Practical Application of Levothyroxine-Based Therapy

Takashi Akamizu

Levothyroxine (LT4) is a natural, endogenous hormone. Adverse events associated with this treatment are mostly symptoms of over-treatment (a state of functional thyrotoxicosis), which can be avoided by careful titration of the LT4 dosage to keep thyrotropin within an appropriate reference range that is relevant to the needs of the individual patient.

1 Introduction

The intention of this chapter is to complete this book on the role of levothyroxine (LT4) in the management of thyroid dysfunction, with a summary of the practical application of this treatment. The focus of the chapter will be on the management of hypothyroidism; for information relating to the implications of TSH-suppressive doses of LT4, the reader should consult chapter “Levothyroxine and Bone” and chapter “Levothyroxine and Cancer”. I will consider how to dose LT4, how patients should take it and the tolerability and safety implications long-term LT4-based therapy. This approach will involve reviewing important information from prescribing documentation for preparations of LT4 from Europe [1] and the USA [2], as these impact on clinical practice across a large area of the world beyond the borders of those regions. For example, physicians in Middle-Eastern countries are influenced by, but not bound by, labelling from both of these regions. Physicians should always consult their local labelling, where available, before prescribing LT4, however. Finally, the chapter will provide a resource of guidelines for the management of hypothyroidism around the world.

T. Akamizu (✉)

Wakayama Medical University, Wakayama, Japan

Kuma Hospital, Kobe, Japan

e-mail: akamizu@wakayama-med.ac.jp, akamizu@kuhp.kyoto-u.ac.jp

© The Author(s) 2021

G. J. Kahaly (ed.), *70 Years of Levothyroxine*,
https://doi.org/10.1007/978-3-030-63277-9_10

2 Safety and Tolerability of Levothyroxine

2.1 Avoiding Symptoms of Thyroid Dysfunction

The prescribing documentation for levothyroxine (LT4) products for use in patients with hypothyroidism notes that the adverse events associated with this treatment generally refer to over-treatment with LT4, which induces a state of thyrotoxicosis. Alternatively, inadequate correction of TSH leaves the hypothyroid patient at risk of a range of adverse outcomes, including major adverse cardiovascular events and premature death (see chapter “Levothyroxine and the Heart” for more details) [3, 4]. Accordingly, both over-treatment and under-treatment with LT4 leave the patient with hypothyroidism at increased risk of adverse long-term clinical outcomes, as well as troublesome symptoms of thyroid dysfunction (summarised in Fig. 1).

Fig. 1 Overview of symptoms arising from suboptimal dosing of levothyroxine in patients with hypothyroidism. Symptoms of hyperthyroidism/thyrotoxicosis were from ^athe European Summary of Product Characteristics [1] and ^bUS Prescribing Information [2] for levothyroxine (LT4) products. Symptoms of hypothyroidism were as listed by the United Kingdom National Health Service [3]

The goal of LT4 management is thus to optimise the LT4 dosage [1–5]. It is important to note that symptoms of thyroid dysfunction are often non-specific in nature, and in some cases similar symptoms are identified for both under- and over-treatment with LT4.

Increased actions of catecholamines are a feature of thyrotoxicosis, including following an overdose of LT4 [6]. Accordingly, a number of adverse consequences of thyrotoxicosis following over-treatment with LT4 are mediated via over-stimulation of β -adrenoceptors, such as tachycardia, anxiety, agitation and hyperkinesia. Treatment with a β -blocker may be helpful here. The European prescribing documentation also warns that over dosage of LT4 may increase the risk of acute psychosis (especially in patients at risk of this condition), and that long-term abuse of LT4 has been associated with cardiovascular death. Seizures are another rare complication of LT4 therapy [2].

The possibility of increased risk of cardiovascular events (see chapter “Levothyroxine and the Heart”), or of osteoporotic fractures (see chapter “Levothyroxine and Bone”), are among the more serious long-term consequences of thyrotoxicosis. This is a particular concern where TSH-suppressive doses of LT4 are administered. Long-term treatment with high doses of LT4 may be administered after total thyroidectomy for well-differentiated thyroid carcinoma in order to suppress secretion of TSH from the pituitary (e.g. see chapter “Levothyroxine and Cancer”), which induces a thyrotoxic status similar to a chronic form of subclinical hyperthyroidism [7–9]. These patients are likely to be at elevated risk of long-term adverse effects, such as those in the cardiovascular system (possible increased risk of adverse cardiovascular events, see chapter “Levothyroxine and the Heart”) or the skeleton (possible increased risk of osteoporosis and fractures, especially in those at increased risk, such as postmenopausal women—see chapter “Levothyroxine and Bone”).

2.2 Adverse Reactions to the LT4 Tablet Itself

Additionally, as with any medicinal product, hypersensitivity reactions in the skin or respiratory system may occur rarely in response to components of the LT4 tablet, possibly including LT4 itself [1, 2]. Such reactions tend to manifest with symptoms, such as urticaria, eczema-like rashes, fever and disturbances of liver function tests, and may persist when different LT4 products are prescribed [10–13]. Excipients vary somewhat between LT4 preparations, and so changes the brand of LT4 may help to resolve the issue; however, hypersensitivity to LT4 itself may effectively prevent the effective management of hypothyroidism [14]. Procedures for oral desensitisation have been described, where administration of successively increasing LT4 dosages (e.g. at 30-min intervals, from an initial dose as low as 0.01 μg) enable subsequent chronic therapy with doses of LT4 that are clinically effective [10–13].

3 How to Prescribe and Take Levothyroxine

Hypothyroidism usually requires patients to take LT4 for life. Accordingly, patients must be educated on how to take their LT4 tablets correctly, to have any chance of achieving stable, euthyroid-like thyroid hormone function over the long term (Table 1). Food has a markedly inhibitory effect on the absorption and bioavailability of LT4 (see chapter “Administration and Pharmacokinetics of Levothyroxine”). Accordingly, it is important that LT4 is taken on an empty stomach, and that no

Table 1 How to take levothyroxine (LT4): examples from products available in Europe and in the USA

	Europe	USA
Dosing frequency for the management of hypothyroidism	One tablet, once-daily	One tablet, once-daily
When to take LT4	30 min before breakfast on an empty stomach	30–60 min before breakfast on an empty stomach
Typical starting doses		
Adults with hypothyroidism	25–50 µg ^a	100–125 µg (70 kg adult) ^c
Elderly	12.5 µg ^a	12–25 µg
Adults with hypothyroidism + CHD	12.5 µg	12–25 µg
Infants/neonates with CH ^b	10–15 µg/kg	10–15 µg/kg ^{b,f}
Children	12.5–50 µg	Varies ^f
Typical dose adjustments	Every 2–4 weeks (elderly: 12.5 mg every 2 weeks)	12.5–25 µg every 4–6 weeks (6–8 weeks for elderly)
Typical maintenance doses		
Adults with hypothyroidism	100–200 µg/day	About 1.6 µg/kg
Adults with hypothyroidism + CHD	As above, possibly lower ^c	May be <1 µg/kg (elderly + CHD)
Children	100–150 µg/m ²	Varies ^f
Elderly	As for adults, possibly lower	May be <1 µg/kg
TSH suppression post-surgery for well-differentiated thyroid cancer	150–300 µg	Usually >2 µg/kg
Contraindications to LT4	<ul style="list-style-type: none"> • Hypersensitivity to LT4 or excipients • Untreated: <ul style="list-style-type: none"> – Adrenal insufficiency – Pituitary insufficiency – Thyrotoxicosis • Acute MI • Acute myocarditis • Acute pancreatitis • Use with anti-thyroid agent during pregnancy 	<ul style="list-style-type: none"> • Untreated adrenal insufficiency

Table 1 (continued)

	Europe	USA
Special warnings and precautions	<ul style="list-style-type: none">• Exclude/treat diseases of:<ul style="list-style-type: none">– CV system^d– Pituitary– Adrenals• TSH autonomy• Psychosis• Risk of osteoporosis	<ul style="list-style-type: none">• Patients with CHD (especially elderly)• Myxoedema coma• Acute adrenal crisis (patients with adrenal insufficiency)• Worsened glycaemic control• Risk of osteoporosis

Compiled from information presented in Refs. [1, 2]

^aThe exact starting dose depends on other factors, such as thyrotropin (TSH) level and body weight

^bFor the first 3 months of life

^cStart low, go slow in adults with hypothyroidism and CHD, and consider the possibility of a lower maintenance dose than in an adult without CHD

^dAngina, arteriosclerosis, hypertension

^eHealthy, non-elderly patients with recent onset hypothyroidism

^fGuidance on doses for children of different ages is provided

food, coffee, etc. is consumed for at least 30 min (according to European guidance, and up to 1 h, according to guidance from the USA) after taking the LT4 tablet (half a glass of water or so is permitted to allow the tablet to be taken). The usual recommendation is to take LT4 first thing in the morning, so that the 30 min before needing to eat is occupied by the usual morning rituals of bathing, etc. In principle, LT4 can be taken at bedtime although the need to wait for 3 h after the evening meal before taking the tablet [15, 16] may be difficult to maintain consistently, with a consequent reduction in the stability of LT4’s biological actions.

The administration of LT4 in the management of hypothyroidism is tailored to the individual needs of the patient, according to an individually determined target for thyrotropin (thyroid-stimulating hormone, TSH) [17, 18]. Starting and maintenance doses (Table 1) vary according to a number of factors, including the therapeutic indication for LT4, age and comorbidity (especially where there is concomitant cardiovascular disease). Starting doses of LT4 for the management of hypothyroidism, and perhaps long-term targets for the TSH level, are likely to be lower in patients with certain comorbidities. US labelling for LT4 permits initiating treatment at the estimated full LT4 dose for T4 replacement in a patient with recent onset hypothyroidism uncomplicated by comorbidities, however. The speed at which the LT4 dose is titrated to achieve control of TSH also varies with the characteristics of the individual patient.

Contraindications and warnings associated with LT4 usually relate to use in patients with comorbidities where the potential harm of accidental over-treatment with LT4 is highest. These relate especially to comorbidities in the cardiovascular and adrenal systems and the risk of osteoporosis (Table 1).

4 Overview of Guidelines on the Management of Hypothyroidism

This book has drawn on major guidelines from Europe and the USA to summarise the current role of LT4 in the management of hypothyroidism, as described in its individual chapters. Many other sources of guidance are available; however, we have listed some of these in Table 2, alongside those from Europe and the USA, as a resource our readers in these areas [17–32]. For clarity and brevity, we have restricted this list to guidelines that impact on the management of hypothyroidism: please consult chapter “Levothyroxine and Cancer” for detailed information on the use of LT4 in the management of differentiated thyroid cancer.

Table 2 Selection of guidelines for the management of hypothyroidism

Ref.	Country/region	Sponsor	Year	Scope
[20]	International	Expert panel	2019	• Thyroid hormone treatment for subclinical hypothyroidism
[21]	International	ES	2012	• Management of thyroid dysfunction in pregnancy and post-partum
[22]	Europe	ETA	2014	• Subclinical hypothyroidism in pregnancy and in children
[17]	Europe	ETA	2013	• Subclinical hypothyroidism, in younger (<65 years) and elderly patients
[18]	USA	ATA	2017	• Thyroid disease in pregnancy and post-partum • Includes content on iodine deficiency, and management of overt and subclinical hypothyroidism
[19]	USA	ATA	2014	• Broad in scope: Includes hypothyroidism associated with iodine deficiency, and management of congenital, overt and subclinical hypothyroidism • Includes special populations (paediatric subjects, elderly, pregnancy, patients who are non-adherent to LT4)
[23]	USA	AACE/ATA	2012	• Broad scope covering multiple aspects of hypothyroidism
[24]	Latin America	LATS	2013	• Includes hypothyroidism associated with iodine deficiency, and management of overt and subclinical hypothyroidism • Includes special populations (elderly, pregnancy)
[25]	Japan	JTA	NA	• Diagnosis of hypothyroidism (and other aspects of thyroid dysfunction)
[26]	UK	NICE	2019	• Thyroid dysfunction, including primary hypothyroidism, subclinical hypothyroidism, hyperthyroidism, thyroid enlargement
[27]	UK	BTA	2016	• Management of primary and overt hypothyroidism
[28]	UK	BTA	2007	• Use of thyroid extract and LT4 + LT3 combinations
[29]	UK	ACB, BTA, BTF	2006	• Use of thyroid function tests

Table 2 (continued)

Ref.	Country/region	Sponsor	Year	Scope
[30]	Canada (Alberta)	TOP	2014	• Concise, at-a-glance summary of management options for primary hypothyroidism
[31]	Australia	DoH	2019	• Management of hypothyroidism during pregnancy
[32]	Australia, New Zealand	RCGPA	2019	• Thyroid function testing in adults

Guidelines published in or after 2010 are considered here. *AACE* American Association of Clinical Endocrinologists, *ACB* Association for Clinical Biochemistry, *ATA* American Thyroid Association, *BTA* British Thyroid Association, *BTF* British Thyroid Foundation, *DoH* Department of Health, *ES* Endocrine Society, *ETA* European Thyroid Association, *JTA* Japan Thyroid Association, *LATS* Latin American Thyroid Association, *NA* not available from source, *RCPA* Royal College of Pathologists of Australia, *TOP* towards optimised practice, *LT4* levothyroxine

Guidelines from the American Thyroid Association tend to be comprehensive and cover multiple aspects of thyroid dysfunction, while those from the European Thyroid Association tend to focus on specific aspects, such as subclinical hypothyroidism in special patient populations. Hypothyroidism is especially difficult to manage in the setting of pregnancy and breastfeeding, and guidelines from these expert societies address this need. Regional guidelines are available from Latin America, also, as well as individual countries including the UK and Japan.

5 Conclusions

The LT4 molecule is identical chemically with the endogenous thyroid hormone, T4. Accordingly, other than rare hypersensitivity reactions to excipients or other pharmaceutical components of the LT4 tablet, symptoms reported by people with hypothyroidism receiving LT4 treatment will relate to the dosage of LT4 they receive, and the severity of their thyroid dysfunction. Novel, re-engineered formulations of LT4 have the potential to increase the reproducibility and constancy of exposure to LT4 during long-term management, which may help to achieve optimal dose titration of LT4 (see chapter “Administration and Pharmacokinetics of Levothyroxine” for an example). Some patients are given supra-physiologic doses of LT4 as a deliberate part of their management, such as those undergoing LT4-based suppression of TSH levels to reduce the risk of disease recurrence after thyroidectomy for thyroid cancer, or to reduce the growth and potential for malignancy of thyroid nodules. Research is continuing to determine the most appropriate LT4-based management algorithms for these patients, to optimise their long-term clinical outcomes.

We, the authors, hope that you have enjoyed reading this book, and that you have found it useful in your clinical practice.

References

1. Merck KgAA. Euthyrox®. Summary of product characteristics.
2. US Prescribing Information for Synthroid®, a trademark of AbbieVie Inc. Available at www.synthroid.com. Accessed Jul 2020.
3. Thayakaran R, Adderley NJ, Sainsbury C, et al. Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study. *BMJ*. 2019;14892:366.
4. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. *Thyroid*. 2018;28:566–74.
5. National Health Service. Symptoms—underactive thyroid (hypothyroidism). Available at <https://www.nhs.uk/conditions/underactive-thyroid-hypothyroidism/symptoms/>. Accessed May 2020.
6. Silva JE, Bianco SD. Thyroid-adrenergic interactions: physiological and clinical implications. *Thyroid*. 2008;18:157–65.
7. Biondi B, Filetti S, Schlumberger M. Thyroid-hormone therapy and thyroid cancer: a reassessment. *Nat Clin Pract Endocrinol Metab*. 2005;1:32–40.
8. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. *Thyroid*. 2010;20:135–46.
9. Heemstra KA, Hamdy NA, Romijn JA, Smit JW. The effects of thyrotropin-suppressive therapy on bone metabolism in patients with well-differentiated thyroid carcinoma. *Thyroid*. 2006;16:583–91.
10. Dortas SD, De Araujo FM, Souza CR, et al. Drug rash induced by levothyroxine and oral desensitization. *World Allergy Organ J*. 2015;8:A21. Available at <https://waojournal.biomed-central.com/articles/10.1186/1939-4551-8-S1-A21>. Accessed Jul 2020.
11. Fevzi D, Mustafa G, Ozgur K, et al. Successful oral desensitization to levothyroxine. *Ann Allergy Asthma Immunol*. 2013;111:146–7.
12. Guzmán MA, Sepúlveda C, Liberman C, et al. Desensibilización a levotiroxina. Caso clínico [Successful oral desensitization to levothyroxine. Report of one case]. *Rev Med Chil*. 2018;146:394–8.
13. Sala A, Labrador-Horrillo M, Guilarte M, Luengo O, Rueda M. Immediate-type hypersensitivity reaction to levothyroxine and desensitization. *Ann Allergy Asthma Immunol* 100. 5:P513–4.
14. Siddiqui MS, Shotliff K. Levothyroxine—not all tablets are the same. *Prescriber* 15 Jul 2019. Available at <https://www.prescriber.co.uk/article/levothyroxine-not-all-tablets-are-the-same>. Accessed Jul 2020.
15. Benvenga S, Bartolone L, Squadrito S, Lo Giudice F, Trimarchi F. Delayed intestinal absorption of levothyroxine. *Thyroid*. 1995;5:249–53.
16. Wenzel KW, Kirschsieder HE. Aspects of the absorption of oral L-thyroxine in normal man. *Metabolism*. 1977;26:1–8.
17. Pearce SH, Brabant G, Duntas LH, et al. ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2:215–28.
18. Alexander EK, Pearce EN, Brent GA, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27:315–89.
19. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24:1670–751.
20. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ*. 2019;12006:365.
21. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:2543–65.

22. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3:76–94.
23. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;22:1200–35.
24. Brenta G, Vaisman M, Sgarbi JA, et al. Clinical practice guidelines for the management of hypothyroidism. *Arq Bras Endocrinol Metabol*. 2013;57:265–91.
25. Japan Thyroid Association. Guidelines. Available at <http://www.japanthyroid.jp/en/guidelines.html>. Accessed Jul 2020.
26. Thyroid disease: assessment and management. NICE guideline [NG145]. Nov 2019. Available at <https://www.nice.org.uk/guidance/ng145/chapter/Recommendations>. Accessed Jul 2020.
27. Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)*. 2016;84:799–808.
28. British Thyroid Association Executive Committee. Armour thyroid (USP) and combined thyroxine/tri-iodothyronine as thyroid hormone replacement. Feb 2007. Available at https://www.british-thyroid-association.org/sandbox/bta2016/bta_statement_on_the_use_of_armour_thyroid_and_combined_t4_and_t3.pdf. Accessed Jul 2020.
29. Association for Clinical Biochemistry, British Thyroid Association, British Thyroid Foundation. UK guidelines for the use of thyroid function tests. Available at https://www.british-thyroid-association.org/sandbox/bta2016/uk_guidelines_for_the_use_of_thyroid_function_tests.pdf. Accessed Jul 2020.
30. Toward Optimized Practice (TOP) Endocrine Working Group. Investigation and management of primary thyroid dysfunction. Clinical practice guideline. April 2014. Available at <https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/thyroid-guideline.pdf>. Accessed Jul 2020.
31. Australian Government Department of Health. Pregnancy Care Guidelines. 46 Thyroid dysfunction. Available at <https://www.health.gov.au/resources/pregnancy-care-guidelines/part-g-targeted-maternal-health-tests/thyroid-dysfunction>. Accessed Jul 2020.
32. Royal College of Pathologists of Australia. Position Statement. Thyroid function testing for adult diagnosis and monitoring. Available at <https://www.rcpa.edu.au/Library/College-Policies/Position-Statements/Thyroid-Function-Testing-for-Adult-Diagnosis-and-M>. Accessed Jul 2020.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.