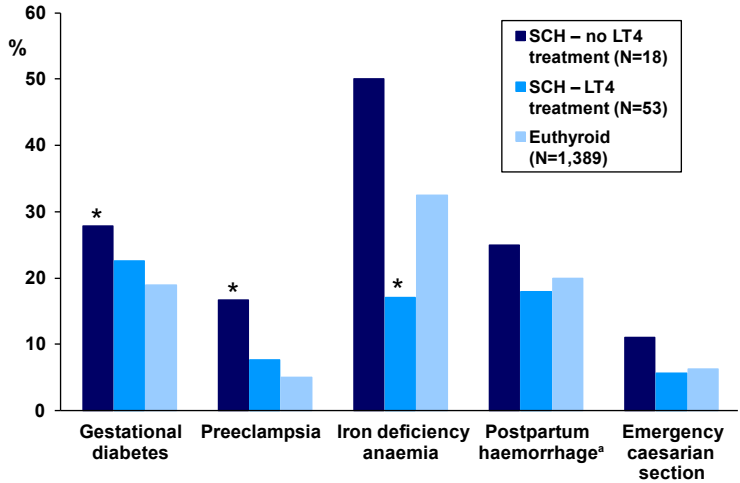
reference ranges. Conversely, omission of LT4 treatment, compared with intervention with LT4, predicted a higher miscarriage rate (relative risk [RR] 1.72 [1.13 to 2.25]) and premature birth (RR 1.66 [1.18 to 2.34]) in an observational study of "euthyroid" women with TPOAb.[61] The quotes around "euthyroid" here reflect the observation that mean TSH in the untreated group had increased to 3.5 mIU/L by the time of delivery, with 19% of these subjects having TSH above their reference range; mean TSH in the LT4-treated group remained similar to that in a euthyroid control group throughout.

The effects of LT4 50 μg were studied in 49 pregnant women with TPOAb and pretreatment TSH >1 mU/L, compared with a control group of 47 untreated women with lower pretreatment TSH. About one in six untreated women (16%) reported a miscarriage, compared with no LT4-treated women (p=0.02).[62] The miscarriage rate in the LT4 group did not differ from that observed in a TPOAb– reference group (8%, p=0.17). Finally, clinical evidence on the effects of intervening with LT4 in women with SCH but no TAI continues to accumulate. For example, a recent (2023) study evaluated the effects of LT4 in 71 women with SCH but no TAI; 53 women were treated with LT4 from a median of 13 weeks' gestation, while 18 did not receive LT4.[63] A reference group of 1,389 euthyroid women was also included. The control group were more likely to have preeclampsia or gestational diabetes than the euthyroid reference group, while the LT4-treated women were not (Figure 1).

The place of modern levothyroxine formulations

LT4 is described as a "narrow therapeutic index drug" because even small changes in the dose given to a patient have the potential to produce clinically significant changes in their thyroid homeostasis (see Chapters 1 and 2 of this book for further information). Modern, updated formulations of LT4 with a tightened specification can deliver an actual dose that is much closer to the dose stated on the pack (between 95% and 105% of the intended dose throughout the shelf-life of the tablet) than before. Practically, this improved precision has allowed closer spacing of LT4 tablet strengths, which provide smaller titration steps during intensification of treatment.

Figure 1 Pregnancy outcomes in women with subclinical hypothyroidism (SCH) with or without treatment with levothyroxine (LT4) in comparison with a euthyroid reference group.



*Significantly different from the euthyroid reference group (p=0.025).
[a]Blood loss of at least 500 mL at delivery.
Compiled from information presented in ref 63.

This is useful for a physician faced with a patient with hypothyroidism who falls pregnant, is planning a pregnancy or who acquires a diagnosis of hypothyroidism post-conception. Guidelines for the management of hypothyroidism during pregnancy mandate tight control of TSH according to a reference range that is lower than for non-pregnant patients, especially during the first trimester (summarised above). This requires careful titration of the LT4 dose to provide adequate TH replacement and to avoid iatrogenic thyrotoxicosis as a result of over-treatment, especially as the LT4 requirement may increase during the first trimester. The current US guideline in this area anticipates that a pregnant woman with SCH is likely to require a maintenance dose of LT4 of 50 μg.[6] Draft UK guidance recommends that women with OH or severe SCH (TSH >10 mIU/L) during pregnancy should be started on LT4 at a dose of 1.6 μg/kg/day, while a woman with SCH at TSH <10 mIU/L should start on LT4 of 1.0–1.2 μg/kg/day.[7] These recommendations suggest that many pregnant (or soon to be pregnant) women with hypothyroidism

(especially SCH) will be taking LT4 doses of between about 25 mg and 100 mg each day. These guidelines fit well with recent real-world observations of cohorts of pregnant women who were receiving TSH-guided dosages in this general range.[64–66] Smaller titration steps may help in achieving optimal TH replacement for these patients.

Is LT4 underused in pregnancy?

Within the real-world studies described above, only 10% of a large cohort of pregnant women with SCH in the UK (6,757 pregnancies, 1998–2017) received LT4, with little sign of increased likelihood to receive LT4 in the later years of this study period.[64] This was a similar proportion to the 16% of pregnant women with SCH who received LT4 in the USA (2010–2014).[67] A higher proportion of pregnant women with "thyroid hypofunction" in Italy received LT4, but this proportion fell steadily between the periods before 2011 (77% received LT4), 2011–2018 (66% received LT4) and 2018 onwards (54% received LT4).[66] Recent data from Finland showed that only about half of women with a diagnosis of hypothyroidism received LT4 in 2016, although the absolute numbers of women receiving LT4 had increased 5-fold since 2004 due to more frequent diagnoses of hypothyroidism in this population.[68] It appears likely that LT4 is underused in this setting.

Conclusions

Pregnancy is a challenging time for thyroid homeostasis, with increased demand for maternal TH, especially during early foetal development. This stress can prompt a new diagnosis of hypothyroidism or exacerbate existing thyroid dysfunction. Hypothyroidism, including SCH, is associated with a range of adverse pregnancy outcomes. There is considerable evidence that TH replacement with LT4 may reduce the risk of some of these outcomes, including pregnancy loss, preterm birth and pre-eclampsia, although not all analyses have shown this and more research is needed. Pregnant women with hypothyroidism need to have their TSH controlled carefully to within pregnancy-specific reference ranges

appropriate for each trimester. Most pregnant women with hypothyroidism will receive daily doses of LT4 in the range 25–100 μg/day. The use of modern formulations of LT4, with better accuracy of dosing and closer-spaced dosage intervals, can add useful precision to the titration of LT4 at these relatively low doses.

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Chapter 6

Hypothyroidism and Infertility in the Modern Era

Zhongyan Shan
Department of Endocrinology, the First Hospital of China Medical University, Shenyang, China

Hypothyroidism in women impairs their ability to conceive, with the magnitude of the impairment proportional to the severity of elevation of thyrotropin (thyroid-stimulating hormone [TSH]). Current clinical evidence supports a role for thyroid hormone replacement with levothyroxine (LT4) to control TSH to <2.5 mIU/L for a woman who is trying to become pregnant. This approach will not only help to address the reduced fertility associated with hypothyroidism, but will also protect a subsequent pregnancy from potentially damaging exposure to hypothyroidism as the developing foetus places extra demands on the mother's thyroid homeostasis. The use of modern LT4 preparations with tightened specifications for manufacturing, dosing accuracy, stability and dose form proportionality between tablet strengths may facilitate the fine-tuning of the LT4 dose needed to maintain euthyroidism on either side of conception.

Introduction

In 1947, an expert review showed that hypothyroidism is associated with adverse effects on fertility and reproduction.[1] Today, hypothyroidism is known to reduce the chances of a successful pregnancy through adverse effects on cyclicity, prematurely reduced ovarian reserve, and interference with the development of ovarian follicles, fertilisation and implantation of the fertilised ovum.[2,3] This chapter summarises the latest epidemiological data on this relationship. It also summarises the results of key studies and meta-analyses that have evaluated the effects of treatment with levothyroxine (LT4) in women with hypothyroidism and impaired fertility, including studies conducted in women undergoing assisted reproduction technologies (ART). Please note that this chapter focuses mainly on the impact of thyroid homeostasis and thyroid hormone replacement prior to conception; the impact of hypothyroidism and thyroid hormone replacement with LT4 on pregnancy outcomes, including early pregnancy loss, is described in the previous chapter.

Burden of infertility in women with hypothyroidism

Impact of hypothyroidism on infertility

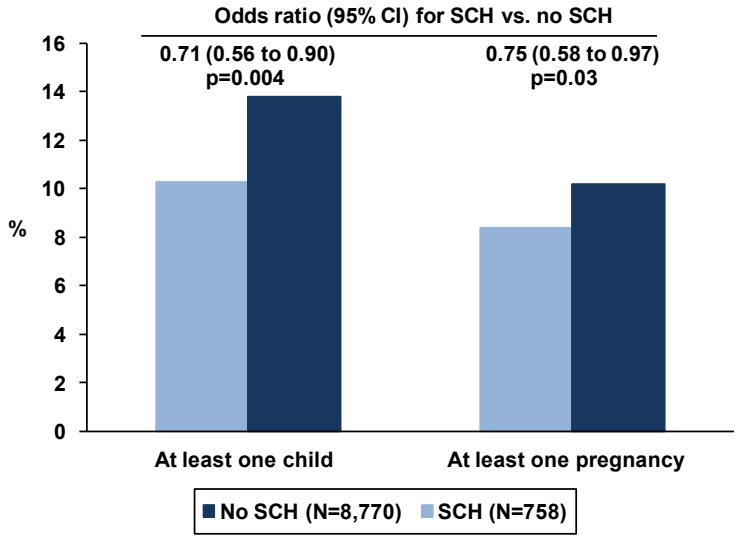
The precise prevalence of infertility among women with hypothyroidism remains unclear.[4] The prevalence of hypothyroidism varies in populations of women undergoing treatment for infertility, for example in India (22–27%),[5–7] Pakistan (35%),[8] Nigeria (12% vs. 3% of a control group had subclinical hypothyroidism [SCH]),[9] Argentina (14% of infertile women had SCH vs. 4% of a fertile control group)[10] and Finland (abnormal thyroid-stimulating hormone [TSH] levels were found in 6.3% of women with ovulatory dysfunction and 4.8% of women with unexplained infertility).[11] In another study, 20% of infertile women had "thyroid abnormalities".[12] Further data from Iran showed that one-quarter (24.5%) of a cohort of women with recurrent miscarriage had anti-thyroid antibodies,

a figure that was twice that found in a control group of women without a history of miscarriage (12.6%).[13]

Other studies suggested a similar prevalence of SCH in women with and without infertility. A screening study of 704 women without a prior diagnosis of thyroid dysfunction who had complained of infertility for at least one year found that only 2.3% had elevated TSH, although 69% of these women presented with ovulatory dysfunction.[14] Elsewhere, the proportion of women with TSH above the reference range did not differ between fertile and infertile women, although mean TSH was higher in the infertile group.[15]

Large observational studies have explored the relationships between indices of thyroid function and fertility. A retrospective study involving 11,254 patients in Denmark with data on TSH found that compared with euthyroid women, those with thyroid parameters consistent with SCH had a 25% reduction in the chance of becoming pregnant, as well as a reduction in the odds of carrying a pregnancy to term (Figure 1).[16] A cut-off value for TSH of 3.7 mIU/L was used to define the upper limit of the TSH reference range. The TSH level was correlated significantly and inversely with the odds of women with SCH becoming pregnant (i.e. higher TSH meant lower fertility). "Prevalent" hypothyroidism (women with a self-reported history of hypothyroidism or receipt of LT4) was not associated with infertility in this study, although only a minority of women met these criteria (9.4%) and it was unclear to what extent LT4 had been used within this population. The presence of self-reported "thyroid disease" (not explained further) predicted infertility (odds ratio [OR] 1.44; 95% confidence interval [CI] 1.00 to 2.08) in a survey of 986 Korean women attending fertility clinics, compared with an age-matched control group.[17] A retrospective analysis of 189 women with unexplained infertility showed that, compared with a control group of women without reduced fertility, the average TSH level was higher and twice as many women had TSH $\geq$2.5 mIU/L (26.9% vs. 13.5%, $p<0.05$).[18] Analysis of data from a UK primary care database relating to 7,978 pregnancies found that 62.8% had TSH >2.5 mIU/L (a typical upper limit for the first trimester reference range for TSH), and 7.4% had TSH >10 mIU/L at this time, which was associated with an increased risk of pregnancy loss.[19]

Figure 1 Impact of subclinical hypothyroidism (SCH) on fertility from a large real-world study in Denmark.



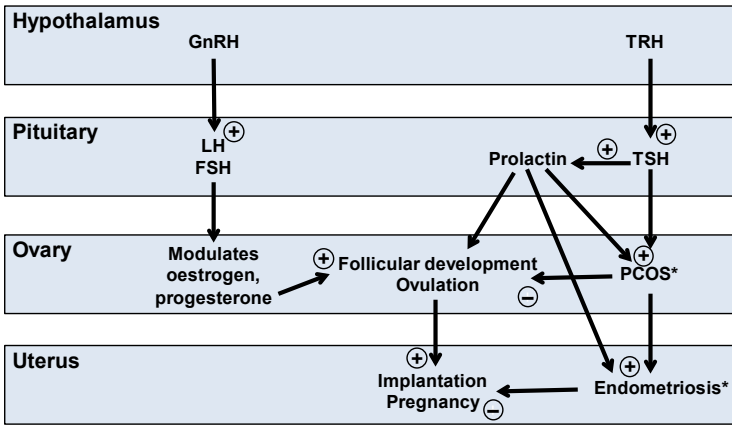
Significance values were fully adjusted. Drawn from data presented in ref 16.

Overall, there appears to be a clinically significant association between hypothyroidism (either overt or subclinical) and infertility, especially where TSH is >4 mIU/L.[3,20]

Mechanisms

There is considerable crosstalk between the parts of the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-ovarian axes that influence female fertility (Figure 2). Specifically, thyroid hormones (thyroxine [T4] and triiodothyronine [T3]) facilitate both the secretion of gonadotrophin-releasing hormone (GnRH), and the action of GnRH in increasing secretion of luteinising hormone (LH) and follicle-stimulating hormone (FSH).[2] The net result is enhancement of production of sex hormones by the ovary and the development of ovarian follicles. Increased secretion of thyrotropin-releasing hormone (TRH) in the setting of hypothyroidism also increases secretion of prolactin, which can reduce fertility by limiting the chances of successful ovulation, among other mechanisms.[2,21]

Figure 2 Simplified schematic illustration of key mechanisms of crosstalk between the hypothalamic-pituitary-ovarian axis and the hypothalamic-pituitary-thyroid axis in the regulation of fertility in women.



See ref 2.

Levels of TSH correlate moderately with levels of prolactin in the setting of infertility, consistent with these observations.[20,22] Low levels of free T3 (fT3) in women with hypothyroidism managed with LT4 were implicated as a contributor to infertility on one study.[23]

Hypothyroidism has also been associated with an increased risk of other conditions that can promote or exacerbate infertility, including endometriosis (especially where elevations of TSH are mild) and polycystic ovary syndrome (PCOS).[24] Hypothyroidism may also exacerbate metabolic dysfunction associated with PCOS, with more severe insulin resistance and associated hyperandrogenism, contributing further to infertility.[25]

It is unclear whether the increased risk of PCOS or other drivers of infertility in the setting of hypothyroidism are mediated by hypothyroidism per se or by the presence of thyroid autoimmunity.[23] Molecular components required for the production of thyroid hormones are present in the placenta,[26] and antibodies directed against thyroid peroxidase (TPOAb) or thyroglobulin (TgAb) have been observed in follicular tissues as well as in the thyroid gland, and at similar concentrations compared with the serum.[27] This has adverse consequences for fertility, as shown by a

study in 52 women undergoing ART where the presence versus absence of TPOAb or TgAb greatly reduced the pregnancy rate (OR 0.036; 95% CI 0.004 to 0.347; p=0.004), despite average serum TSH and free thyroxine (fT4) being essentially identical between these groups.[28] A recent (2022) meta-analysis confirmed these findings, with an OR for implantation of an embryo during ART of 0.72 (95% CI 0.59 to 0.88; p=0.001) for women with versus without thyroid autoimmunity.[29] Autoimmune damage to the ovaries or other components of the reproductive system, as well as a localised manifestation of hypothyroidism in the reproductive tissues, may contribute to these effects.[30] The effects of thyroid autoimmunity on fertility among women undergoing ART depends on the ART protocol used, however, the presence of anti-thyroid antibodies does not appear to adversely affect pregnancy rates in women undergoing intracytoplasmic sperm injection.[31] Variation in TSH levels within the reference range did not affect ART outcomes in euthyroid women without thyroid autoimmunity, according to a meta-analysis.[32]

Thyroid hormones may contribute to spermatogenesis.[33] Accordingly, hypothyroidism may contribute to male infertility, with adverse effects on erectile function, as well as sperm morphology and motility.[34] SCH was associated with damage to DNA in spermatozoa in one cross-sectional study in 5,401 men seeking treatment for infertility.[35]

Effects of thyroid hormone replacement with levothyroxine on fertility

Women with hypothyroidism

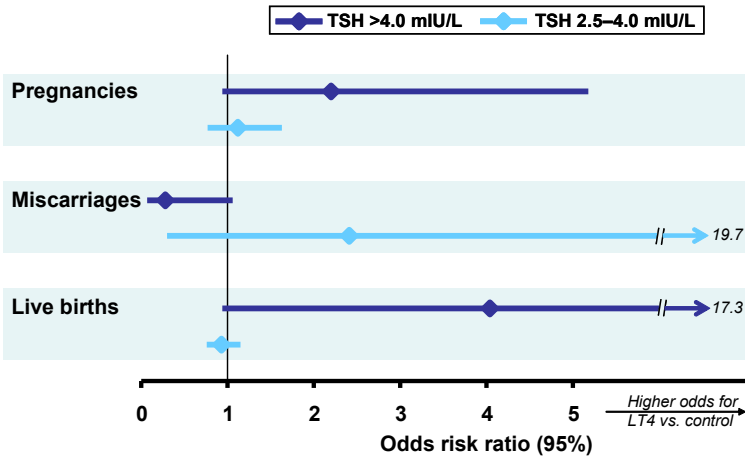
It is generally accepted that overt hypothyroidism reduces fertility, and that correction of overt hypothyroidism improves fertility.[19,36] Randomised, placebo-controlled evaluations of LT4 in populations with overt hypothyroidism are not feasible for ethical reasons, as guidelines in this area are clear that all women with overt hypothyroidism should receive LT4. The situation regarding SCH is more nuanced, and the evidence base for intervention with LT4 in this population to reverse infertility is discussed below.

A prospective, randomised trial showed that LT4 treatment of infertile women with SCH undergoing ART increased the quality of embryos, with more Grade I or II embryos in the LT4 group (mean 3.3 for LT4 vs. 2.2 for placebo, p=0.007).[37] The rate of embryo implantation was also higher for LT4 (26.9% vs. 14.9% for placebo, p=0.044). There was only a non-significant trend towards a higher clinical pregnancy rate for the LT4 (53.3%) versus placebo (37.5%) groups; however, the live birth rate in the LT4 group was double that in the placebo group (53.1% vs. 25.0%, p=0.039). Another randomised trial found that the clinical pregnancy rate in women undergoing ART was significantly higher in those receiving LT4 (35%) versus placebo (26%), despite no difference between groups in the number of oocytes retrieved.[38] These studies are consistent with the finding of superior quality embryos in women with SCH who were treated versus not treated with LT4 at the time of their ART intervention.[39] This systematic review that focussed on four studies in women with a diagnosis of SCH and autoimmune thyroiditis concluded that intervention with LT4 improved embryo quality, implantation rate and live birth rate following ART.[39]

The results of systematic reviews and meta-analyses in this area have been variable, partly because of their design. The most recent (2023) meta-analysis in this area available at the time of writing included an evaluation of the effects of LT4 given before pregnancy to women with SCH (based on five randomised trials) and did not report an increased pregnancy rate for the LT4 group overall.[40] However, there was a strong trend towards an improvement in pregnancy rate for women with TSH >4 mIU/L (Figure 3). This analysis also reported an increase in the live birth rate associated with a decrease in the miscarriage rate (Figure 3); while these additional outcomes are described more fully in the preceding chapter, it is important to note that intervention with LT4 appears to improve the prospects for a successful pregnancy at multiple stages from before conception to delivery. However, an earlier (2017) meta-analysis did report an improved clinical pregnancy rate in women with "thyroid dysfunction" who received LT4.[41]

The impact of LT4 treatment on fertility has been studied extensively in women with SCH who underwent ART. A Cochrane review reanalysed

Figure 3 Impact of preconception thyroid hormone replacement with levothyroxine on fertility and pregnancy outcomes in women with subclinical hypothyroidism according to the level of thyrotropin (TSH).



Drawn from data presented in ref 40.

data from a randomised study in women with SCH (± thyroid autoimmunity) undergoing ART, described above,[37] and concluded that the risk ratio (RR) associated with achieving a pregnancy with versus without LT4 was 2.13 (95% CI 1.07 to 4.21).[42] There is one meta-analysis from 2018 which pooled data from four randomised trials conducted in women undergoing ART, of which two recruited women with SCH and two recruited women with thyroid autoimmunity.[43] The overall effect of LT4 was statistically neutral for the clinical pregnancy rate, with an RR for achieving pregnancy of 1.46 (95% CI 0.84 to 2.48) associated with LT4 treatment. An earlier meta-analysis reported a similar conclusion regarding the effect of LT4 on the pregnancy rate in women undergoing ART (RR 1.75; 95% CI 0.90 to 3.38; p=0.098).[44]

Retrospective data from a population of women undergoing ART suggested that women with hypothyroidism maintained lower pregnancy rates compared with euthyroid women despite treatment with LT4.[45] Another observational study of 1,418 pregnancies did not support intervention with LT4 in women with SCH and recurrent pregnancy loss.[46]

Hyperprolactinaemia plays a part in the pathophysiology of infertility associated with hypothyroidism, as described above. A randomised trial in 63 women with SCH found that treatment with LT4 versus placebo significantly reduced basal and peak levels of prolactin during 48 weeks of treatment.[47] Larger effects were observed in women with elevated prolactin at baseline.

Euthyroid women

Randomised trials have shown that levothyroxine does not influence pregnancy rates or live births in euthyroid women with thyroid autoimmunity, in the setting of spontaneous conception[48,49] or ART.[50,51]

What the guidelines say

European Thyroid Association guidelines for the management of SCH (2014) acknowledged the need for further clinical evidence regarding the relationship between SCH, fertility and associated outcomes, but considered that it is reasonable to control TSH to below 2.5 mIU/L with LT4 for a woman who is planning to become pregnant, especially if thyroid autoimmunity is present.[52] Elsewhere in Europe, a more recent draft guideline (2023) from the UK Royal College of Gynaecologists recommended the same preconception TSH target of <2.5 mIU/L.[53]

A guideline from the American Thyroid Association (2017) also supported this approach.[54] However, this guideline goes further in considering that controlling preconception TSH to <1.5 mIU/L may represent a worthwhile goal, even in the absence of evidence for improved outcomes with this approach. The rationale for tighter control of TSH before pregnancy is that it may reduce the risk of hypothyroidism developing once a pregnancy is established and the demand for thyroid hormones increases (see Chapter 5 of this book for more information on thyroid homeostasis and the management of hypothyroidism during pregnancy). Another US guideline, from the American Society for Reproductive Medicine, concluded that there is insufficient evidence that SCH per se is associated with reduced fertility.[55] The same guideline concluded that clinical evidence supports a benefit for intervention with LT4 for

increasing pregnancy rates (and reducing subsequent rates of pregnancy loss) where women with SCH have TSH >4 mIU/L, while further evidence is needed to support the management of women with SCH and TSH 2.5–4 mIU/L with regard to optimising fertility.

Other important recommendations from these guidelines are:[55]

a) All women with overt hypothyroidism require thyroid hormone replacement with LT4 irrespective of their needs or intentions for family planning.
b) No support is provided for the use of LT4 to manage euthyroid women with anti-thyroid antibodies, consistent with the lack of evidence for improved fertility or pregnancy outcomes described above.
c) The management of thyroid function is conducted via thyroid hormone replacement with LT4, guided by the TSH level; there is no role for additional use of preparations at this time (see Chapter 8 of this book for current and future prospects for a role of T3 in the management of hypothyroidism).

Finally, an international expert panel produced a guideline in 2019 that was critical of the concept of SCH in general and recommended that most adults with a diagnosis of SCH do not require treatment with LT4.[56] However, the authors were clear that their recommendation did not apply to women who were trying to become pregnant, or to women at high risk of an unplanned pregnancy, in line with the evidence summarised above and in Chapter 5 of this book.

Conclusions

Hypothyroidism promotes infertility, especially if TSH is more markedly elevated. Clinical evaluations of LT4 have focussed more on the management of pregnancy per se, rather than the impact of preconception LT4 on a woman's ability to become pregnant. Nevertheless, there is evidence that LT4 treatment may improve fertility; this is true not only for women with overt hypothyroidism (who all need treatment with LT4), but also for women with SCH, when TSH is above the non-pregnant reference range.

It is important to remember that careful control of preconception TSH will protect a subsequent pregnancy from adverse outcomes such as early pregnancy loss (see Chapter 5). Indeed, current management guidelines from Europe and the USA have emphasised the importance of monitoring TSH carefully before and after conception in women with hypothyroidism who are trying to achieve a pregnancy. This is largely because the achievement of euthyroid-like levels of TSH before the pregnancy is likely to facilitate the successful titration of the LT4 dosage as the demand for thyroid hormones increases during the first trimester.

In practice, most of these women have SCH and will require a relatively low and carefully titrated dose of LT4, especially when setting out to achieve a TSH level within the lower half of the usual, non-pregnant reference range, as advocated by management guidelines. Modern LT4 preparations with tightened specifications for dosing accuracy (described in detail in Chapters 1 and 2 of this book) have permitted the introduction of a larger range of dosage strengths for the same LT4 preparation, which facilitates accurate dose titration, usually with the need to take only one tablet per day.[57,58] In addition, bioequivalence between tablet strengths with the new formulation of LT4 facilitates further adjustments to the LT4 dosage that are likely to be needed once a pregnancy is established.

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Chapter 7

Safety and Tolerability of Modern Levothyroxine Tablets

Ulrike Gottwald-Hostalek and Yorki Tayrouz
Merck Healthcare KGaA, Darmstadt, Germany

Levothyroxine (LT4) is chemically identical to the endogenous thyroid hormone thyroxine, and considered as a narrow therapeutic index drug. Thus, under-treatment with LT4 risks the continuation of the distressing side effects of hypothyroidism as well as potential adverse effects on fertility and pregnancy outcomes. Over-treatment risks inducing the symptoms of hyperthyroidism (thyrotoxicosis), with increased risk of serious adverse outcomes associated with cardiac and bone health. Optimising the safety and tolerability of LT4 treatment is therefore synonymous with optimising the management of hypothyroidism. The use of modern preparations of LT4 can facilitate hypothyroidism management by providing better precision of LT4 exposure and more flexible LT4 dose adjustment, compared with older formulations.

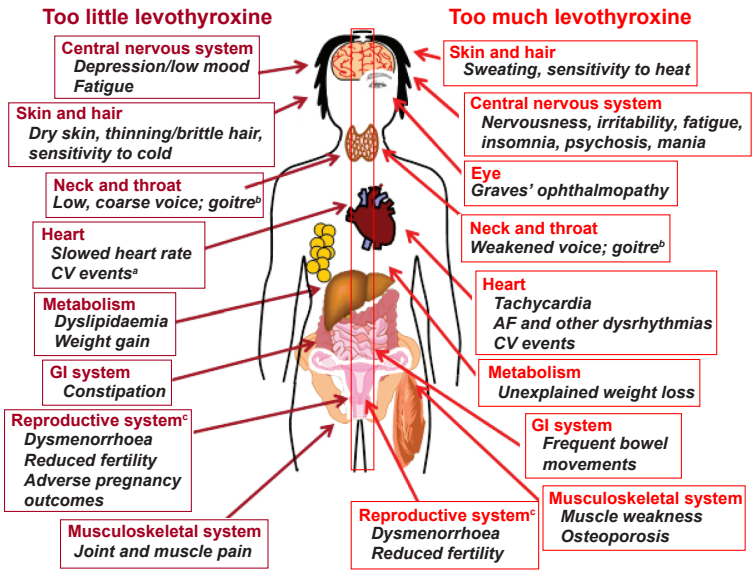
Introduction

Levothyroxine (LT4) is one of the most commonly prescribed medicines in the world.[1–4] For example, there were about 120 million prescriptions of LT4 in the United States of America (USA) in 2014 and almost 7% of the commercially or Medicare-insured population in the USA redeemed at least one prescription for LT4 in 2016 alone.[3] Similarly, about 30 million prescriptions for LT4 were dispensed in the United Kingdom (UK) in 2017.[4] LT4 was the first and second most prescribed drug in these countries, respectively.[3,4] Ensuring the safety of treatment with LT4 is paramount, given the relatively high prevalence of hypothyroidism and thus the relatively widespread exposure of the population to this treatment. The status of LT4 as a narrow therapeutic index drug (see Chapters 1 and 2 of this book) adds urgency to this situation, as small changes in the exposure to LT4 of a patient with hypothyroidism during routine treatment can lead to clinically significant changes in the biological effect of the treatment. This chapter reviews the safety and tolerability of LT4 in the management of hypothyroidism, with reference to both long-term management of these patients and with special references to the potential of newer formulations of LT4 to facilitate initial treatment and long-term management.

Managing the symptoms of hypothyroidism

The resolution of symptoms and maintenance of good quality of life for patients with hypothyroidism is a principal goal of the management of the disorder.[5] Accordingly, giving too little or too much LT4 may induce the adverse effects of hypothyroidism or hyperthyroidism, respectively. Figure 1 shows common symptoms associated with hypothyroidism (including under-treatment of this condition with LT4) and over-treatment with LT4 (thyrotoxicosis).[6–14] Often, under- and over-treatment with LT4 produce opposite effects, as expected. For example, the hypothyroid state in the central nervous system (CNS) is associated with low mood or depression, while thyrotoxicosis is associated with nervousness, irritability

Figure 1 Overview of common symptoms associated with under-treatment and over-treatment (thyrotoxicosis) of hypothyroidism with levothyroxine.



[a]Controversial for subclinical hypothyroidism. [b]May also be present in hypothyroidism. [c]Female reproductive system is represented here but thyroid dysfunction may also adversely affect male fertility. Compiled from information presented in refs 6–14. See also Chapters 3–6 for more information on the LT4-based management of hypothyroidism, including the use of modern formulations with tightened specification.

and, in severe cases, psychosis or mania. Similarly, these states are associated with a slow heart rate vs. tachycardia and an increased risk of tachyarrhythmias, respectively, increased sensitivity to cold and heat, respectively, or constipation vs. increased frequency of bowel movements, respectively. The situation is more complex in other areas. For example, both states may be associated with increased risk of cardiovascular events and with dysmenorrhoea and reduced fertility, arising via different pathological mechanisms. Finally, Graves' ophthalmopathy (bulging eyes with retracted eyelids) and osteoporosis are characteristic of thyrotoxicosis, with no corresponding opposite presentation associated with hypothyroidism.

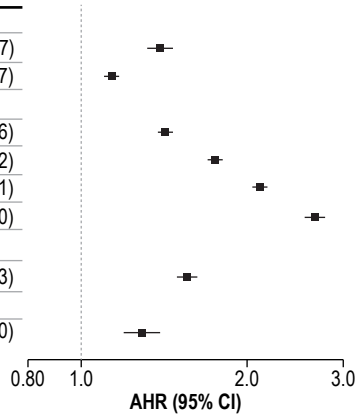
The importance of accurate titration of the LT4 dose

The routine management of hypothyroidism involves careful adjustment of the LT4 dose to bring the serum level of thyrotropin (thyroid-stimulating hormone [TSH]) to within a pre-specified reference range defined in a population without thyroid dysfunction.[5,15] A TSH level above the upper limit of this range is diagnostic of hypothyroidism, although minor elevations of TSH should be considered with caution, as many common personal characteristics (e.g. increasing age, obesity), medical conditions (especially involving intestinal malabsorption), drugs, foodstuffs and dietary supplements can either modulate the level of TSH or interfere with the functioning of the TSH test.[15] Specific TSH reference ranges also apply separately to each trimester of pregnancy (see Chapter 6 of this book).[16]

Either a hypothyroid or hyperthyroid state may be distressing and reduce patients' quality of life, requiring careful and accurate titration of the LT4 dose, with appropriate adjustment from time to time, as required. Inappropriately managed patients with TSH out of range are at risk of serious consequences of thyroid dysfunction, including an increased risk of cardiovascular disease or premature mortality.[17–19] Figure 2 summarises the effects of over- or under-treatment with thyroid hormones on cardiovascular mortality outcomes from a recent (2022) study in a population of >700,000 US military veterans.[19] Both over-treatment (low TSH, high free thyroxine [fT4]) and under-treatment (high TSH, low fT4) were adjusted with an increased risk of mortality, compared with individuals having these parameters within the reference range.[19] Another study based on 235,168 patients with hypothyroidism from a registry showed that each 6-month period of elevated TSH (vs. TSH within the reference range) was associated with increased mortality, whether or not the patient received LT4 (hazard ratio [HR] 1.05; 95% confidence interval [CI] 1.02 to 1.07 for each group).[18] Six months of low TSH during LT4 treatment (thyrotoxicosis) was associated with a greater risk of mortality in this study (HR 1.18; 95% CI 1.15 to 1.21).

Figure 2 Adjusted hazard ratios (AHR) for cardiovascular mortality associated with under- or over-treatment of hypothyroidism with levothyroxine from a study of 705,307 US military veterans who received thyroid hormone treatment.

Thyroid function test	AHR (95% CI)
Thyrotropin level, mIU/L	
<0.1	1.39 (1.32–1.47)
0.1 to <0.5	1.13 (1.09–1.17)
0.5 to 5.5	1 [Reference]
>5.5 to <7.5	1.42 (1.38–1.46)
7.5 to <10	1.76 (1.70–1.82)
10 to 20	2.13 (2.05–2.21)
>20	2.67 (2.55–2.80)
Free thyroxine level, ng/dL	
<0.7	1.56 (1.50–1.63)
0.7 to 1.9	1 [Reference]
>1.9	1.29 (1.20–1.40)



AHRs were adjusted for age, gender and cardiovascular risk factors. Reproduced from ref 19 according to the CC-BY licence (https://jamanetwork.com/pages/cc-by-license-permissions).

Moreover, the prescription of inappropriate dosages of LT4 for people with hypothyroidism is not uncommon. A study from Germany showed that 18% of a population of patients with hypothyroidism were over-treated with LT4 and 4% were under-treated, according to their TSH levels, during the years 2016–2020.[20] Other studies reported rates of under-treatment and over-treatment with LT4 of 3% and 1.3%, respectively, in the primary care setting in Germany (2005–2018)[21] and 7.4% and 4.7%, respectively, in Denmark (2001–2012).[22] These studies attest to the importance of accurate dose titration of LT4 during the management of hypothyroidism. In addition, frequent unawareness and under-diagnosis of hypothyroidism in routine clinical practice compounds these issues.[23] The potential contribution of modern LT4 formulations to optimising the management of hypothyroidism is discussed later in this chapter.

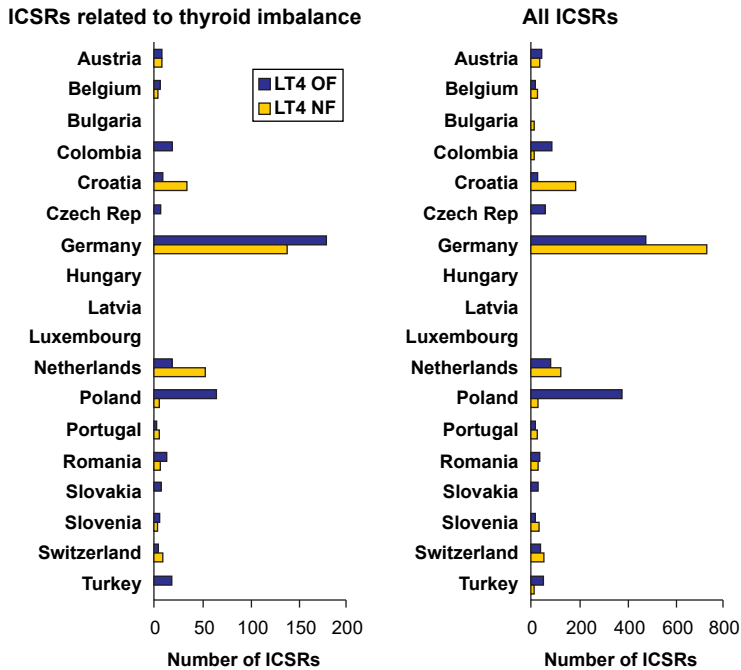
Maintaining safety and quality of life when switching to a modern LT4 formulation

Increasingly stringent regulatory requirements have driven the introduction of improved formulations of LT4 into routine clinical practice (see Chapters 1 and 2 of this book). These formulations have tightened specifications for the accuracy of the stated LT4 content, improved stability and shelf life, and more precisely defined bioequivalence between different tablet strengths that may be combined to make up a daily dose of LT4.[24,25]

This new regulatory approach to the production of LT4 tablets has required patients to be switched from the old to the new formulations. The introduction of the new formulation in France produced a marked increase in the number of spontaneous adverse event reports in the year after the switch;[26] this was unexpected, as formal bioequivalence had been demonstrated between the new and old LT4 formulations,[24,25] and switches were conducted on a dose-for-dose basis. No new safety signals associated with LT4 treatment emerged from analysis of the reports and evaluation of medically confirmed cases.[26]

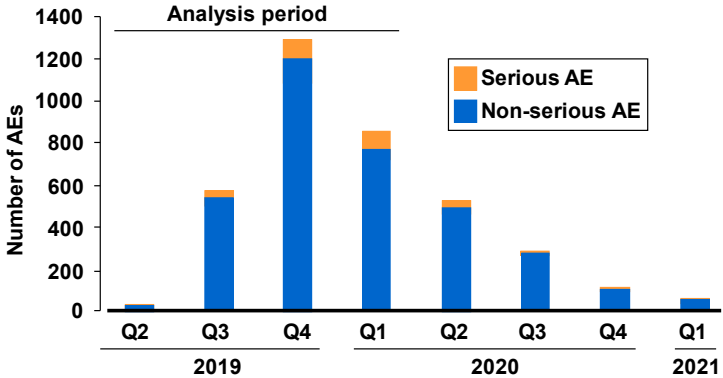
A similar phenomenon had occurred previously following the switching of patients from an older formulation of LT4 to an updated one in New Zealand: the spike in adverse event reporting appeared to be associated with intense interest and speculation on social and news media.[27] The implications of this switch for tolerability and safety were evaluated further in a larger real-world study that evaluated individual case safety reports (ICSRs) for the year before and the year after the switch in 18 other countries.[28] The pattern of ICSRs reporting varied considerably between countries, with a low number of ICSRs before and after the switch for most (Figure 3). A high incidence of ICSRs in Germany likely reflected the large pharmaceutical market of that country (Figure 3). Altogether there were 1,259 ICSRs for the year before the switch and 1,334 ICSRs for the year after, with 259 and 350 ICSRs, respectively, that related specifically to thyroid imbalance. Again, no new safety concerns relating to the therapeutic use of LT4 were revealed in this analysis.[28]

Figure 3 Numbers of individual case safety reports (ICSRs) in 18 countries in Europe the year before and after switching from an old formulation (OF) of levothyroxine (LT4) to an updated formulation with tightened specifications (NF).



The switch between LT4 formulations was necessary, as described above, and this study provided reassurance that the switch caused minimal disturbance to the routine management of hypothyroidism overall.[287] The number of ICSRs during each quarter of the year following the switch was also analysed: the number of reports peaked at about 9 months following the switch and declined towards baseline gradually thereafter (Figure 4).[28] An updated analysis from 76 countries, grouped into World Health Organization regions,[29] provided similar data (Figure 5).[30] The largest difference in the number of ICSRs for the period before and after the switch occurred in the European Region (+2,869); this was mostly accounted for by a higher number from several countries, such as Germany (+793), Croatia (+694), Italy (+503), Spain (+261)

Figure 4 Time course of individual case safety reports (ICSRs) after switching from an old formulation of levothyroxine to an updated formulation with tightened specifications in Germany.



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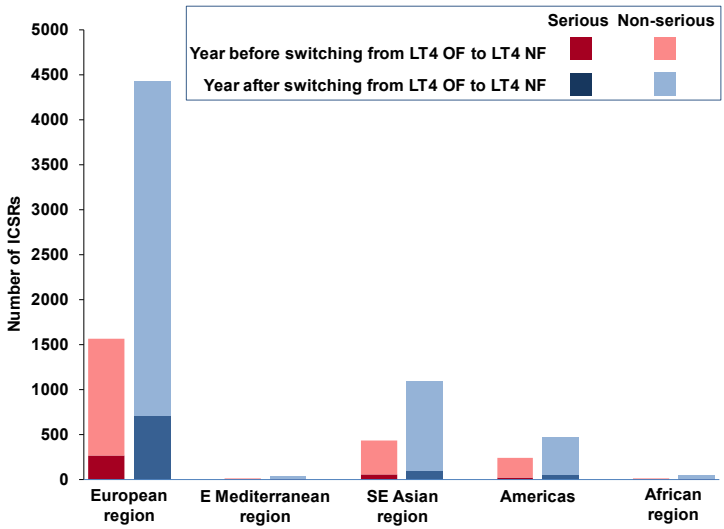
and the Netherlands (+150).[29] It should be noted that many millions of prescriptions for LT4 are issued every year. For example, LT4 has been the fourth most frequently prescribed medicine in Germany in recent years, approaching 9 million prescriptions issued there in 2019.[20] The increase of about 250 ICSRs from before to after the switch in Germany in the first analysis[27] and the increase in the European Region in the more recent analysis[29] should be interpreted within this context.[29]

It is not possible to exclude the possibility of genuine disturbance of thyroid homeostasis for some patients after the switch. As described above, the new formulation has tightened specifications for stability of the LT4 content over its full shelf life. Accordingly, patients who received their last prescription of the old LT4 formulation from a batch near the end of its shelf life and with LT4 content close to the lower limit of the labelled dose according to the old criteria for dosing accuracy, may conceivably have received a higher-effect dose of LT4 from the new, more accurate formulation. Other mechanisms may also be at play here, for example, even switches between placebos have provoked changes in physiological biomarkers such as blood pressure in patients who believed they were receiving different active formulations.[31] These phenomena are unlikely to have long-term implications for patient care as any genuine disturbance of

Figure 5 Updated analysis of individual case safety reports (ICSRs) relating to a switch from the older LT4 formulation (LT4 OF) to the updated formulation with tightened specifications (LT4 NF) from 76 countries grouped into World Health Organization regions.



Countries with data: ***European region***: Albania, Armenia, Austria, Azerbaijan, Belarus, Belgium, Bosnia, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Georgia, Germany, Greece, Hungary, Iceland, Italy, Kazakhstan, Kyrgyzstan, Latvia, Luxembourg, Macedonia, Moldova, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, Uzbekistan; ***Eastern (E) Mediterranean region***: Bahrain, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates; ***South East (SE) Asian region***: Bangladesh, Brunei, China, Indonesia, Macao, Malaysia, Mauritius, Philippines, Singapore, Sri Lanka, Thailand; ***Americas***: Brazil, Colombia; ***African region***: Angola, Botswana, Kenya, Namibia, South Africa, Sudan.
Data on file, Merck Healthcare KGaA, Darmstadt, Germany.

thyroid homeostasis should be corrected during routine patient monitoring and follow-up. Careful counselling of patients is important when switching formulations of a treatment, to reassure them regarding the need for the switch, and the similarity of effects of the old and new treatments.

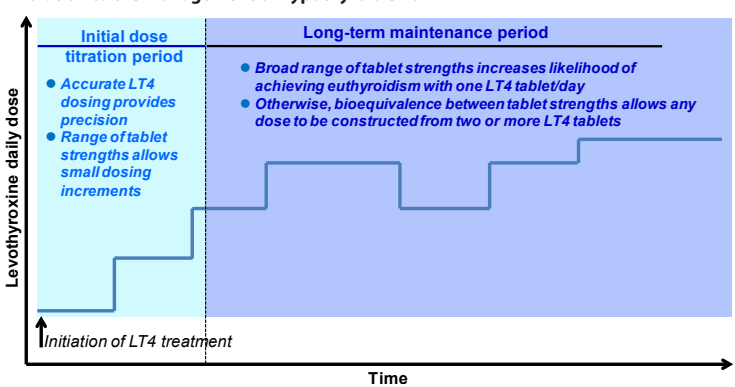
Optimising the safety of levothyroxine

Exogenously administered LT4 is chemically identical to the naturally occurring thyroid hormone thyroxine. Thus, optimising the management of hypothyroidism is functionally synonymous with optimising the

tolerability of the treatment for a patient who requires LT4 administration. LT4 is initiated at a low dose (e.g. 25–50 μg/day) for some patients, especially those with subclinical hypothyroidism and/or significant (especially cardiac) comorbidities.[5] Modern formulations with tightened manufacturing specifications and greater accuracy of LT4 content can support a greater number of tablet strengths, especially in the range 25–100 mg, which may aid titration of the LT4 dose at these relatively low overall daily dosages (Figure 6).[32] The availability of more tablet strengths is also an advantage during the longer-term management of hypothyroidism, when only occasional dose adjustments will be necessary as dictated by the results of routine monitoring of TSH, as the likelihood of being able to maintain a patient on a single tablet per day is increased. Where this is not possible, dose equivalency between different tablet strengths means that any two tablets can be combined to provide the correct daily dose without the need for breaking tablets.

Maintaining adequate adherence to LT4 treatment is also essential for optimal and stable long-term outcome. Observational studies conducted in populations of patients with hypothyroidism have shown that adherence to LT4 is variable, and often low, and this is frequently associated with a lack of knowledge about hypothyroidism and the importance of achieving and maintaining a euthyroid state.[33–37] A levothyroxine absorption test can be useful in some cases for distinguishing non-adherence

Figure 6 Schematic representation of the potential contribution of a modern, updated LT4 formulation to the management of hypothyroidism.



from other issues, such as malabsorption of LT4.[38] The long elimination half-life of LT4 (of about one week) makes it possible to use alternative dosing strategies to the standard once-daily regimen. These strategies may help some patients adhere to their LT4 regimen, such as once-, twice- or thrice-weekly administration of LT4, or making up for a missed dose by taking it the next day, so that a week's worth of LT4 is taken across the duration of each week.[32,39,40]

Conclusions

Optimising the tolerability and safety of LT4 in the management of hypothyroidism is synonymous with achieving optimal management of thyroid function, thus avoiding the distressing symptoms or risk of adverse outcomes associated with under- or over-treatment with LT4. Compared with older formulations of LT4, modern LT4 preparations can facilitate the management of these patients by providing better precision and more flexible dose adjustment.

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Chapter 8

Current and Future Prospects for the Role of Triiodothyronine in the Management of Hypothyroidism

Antonio C. Bianco, M.D., Ph.D.
Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism,
The University of Chicago, Chicago, USA

The thyroid gland secretes two principal thyroid hormones: thyroxine (T4) and triiodothyronine (T3). T4 is a prohormone that must be activated to T3 outside of the thyroid gland by specific iodothyronine deiodinases. Thyroid hormone replacement therapy with levothyroxine (LT4) for patients with hypothyroidism does not adequately restore circulating levels of T3 in all patients and could explain why some patients remain symptomatic despite normalisation of thyroid-stimulating hormone. In addition, genetic polymorphisms in the deiodinases or other components of thyroid homeostasis could exacerbate this situation. Given that T3 is the biologically active thyroid hormone, a consensus is building that restoring optimal T3 homeostasis is central to the management of hypothyroidism. Two meta-analyses of 18 randomised controlled trials (RCTs) that evaluated patient-reported outcomes (PROs) in patients receiving liothyronine (LT3) + LT4 versus LT4 alone did not identify differences

between both therapies, but did find a strong preference for LT4 + LT3 versus LT4 alone. However, these trials did not focus on patients exhibiting residual symptoms. One recent secondary analysis of an RCT found that patients with residual symptoms benefit the most from combination therapy with LT4 + LT3. Thus, new RCTs focussed on patients more likely to benefit from LT3, and using PROs and preferences should adequately address the hypothesis that adding LT3 to LT4 can resolve symptoms and improve quality of life in some people with hypothyroidism.

Introduction

Thyroxine (T4) and triiodothyronine (T3) are the two main hormones secreted by the thyroid gland, capable of triggering biological effects in almost every system within the body. The guideline-driven management of hypothyroidism is focussed strongly on the therapeutic use of levothyroxine (LT4) monotherapy, titrated to a dose that brings the level of thyrotropin (thyroid-stimulating hormone [TSH]) to within a pre-specified "normal" reference range. Nonetheless, a minority of LT4-treated patients continue to report residual symptoms reminiscent of hypothyroidism, despite being in a state of biochemical euthyroidism according to their TSH levels. There has been considerable clinical interest over the years in the potential of combination treatment with liothyronine (LT3) alongside LT4. To date, this approach has not gained traction in clinical guidelines, although there has been consistent support for a therapeutic trial of additional LT3 administration for some of these patients. This chapter reviews the current evidence base and future prospects for adding LT3 to LT4 therapy in patients with hypothyroidism.

The pathophysiological basis for combination treatment with LT4 + LT3

The deiodinases and thyroid hormone action

The rate of T4 secretion from the human thyroid gland outstrips that of T3 by a variable amount, from about 14:1 to 8:1, depending on the TSH levels. Nevertheless, T3 is the biologically active hormone: deiodinases inside and outside the thyroid parenchyma convert T4 to T3 (mainly the deiodinase 2 [DIO2] isoform, with some contribution from the DIO1 isoform), which reaches the circulation and acts systemically. In addition, T3 generated via DIO2 acts locally to influence the transcription of a wide range of genes (Table 1).[1–3] The deiodinases also mediate the conversion of T4 and T3 to inactive metabolites (DIO3 isoform), such as reverse T3 and 3,3'-diiodothyronine (T2), respectively. In practice, numerous metabolites of thyroid hormones have been found in the circulation, but their physiological role, if any, remains to be established.[4–7] DIO2 is also closely involved in the feedback mechanisms in the hypothalamus and pituitary gland, by which a relatively small change in the circulating T4 level causes a much larger change in TSH secretion.[8] This is illustrated through the observation that DIO2 inhibition by treatment with amiodarone increases TSH secretion.[9]

Pathophysiological consequences of polymorphisms in deiodinase genes

Polymorphisms or mutations in the genes encoding the deiodinases may affect the activity of these enzymes. For example, the *DIO2* Thr92Ala polymorphism was associated with a significantly lower T3 level in post-thyroidectomy patients receiving thyroid hormone replacement therapy with LT4.[10] The reduced T3 level was apparently due to a reduction in the stability of the DIO2 protein, which in turn caused a lower rate of conversion of T4 to T3.[11] This polymorphism has also been associated with hypothyroidism localised to the brain.[11] Other cross-sectional data demonstrated a significant effect of a *DIO1* polymorphism (rs2235544) on the LT4 dosage required to control hypothyroidism in a

Table 1 Overview of the metabolism of thyroxine by peripheral deiodinases.

	Deiodinase D1	Deiodinase D2	Deiodinase D3
Mainly expressed in	Liver, kidney, thyroid	Brain, pituitary, skeletal muscle, heart	Widely expressed
Principal reaction	T4 → T3	T4 → T3	T4 → rT3
Other important reactions	T4 → rT3 T3 or rT3 → T2	rT3 → T2	T3 → T2
Summary of physiological importance	• Important source of plasma T3 • Recovery of iodine from inactive thyroid hormone metabolites	• Regulation of local cellular T3 levels • Maintaining pituitary/hypothalamic feedback for thyroid hormone production	• Regulation of local cellular D3 levels, independent of local T3 or T4 levels • Degradation of thyroid hormones

rT3: reverse triiodothyronine; T2: 3,3′-diiodothyronine; T3: triiodothyronine; T4: thyroxine.

cohort of 76 patients.[12] A recent study in 200 LT4-treated women with primary hypothyroidism measured levels of thyroid hormones according to the presence of a single nucleotide polymorphism (SNP) in the *DIO3* gene.[13] There were significant differences in the serum levels of T2, T3 and T4 among three groups of women who had wild-type *DIO3*, or who were homozygous or heterozygous for the SNP. On the other hand, a cross-sectional study from the UK Biobank failed to find a significant association between any of three *DIO2* polymorphisms and a range of outcomes related to psychological well-being, cognitive function and cardiovascular risk. Polymorphisms of thyroid deiodinases have also been associated with an increased risk of other diseases, such as early-onset obesity, several cancer types, neurodegenerative diseases, bone diseases, hypertension and schizophrenia, among others.[10,14–18] The importance of polymorphisms of other proteins involved in thyroid homeostasis, such as thyroid hormone receptors and transfer proteins, remains an active area of research.[19]

It is possible that a given circulating level of T4, e.g. during treatment for hypothyroidism with exogenous LT4, may drive sufficient production of T3 in one organ system, but not in another.[20] For example, a state of local T3 deficiency in the heart (perhaps driven by up-regulation of DIO3,[21] which degrades T3 to T2 [Table 1]) has been implicated as a possible driver of adverse clinical outcomes in patients with heart failure.[22] Low T3 is commonly observed among populations with heart failure,[23,24] and intervening to improve T3 homeostasis has been suggested as a therapeutic approach to the management of heart failure with preserved ejection fraction.[25] Isolated low T3 ("euthyroid sick syndrome") is a risk factor for increased mortality in patients with various cardiac conditions.[26–28] Overall, it is clear that polymorphisms in deiodinases may underlie an inability of LT4 treatment to achieve a euthyroid state in peripheral tissues in some hypothyroid patients.[198]

The inability of LT4 to normalise T3 production in all patients with hypothyroidism

Several studies have reported that a low level of free T3 (fT3) persists in some patients who receive thyroid hormone substitution with LT4 that is sufficient to bring TSH and free T4 (fT4) to within their reference ranges.[29–33] For example, the recent Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) showed that LT4 treatment for hypothyroidism normalised serum TSH levels and increased average fT4 levels, as expected, but the mean fT3 level was reduced by 7%, with 15.6% of patients reporting at least one fT3 test result below its reference range during the average follow-up of 8 years.[31] An observational study in 9,850 LT4-managed adults with hypothyroidism found a non-linear relationship between levels of fT3 and fT4 such that there was little change in fT3 at higher levels of fT4.[34] Thus, increasing the LT4 dose was effective in reducing TSH and increasing fT4, but had little effect on fT3 beyond a certain level.[34] A meta-analysis comparing well-controlled patients with hypothyroidism (according to the TSH level) with a euthyroid control group showed that modest but statistically significant elevations of total cholesterol (mean difference +9.6 mg/dL [0.25 mmol/L]) and LDL-cholesterol (+3.3 mg/dL [0.09 mmol/L]) persisted in the hypothyroid group.[35]

The problem of persistent symptoms in some patients with hypothyroidism

The observation that TSH-guided thyroid hormone replacement for patients with hypothyroidism may not always establish effective euthyroidism (i.e. normalised levels of TSH, fT4 and fT3, see above) has refocused interest on the minority of patients who continue to experience hypothyroidism symptoms, e.g. impaired quality of life, even after the restoration of TSH to within its reference range.[36–40] Observational data suggest that people with hypothyroidism report a lower quality of life than their euthyroid peers, even if their TSH is well-controlled, and after adjustment for age, gender, comorbidities and associated medication use.[41] Elsewhere, quality-of-life scores provided by patients with well-controlled hypothyroidism were shown to correlate with levels of TSH

and fT4 within the normal range, but not with levels of fT3.[42] Finally, an RCT showed that additional LT4 administration did not improve psychological well-being or cognitive function in patients with symptoms reminiscent of hypothyroidism but a TSH level within the reference range.[43]

It should be noted that symptoms of hypothyroidism are non-specific and may arise from multiple comorbidities or their treatments, and exhaustive work-up is needed before these symptoms can be confidently associated with residual hypothyroidism.[35,36,38] Hypothyroid-like symptoms such as fatigue may arise from deficiencies of vitamins and minerals (especially B_{12}, folate and iron), menopause, coeliac disease and overweight/obesity with obstructive sleep apnoea.[38] Nevertheless, it is rational to hypothesize that correction of fT3 in addition to TSH and fT4 could be an effective strategy to improve the quality of life of patients with hypothyroidism who do not respond fully to LT4 monotherapy. The evidence base for intervention with LT3 in this population is summarised in the following section.

Clinical evaluations of LT4 and LT3 in combination

Randomised trials and meta-analyses

Table 2 summarises the main findings of numerous randomised trials that have evaluated combinations of LT4 + LT3 in comparison with LT4 alone in patients with hypothyroidism.[44–66] Several features of these trials are immediately striking: most were published more than 15 years ago, most are small and employed a relatively short treatment duration and – especially – most reported no differences in outcome between LT4 + LT3 treatment versus LT4 alone. A 2006 meta-analysis, after most of these trials had been published, found no overall differences between combination therapy versus LT4 monotherapy for bodily pain, depression, anxiety, fatigue, quality of life, body weight, any lipid parameter or adverse events.[67] Further meta-analyses published as recently as 2021 demonstrated no differences between LT3 + LT4 versus LT4 alone on symptoms, fatigue, quality of life, mood or cognition, which was unsurprising, given the number of neutral trials published at least 20 years ago.[68–71]

Table 2 Summary of randomised controlled trials that compared monotherapy with levothyroxine (LT4) with combinations of LT4 and liothyronine (LT3) in adult patients with hypothyroidism.

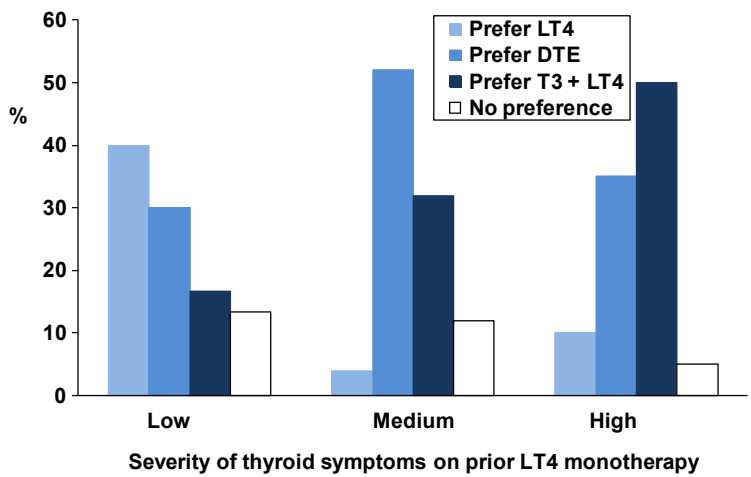
Ref	Year published	Duration (w)	N	Summary of main results
[44]	1970	8	99	18% preferred the combination vs. 33% for LT4; combination therapy was associated with troublesome side effects.
[66]	1999	5	33	Benefit for combination on 6/17 tests for cognitive function or mood and in 10/15 VAS assessments of mood and physical status; no changes in blood pressure or lipids.
[45]	2000	5	26	"Clear" improvement in cognition and mood on the combination.
[46]	2002	5	13	Trend to decreased symptoms and improved mood scores on the combination; no effect on cognition.
[58]	2003	10	110	No clear difference between LT4 and LT4 + LT3 for cognitive function, QoL, thyroid symptoms or subjective treatment satisfaction.
[59]	2003	16	46	No significant between-group differences for weight, lipids, QoL scores or neuropsychological tests.
[60]	2003	15	40	No significant between-group improvement in self-rated mood and well-being scores (Symptom Checklist-90, Comprehensive Epidemiological Screen for Depression, Multiple Outcome Study).
[47]	2004	12	23	No benefit of combination for mood and cognition scores.
[48]	2004	16	40	No additional effect of the combination on mood or well-being scores in patients with depressive symptoms on stable LT4.
[49]	2005	52	697	Transient improvement in QoL questionnaire scores at 3 months for the combination, but no sustained effect on these or on symptoms at 12 months.
[61]	2005	15	141	41.3% (10:1) and 52.2% (5:1) preferred the combination vs. LT4 alone (29.2%; p=0.024); this was the primary outcome. No difference for QoL questionnaires or neurocognitive tests.
[50]	2005	24	58	LT4 was associated with "unphysiologically" high fT4 and low fT3; LT3 supplementation had little effect on fT3.
[51]	2005	15	28	No benefit for the combination on most QoL or psychometric tests; 18 preferred the combination vs. 2 for LT4 alone.
[62]	2005	6	27	No between-group difference for fatigue, depression, working memory.

Ref	Year published	Duration (w)	N	Summary of main results
[52]	2009	16	71	Small reduction in anxiety/insomnia for the combination, but no between-group difference for other psychosocial scores, weight, heart rate, blood pressure and lipids.
[63]	2009	12	59	Benefit for combination on 7/11 scores for QoL or depression; 49% preferred the combination and 15% preferred monotherapy (p=0.002).
[53]	2010	24	36	No between-group difference for symptoms or bone function markers; some improvement in lipids on the combination.
[64]	2016	8	32	No effect of the combination on lipids, body weight or QoL; the combination increased mean heart rate but not blood pressure.
[54]	2017	12	45	60% of patients with biochemical euthyroidism on LT4 preferred LT4 + LT3; this increased to 100% for patients with polymorphisms in *DIO2* (Thr92Ala) and MC10 (rs17606253).
[65]	2021	22	72	No between-group difference for neurocognitive, QoL, psychosocial scores or patient preferences; however, patients with the most severe symptoms had improved questionnaire scores and expressed strong preference for the combination.
[55]	2022	12	59	Improvement for the combination in 12/13 domains of the ThyPRO thyroid-specific QoL instrument questionnaire (physical, mental and social domains) in patients with symptoms despite optimised LT4.
[56]	2023	52	38	Significant improvement in diastolic function with the combination group that correlated with improvement in fT3.
[57]	2024	24	141	No difference in QoL or preference for combination therapy vs. LT4 alone.

Duration refers to randomised treatment duration in weeks. Studies in patients with central hypothyroidism and of desiccated thyroid extract are not included here.
Abbreviations: DIO2: deiodinase 2; fT3: free triiodothyronine; fT4: free thyroxine; LT3: liothyronine; LT4: levothyroxine; N: number randomised; QoL: quality of life; VAS: visual analogue scale.

Nevertheless, a 2022 meta-analysis showed that patients expressed a significant preference for LT4 + LT3 combination therapy versus LT4 alone (risk ratio 2.47; 95% confidence interval [CI] 1.31 to 4.67).[68] In one of the studies summarised in Table 2, the use of inclusion criteria requiring patients to have LT4-resistant symptoms of hypothyroidism led to the demonstration of a benefit for the combination in 12/13 domains of a thyroid-specific quality-of-life questionnaire (ThyPRO).[65] Another study asked patients to rank three study treatments in order of preference; numerically more patients allotted rank 1 (best) to LT4 + LT3 (32%) or desiccated thyroid extract (45%; this preparation also contains T4 and T3), compared with LT4 (23%), although there were no significant differences within this dataset.[64] However, when the population was stratified for the severity of residual symptoms on their prior LT4 monotherapy, those with the most severe symptoms expressed a clear and significant preference for the LT3-containing regimens (Figure 1). The highest versus lowest severity of symptoms at baseline was also associated with significant benefits for LT3 + LT4 versus LT4 monotherapy relating to scores derived from the Thyroid Symptom Questionnaire-36,

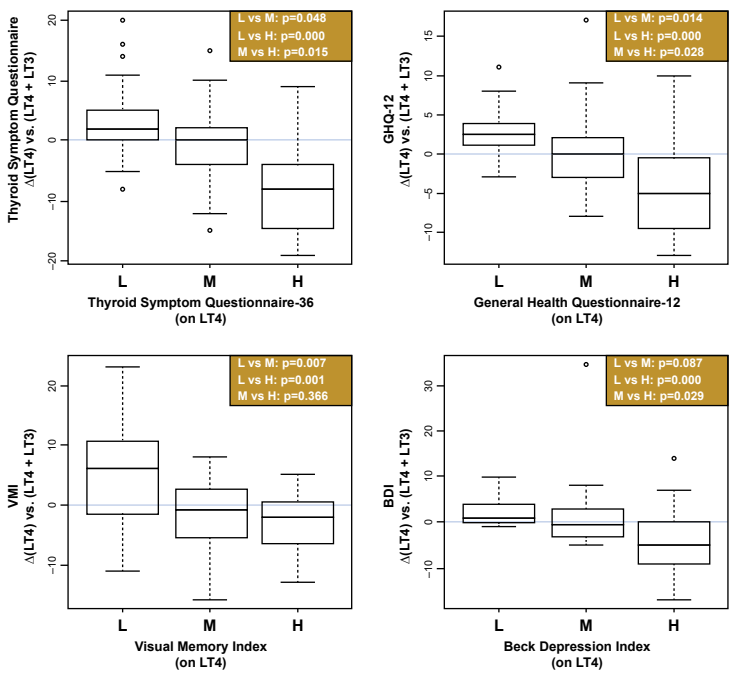
Figure 1 Patient preferences for levothyroxine (LT4), desiccated thyroid extract (DTE) or liothyronine (LT3) + LT4, according to the severity of hypothyroid symptoms during prior LT4-based monotherapy from a randomised trial in patients with hypothyroidism.



Drawn from data presented in ref 64.

the General Health Questionnaire, the Beck Depression Inventory and the Visual Memory Index (Figure 2). Finally, a study published in 2016 in 45 patients with overt hypothyroidism rendered biochemically euthyroid by LT4 monotherapy compared the effects of LT3 and placebo as add-on treatment, with patient preference as the main study outcome.[64] The impact of polymorphisms of *DIO2* (Thr92Ala) and the thyroid hormone transport protein MC10 (rs 17606253) on patient preference was evaluated. The proportions of patients preferring the combination (60% overall) were 42% for those with neither polymorphism, 63% for those with one polymorphism and 100% for those with both polymorphisms.

Figure 2 Thyroid symptoms and patient-reported outcomes according to the severity of hypothyroid symptoms during prior LT4-based monotherapy from a randomised trial in patients with hypothyroidism.



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"L", "M" and "H" refer to low, medium and high severity of hypothyroid symptoms on prior LT4 monotherapy.

Limitations of the current evidence base

An expert review from 2009 posed the question in its title, "*Do we need still more trials on T4 and T3 combination therapy in hypothyroidism?*".[72] The author's answer was "Yes – but not more of the same", acknowledging the multiple limitations inherent in the available clinical evidence base, especially:

- The short pharmacokinetic half-life of LT3 (hours), compared with the long half-life of LT4 (days), effectively precluded the establishment of a stable euthyroid-like physiological balance of T3 and T4. Wide variations in peak-to-trough levels of fT3 occur with the use of immediate-release LT3 preparations.[73] Extended-release formulations of LT3 are in clinical development, which may facilitate the establishment of biochemical euthyroidism based on fT3 levels, as well as fT4 and TSH.[74–76] Importantly, serum levels of fT3 have been shown to reflect tissue levels of fT3 sufficiently accurately that serum fT3 is suitable as a biomarker for systemic T3 status, which will aid the conduct and interpretation of future clinical trials in this area.[77]
- Trial participants were relatively unselected populations with hypothyroidism, mostly with no attempt to recruit patients likely to benefit from LT4 + LT3 combinations, such as those with documented polymorphisms of key proteins that might predispose to low T3 levels, and/or those with symptoms of hypothyroidism that were resistant to prior TSH-directed LT4 monotherapy.

A recent review of the literature echoed these concerns and concluded that clinical comparisons of LT4 with LT4 + LT3 in hypothyroidism were usually underpowered and failed to recruit sufficient patients with residual symptoms of hypothyroidism on prior LT4 monotherapy.[38] These authors also concluded that more recent studies that did recruit populations of patients with residual hypothyroid symptoms on LT4 reported benefits relating to reduced symptoms and/or improved quality of life for patients receiving the LT4 + LT3 combination rather than LT4 monotherapy, as described above.[38]

A computer modelling approach set out to define the conditions for successful intervention with LT4 and LT3.[78] The authors concluded that

the amount of residual thyroid function in each individual was key to optimising thyroid homeostasis with this combination and made recommendations on starting doses of LT4/LT3 for residual thyroid function of <10% (100 μg/10–12.5 μg), 10–20% (100 μg/7.5–10 μg) and >20% (87.5 μg/7.5 μg). Residual thyroid function appears to be another parameter that may be a source of variability in the therapeutic response to LT3-containing interventions in the management of hypothyroidism that needs to be controlled more carefully in clinical trials.

Current guidelines

Unsurprisingly, major guidelines have not provided strong support for the use of LT3 in the management of hypothyroidism, given the neutral results of the older clinical studies summarised above. Nevertheless, the European Thyroid Association (ETA) provided good evidence for the combination approach in a guideline published in 2012.[72] According to the ETA, additional LT3 may be given "*solely as an experimental treatment modality*" with specialist physician supervision for patients with hypothyroid symptoms despite good adherence to optimised LT4 therapy, with the treatment withdrawn after 3 months if there is no benefit. LT3 should be given twice daily at an LT3:LT4 ratio between 13:1 and 20:1. Pregnant women and patients with cardiac arrhythmias should not receive LT3. The stated goal of treatment is to improve or optimise levels of TSH, fT3, fT4 and the fT4:fT3 ratio, measured in a morning blood sample before taking any thyroid hormone tablets. A 2015 position statement from the British Thyroid Association supported this approach.[79]

The American Thyroid Association (ATA) 2014 guideline for the management of hypothyroidism provides a weak (due to lack of evidence) recommendation to avoid the routine use of LT3 + LT4.[80] There is also no recommendation on the suitability of add-on LT3 for patients with residual hypothyroid symptoms despite optimised LT4, and no support for the use of thyroid extracts, which contain T4 and T3. The ATA updated its guidance on the therapeutic use of LT3, with a consensus statement published in 2021.[81] The ATA recognised that LT4 monotherapy produces a lower fT3:fT4 ratio than is seen in euthyroid individuals, and that this can be corrected with LT4 + LT3 combination therapy (to some extent, at

least, with available immediate-release LT3 preparations). Importantly, the consensus recognises that generic quality-of-life instruments are likely to miss some classic hypothyroid-related symptoms, such as tiredness and emotional instability, and that thyroid-specific instruments should be used in future.

Where next?

The report from the ATA, described above, recognised that patients most likely to benefit from LT4 + LT3 combination therapy "*may not yet have been included in trials in sufficient numbers to provide adequate power for detecting a response*", particularly those dissatisfied with, or with residual symptoms on, LT4 monotherapy.[80] Accordingly, the hypothesis that adding LT3 to LT4 may improve the management of some people with hypothyroidism has not been adequately tested so far, and new and more appropriately designed trials are needed. Box 1 summarises the results of a formal consensus procedure undertaken by the ATA to provide guidance on the conduct of new clinical trials in this area that will avoid the design pitfalls described above.[80] The statement addresses the need for: recruitment of patients with residual symptoms on LT4 alone; robust, randomised trial designs; validated, thyroid-specific patient-reported outcomes as primary outcomes; and sustained-release LT3 preparations; and the potential for impact of polymorphisms in deiodinases and thyroid receptors on outcomes from thyroid hormone replacement, among other recommendations. A 2023 UK expert consensus provided similar recommendations, focussing on patients with the loss-of-function *DIO2* Thr92Ala polymorphism as a population likely to have a high symptom burden and a strong biological rationale for intervention with LT3 in addition to LT4.[76]

The results of trials designed to address these issues will finally answer the outstanding questions relating to the efficacy of additional LT3 for patients who are uncontrolled or unwell on LT4 monotherapy. A double-blind RCT in the Netherlands (T3-4-Hypo) is currently comparing LT4 + LT3 and LT4 monotherapy in adults with autoimmune hypothyroidism, ≥3 months of TSH within reference on LT4 ≥1.2 μg/kg and tiredness unexplained by other conditions.[82] Treatment is for 1 year, and the study is powered to detect treatment effects on the ThyPRO

Box 1 Abbreviated overview of key outcomes from a consensus process on the design of new trials evaluating LT4 + LT3 in the management of hypothyroidism conducted by the American Thyroid Association.

Level of consensus: **90–100%;** **70–90%;** **50–70%**

- Need for **double-blind, randomised, placebo-controlled, parallel-group** trials **of ≥1 year**
- Consider powering trials to **study effects of polymorphisms** in deiodinases and TH receptors
- Consider measuring **canonical and non-canonical TH pathways** (e.g. TG levels, cardiac function)
- **Include patients with comorbidities** so that results can be generalised to the wider population
- **Standardise interactions of patients with physicians** as this influences treatment satisfaction
- **Slow-release LT3 is needed** for future trials (for now, give immediate-release LT3 twice daily)
- Trials should use **validated thyroid-specific PROs** at baseline and be powered to detect changes (especially ThyPRO-39) as primary outcomes with patient preference as a secondary outcome
- **ThyPRO-39 or the tiredness scale of 85-item ThyPRO** can be used to measure fatigue
- **Body weight and lipids should be key metabolic outcomes** (REE is a secondary measure)
- Include **HR for cardiac efficacy**, **fluid cognition testing (NIH Toolbox) for cognition** outcomes (ideally these can measure changes in "brain fog") and **bone biomarkers for musculoskeletal outcomes** (DXA scan if the trial is >12 months' duration
- **Measure thyrotoxicosis, hypothyroid and general AE**
- **ECG monitoring at baseline** and 3-monthly intervals
- **Measure trough fT4 and total T3 and peak T3** in a nested PK study in combination trials
- **Specifically recruit patients with LT4-resistant symptoms** for trials (eligible patients should be on at least 1.2 µg/kg/day of LT4)
- Consider a **qualitative study to explain patient preferences for TH**
- Future trials should **aim at achieving a physiological fT3/fT4 ratio**
- **Consider a 2x2 factorial design** with TH and lifestyle intervention arms
- Consider including **an arm evaluating DTE**
- **Recruit patients with low T3 on LT4** and stratify results based on changes in T3 on LT4 + LT3
- **Pilot studies could explore additional outcomes of interest** within a larger trial

Consensus statements have been abbreviated and similar statements have been merged for conciseness. Colour coding for level of consensus and use of bold text is arbitrary to aid visual interpretation and applied by the author of this chapter. Statements with consensus <50% were omitted. Abbreviations – AE: adverse event(s); DTE: desiccated thyroid extract; DXA: dual-absorption X-ray absorptiometry scan; ECG: electrocardiogram; fT3: free triiodothyronine; fT4: free thyroxine; HR: heart rate; LT4: levothyroxine; NIH: National Institutes of Health; PROs: patient-reported outcomes; REE: resting energy expenditure; T3: triiodothyronine/liothyronine; TG: triglyceride(s); TH: thyroid hormone(s). Compiled from information presented in ref 80.

tiredness scale (the main study outcome), as well as the impact of the *DIO2* Thr92Ala polymorphisms and the polymorphism of the MC10 thyroid hormone transporter. Accordingly, this study incorporates the key design requirements for new trials proposed by international experts in thyroid research, as described above.

Safety of LT4 + LT3 combination therapy

Establishing the safety of a medication is paramount, especially for a lifelong condition that is prevalent in a relatively young population, some of whom will be exposed to the treatment for decades. The safety of therapy with LT4 or the LT4 + LT3 combination depends on avoiding under- or over-treatment with thyroid hormones, as per the usual management of hypothyroidism (Chapter 7 of this book summarises the clinical consequences of under- or over-treatment). Meta-analytic evidence shows that the incidence of adverse events is similar for populations receiving LT3 + LT4 and LT4 monotherapy, including for thyroid extracts.[69,83] A recent meta-analysis has revealed that treatment with LT3 is safe for patients undergoing cardiac surgery, although more data on this population are needed.[84,85]

Conclusions

T3 is the active thyroid hormone, and a consensus is building that establishing optimal homeostasis of this hormone is central to the optimal management of hypothyroidism.[86,87] The use of LT3 + LT4 in the treatment of hypothyroidism is as safe and effective as LT4 alone, as verified in a series of RCTs. However, most of these trials did not recruit the patients most likely to benefit from LT3 treatment and did not employ appropriate thyroid-specific instruments to measure effects on symptoms and quality of life. There is evidence from more recent, well-designed studies that patients with residual symptoms of hypothyroidism on optimised LT4 monotherapy express a strong preference for the LT4 + LT3

combination versus LT4 alone. A new series of clinical trials, designed using the lessons learned over the past two decades, will adequately address the hypothesis that adding LT3 to LT4 can improve symptoms and quality of life in some people with hypothyroidism.

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