Title: Prevalence, Diagnosis, and Management of Hypothyroidism: An Update

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Abstract

Hypothyroidism impacts approximately 5% of the general population, with an additional 5% of individuals remaining untreated. Primary hypothyroidism is prevalent in over 99% of individuals who are affected. Women are more susceptible to this condition than men, and its prevalence increases as they age. The primary cause of a variety of thyroid disorders, including hypothyroidism, is the global iodine deficiency. Nevertheless, in regions where iodine levels are sufficient, Hashimoto's disease (chronic autoimmune thyroiditis) is the primary cause of thyroid dysfunction. Hypothyroidism is identified through biochemical analysis. Serum thyroid-stimulating hormone (TSH) levels that exceed the normal reference range and thyroxine levels that fall below the normal range are indicative of overt primary hypothyroidism. The symptoms of hypothyroidism are non-specific and may be mild, particularly in elderly individuals. Cardiovascular disease and increased mortality rates may result from hypothyroidism that is either untreated or inadequately treated. The most precise laboratory measure for assessing thyroid function is the serum thyroid-stimulating hormone test. The notion that screenings on individuals without symptoms result in enhanced outcomes is not supported by scientific data. The administration of synthetic levothyroxine orally may alleviate symptoms for the majority of individuals, and it is typically necessary to take the medication for the duration of their lives. It is not recommended to use a combination of triiodothyronine and thyroxine in treatment, as there are no benefits compared to using thyroxine alone. Individuals who have been diagnosed with subclinical hypothyroidism, which is defined by thyroid-stimulating hormone levels exceeding 10 mIU/l and elevated thyroid peroxidase antibody titres, are at an increased risk of developing clinical illness and may obtain therapeutic benefits from medication. The treatment of hypothyroidism has been successful with non-pharmacological therapies, such as physiotherapy, yoga, and dietary modifications.

Keywords: hypothyroidism, thyroid dysfunction, biomarkers, symptoms, levothyroxine
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Introduction

Insufficient thyroid hormone synthesis by the thyroid gland, which leaves the body with insufficient supplies to meet its metabolic demands, is the hallmark of hypothyroidism. Data from the National Health and Nutrition Examination Survey (NHANES III) indicate that around 1 in 300 Americans suffer with hypothyroidism [1]. Women are more likely than men to have this disorder, and its prevalence rises with age. Hypothyroidism is thought to affect 13 million Americans without a diagnosis. In the overall US population, 0.3% of people have clinical hypothyroidism [2], with a higher incidence among those 65 and older [5–7]. The prevalence of this illness is seven times greater in girls than in boys, with 40 instances per 10,000 females and six cases per 10,000 males. A number of autoimmune endocrinopathies, coeliac disease, autoimmune gastric atrophy, and type 1 diabetes mellitus are additional risk factors [3]. Additionally regarded as risk factors include Turner syndrome and Down syndrome.

Insufficient pituitary or brain stimulation of the thyroid gland or primary gland failure may cause hypothyroidism. Primary gland failure may be caused by infiltrative illnesses, autoimmune disorders (such as Hashimoto's disease), congenital anomalies, and iodine deficiency. Thyroid autoimmune disease is the primary cause of hypothyroidism.

Poorly managed or untreated hypothyroidism may lead to musculoskeletal issues, neurological diseases, cardiovascular illness, and infertility [2,4]. The most common cause of thyroid disorders, including hypothyroidism, globally is environmental iodine shortage. In contrast, the primary cause of hypothyroidism in regions where iodine sufficiency is prevalent is autoimmune thyroiditis, sometimes known as Hashimoto's disease. Hypothyroidism is linked to worse quality of life, more sick days, and reduced mortality. Lower blood levels of FT4 along with high thyrotropin (TSH) levels are used to diagnose thyroid disorders when they are the main cause of the problem. TSH levels for secondary (pituitary) or tertiary (hypothalamic) sources might be low or normal. Subclinical hypothyroidism is the condition that arises when FT4 levels are within the normal range but TSH levels are higher than usual. Primary hypothyroidism in adults is the main topic of this essay [5].

Methods

The evaluation of the narrative review on hypothyroidism was conducted transparently and methodically by adhering to the SANRA Scale for the Assessment of Narrative Review Articles checklist (SANRA) [6]. By adhering to SANRA requirements, the review probably showed clarity in conducting a thorough literature search and using suitable criteria for included research. The articles were obtained from the databases PubMed, Web of Science, Scopus, and Google Articles were obtained from the databases. The search specifically targeted systematic reviews and/or meta-analyses and was limited to items published in English. The keywords used included "hypothyroidism," "thyroid function," "thyroid hormones," "treatment" "cardiorespiratory fitness.

Prevalence and Incidence

It is known that the geographic incidence of hypothyroidism varies due to a number of reasons, such as shifting definitions of the condition, poorly described and diverse populations under investigation, variations in the sensitivity of thyroid function tests in the past, and iodine intake. According to estimates, between 0.2% and 5.3% of Europeans in the general population suffer with symptomatic hypothyroidism [7]. A meta-analysis of seven studies from nine European countries estimated that around 5% of people had undiagnosed hypothyroidism, which includes both overt and subclinical hypothyroidism [7,8]. The incidence rate is 226.2 (with a range of 222.26–230.17) per 100,000 people year, according to the meta-analysis. The prevalence of both overt and covert hypothyroidism in the US has been estimated to be 0.3% and 4.3%, respectively [9].

Causes of Hypothyroidism

As discussed before, the absence of T4 and T3 hormones is a characteristic of hypothyroidism. Although T3 is produced in smaller amounts, T4 is the main hormone that the thyroid gland produces. Just 20% or less of the T3 hormone present in peripheral tissue is produced by the thyroid gland. Within the designated tissues, T4 is enzymatically converted to T3 to provide the remaining part [10]. Via a negative feedback mechanism, the pituitary gland increases the release of thyroid-stimulating hormone (TSH) when the thyroid gland is unable to synthesise T4 and T3. Over 99 percent of cases have primary hypothyroidism, which is caused by the thyroid gland's inability to produce thyroid hormones. The remaining 5 percent of people suffer from hypothyroidism for a variety of reasons, including peripheral (extra-thyroidal) hypothyroidism, tertiary hypothyroidism brought on by a lack of thyrotropin-releasing hormone, and secondary hypothyroidism, which is brought on by the pituitary gland's inadequate production of TSH [11].

Not as much Common causes were congenital hypothyroidism (1.6%), lithium-associated thyroid failure (1.6%), subacute thyroiditis (1.8%), and previous thyroid radiation or surgery (1.8%). These days, a number of immunotherapies are leading to a growing number of iatrogenic causes [12]. Less frequent causes include thyroid hormone resistance, secondary or primary congenital hypothyroidism, overuse of antithyroid medicines, or adverse drug reactions. Hypothyroidism may also occur as a result of goitrogenic dietary consumption (such as veganism) and radiation exposure from treatments or the environment.

<<Figure 1: Causes of Hypothyroidism>>

Pathophysiology

Thyroid hormone is controlled by a powerful negative feedback system. Thyrotropin-releasing hormone, which is produced by the brain, controls the anterior pituitary gland's release of thyroid-stimulating hormone (TSH). This then controls how the thyroid gland secretes the thyroid hormones thyroxine [T4] and triiodothyronine [T3]. Numerous cells and organs' metabolism and functions are impacted by thyroid hormone. The signs and symptoms

of thyroid dysfunction clearly demonstrate its importance. Through negative feedback to the pituitary gland and brain, the thyroid hormone controls thyroid metabolism. Depending on the level of thyroid hormone in the blood, the hypothalamus controls the release of thyrotropin-releasing hormone. Together, these hormones control how much TSH the anterior pituitary gland secretes. Thyroid hormone levels in the blood are controlled by this operational feedback loop within a reasonable range [13].

<<Figure 2: Overview of thyroid hormone actions [14] here>>

Clinical Presentation

Thyroid hormone receptors govern several crucial physiological functions. As a consequence, hypothyroidism may lead to a wide range of clinical indications and symptoms. The intensity of these symptoms often corresponds to the extent of thyroid malfunction and the progression of hypothyroidism over time [15]. The Symptoms often linked to hypothyroidism are typically vague and not unique to the condition. These Symptoms include weight gain, weariness, impaired focus, depression, widespread muscular discomfort, and abnormalities in menstrual cycles. Specific symptoms of hypothyroidism include constipation, sensitivity to low temperatures, dry skin, weakness in the muscles closest to the body's core, and thinning or loss of hair. The Symptoms of hypothyroidism might differ depending on the individual's age and gender. Menstrual abnormalities and infertility may be seen in women with hypothyroidism [16]. Common examination findings in hypothyroidism include goitre, delayed relaxation phase of deep tendon reflexes, thin or brittle hair, dry skin, and peripheral oedema. Typical electrocardiography results include a slow heart rate, flattened T waves, and reduced electrical activity. Severe hypothyroidism may manifest in patients with pericardial effusion, pleural effusion, megacolon, hemodynamic instability, and coma [17].

<<Table 1: Signs & Symptoms of Hypothyroidism. Table made with references [4, 9, 16] here>>

The clinical manifestation is often mistaken for septic shock. Infants and toddlers may often exhibit symptoms of lethargy and failure to grow. be seen in women with hypothyroidism. Cognitive impairment may be the only indication in elderly individuals. of deep tendon reflexes, thin or brittle hair, dry skin, and peripheral oedema. slow heart rate, flattened T waves, and reduced electrical activity. manifest in patients as pericardial effusion, pleural effusion, megacolon, hemodynamic instability, and coma. clinical manifestation is often mistaken for septic shock [16,17]. Myxoedema coma, a condition characterized by severe physiological breakdown due to hypothyroidism, is an uncommon occurrence, with an annual occurrence rate of 0.22 per million. Common laboratory Results in hypothyroidism may consist of low sodium levels (hyponatremia), high carbon dioxide levels (hypercapnia), low oxygen levels (hypoxia), normal-sized red blood cells (normocytic anaemia), increased levels of creatine kinase, high levels of prolactin (hyperprolactinemia), and high levels of lipids in the blood (hyperlipidemia) [18].

Screening and diagnosis

The diagnosis of hypothyroidism relies only on repeated biochemical results. An imbalance in the levels of reactive oxygen species and the antioxidant defence system, resulting in increased oxidative stress, has been shown in both human and animal models of hypothyroidism [19, 20]. Hypothyroidism may create a pro-oxidant environment that may contribute to the development of atherosclerosis, a disease often associated with this thyroid disorder. In a hypothyroidism experimental model, there was an increase in the overall activity of nitric oxide synthase (NOS), and significant alterations were seen in the mRNA and protein expression of all three isoforms of NOS. Currently, diagnostic Evaluations for hypothyroid patients do not often involve blood tests to measure levels of pro-oxidant and anti-oxidant species [21].

<< Figure 3: Flow chart of Evaluation for suspected hypothyroidism. Flow chart made with references [6,11, 22] here>>

Overt primary hypothyroidism is characterized by serum TSH levels that are higher than the normal reference range, and free thyroxine levels that are lower than the usual reference range. It is worth mentioning that reference ranges are now a topic of continuing discussion and vary depending on the specific assay performed, as well as the age, sex, and ethnic background of the patient [23]. The top threshold of the TSH reference range often rises with ageing in humans. Furthermore, each person has a unique TSH reference range, which adequately encompasses just a quarter of the reference range for the total population.

Treatment

Pharmacological Treatment

Most people with hypothyroidism will need thyroid hormone therapy for the duration of their treatment. Triiodothyronine (T3) and thyroxine (T4) are the two thyroid hormones that are normally produced by the thyroid gland. Although T4 is produced in greater amounts, T3 is the biologically active form [24]. The peripheral conversion of thyroxine (T4) by deiodinase enzymes yields around 80% of triiodothyronine (T3) [25]. The main therapy for hypothyroidism is often restricted to once-daily administration of synthetic thyroxine preparations because of the short biologic half-lives of T3 preparations. Like endogenous thyroxine, synthetic thyroxine undergoes deiodination after absorption to produce the more physiologically active T3 [26]. There Synthetic thyroxine comes in both brand-name and generic varieties. The US Food and Drug Administration (FDA) approved the substitution of generic levothyroxine for brand-name levothyroxine in 2004. However, the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists challenged the FDA's claim that generic forms of levothyroxine were bioequivalent to brand-name ones [27]. When compared to brand-name levothyroxine medications, the researchers found that the use of potentially flawed pharmacokinetic methodologies and the lack of TSH tests to establish bioequivalence could lead to significant underestimations and overestimations of generic equivalency. It is thus recommended that

patients begin and maintain their medication with either generic or brand-name levothyroxine preparations, without switching between the two. To ensure that their TSH and free T4 levels are within the normal range, patients who switch products should have further testing done six weeks later. For young, healthy individuals, 1.6 µg/kg/day is the first levothyroxine dosage required for complete replacement [28]. Thyroid hormone administration is often advised in the morning, around half an hour before eating anything. Since calcium and iron supplements may decrease thyroid hormone absorption, it is not advised to take them within four hours after taking levothyroxine [29]. The main cause of persistently elevated TSH levels in people taking adequate amounts of thyroid hormone is often noncompliance with levothyroxine treatment.

The Dosage of levothyroxine for babies and children is determined based on their weight and varies depending on their age. Adjustments to the dosage should be made according to the patient's clinical response and the results of laboratory tests. Patients experiencing challenges with the morning administration of levothyroxine may discover that taking the medication after nighttime is a viable and successful option [30]. A well-organized trial carried out in the Netherlands found that administering levothyroxine at bedtime led to decreased TSH levels and increased free T4 levels, without any discernible impact on quality of life. Patients who struggle to adhere to a daily levothyroxine regimen may safely take their week's prescription of levothyroxine once a week [31].

<<Table 2: Initial Dosing of Levothyroxine in Adults with Primary Hypothyroidism. Table made in reference to [30,31] here>>

Non- Pharmacological Treatment

Non-pharmaceutical interventions for treating Hypothyroidism have also been tested, such as dietary modifications, physical activity, and lifestyle adjustments. Certain studies demonstrate the feasibility of restoring TSH scores to a euthyroid state, while others just alleviate unwanted symptoms [32]. Thyroid function is strongly correlated with sleep, smoking, food, and exercise. Research has shown that experiencing poor sleep quality is associated with a higher likelihood of developing Hypothyroidism [33]. Similarly, it was shown that a diet that is either low or excessively rich in iodine might elevate an individual's risk. It is crucial to acknowledge that the defining symptoms of hypothyroidism, such as tiredness, weight gain, and sadness, decrease the likelihood of patients adopting some advantageous lifestyle behaviours, such as frequent exercise [34]. A cross-sectional research examining physical activity in women discovered that the group of women with subclinical hypothyroidism (SCH) had lower levels of physical activity duration, daily step count, and muscular strength compared to those with normal thyroid function [35]. It is evident that sedentary lives are linked to elevated TSH scores, and conversely, higher TSH scores worsen sedentary lifestyles. Reduced physical capacity is therefore a significant barrier to following well-meaning medical recommendations [35,36].

Consequently, altering one's diet seems to be a more practical starting point for making improvements. A randomised control trial of SCH in 62 children demonstrated that consuming specific foods, such as green vegetables, beef, whole milk, and butter, for a period of six months, without any other changes to their diet, resulted in a significant improvement in their primary complaint of fatigue, as compared to the control group. It is worth noting that this study did not include women. The dietary adjustments did not have a negative impact on the lipid profile or BMI of the intervention group [37]. European research discovered that selenium administration effectively regulated or reduced TSH levels. Additionally, it decreased thyroid antibodies, the ratio of T4 to T3, as well as overall levels of oxidative stress and inflammation. Iodine is a mineral that has been extensively researched in relation to thyroid function [38]. Three studies provided considerable data indicating that an imbalance of iodine, either in shortage or excess, increased the likelihood of developing Hypothyroidism. Observational research examining the impact of lifestyle on thyroid function revealed that an imbalance in iodine levels had a notable influence on the ability of the thyroid gland to produce hormones. Both a deficit and an excess of iodine were associated with a higher likelihood of developing Hypothyroidism [39,40]. Researchers conducted a study on two Chinese villages that had varied amounts of iodine consumption. They discovered that those living in the community with higher iodine intake had a considerably greater chance of developing subclinical hypothyroidism (SCH) compared to those in the town with lower iodine intake. Researchers deduced that an excessive consumption of iodine served as a precursor for subclinical hypothyroidism (SCH) and eventual overt hypothyroidism. This finding was corroborated by comprehensive research involving a large group of individuals with subclinical hypothyroidism (SCH) living in an area with sufficient iodine levels. These individuals were instructed to limit their iodine intake to the recommended daily allowance (RDA) of 150 µg/day. As a result, they were able to reduce their TSH levels and, in some instances, achieve complete normalisation. The experimental group had a notable enhancement in TSH levels and an elevation in T4 levels, as opposed to the two control groups that did not undergo iodine restriction. The researchers determined that limiting excessive iodine consumption might serve as a major therapeutic approach for people with subclinical hypothyroidism (SCH) [41].

On the other hand, providing additional iodine to individuals with subclinical hypothyroidism (SCH) who have diets naturally lacking in this mineral shows encouraging outcomes [42]. A single case study demonstrated significant improvement in subclinical hypothyroidism (SCH) with the addition of iodine supplementation to a patient's diet, which was initially deficient in this nutrient. This report documents the one-month monitoring of a postmenopausal woman who had subclinical hypothyroidism (SCH), dyslipidemia, and obesity. During this period, the lady consumed the recommended daily allowance (RDA) of iodine. She was provided with advice on foods that are abundant in minerals and how to effectively include them in her diet. The outcomes were quite encouraging. In addition to improving her TSH level, she saw a drop in her total cholesterol and a reduction in her body mass index from 30.13 to 28.5 kg/m2. The patient found these outcomes invigorating. Her improvement would likely facilitate the adoption of other advantageous lifestyle behaviours, such as heightened physical

activity, resulting in more comfort and enjoyment [43]. By evidences, it is clear that lifestyle alterations have a significant effect on thyroid function and might potentially alleviate symptoms of subclinical hypothyroidism (SCH). Nevertheless, conducting more focused research would provide more evidence to support this assertion [44,45].

Conclusion

In conclusion, additional research ought to be conducted to determine the precise prevalence of hypothyroidism in the general population, optimise the dosage of levothyroxine substitution and determine the ideal course of treatment. Furthermore, it is important to promote non-pharmacological interventions such as physiotherapy, yoga, and food management to achieve optimal outcomes.

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References

1. Chaker, L., Razvi, S., Bensenor, I.M. *et al*. Hypothyroidism. *Nat Rev Dis Primers* 8, 30 (2022). https://doi.org/10.1038/s41572-022-00357-7
2. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012 Aug 1;86(3):244-51.
3. Angum F, Khan T, Kaler J, Siddiqui L, Hussain A. The Prevalence of Autoimmune Disorders in Women: A Narrative Review. Cureus. 2020 May 13;12(5):e8094. doi: 10.7759/cureus.8094. PMID: 32542149; PMCID: PMC7292717.

4. Amr NH. Thyroid Disorders in Subjects with Down Syndrome: An Update. Acta Biomed. 2018 Mar 27;89(1):132-139. doi: 10.23750/abm.v89i1.7120. PMID: 29633736; PMCID: PMC6357620.
5. Devaraj, T. V.; Salina, S.1,. Prevalence of hypothyroidism in Kannur; a coastal district in Kerala. Thyroid Research and Practice 18(2):p 55-60, May–Aug 2021. | DOI: 10.4103/trp.trp_1_22
6. Baethge, C., Goldbeck-Wood, S. & Mertens, S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* **4**, 5 (2019). https://doi.org/10.1186/s41073-019-0064-8
7. Chiovato L, Magri F, Carlé A. Hypothyroidism in Context: Where We've Been and Where We're Going. Adv Ther. 2019 Sep;36(Suppl 2):47-58. doi: 10.1007/s12325-019-01080-8. Epub 2019 Sep 4. PMID: 31485975; PMCID: PMC6822815.
8. Ane Garmendia Madariaga, Silvia Santos Palacios, Francisco Guillén-Grima, Juan C. Galofré, The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis, *The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 3, 1 March 2014, Pages 923–931, https://doi.org/10.1210/jc.2013-2409
9. Moleti M, Aversa T, Crisafulli S, Trifirò G, Corica D, Pepe G, Cannavò L, Di Mauro M, Paola G, Fontana A, Calapai F, Cannavò S and Wasniewska M (2023) Global incidence and prevalence of differentiated thyroid cancer in childhood: systematic review and meta-analysis. Front. Endocrinol. 14:1270518. doi: 10.3389/fendo.2023.1270518
10. G. Omuse, D. Kawalya, P. Mugaine, A. Chege, D. Maina, Neonatal reference intervals for thyroid stimulating hormone and free thyroxine assayed on a Siemens Atellica® IM analyzer: a cross sectional study. BMC Endocr. Disord. 23(1), 112 (2023)
11. . G. Effraimidis, T. Watt, U. Feldt-Rasmussen, Levothyroxine therapy in elderly patients with hypothyroidism. Front. Endocrinol. 12, 641560 (2021)
12. A. Busnelli, F. Cirillo, P.E. Levi-Setti, Thyroid function modifications in women undergoing controlled ovarian hyperstimulation for in vitro fertilization: a systematic review and metaanalysis. Fertil. Steril. 116(1), 218–231 (2021)
13. Angell, T.E., Huang, S.A., Alexander, E.K. (2018). The Thyroid. In: Belfiore, A., LeRoith, D. (eds) Principles of Endocrinology and Hormone Action. Endocrinology. Springer, Cham.https://doi.org/10.1007/978-3-319-44675-2_14
14. Feldt-Rasmussen U, Effraimidis G, Bliddal S, Klose M. Consequences of undertreatment of hypothyroidism. Endocrine. 2024 May;84(2):301-308. doi: 10.1007/s12020-023-03460-1. Epub 2023 Aug 9. PMID: 37556077; PMCID: PMC11076368.
15. El-Shafie KT. Clinical presentation of hypothyroidism. Journal of Family and Community Medicine. 2003 Jan 1;10(1):55-8.
16. Surks MI, Ross D, Mulder J. Clinical manifestations of hypothyroidism. Uptodate. Waltham, MA. Retrieved from http://www. uptodate. com. 2012.
17. Park S, Jeon MJ, Song E, Oh HS, Kim M, Kwon H, Kim TY, Hong SJ, Shong YK, Kim WB, Sung TY. Clinical features of early and late postoperative hypothyroidism

after lobectomy. The Journal of Clinical Endocrinology & Metabolism. 2017 Apr 1;102(4):1317-24.
18. Pluta RM, Burke AE, Glass RM. JAMA patient page. Subclinical hypothyroidism. JAMA. 2010;304(12):1402
19. Casey BM, Thom EA, Peaceman AM, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal– Fetal Medicine Units Network. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. N Engl J Med. 2017;376(9):815-825.
20. Loh HH, Lim LL, Yee A, et al. Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry. 2019;19(1):12.
21. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ. 2019; 365:I2006.
22. Hueston WJ. Treatment of hypothyroidism [published correction appears in Am Fam Physician. 2002;65(12):2438]. Am Fam Physician. 2001;64(10):1717-1725. Accessed December 9, 2020. https://www.aafp. org/afp/2001/1115/p1717.html
23. J. Jonklaas, A.C. Bianco, A.R. Cappola, F.S. Celi, E. Fliers, H. Heuer et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. Eur. Thyroid J. 10(1), 10–38 (2021)
24. R.P. Peeters, A. Boelen, Non-thyroidal illness (NTI). In Oxford Textbook of Endocrinology and Diabetes, 3rd edn. ed. by J.A.H. Wass, P.M. Stewart, S.A. Amiel, M. Davies (Oxford University Press, Oxford, UK, 2021)
25. U. Feldt-Rasmussen, Laboratory measurement of thyroid-related hormones, proteins, and autoantibodies in serum. In Werner and Ingbar's the Thyroid: A Fundamental and Clinical Text, 11th edn. ed. by L.E. Braverman, D.S. Cooper, P. Kopp (Lippincott, Williams & Wilkins, Philadelphia, 2020) p. 868–907
26. D. Yaniv, I. Vainer, I. Amir, E. Robenshtok, D. Hirsch, T. Watt et al. Quality of life following lobectomy versus total thyroidectomy is significantly related to hypothyroidism. J. Surg. Oncol. 126(4), 640–648 (2022)
27. S. Garasto, A. Montesanto, A. Corsonello, F. Lattanzio, S. Fusco, G. Passarino et al. Thyroid hormones in extreme longevity. Mech. Ageing Dev. 165(Pt B), 98–106 (2017)
28. R. Buffenstein, M. Pinto, Endocrine function in naturally longliving small mammals. Mol. Cell Endocrinol. 299(1), 101–111 (2009)
29. J. Bowers, J. Terrien, M.S. Clerget-Froidevaux, J.D. Gothié, M.P. Rozing, R.G.J. Westendorp et al. Thyroid hormone signaling and homeostasis during aging. Endocr. Rev. 34(4), 556–589 (2013)
30. J.M. Evron, S.L. Hummel, D. Reyes-Gastelum, M.R. Haymart, M. Banerjee, M. Papaleontiou, Association of thyroid hormone treatment intensity with cardiovascular mortality among US veterans. JAMA Netw. Open 5(5), e2211863 (2022)
31. B. Biondi, The management of thyroid abnormalities in chronic heart failure. Heart Fail. Clin. 15(3), 393–398 (2019)
32. L. Persani, Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J. Clin. Endocrinol. Metab. 97(9), 3068–3078 (2012)

33. L. Persani, G. Brabant, M. Dattani, M. Bonomi, U. Feldt-Rasmussen, E. Fliers et al. 2018 European Thyroid Association (ETA) guidelines on the diagnosis and management of central hypothyroidism. Eur. Thyroid J. 7(5), 225–237 (2018)
34. U. Feldt-Rasmussen, G. Effraimidis, M. Klose, The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Mol. Cell Endocrinol. 525, 111173 (2021)
35. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 ? L-T3 in the treatment of hypothyroidism. Eur Thyroid J. 2012;1:55–71.
36. Biondi B, Bartalena L, Chiovato L, et al. Recommendations for treatment of hypothyroidism with levothyroxine and levotriiodothyronine: a 2016 position statement of the Italian Society of Endocrinology and the Italian Thyroid Association. J Endocrinol Invest. 2016;39:1465–74.
37. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012;72:17–33.
38. Andersen SL, Carle A, Olsen J, Laurberg P. Hypothyroidism incidence in and around pregnancy: a Danish nationwide study. Eur J Endocrinol. 2016;175:387–93.
39. Sweeney LB, Stewart C, Gaitonde DY. Thyroiditis: an integrated approach. Am Fam Physician. 2014;90:389–96.
40. Thvilum M, Brandt F, Brix TH, Hegedus L. Hypothyroidism is a predictor of disability pension and loss of labor market income: a Danish registerbased study. J Clin Endocrinol Metabol. 2014;99:3129–35.
41. Thvilum M, Brandt F, Almind D, et al. Excess mortality in patients diagnosed with hypothyroidism: a nationwide cohort study of singletons and twins. J Clin Endocrinol Metabol. 2013;98:1069–75.
42. Guglielmi R, Grimaldi F, Negro R, et al. Shift from levothyroxine tablets to liquid formulation at breakfast improves quality of life of hypothyroid patients. Endocr Metab Immune Disord Drug Targets. 2018;18:235–40.
43. Garmendia Madariaga A, Santos Palacios S, GuillenGrima F, Galofre JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014;99:923–31.
44. Magri F, Zerbini F, Gaiti M, et al. Poverty and immigration as a barrier to iodine intake and maternal adherence to iodine supplementation. J Endocrinol Invest. 2019;42:435–42.
45. Collet TH, Bauer DC, Cappola AR, et al. Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis. J Clin Endocrinol Metabol. 2014;99:3353–62.

Tables

Table 1: Signs & Symptoms of Hypothyroidism. Table made with references [4, 9, 16]

System	Clinical Features	Description
General	Fatigue, Weakness, Lethargy	Patients often feel tired, weak, and lacking energy due to slowed metabolism
Cold Intolerance	Sensitivity to cold temperatures	Patients feel excessively cold because of reduced heat production by the body
Skin	Dry, Coarse Skin; Pale Skin; Hair Loss	The skin becomes dry and rough due to decreased sweat and sebaceous gland activity; hair may thin and become brittle
Cardiovascular	Bradycardia, Hypertension (Diastolic), Pericardial Effusion	Slowed heart rate (bradycardia) and increased peripheral resistance lead to diastolic hypertension; fluid accumulation can cause pericardial effusion
Musculoskeletal	Muscle Weakness, Myalgia, Arthralgia, Slow Reflexes	Patients may experience muscle pain, weakness, joint pain, and delayed reflexes due to the general slowing of body functions
Psychiatric	Depression, Apathy, Psychomotor Retardation	Mood changes, apathy, and slowed movement or thought processes are common
Metabolic	Hyperlipidemia, Hyponatremia	Decreased clearance of cholesterol leads to high levels of lipids in the blood;

		impaired free water clearance can cause low sodium levels

Table 2: Initial Dosing of Levothyroxine in Adults with Primary Hypothyroidism. Table made in reference to [30,31]

Patient group	**Dosing**
Age younger than 60 years	Start with 1.5 to 1.8 mcg per kg per day
Age 60 years or older; known or suspected heart disease	Start with 12.5 to 50 mcg per day
Pregnant on a previously stable dose	Increase to nine doses per week; endocrine referral

Figure 1: Causes of Hypothyroidism
Figure 2:Overview of thyroid hormone actions
Figure 3: Flow chart of Evaluation for suspected hypothyroidism