Hypothyroidism: An Overview of the Disease and Current Treatment Approach

By

Sadia Afrin

21346076

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements of the degree of

Bachelor of Pharmacy (Hons.)

School of Pharmacy

BRAC University

February 2026

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at BRAC University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

_____

Sadia Afrin

21346076

Approval

The thesis/project titled “Hypothyroidism: An Overview of the Disease and Current Treatment Approach” submitted by Sadia Afrin (21346076) of Spring 2026 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

_____

Dr. Zara Sheikh, PhD

Assistant Professor, School of Pharmacy

BRAC University

Approved By:

Chairman _____

Professor Sharmind Neelotpol, PhD

Chairperson, School of Pharmacy

BRAC University

Ethics Statement

This project does not involve any kind of animal and human trial**.**

Abstract

Hypothyroidism (underactive thyroid) is a condition where the thyroid gland does not produce enough thyroid hormones to meet the body's needs. As these hormones regulate how the body uses energy (metabolism), their deficiency causes many body functions to slow down. Common causes include Hashimoto's disease (autoimmune attack), iodine deficiency, or post-treatment effects. Symptoms develop slowly, including fatigue, cold intolerance, weight gain, constipation, dry skin/hair, hoarse voice, depression, and memory issues. Levothyroxine monotherapy is the standard treatment for hypothyroidism. Nonetheless, numerous unclear inquiries remain about patients who are biochemically stable yet dissatisfied with their therapy results. The present review is to give an overview of hypothyroidism disease, epidemiology of the disease, causes of hypothyroidism, highlighting the key considerations in diagnosis and current treatment of hypothyroidism along with providing future directions for research and improve management of the disease. Future research should investigate whether alternate regimens could offer a solution for a particular group of people with remaining symptoms. Investigation of the efficacy of new formulations (e.g., slow-release liothyronine) or increased administration frequency of levothyroxine-liothyronine combination therapy (e.g., tri-daily liothyronine) in alleviating patient symptoms, alongside the identification of patient subgroups that may benefit from alternatives to levothyroxine monotherapy (e.g., through the identification of additional genetic polymorphisms that could elucidate the individual thyroid set-point) could provide a new dimension to hypothyroidism management.

Keywords: Hypothyroidism; Hashimoto's disease; Levothyroxine; Liothyronine; Combination therapy; Genetic polymorphisms.

Dedication

Dedicated to my Supreme Creator, beloved parents, and my siblings who constantly support me on this journey. I also extend my sincere gratitude to a special person and to my friends (Abrar, Adrita, Noman, Prity) for their constant encouragement, motivation, and support during the completion of this work.

Acknowledgement

I am sincerely grateful to my respected supervisor, Dr. Zara Sheikh, PhD, Assistant Professor at the School of Pharmacy, BRAC University, for her invaluable guidance, constructive feedback, and unwavering support throughout this project. Her patience, encouragement, and insightful mentorship greatly helped me overcome challenges and successfully complete this thesis.

I would like to express my heartfelt gratitude to Professor Arshad Mahmud Chowdhury, PhD, Dean and Professor Sharmind Neelotpol, PhD Chairperson, for their encouragement and leadership, as well as all faculty members.

Table of Contents

List of Tables

List of Figures

List of Acronyms

T3 – Tri-iodothyronine

T4 – Thyroxine

FT3 – Free Tri-iodothyronine

FT4 – Free Thyroxine

TSH – Thyroid-Stimulating Hormone (Thyrotropin)

TRH – Thyrotropin-Releasing Hormone

TH – Thyroid Hormone

TPO-Ab – Thyroid Peroxidase Antibody

CH – Central Hypothyroidism

MPHD – Multiple Pituitary Hormone Deficiencies

DIO2 – Deiodinase Type 2 Gene

IGSF1 – Immunoglobulin Superfamily Member 1

TSHB – Thyroid-Stimulating Hormone Beta Subunit Gene

TRH-R – Thyrotropin-Releasing Hormone Receptor

IRS4 – Insulin Receptor Substrate 4

TBL1X – Transducin Beta Like 1 X-Linked

ETA – European Thyroid Association

BA – British Association (context likely British Thyroid Association)

LEV / L-T4 – Levothyroxine

FDA – Food and Drug Administration

mIU/L – milli-International Units per Liter

Chapter 1

Introduction

Chapter 1

1.1 Introduction

Hypothyroidism is a well-known and common medical condition in every corner of the world, and it is caused by the lack of thyroid hormones, mainly comprising T4 (thyroxine) and T3 (tri-iodothyronine), that is exclusively having ugly consequences on health and may even lead to death without proper remedy (1). The diagnosis of the very disease given the dynamic nature of the symptoms and the absence of clear and specific symptoms of hypothyroidism is biochemical in nature and largely relies on the presence of thyroid-function tests Free tri-iodothyronine (FT3) and free thyroxine (FT4), which leads to the elevated and inversed change in the concentration of the pituitary gland hormone thyrotropin (thyroid-stimulating hormone (TSH) (2) and, consequently, the monitored change of the concentration of TSH levels the most popular primary (3).Hypothyroidism is typically a primary process which occurs when the thyroid gland fails to secrete sufficient amounts of thyroid hormone (4). As a result, open hypothyroidism is presented as a TSH level surpassing and an FT4 level that shows the state of being under the normal range, which is known as subclinical hypothyroidism, in which the thyroid gland is generally normal, but is not stimulated sufficiently owing to low secretion of thyrotropin by the pituitary (5,6). In Tertiary hypothyroidism, inadequate secretion of thyrotropin-releasing hormone (TRH) by the hypothalamus prompts inadequate secretion of TSH, which in turn leads to inadequate thyroid stimulation (7).

Whether or not thyroid dysfunction is to be determined based on the already available reference ranges of free thyroxine and TSH is debated. This is a clinically problematic issue because the reference ranges typically serve as a therapy threshold. In individuals with hypothyroidism, replacement by levothyroxine remains the gold standard or sole approach to hypothyroidism

treatment. The issue of whether all patients should be treated with levothyroxine or there should be some alternative therapies (combinations with liothyronine preparations) has identified as whether a definite percentage of patients treated with levothyroxine should still complain despite the attainment of the target levels in the biochemical therapy.

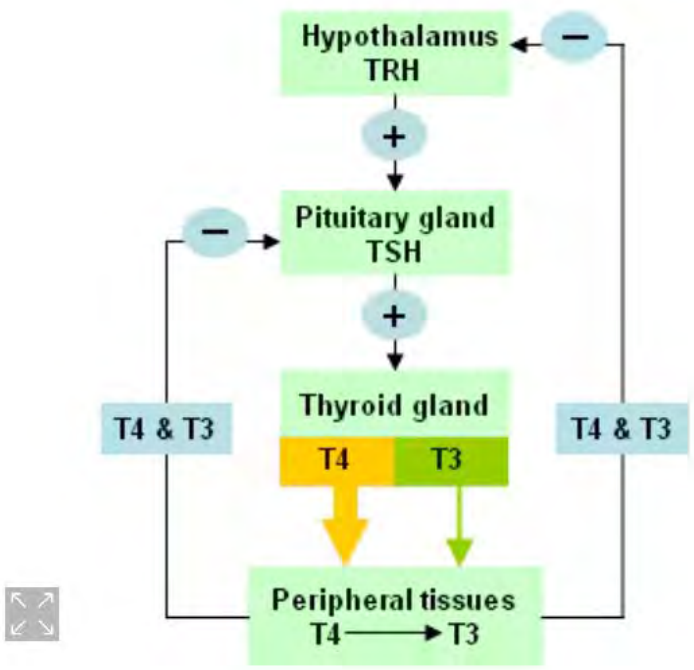

Figure 1. A complex feedback system involving the hypothalamus and pituitary gland regulates the circulating thyroid hormones.

1.2 Aim

The aim of the review is to give an overview of hypothyroidism disease, epidemiology of the disease, causes of hypothyroidism, highlighting the key considerations in diagnosis and current treatment of hypothyroidism, along with providing future directions for research and improving management of the disease.

Chapter 2

Methodology

Chapter 2

2.1 Methodology

This review article includes original published studies, systematic reviews, meta-analyses, and international health documentation, all contributing to an overall understanding of hypothyroidism, prevalence of the disease, causes and current management of the disease. Standardized protocol and flexible method have been followed to get access to relevant scholarly articles from reputable scientific databases, including PubMed, ScienceDirect, Google Scholar, MedLine, Embase, Cochrane Database and the World Health Organization (WHO) publications. The search included specific terms ("hypothyroidism," "epidemiology of hypothyroidism," "risk factors," "causes of hypothyroidism," "treatment", "modalities," "management," "advanced treatment strategies of hypothyroidism"), relying on applicable articles as well. This article includes publications from the beginning of hypothyroidism research to the most current findings available in 2025, to provide historical depth and current relevance. Parameters for source selection criteria were based on scientific enforcement, citation frequency, relevance to the study's subtopics, and publication in peer-reviewed journals to ensure accuracy and utility. Publications that specifically deal with the classification of hypothyroidism (Example: primary hypothyroidism, overt and subclinical hypothyroidism, secondary hypothyroidism), signs and symptoms of the diseases, and standard treatment of hypothyroidism were prioritized. After a thorough search and analysis of relevant papers from reliable sources, relevant and updated information was gathered, and "Hypothyroidism: An Overview of the Disease and Current Treatment Approach" was compiled and prepared. Finally, accurate citation has been used in order to give full attribution to the original author of the work, and all the articles have been cited to provide additional details in the Reference list.

Chapter 3

Epidemiology and Causes of Hypothyroidism

Chapter 3

Epidemiology and Causes of Hypothyroidism

3.1 Prevalence and Risk Factors

In the vast majority of cases of primary hypothyroidism in the world, the disease is caused by Hashimoto thyroiditis, an autoimmune disease, but in the past, the absolute most common cause of the disease was severe iodine deficiency .The thyroiditis in Hashimoto's is a gradual, progressive thyroid failure, which is due to the infiltration of the lymphocytes that causes immune-mediated destruction of the thyroid gland (8).A high level of antibodies to thyroid peroxidase (TPO-Ab) is characteristic of the thyroiditis of the hashimoto’s and it occurs in about 11% of the general population. TPO-Ab also happens to be regarded as a considerable danger factor for blatant hypothyroidism potential to induce gradual transformation of subclinical hypothyroidism to overt disease (9) . The rate of occurrence of the Hashimoto thyroiditis has been steadily rising due to the interplay of genetic sensitivity and other environmental signals like excess of the iodine element, pregnancy, sex-related hormones and steroids, deficiency and exposure to radiations etc (10), chemokines have also been proven to play a central role in developing the Hashimoto thyroiditis with the recent discoveries that both genetic and the environment factor to influence the increase in DNA methylation of several genes involved in immune system regulation which increases the risk of hypothyroidism further (11-13).

Overt hypothyroidism reaches about 1-2 per cent prevalence in countries in which the requirements of iodine are fulfilled to adequate levels (14,15). It occurs in both overt and subclinical forms of hypothyroidism (primary forms of hypothyroidism) (14), with major prevalence in elderly individuals, where they constitute almost 7% in people aged 85-89 years (16).

Hypothyroidism is more prevalent among patients with Type 1 diabetes, autoimmune gastric atrophy, coeliac disease, Addison's disease, rheumatoid arthritis and other autoimmune endocrinopathies than in the general population (17). Hypothyroidism is also more likely to develop among individuals with Down syndrome or Turner's syndrome (18). Conversely, moderate alcohol and tobacco smoking are linked to a low risk of hypothyroidism (19,20). Depending on the criteria, the general population's prevalence of hypothyroidism (subclinical and overt) ranges from 0.3% to 3.7% in the USA and from 0.2% to 5.3% in Europe (20-25). According to a meta-analysis of research (5) conducted in nine European nations, the prevalence of undiagnosed hypothyroidism, which includes both overt and mild instances, is approximately 5% (26). Hypothyroidism is common in India, affecting around 1 in 10 adults, with prevalence rates between 9% to 11%, significantly higher in females and older individuals, and varying geographically, showing higher rates inland than coastal areas, though it's a growing concern despite iodized salt efforts. A major 2013 study conducted in eight major cities of India (Bangalore, Chennai, Delhi, Goa, Mumbai, Hyderabad, Ahmedabad and Kolkata) demonstrated a 10.95% prevalence on the whole, with females at 15.86% and older adults disproportionately affected. Autoimmune mechanisms were observed to play an etiological role in a significant proportion of patients reported in this study (27). Hypothyroidism is the most common thyroid disorder in Bangladesh; precise nationwide prevalence data for 2026 remain limited. Current research indicates that approximately 20% of the general population in Bangladesh suffers from some form of thyroid disorder (28).

General Population Prevalence of Hypothyroidism in Bangladesh:

Small-scale and community-based studies provide varying estimates for hypothyroidism:

- **Dhaka District:** A study among adults found a prevalence of **7.0%** in Dhaka district according to a 2010 report, with a combined prevalence of 3.8% overt hypothyroidism and 3.46 % of subclinical hypothyroidism (29). However, no recent data is available, suggesting the need for an epidemiological study on the prevalence of hypothyroidism in Dhaka as well as in other cities of Bangladesh.
- **Khulna District:** A community-based study of 925 individuals identified a **4.97%** prevalence of overt hypothyroidism and **6.59%** for subclinical hypothyroidism.
- **Southeastern Region:** Research published in 2025 indicates hypothyroidism remains a major concern, with some clinical surveys showing rates as high as **33%** among specific patient groups (30).

3.2 Causes of Hypothyroidism

Hypothyroidism comes in four types: primary (resulting from insufficient production by the thyroid gland, resulting in the lack of thyroid hormone), secondary (resulting from a deficiency of TSH by the pituitary gland), tertiary (resulting from a deficiency of thyrotropin-releasing hormone by the hypothalamus), and peripheral (caused by extra-thyroidal or genetic mutations of causing thyroid-hormone resistance) (1). Less than 1% of the cases worldwide are secondary and tertiary hypothyroidism, also known as the central hypothyroidism and extrathyroidal hypothyroidism.

3.2.1 Primary hypothyroidism

Chronic autoimmune thyroiditis is the most prevalent cause of hypothyroidism in adequately iodinated areas, and can be described as Hashimoto's disease. Most patients of autoimmune

thyroiditis have high levels of anti-thyroid antibodies, mainly consisting of thyroid peroxidase antibodies and anti-thyroglobulin antibodies. The level of thyroid peroxidase antibody is also increased in approximately 11% of the general population (31). Thyroid peroxidase antibody in patients with subclinical hypothyroidism can be used to establish whether a patient will have the full-fledged disease or not (32,33). Although it is not clear what causes autoimmune thyroiditis, environmental and genetic factors play a great role in this condition (34,35). There is also a low level of thyroid peroxidase antibody in smokers compared with non-smokers, and autoimmune thyroiditis is increasing following cessation of smoking (36,37). Moderate consumption of alcohol intake, lack of vitamin D and selenium, among other environmental influences, are also linked to autoimmune thyroiditis (38).

The thyroid hormone contains iodine. Lack of iodine may result in hypothyroidism, thyroid nodules and goitre. The most severe consequence of iodine deficiency is cretinism (retarded mental and physical growth in the womb and childhood). One of the cheapest and non-toxic public health interventions in the prevention of cognitive and physical impairment is Iodine fortification (39,40). The efforts remain unsuccessful in eradicating large regions of Africa and Asia, and individual sub-populations within certain countries with a high incidence of income, most obtruded being expectant women in certain areas of Italy, the United States, and the United Kingdom, continue to experience inadequate quantities of iodine despite the activities (41-43). The prevalence of autoimmune hypothyroidism is higher in populations that alternate between mildly deficient and optimally or excessively high levels of iodine, and the prevalence rate of hypothyroidism is lower in populations that alternate between severely deficient amounts and mildly deficient amounts (44,45).

The prescribed medication amiodarone contains Iodine which leads to thyroid hormone inhibition through Iodine accumulation, which terminates thyroid hormone creation (the Wolff-Chaikoff effect). The treatment of amiodarone results in hypothyroidism for approximately 14% of patients (46). Lithium produces two different effects, which include its impact on thyroid hormone production and release (47), leading to the development of hypothyroidism. The population-based cohort study identified 6% of leishmaniasis patients who required open lithium therapy treatment over the 18-month study period (48). The tyrosine kinase inhibitors are used in targeted therapy of various malignancies. The Food and Drug Administration's adverse event reporting system (49) examined clinical reports, which showed that patients who used sunitinib had a higher chance of developing hypothyroidism compared to patients who used sorafenib. Primary hypothyroidism can occur through the use of thalidomide, interferon-alfa and certain monoclonal antibodies, antiepileptic drugs and second-line medications for multidrug-resistant tuberculosis (Box 1).

After the administration of radioiodine, hemithyroidectomy, neck radiation therapy, or cancer surgery, hypothyroidism may also be common (50-54). With causes of Graves' disease, even low doses of radioiodine can cause hypothyroidism in nearly 80% of all individuals who undergo the treatment. Reported statistics indicate that some 8 percent patients undergoing treatment of solitary toxic nodules and 55 percent patients undergoing treatment of toxic nodular goitre develop hypothyroidism (50). A meta-analysis of 32 studies (55) found that 20% of patients who underwent a hemithyroidectomy experienced hypothyroidism (53). Other causes of primary hypothyroidism are infiltrative illness and temporary thyroiditis (Box 1).

3.2.2 Central hypothyroidism

CH is unusual, as well as it is common, in both genders. The latter are usually concomitant to the former, yet its pituitary troubles (not the hypothalamic ones) (56). The features of the central hypothyroidism are described as low or low to normal TSH and correspondingly low amount of free thyroxine (57). In some cases, there occurs a slight rise in TSH levels, which is likely to be a result of a decline in bioactivity. Pituitary adenoma causes more than half of all the cases of central hypothyroidism (56). Incentives to central hypothyroidism are Sheehan syndrome, pituitary apoplexy, pituitary or hypothalamus disease due to head trauma, surgery, radiation therapy, genetic and infiltrative disease. Several known medications can potentially influence the hypothalamic pituitary- thyroid axis (Box 1) (58,59).

The pathogenesis of CH is heterogeneous and can be expounded because of Iatrogenic response, trauma, autoimmune disorders, or congenital defects. Additionally, there can be several pituitary hormone deficiencies (MPHD) or isolated CH. CH is rich in clinical manifestations and is not just a combination of the signs of hypothyroidism because of its different causes. The clinical picture of patients is determined by MPHD aetiology, a symptom of endocrine deficiencies in most endocrine axes, a history of craniospinal irradiation, or pituitary adenoma. IGSF1, TBLIX, and IRS4 mutations with a direct causative role in CH were recently suggested as mutations and were reported in the already known reported mutations in TRH-R and TSHB (60-64). The mutation causes CH, Macro orchidism and TBLIX mutation mutation that impacts hearing ability caused by the mutation of IGSF1 by a mutable gene, which is IGSF1. This may be utilised as a guideline in such discriminative characteristics to CH cause(65).

Normal or low TSH of CH patients fails to relate to the status of TH due to the central deregulation of the thyroid gland in CH. FT4 thus becomes a requirement in the diagnosis and treatment of CH.

In the majority of the newborn screening programmes dealing with congenital hypothyroidism, TSH is the first test. This method of approach can be considered a challenge in detection since CH is usually characterised by low/ normal TSH. Even the milder forms of CH are harder to detect since some of them can appreciate an F14 of even up to the lower part of the limits. The only correct way of diagnosing the case of congenital CH is the initial T4 measurements in the first cassettes of newborn screening. A newborn screening conducted using TSH is far more prevalent, and it will not diagnose newborn children with CH. Levothyroxine is the most common CH treatment, and it should be considered whether a person uses the evidence-based treatment or not. The treatment with levothyroxine in congenital cases of CH should be started as early as possible so that children may be able to develop neurodevelopment optimally. On the other hand, however, LEVOTHYROXINE treatment is to be doubted and may not be obligatory in milder instances of (congenital) CH or where, e.g. in older patients with only slightly depressed FT level on account of a TBLIX mutation, only slightly depressed pates are concerned. LEVOTHYROXINE should be taken regularly at a low dose at the beginning to minimize the proliferation of chances of being over-treated. Most information about the state of TH relies on examination of FT; therefore, TSH cannot prove to be a system of usefulness in examining the success of Levothyroxine therapy. EVOTHYROXINE ingestion time depends on the concentrations of FT. To ascertain the right outcomes, the European Thyroid Association (ETA) recommendation guideline on diagnosis and treatment of CH is categorical in that a state of blood sample must be taken before or at least four hours after the intake of L.-T4 (66). The FT4 concentration tends to be higher in patients on levothyroxine. In an event that the symptoms of hypothyroidism are present and the values obtained on FT4 fall on the lower half of the reference space, then hypothyroidism is not adequately treated (66).

3.2.3 Peripheral Hypothyroidism

Peripheral hypothyroidism is a far less prevalent form of hypothyroidism, and to determine it, a high degree of clinical suspicion is needed since it does not demonstrate any typical course of abnormal portrayal of hypothyroidism in the plasma thyroid hormone. Thyroid hormone receptor 8 resistance, characterised by accumulating severe hypothyroidism of bones, gastrointestinal, and nervous systems, including retarded growth, anaemia, constipation, intellectual retardation and slow cognition, skeletal dysgenesis, and normal or near normal serum thyroid activity (67,68,1). Type 3 deiodinase is an incredibly rare cause of consumptive hypothyroidism due to ectopic over-expression, and has been shown to cause patients with gastrointestinal stromal tumors and other vascular fibrotic tumors (69).

Table 1. Causes of Hypothyroidism

Primary Hypothyroidism

- Chronic autoimmune thyroiditis (also known as Hashimoto's thyroiditis)
- Iodine -severe iodine deficiency, mild and severe iodine excess
- Drugs such as amiodarone, lithium, tyrosine kinase inhibitors, interferon-alfa, thalidomide, monoclonal antibodies (e".g."Ipilimumab and nivolumab), antiepileptic drugs (e.g., valproate), drugs for second-line treatment of multidrug-resistant tuberculosis
- Iatrogenic—radioiodine treatment (e.g., for Graves' disease or toxic nodular disease), hemithyroidectomy, radiotherapy or surgery in the neck or head region
- Transient thyroiditis—viral (De Quervain's syndrome), post-partum, silent thyroiditis, destructive thyroiditis
- Thyroid gland infiltration*—infectious (e.g., mycoplasma), malignant (eg, thyroid malignancy, lymphoma, metastasis of malignancy elsewhere), autoimmune (e.g., sarcoidosis), inflammatory (e.g., Riedels's thyroiditis)
- Genetic*—autoimmunity-related genes (eg, HLA class I region, PTPN22, SH2B3, and VAV3), general and thyroid-specific genes (eg, FOXE1, ATXN2, and PDE8B)

Central Hypothyroidism

- Pituitary tumours (secreting or non-secreting)
- Pituitary dysfunction (eg, Sheehan's syndrome)
- Hypothalamic dysfunction (eg, post-traumatic)
- Resistance to thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone
- Drugs (eg, dopamine, somatostatins, glucocorticosteroids, and retinoid X receptor selective ligands)
- Increased TSH concentration due to leptin stimulation

Peripheral (extra- thyroidal) hypothyroidism

- Consumptive hypothyroidism
- Tissue-specific hypothyroidism due to decreased sensitivity to thyroid hormone (eg, mutations in MCT8 [also known as SLC16A2], SECISBP2, THRA, THRB)

*Rare causes of primary hypothyroidism. †Evidence mainly from animal models.

Chapter 4

Signs and Symptoms of Hypothyroidism

Chapter 4

Signs and Symptoms of Hypothyroidism

4.1 Interpretation of symptoms in diagnosing and treating overt hypothyroidism

The association between low FT level and high TSH level is referred to as overt hypothyroidism. Clinical manifestation is very different in every individual based on age, sex, and duration between onset and diagnosis (70). More importantly, such symptoms are not specific to the diagnosis of hypothyroidism. Fatigue with 81%, dry skin with 63%, and dyspnea with 51% were the most common problems in the hypothyroid patients in a population-based case-control study. Only 13 out of the 34 symptoms investigated in hypothyroidism were statistically overrepresented. None of the 34 symptoms that were related to hypothyroidism was helpful in the diagnosis of hypothyroidism (71). These outcomes all render the association of symptoms with the causes challenging.

However, it is not a secret that untreated overt hypothyroidism may affect most of the organs, with the cardiovascular system being among them, with higher vascular resistance, reduced cardiac output and left ventricular performance, and alterations in many other cardiovascular contractility measurements (72). Proper research study indicates that loss of myocardial diffusion is a common occurrence in patients with hypothyroidism (73). The assortment of nonspecific symptoms of hypothyroidism and the potential negative impact of overt hypothyroidism on the functioning of vital organs, combined with the availability of a reasonably priced and reliable diagnostic test. TSH test has caused the policy of even a slight suspicion, leading to a blood test, and levothyroxine (LEVOTHYROSINE) is now amongst the most frequently recommended medications, which might have been due to this, even when thyroid function tests are normal (74). Whether there are

symptoms or not, all patients should be treated with a combination of high TSH and low FT4 concentration according to the guidelines. Effective discontinuation has been reported, although discontinuation is generally considered a lifelong replacement therapy. A meta-analysis and systematic analysis of the clinical outcomes of 1103 patients after the discontinuation of thyroid hormone replacement therapy was done by Burgos et al. (75). However, of the patients that went through discontinuation of thyroid hormone replacement therapy, about one-third of patients remained euthyroid after the study. As opposed to those that had earlier been diagnosed with subclinical hypothyroidism (35.6%), those that had been previously diagnosed with overt hypothyroidism were less likely to be left euthyroid (11.8%). Thus, the systematic management plan might be needed to assist clinicians reconsider their patient and her necessity to receive levothyroxine to avoid overtreatment.

4.2 Interpretation of symptoms in diagnosing and treating subclinical hypothyroidism

Asymptomatic patients with subclinical hypothyroidism generally have none of the symptoms, but those who do have the symptomatology tend to report it more frequently compared to overt hypothyroidism patients; and it is certainly less alarming than patients who have overt hypothyroidism (76,77,78). Although subclinical hypothyroidism has been found to prevail in some studies in comparison to higher rates of depressive symptoms, additional symptoms also exist, such as reduced quality of life, cognition, and memory (79-81) and fatigue, muscle weakness, weight gain, cold intolerance, and constipation (82). It should be brought into consideration that the symptoms that were stated in certain of these studies just examined the patients with a small number of TSH levels, or the sample size thereof was not very large. A mild rise in TSH can be seen in up to 46% of patients with subclinical hypothyroidism and can be retested and then

eliminated through a repeat examination after 2 to 3 months (83). The circadian TSH rhythm, obesity or unique mutations to the TSH receptor may slightly elevate TSH, not necessarily necessitating levothyroxine medication .

BA and ETA present knowledge indicates that, should TSH be greater than/equals 10 mIU/L, or should TSH be greater than/equals 4-4.5 mIU/L, in combination with signs and/or comorbidities, then Levothyroxine must be prescribed to treat subclinical hypothyroidism, considering the age factor (84,85). A TSH level exceeding 10 mlU/L was found to be correlated with increased mortality and poor cardiovascular conditions (86). A newer guideline, however, suggested that subclinical hypothyroidism should not be treated using thyroid hormones (87). In one of their debate articles, Peeters and Brito (88) observed that it remains a challenge to treat patients who have mild symptoms of subclinical hypothyroidism. The patient could perceive it as insensitive when failing to rectify the laboratory abnormality, but the same could be defined when a laboratory test is done with the aim of not benefiting the patient and ameliorating his/her symptoms. The authors recommended the same to improve compliance with the existing standards set by the scientific societies to avoid further rise in the number of unjustified prescriptions of Levothyroxine. They also highlighted how clinicians need to become more skillful in treating symptomatic conditions that are not usually associated with clear pathological correlates, especially in cases of simple TSH increases (88). In the case of the lack of understanding of the mechanism and meaning of mild symptoms in individuals with subclinical hypothyroidism, it might be appropriate to elect to do a 6-month treatment trial along with Levothyroxine. Symptoms must be reassessed periodically and, in case of no improvement, the medication must be terminated (85).

Alongside persistent symptoms of thyroid disease on continued medication with Levothyroxine, several other patients have similar symptoms when changing to a different brand of Levothyroxine. One recent study was a study of the impact of the unavailability of the Levothyroxine brand Thyrax in the Netherlands and the consequent replacement of this specific brand with another dose-equivalent replacement. To begin with, according to the Netherlands Pharmacovigilance Centre Lareb, the number of symptoms reported has gone up. With the PHARMO Database Network and the Nivel Primary Care Database, it was established that TSH was out of range in +/-20% >6 weeks following the euthyroid patients who remained on the Levothyroxine drug Thyrax at the same dosage. It is worth noting that a much larger proportion of patients (24-63%) had biochemically indicating signs of overdose following a dose-equivalent replacement between Levothyrax and Thyrax and alternate brands of Levothyroxine. Therefore, a dose adjustment can be necessary among several persons when they change to the dose-equivalent Levothyroxine brand (89). As per the existing recommendations, changing Levothyroxine brands is not encouraged before the absolute necessity, and in case it is necessary, TSH levels must be monitored 6 weeks later (90,91). The fact that the outcomes of the recent study by Brito et al. (92) were different is worthy of mentioning since these researchers observed no alteration in serum TSH levels following the brand change of Levothyroxine. Thus, the effects of the switch of the brand of Levothyroxine on the TSH level are likely to be conditional on the brand change. As symptoms of thyroid disease have not been taken into account in either of the Brito et al. or Flinterman et al. trials, it is still unknown whether an increase in symptoms and a TSH alteration after transitioning to the brand are causally related. Therefore, further research has to be conducted to come up with conclusive results.

Chapter 5

Treatment of Hypothyroidism

Chapter 5

Treatment of Hypothyroidism

5.1 Standard treatment

Levothyroxine monotherapy in solid form and emptied stomach is the standard on which the care is followed. The treatment is a prerequisite to the situation where there are clinical signs of hypothyroidism and the biochemical confirmation of the overt hypothyroidism. Another option is not to avoid prescribing generic formulations, but re-prescription of the levothyroxine product is contraindicated in already stable patients (93). The ideal dose of overt hypothyroidism is 1.5-1.8 mg /kg. of body weight (93-95). The usual dose of Follicle-stimulating hormone in patients with coronary artery disease begins at 12.5-25.0mg/day, although it needs to be slowly advanced depending on the symptoms and TSH (93). The older adult typically uses the regimen, especially in cases where he has several co-morbidities (93,94). Young patients with no comorbidities can usually be started on the entire dosage at the start and followed up appropriately to prevent the possibility of over-treatment. After the first stage of therapy is over, TSH levels need to be measured after 4-12 weeks, after every six months and finally after one year when the levels have stabilized. There must be some form of change based on the lab result, as in some patients (e.g., low body weight or old age), a small dose will cause a huge impact on serum TSH levels. Since there are normal tri-iodothyronine and TSH concentrations, it is not clear whether low tri-iodothyronine concentration has clinical significance in some patients. Tri-iodothyronine is not regularly quantified to determine the efficacy of treatment (96). The physiological modifications involved during pregnancy demand higher doses of levothyroxine to ensure euthyroidism (97). Women who are of childbearing age and who are hypothyroid and on levothyroxine must also be

advised to triple their dosage during pregnancy and also consult their physician regarding additional advice (98).

5.2 Treatment Targets

The treatment goals include normative values of TSH levels and remission of physical and mental symptoms, and both under- and overtreatment should be prevented (93). But even with levothyroxine treatment, only between 35-60% of patients may achieve the desired level of TSH and may be over- or under-treated (99,100). A retrospective cohort study of UK patients under levothyroxine therapy has demonstrated that nearly 6 per cent of all such patients have TSH under 01 mIU/L following 5 years of therapy, and that over 10 per cent of all such patients have TSH above 100 mIU/L (99). Adverse health outcomes, including atrial fibrillation and osteoporosis, may be a consequence of over-treatment, which is a consequence of iatrogenic subclinical or overt hyperthyroidism. It should not be applied particularly in old people and post-menopausal women. Continuous insufficient thyroid hormone could lead to high cardiovascular disease and inexhaustible signs and symptoms, and underuse. The objectives of central hypothyroidism treatment differ from those of primary hypothyroidism since clinicians are not capable of banking on the reflex TSH approach.

5.3 Failure to reach treatment objectives

Underdose, combination with supplements or drugs, comorbidity, and non-adherence to therapy are the factors which fail to attain therapy. The level of TSH secretion among the elderly requires reduced doses of levothyroxine, but higher doses are required after a thyroidectomy.

The absorption of levothyroxine occurs in the small intestine, and it is recommended to take the drug in the mornings, 30-60 minutes before breakfast. Pre-bedtime intake 2-3 hours since the last meal) can enhance absorption, and it can be regarded as a way of raising compliance (101). Levothyroxine absorption, bioavailability, or metabolism may be affected by other drugs. Gastrointestinal diseases that affect the absorption of levothyroxine are helicobacter pylori gastritis, coeliac disease and autoimmune atrophic gastritis. Some studies pointed out that liquid and soft gel preparations of levothyroxine are independent of gastric pH being absorbed, and thus there would be a way out for patients who cannot swallow levothyroxine 30-60 minutes before a meal (102-103). This was performed in a randomized crossover but in two blind trials (104) consisting of 77 untreated hypothyroid patients, where the outcomes did not show a significant difference in the use of liquid thyroxine at breakfast, then 30 minutes before breakfast, as based on the thyroid functional tests. Nevertheless, no studies have compared the liquid gel preparations of levothyroxine and the solid preparations in clinical outcomes.

The problem of non-adherence, which is a frequent cause of failures in treatment, must be mentioned in any case of continuing high levels of TSH in the absence of other factors. The fact that levothyroxine pills are taken immediately before the sample may lead to an increase in the TSH and normal or high-normal levels of free thyroxine. A detected thyroxine absorption test needs to be considered so as to differentiate the non-compliance and other reasons for under-treatment (105).

5.4 TSH Level normalization chronic Symptoms

Recurrent symptoms, including depression and compromised mental wellbeing are recorded in approximately 5-10% of biochemically-managed levothyroxine-treated hypothyroidism (106).

Concurrent diseases or perimenopausal status can be attributed to these complaints, and they should be ruled out. There has also been a recommendation that long-term symptoms are caused by autoimmunity (107). The hypothalamic-pituitary thyroid axis regulates thyroid levels in the blood, and a set-point consists of comparatively low intraindividual and high interindividual standard deviation (108). The diffusion of TSH to similar levels of circulating thyroid hormones will also not be the same in various individuals.

Alternatively, the limitations of the levothyroxine monotherapeutic regimen might be the cause of the continuing complaints in certain patients. Levothyroxine usually will keep adequate amounts of thyroxine circulating in the system, which then may be changed to triiodothyronine by deiodinating it using deiodinase 1 and deiodinase 2. In the case of a euthyroid patient, the direct release of the thyroidal secretion results in the formation of approximately 20% of the circulating triiodothyronine. Instead, in levothyroxine monotherapy, the peripheral thyroxine to triiodothyronine conversion provides all the triiodothyronine to the patient. As a result, the ratio of free thyroxine to triiodothyronine in patients under levothyroxine monotherapy is higher compared with patients of the euthyroid group. Certain patients with normalized TSH are observed to have lower than the reference range levels of serum tri-iodothyronine but high levels of free thyroxine serum (109-111). There is no knowledge as to whether this has clinical implications. Levothyroxine monotherapy cannot substitute the physiological doses of tri-iodothyronine or the biological effects of thyroid hormones within all the tissues in the hypothyroid rat (112,113). A normal level of TSH represents euthyroidism of the pituitary but does not necessarily represent euthyroidism of all tissues. The differences in tissue deiodinase 2 inactivation in the tissues may also play a contributing role, resulting in normalization of the levels of triiodothyronine in the

hypothalamus before the total normalization of tri-iodothyronine levels in the rest of the body tissue (112).

5.5 Combination therapy Levothyroxine and Liothyronine

Over the past 15 years, numerous studies have been conducted with a view to providing research on combined levothyroxine-liothyronine therapy (114). Whereas it was found that combination therapy positively influences (115-118), including patient preference, better metabolic profile, the results of patients treated with combination therapy typically do not improve as compared to those treated with levothyroxine monotherapy (119). This may be owing to the insufficiency of doses or administration rates of levothyroxine and liothyronine (119). In addition, the trials were also not life-long and were short (less than 4 months) and employed questionnaires to report on the symptoms of the patients, which may not have been specific or sensitive enough.

Rather, perhaps trials have never been able to establish the related subsets to which combination therapy would be profitable. In most of the studies, there was no specific focus on the patients who showed an adverse response to levothyroxine or special low levels of serum tri-iodothyronine. No particular attention has been paid to genetically different individuals as far as thyroid hormone metabolism is concerned (120). The potential target population group is individuals with extensive genetic variations in the deiodinase 2 (DIO2) gene that transforms thyroxine into tri-iodothyronine locally in various tissues, including those in the brain (121). DiO2 polymorphism of Thr92Ala provides a variant of deiodinase 2 with a more protracted half-life compared to the wild type enzyme, and fuzzy localization in the Golgi apparatus. These results demonstrate that the cerebral cortex expression pattern was perturbed in the patients in the same way as that obtained with the neurodegenerative diseases, and with no indication that the thyroid hormone signaling mechanism

is perturbed (122). A study of 136 patients receiving levothyroxine replacement therapy identified that those with a Thr92Ala polymorphism in DIO2 were more distant in their psychological well-being than those without the polymorphism, who responded better to combination therapy (123). Nonetheless, the outcome of the multiple testing was not noteworthy as the procedure was duly rectified. According to the results of a population-based cohort study, there was no influence of the Thr92Ala polymorphism on any of the cognitive functions or quality of life measures (124). In order to conclude, the prospective randomized controlled trials must be developed accordingly to enable the physicians to make evidence-based decisions.

The European Thyroid Association offers a levothyroxine and liothyronine dosage calculation method and introduces the concept that nonadherent, biochemically normal patients displaying persistent symptoms despite levothyroxine intake can qualify to participate in an experimental study of levothyroxine and liothyronine combination at the doses (125).

It has to be, however, initiated by competent endocrinologists or internal medicine physicians. It should be monitored at all times and canceled in case it is not getting better. However, due to the uncertainty of long-term risk and benefit, the American Thyroid Association does not encourage the use of such studies regularly, other than in formal research and experiments (93). It should be evaluated by long-term randomized controlled trials to establish ratios of risk to benefit, which are required by the American Thyroid Association(93) and the European Thyroid Association (125). These trials would necessitate research on optimal levels of thyroid to be monitored during combination therapy and whether the levels of tri-iodothyronine would be a significant parameter. Phlebotomy time is also a significant element in case the dose of the liothyronine is exceeded once daily. It has little support to lend, with no alternative therapy for hypothyroidism. Thyroid Liothyronine monotherapy should not be used as it is risky. Substitution of Hypothyroidism with

compounded thyroid hormones, nutritional supplements and any non-prescription drug is not recommended.

Chapter 6

Conclusion and Future Directions

Chapter 6

Conclusion and Future Directions

Despite all that is known about the identification, clinical implications, diagnosis and treatment of hypothyroidism, there are grey areas, particularly on the diagnosis and treatment issues. Several risk factors are known to cause increased or decreased TSH levels, levels of free thyroxine and thyroid diseases, although a small proportion of the fluctuation is attributed to it (126). Therefore, risk factor identification is required. Growing evidence is emerging to indicate that endocrine disruptors may be causal agents of endocrine diseases. The causes of the exposure to chemicals affecting the thyroid could also be different, i.e., the environmental sources (e.g., flame retardants) and the dietary (e.g., the packaging of food) ones (127).

Hypothyroidism is associated with cardiovascular disease, and the correlation has been known and confirmed in numerous studies. Nevertheless, the mechanisms of such a relationship are unfamiliar. The correlation between hypothyroidism and other cardiovascular diseases appears to be fragmented from the typical cardiovascular risk factors (128,129,130). Future studies that dwell on emerging cardiovascular risk factors or other mechanisms can clarify some of the pathways, and this would be of utmost importance in establishing the direction to take when it comes to its management, as well as its monitoring strategies among patients with asymptomatic hypothyroidism. Diagnosis of hypothyroidism has now been founded on statistically calculated reference values of TSH and free thyroxine, which cannot give information on the danger of the disease in patients. However, some other grading method has been proposed based on thyroid-function test since the ranges of cutoffs to represent mild and overt hypothyroidism are arbitrary. According to the US Preventive Services Task Force, one of the key issues that thwarted the process involved in making the decision was the arbitrariness of these cutoffs, which led to the

screening of thyroid dysfunction among the patients who had no symptoms (131). The thresholds further influence the management of the disease among the asymptomatic patients of hypothyroidism. The adverse health outcomes that follow in the case of long-term thyroid dysfunction need to be researched. Moreover, it is essential to determine what TSH and free thyroxine concentrations are linked with an increased morbid risk. Such knowledge can be obtained on the basis of collaborative forms of observational cohort studies whose period of observation is long enough.

Levothyroxine monotherapy is the standard practice in the treatment of hypothyroidism. There is, however, a lot of ambiguity in the questions about the biochemically stable patients who are not pleased with the outcome of the therapies. The possibility of a solution, as well as alternative regimens for a specific group of individuals with unexplained symptoms, should be investigated in future research. The gap in the research needed, in urgent form, is the determination of the aetiology of persistent symptoms in biochemically stable patients, and whether this may be improved by an optimal dose (i.e. depending on the levels of serum triiodothyronine of the individual patient, or the serum TSH set-point of the particular patient). Pragmatically, such information can be acquired through exploration of the efficacy of new formulations (e.g., slow-release liothyronine) or deeper, more frequent dosage of levothyroxine-liothyronine combination therapy (e.g., tri-daily liothyronine) into symptom mitigation and also into the discovery of patient subgroups that may respond naturally to alternative types of treatment than to levothyroxine monotherapy (e.g. by the identification of new additional genetic polymorphism that might explain the set-point of the thyroid).

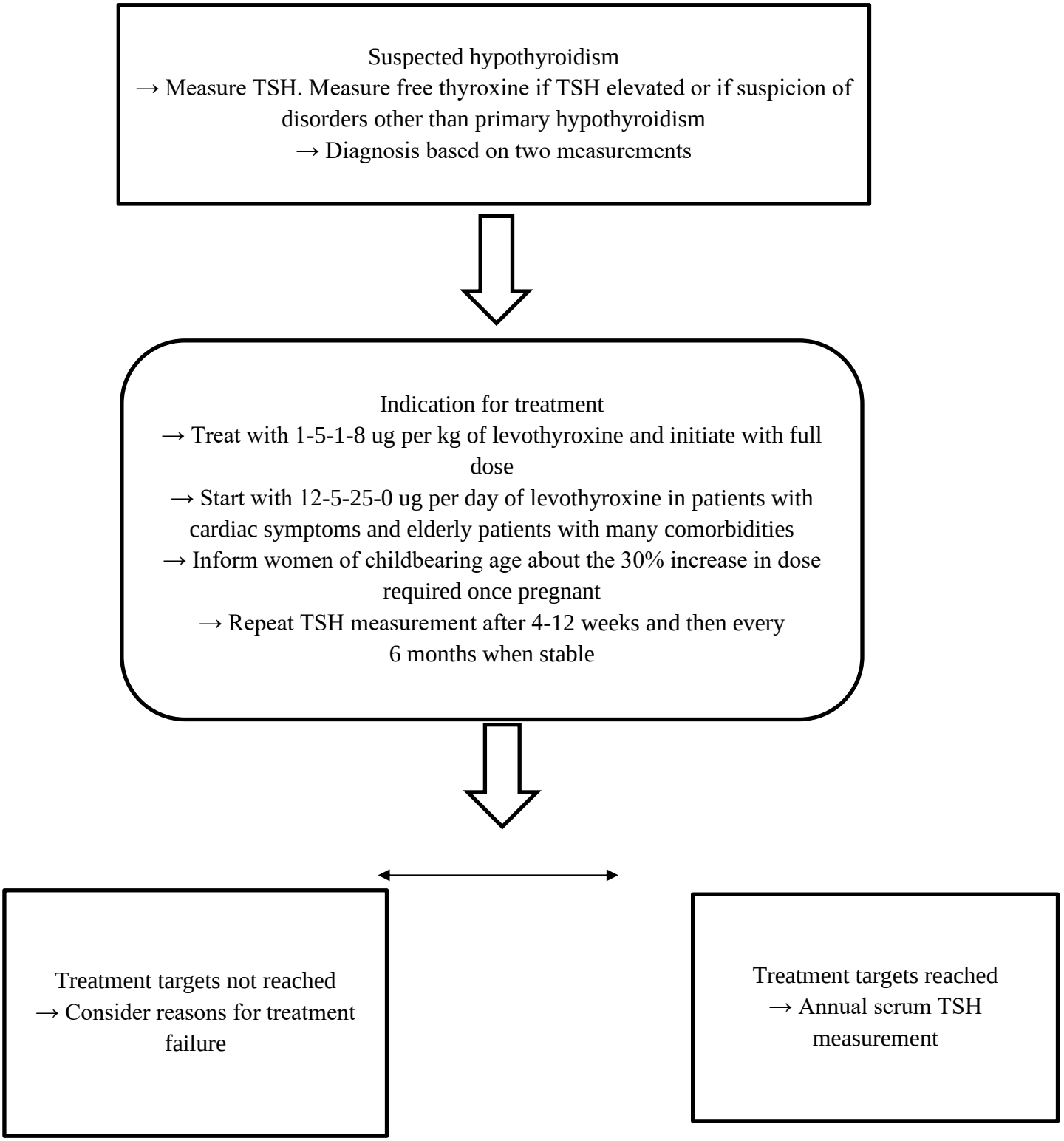

Figure 2: Diagnosis and treatment of Primary Hypothyroidism

Table 2. Clinical Presentation and Implications of Hypothyroidism

	Clinical Presentation	**Signs and implications**
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body-mass index, low metabolic rate, myxedema*, hypothermia*
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidaemia, bradycardia, hypertension, endothelial dysfunction or increased intima-media thickness*, diastolic dysfunction*, pericardial effusion*,hyperhomocysteinemia*, electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurological and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression*, dementia*, ataxia*, Carpal tunnel syndrome and other nerve entrapment syndromes*, myxedema coma*

Gastrointestinal	Constipation	Reduced oesophageal motility, non-alcoholic fatty liver disease*, ascites (very rare)
Endocrinological	Infertility and subfertility, menstrual disturbance, galactorrhoea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin, pituitary hyperplasia*
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman's syndrome*, osteoporotic fracture* (most probably caused by overtreatment)
Haemostasis and haematological	Bleeding, fatigue	Mild anaemia, acquired von Willebrand disease*, decreased protein C and S*, increased red cell distribution width*, increased mean platelet volume*
Skin and hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows*, yellow palms of the hand*, alopecia areata*
Electrolytes and kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatraemia

References

1.Taylor, P. N., Albrecht, D., Scholz, A., Gutierrez-Buey, G., Lazarus, J. H., Dayan, C. M., & Okosieme, O. E. (2018). Global epidemiology of hyperthyroidism and hypothyroidism. Nature Reviews Endocrinology, 14, 301–316

2. Canaris, G. J., Steiner, J. F., & Ridgway, E. C. (2002). Do traditional symptoms of hypothyroidism correlate with biochemical disease? Journal of General Internal Medicine, 17, 1–7.

3.Hadlow, N. C., Rothacker, K. M., Wardrop, R., Brown, S. J., Lim, E. M., & Walsh, J. P. (2013). The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. The Journal of Clinical Endocrinology & Metabolism, 98(7), 2936–2943.

4.Taylor, P. N., Medici, M. M., Hubalewska-Dydejczyk, A., & Boelaert, K. (2024). Hypothyroidism. The Lancet, 404(10460), 1347–1364

5.Zamwar, U. M., & Muneshwar, K. N. (2023). Epidemiology, types, causes, clinical presentation, diagnosis, and treatment of hypothyroidism. Cureus, 15(9), e46241

6. Hollowell, J. G., Staehling, N. W., Flanders, W. D., Hannon, W. H., Gunter, E. W., Spencer, C. A., & Braverman, L. E. (2002). Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). The Journal of Clinical Endocrinology & Metabolism, 87(2), 489–499

7.Walsh, J. P., Bremner, A. P., Feddema, P., Leedman, P. J., Brown, S. J., & O'Leary, P. (2010). Thyrotropin and thyroid antibodies as predictors of hypothyroidism: A 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. The Journal of Clinical Endocrinology & Metabolism, 95(3), 1095–1104

8. Ragusa, F., Fallahi, P., Elia, G., Gonnella, D., Paparo, S. R., Giusti, C., Churilov, L. P., Ferrari, S. M., & Antonelli, A. (2019). Hashimoto' s thyroiditis: Epidemiology, pathogenesis, clinic and therapy. Best Practice & Research Clinical Endocrinology & Metabolism, 33(6), 101367

9.Ferrari, S. M., Ragusa, F., Paparo, S. R., Nasini, F., Nardi, M., Sellari-Franceschini, S., Fallahi, P., & Antonelli, A. (2019). Differential modulation of CXCL8 versus CXCL10, by cytokines, PPAR-gamma, or PPAR-alpha agonists, in primary cells from Graves' disease and ophthalmopathy. Autoimmunity Reviews, 18(7), 673–678

10. Ralli, M., De Virgilio, A., Artico, M., Longo, L., de Vincentiis, M., & Greco, A. (2018). New insights into the etiopathogenesis of Hashimoto's Thyroiditis: The role of genetics and epigenetics. Autoimmunity Reviews, 17(10), 1065–1066

11.Lafontaine, N., Wilson, S. G., & Walsh, J. P. (2023). DNA methylation in autoimmune thyroid disease. The Journal of Clinical Endocrinology & Metabolism, 108(3), 604–613

12. Vanderpump, M. P. J., Tunbridge, W. M. G., French, J. M., Appleton, D., Bates, D., Clark, F., Grimley Evans, J., Hasan, D. M., Rodgers, H., Tunbridge, F., & Young, E. T. (1995). The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. Clinical Endocrinology, 43(1), 55–68

13. Zimmermann, M. B., & Andersson, M. (2021). Global endocrinology: Global perspectives in endocrinology: Coverage of iodized salt programs and iodine status in 2020. European Journal of Endocrinology, 185(1), R13–R21

14.Gussekloo, J., van Exel, E., de Craen, A. J. M., Meinders, A. E., Frölich, M., & Westendorp, R. G. J. (2004). Thyroid status, disability and cognitive function, and survival in old age. JAMA, 292(21), 2591–2599.

15.Conrad, N., Misra, S., Verbakel, J. Y., Verbeke, G., Molenberghs, G., Taylor, P. N., Mason, J., Sattar, N., McMurray, J. J. V., McInnes, I. B., Khunti, K., & Cambridge, G. (2023). Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: A population-based cohort study of 22 million individuals in the UK. The Lancet, 401(10391), 1878–1890

16. Bull, M. J., Trotter, T., Santoro, S. L., Christensen, C., Grout, R. W., & The Council on Genetics. (2022). Health supervision for children and adolescents with Down syndrome. Pediatrics, 149(5), e2022057010

17. Unnikrishnan, A. G., Kalra, S., Sahay, R. K., Bantwal, G., John, M., & Tewari, N. (2013). Prevalence of hypothyroidism in adults: An epidemiological study in eight cities of India. Indian Journal of Endocrinology and Metabolism, 17(4), 647–652.

18.Selim, S., Hasan, K., & Hasan, A. B. M. (2023). Thyroid disorders in Bangladesh: An epidemiological perspective. Bangladesh Journal of Endocrinology and Metabolism, 2(2), 63–64.

19.Carlé A, Pedersen IB, Knudsen N, et al. Moderate alcohol consumption may protect against overt autoimmune hypothyroidism: a population-based case-control study. Eur J Endocrinol 2012; 167: 483–90. [PubMed: 22802427]

20. Asvold BO, Bjøro T, Nilsen TI, Vatten LJ. Tobacco smoking and thyroid function: a population-based study. Arch Intern Med 2007; 167: 1428–32. [PubMed: 17620538]

21.Åsvold BO, Vatten LJ, Bjøro T. Changes in the prevalence of hypothyroidism: the HUNT Study in Norway. Eur J Endocrinol 2013; 169:613–20. [PubMed: 23975540]

22. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid 2007; 17: 1211–23. [PubMed: 18177256]

23.Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526–34. [PubMed: 10695693]

24. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014; 99: 923–31. [PubMed: 24423323]

25.Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T (4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489–99. [PubMed: 11836274]

26.Laurberg P, Cerqueira C, Ovesen L, et al. Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metab 2010; 24: 13–27 [PubMed: 20172467

27.Hossen, M. S., Islam, M. M., Das, A., Ripon, M. A. R., Amin, M. T., Basher, M. A., & Rashid, M. M. O. (2025). Thyroid dysfunction prevalence and risk factors in the southeastern part of Bangladesh: A cross-sectional study. Health Science Reports, 8 (1), e70329

28.Moran, C., Agostini, M., McGowan, A., Schoenmakers, E., Fairall, L., Lyons, G., Rajanayagam, O., & Chatterjee, K. (2017). Contrasting phenotypes in resistance to thyroid hormone alpha correlate with divergent properties of thyroid hormone receptor α1 mutant proteins. Thyroid, 27(7), 973–985.

29.https://nib.portal.gov.bd/sites/default/files/files/nib.portal.gov.bd/page/2c82b665_09b4_4cbb_b6a6_266f5c390c4c/2022-03-13-04-59-a755d58ca3a6b858e9573a78d73b59dd.pdf

30.Bochukova, E., Schoenmakers, N., Agostini, M., Schoenmakers, E., Rajanayagam, O., Keogh, J. M., Henning, E., & Chatterjee, K. (2012). A mutation in the thyroid hormone receptor alpha gene. The New England Journal of Medicine, 366(3), 243–249

31.Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T (4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489–99. [PubMed: 11836274]

32.Effraimidis G, Strieder TGA, Tijssen JGP, Wiersinga WM. Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study. Eur J Endocrinol 2011; 164: 107–13. [PubMed: 20956436]

33. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010; 95: 1095–104. [PubMed: 20097710]

34.Medici M, Porcu E, Pistis G, et al. Identification of novel genetic Loci associated with thyroid peroxidase antibodies and clinical thyroid disease. PLoS Genet 2014; 10: e1004123. [PubMed: 24586183]

35.Schultheiss UT, Teumer A, Medici M, et al. A genetic risk score for thyroid peroxidase antibodies associates with clinical thyroid disease in community-based populations. J Clin Endocrinol Metab 2015; 100: e799–807. [PubMed: 25719932]

36.Effraimidis G, Tijssen JG, Wiersinga WM. Discontinuation of smoking increases the risk for developing thyroid peroxidase antibodies and/or thyroglobulin antibodies: a prospective study. J Clin Endocrinol Metab 2009; 94: 1324–28. [PubMed: 19141579]

37.Belin RM, Astor BC, Powe NR, Ladenson PW. Smoke exposure is associated with a lower prevalence of serum thyroid autoantibodies and thyrotropin concentration elevation and a higher prevalence of mild thyrotropin concentration suppression in the third National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2004; 89: 6077–86. [PubMed: 15579761]

38.Wu Q, Rayman MP, Lv H, et al. Low population selenium status is associated with increased prevalence of thyroid disease. J Clin Endocrinol Metab 2015; 100: 4037–47 [PubMed: 26305620]

39.Bougma K, Aboud FE, Harding KB, Marquis GS. Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. Nutrients 2013; 5: 1384–416. [PubMed: 23609774]

40.WHO. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers, 3rd edn. Geneva: World Health Organization, 2007 http://apps.who.int/iris/bitstream/10665/43781/1/9789241595827_eng.pdf (accessed Jan 30, 2017).

41. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 2013; 382: 331–37 [PubMed: 23706508]

42.Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merrill L, Moye J. Iodine status in pregnant women in the National Children's study and in U.S. women (15—44- years), National Health and Nutrition Examination Survey 2005–2010. Thyroid 2013; 23: 927–37. [PubMed: 23488982]

43.Teng X, Shan Z, Chen Y, et al. More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. Eur J Endocrinol 2011; 164: 943–50. [PubMed: 21444648]

44.Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015; 3: 286–95. [PubMed: 25591468]

45.Zhong B, Wang Y, Zhang G, Wang Z. Environmental iodine content, female sex and age are associated with new-onset amiodarone-induced hypothyroidism: a systematic review and meta-

analysis of adverse reactions of amiodarone on the thyroid. Cardiology 2016; 134: 366–71. [PubMed: 27100205]

46.Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. Lancet 2015; 386: 461–68. [PubMed: 26003379]

47. Shulman KI, Sykora K, Gill SS, et al. new thyroxine treatment in older adults beginning lithium therapy: implications for clinical practice. Am J Geriatr Psychiatry 2005; 13: 299–304. [PubMed: 15845755]

48. Shulman KI, Sykora K, Gill SS, et al. new thyroxine treatment in older adults beginning lithium therapy: implications for clinical practice. Am J Geriatr Psychiatry 2005; 13: 299–304. [PubMed: 15845755]

49.Shu M, Zai X, Zhang B, Wang R, Lin Z. Hypothyroidism side effect in patients treated with sunitinib or sorafenib: clinical and structural analyses. PLoS One 2016; 11: e0147048. [PubMed: 26784451

50.Kahraman D, Keller C, Schneider C, et al. Development of hypothyroidism during long-term follow-up of patients with toxic nodular goitre after radioiodine therapy. Clin Endocrinol 2012; 76: 297–303.

51. Krohn T, Hänscheid H, Müller B, et al. Maximum dose rate is a determinant of hypothyroidism after 131I therapy of Graves' disease, but the total thyroid absorbed dose is not. J Clin Endocrinol Metab 2014; 99: 4109–15. [PubMed: 25033065]

52.Lee V, Chan SY, Choi CW, et al. Dosimetric predictors of hypothyroidism after radical intensity modulated radiation therapy for non-metastatic nasopharyngeal carcinoma. Clin Oncol (R Coll Radiol) 2016; 28: e52–60. [PubMed: 27235379]

53.Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JWA, Dekkers OM. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 2012; 97: 2243–55. [PubMed: 22511795]

54.Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L. Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Cancer 2011; 117: 5250–60. [PubMed: 21567385]

55. Nygaard B, Hegedüs L, Nielsen KG, Ulriksen P, Hansen JM. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol 1999; 50: 197–202

56.Persani L Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab 2012; 97: 3068–78. [PubMed: 22851492]

57.Persani L, Ferretti E, Borgato S, Faglia G, Beck-Peccoz P. Circulating thyrotropin bioactivity in sporadic central hypothyroidism. J Clin Endocrinol Metab 2000; 85: 3631–35. [PubMed: 11061514]

58.Graeppi-Dulac J, Vlaeminck-Guillem V, Perier-Muzet M, Dalle S, Orgiazzi J. Endocrine side effects of anti-cancer drugs: the impact of retinoids on the thyroid axis. Eur J Endocrinol 2014; 170: R253–62. [PubMed: 24616413]

59.Grunenwald S, Caron P. Central hypothyroidism in adults: better understanding for better care. Pituitary 2015; 18: 169–75. [PubMed: 24554165]

60.Sun Y, Bak B, Schoenmakers N, van Trotsenburg ASP, Oostdijk W, Voshol P, et al. Loss-of-Function mutations in Igsf1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. Nat Genet (2012) 44(12):1375–81. doi: 10.1038/ng.2453

61.Heinen CA, Losekoot M, Sun Y, Watson PJ, Fairall L, Joustra SD, et al. Mutations in Tbl1x are associated with central hypothyroidism. J Clin Endocrinol Metab (2016) 101 (12):4564–73. doi: 10.1210/jc.2016-2531

62.Heinen CA, de Vries EM, Alders M, Bikker H, Zwaveling-Soonawala N, van den Akker ELT, et al. Mutations in Irs4 are associated with central hypothyroidism. J Med Genet (2018) 55(10):693–700. doi: 10.1136/jmedgenet-2017-105113

63.Bonomi M, Busnelli M, Beck-Peccoz P, Costanzo D, Antonica F, Dolci C, et al. A family with complete resistance to thyrotropin-releasing hormone. New Engl J Med (2009) 360(7):731–4. doi: 10.1056/NEJMc0808557

64.Bonomi M, Proverbio MC, Weber G, Chiumello G, Beck-Peccoz P, Persani L. Hyperplastic pituitary gland, high serum glycoprotein hormone-a-subunit, and variable circulating thyrotropin (Tsh) levels as hallmarks of central hypothyroidism due to mutations of the tshb Gene1. J Clin Endocrinol Metab (2001) 86(4):1600–4. doi: 10.1210/jcem.86.4.7411

65.Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, et al. European Thyroid association (Eta) guidelines on the diagnosis and management of central hypothyroidism. Eur Thyroid J (2018) 7(5):225–37. doi: 10.1159/000491388

66.Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, et al. European Thyroid association (Eta) guidelines on the diagnosis and management of central hypothyroidism. Eur Thyroid J (2018) 7(5):225–37. doi: 10.1159/000491388

67.Bougma K, Aboud FE, Harding KB, Marquis GS. Iodine and mental development of children 5 years old and under: a systematic review and meta-analysis. Nutrients 2013; 5: 1384–416. [PubMed: 23609774]

68.WHO. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers, 3rd edn. Geneva: World Health Organization, 2007 http://apps.who.int/iris/bitstream/10665/43781/1/9789241595827_eng.pdf (accessed Jan 30, 2017).

69. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 2013; 382: 331–37 [PubMed: 23706508]

70.Doucet J, Trivalle C, Chassagne P, Perol M-B, Vuillermet P, Manchon N-D, et al. Does age play a role in clinical presentation of hypothyroidism? J Am Geriatrics Soc (1994) 42(9):984–6. doi: 10.1111/j.1532-5415. 1994.tb06592.x

71.Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P. Hypothyroid symptoms and the likelihood of overt thyroid failure: A population-based case–control study. Eur J Endocrinol (2014) 171(5):593–602. doi: 10.1530/eje-14-0481

72.Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet (2017) 390 (10101):1550–62. doi: 10.1016/S0140-6736(17)30703-1

73.Gao X, Liu M, Qu A, Chen Z, Jia Y, Yang N, et al. Native magnetic resonance T1 mapping identifies diffuse myocardial injury in hypothyroidism. PloS One (2016) 11(3): e0151266. doi: 10.1371/journal.pone.0151266

74.Brito JP, Ross JS, El Kawkgi OM, Maraka S, Deng Y, Shah ND, et al. Levothyroxine use in the UnitedStates,2008-2018.JAMAInternalMed(2021)181(10):1402–5.doi: 10.1001/jamainternmed.2021.2686

75.Burgos N, Toloza FJK, Ospina NMS, Brito JP, Salloum RG, Hassett LC, et al. Clinical outcomes after discontinuation of thyroid hormone replacement: A systematic review and meta-analysis. Thyroid (2021) 31(5):740–51. doi: 10.1089/thy.2020.0679

76.Carlé A, Karmisholt JS, Knudsen N, Perrild H, Thuesen BH, Ovesen L, et al. Does subclinical hypothyroidism add any symptoms? evidence from a Danish population-based study. Am J Med (2021) 134(9):1115–26. e1. doi: 10.1016/j.amjmed.2021.03.009

77.Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Internal Med (2000) 160(4):526–34. doi: 10.1001/ archinte.160.4.526

78.Zulewski H, Müller B, Exer P, Miserez AR, Staub J-J. Estimation of tissue hypothyroidism by a new clinical score: Evaluation of patients with various grades of hypothyroidism and Controls1. J Clin Endocrinol Metab (1997) 82(3):771–6. doi: 10.1210/ jcem.82.3.3810

79.Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. J Clin Endocrinol Metab (2006) 91(1):145–53. doi: 10.1210/jc.2005-1775

80. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of l-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: Randomized, crossover trial. J Clin Endocrinol Metab (2007) 92(5):1715–23. doi: 10.1210/jc.2006-1869

81. Baldini IM, Vita A, Mauri MC, Amodei V, Carrisi M, Bravin S, et al. Psychopathological and cognitive features in subclinical hypothyroidism. Prog Neuropsychopharmacol Biol Psychiatry (1997) 21(6):925–35. doi: 10.1016/s0278-5846 (97)00089-4

82. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocrine Rev (2008) 29(1):76–131. doi: 10.1210/er.2006-0043

83.Peeters RP. Subclinical hypothyroidism. New Engl J Med (2017) 376(26):2556–65. doi: 10.1056/NEJMcp1611144

84.Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, 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(12):1200–35. doi: 10.1089/thy.2012.0205

85.Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. Eta guideline: Management of subclinical hypothyroidism. Eur Thyroid J (2013) 2(4):215–28. doi: 10.1159/000356507

86. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: A review. JAMA (2019) 322(2):153–60. doi: 10.1001/jama.2019.9052

87.Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid hormones treatment for subclinical hypothyroidism: A clinical practice guideline. BMJ (2019) 365: l2006. doi: 10.1136/bmj. l2006

88.Peeters RP, Brito JP. Subclinical hypothyroidism: To treat or not to treat? Eur J Endocrinol (2020) 183(6): D15–24. doi: 10.1530/eje-20-0621

89.Flinterman LE, Kuiper JG, Korevaar JC, van Dijk L, Hek K, Houben E, et al. Impact of a forced dose-equivalent levothyroxine brand switch on plasma thyrotropin: A cohort study. Thyroid (2020) 30(6):821–8. doi: 10.1089/thy.2019.0414

90.Benvenga S, Carlé A. Levothyroxine formulations: Pharmacological and clinical implications of generic substitution. Adv Ther (2019) 36(2):59–71. doi: 10.1007/s12325 019-01079-1

91.Eric Fliers BD, Bhaseen A, Brix. TH. European Thyroid association (Eta) and thyroid federation international (Tfi) joint position statement on the interchangeability of levothyroxine products in eu countries. Eur Thyroid J (2018) 7:238–42. doi: 10.1159/ 000493123

92.Brito JP, Deng Y, Ross JS, Choi NH, Graham DJ, Qiang Y, et al. Association between generic-to-Generic levothyroxine switching and thyrotropin levels among us adults. JAMA Internal Med (2022) 182(4):418–25. doi: 10.1001/jamainternmed.2022.0045

93.Jonklaas J, Bianco AC, Bauer AJ, et al., for the American Thyroid Association Task Force on Thyroid Hormone Replacement Study Group. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid 2014; 24: 1670–751. [PubMed: 25266247]

94.Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA Guideline: management of subclinical hypothyroidism. Eur Thyroid J 2013; 2: 215–28. [PubMed: 24783053]

95.Roos A, Linn-Rasker SP, van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med 2005; 165: 1714–20. [PubMed: 16087818]

96.Abdalla SM, Bianco AC. Defending plasma T3 is a biological priority. Clin Endocrinol 2014; 81: 633–41.

97.Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004; 351: 241–9. [PubMed: 15254282]

98.Stagnaro-Green A, Abalovich M, Alexander E, et al., for the American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum Study Group. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21: 1081–125. [PubMed: 21787128]

99.Taylor PN, Iqbal A, Minassian C, et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. JAMA Intern Med 2014; 174: 32–39. [PubMed: 24100714]

100.Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men

101.Bolk N, Visser TJ, Nijman J, Jongste IJ, Tijssen JGP, Berghout A. Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial. Arch Intern Med 2010; 170:1996–2003. [PubMed: 21149757]

102. Vita R, Saraceno G, Trimarchi F, Benvenga S. Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors. J Clin Endocrinol Metab 2014; 99: 4481–86. [PubMed: 25259910]

103.Seng Yue C, Benvenga S, Scarsi C, Loprete L, Ducharme MP. When bioequivalence in healthy volunteers may not translate to bioequivalence in patients: differential effects of increased

gastric pH on the pharmacokinetics of levothyroxine capsules and tablets. J Pharm Pharm Sci 2015; 18: 844–55. [PubMed: 26670370]

104.Cappelli C, Pirola I, Daffini L, et al. A double-blind placebo-controlled trial of liquid thyroxine ingested at breakfast: results of the TICO Study. Thyroid 2016; 26: 197–202. [PubMed: 26586610]

105.Koulouri O, Moran C, Halsall D, Chatterjee K, Gurnell M. Pitfalls in the measurement and interpretation of thyroid function tests. Best Pract Res Clin Endocrinol Metab 2013; 27: 745–62. [PubMed: 24275187

106.Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol 2002; 57: 577–85

107.Ott J, Promberger R, Kober F, et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid 2011; 21: 161–67. [PubMed: 21186954]

108.Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T (4) and T (3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002; 87: 1068–72. [PubMed: 11889165]

109.Gullo D, Latina A, Frasca F, Le Moli R, Pellegriti G, Vigneri R. Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. PLoS One 2011; 6: e22552. [PubMed: 21829633]

110.Ito M, Miyauchi A, Morita S, et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. Eur J Endocrinol 2012; 167: 373–78. [PubMed: 22711760]

111.Jonklaas J, Davidson B, Bhagat S, Soldin SJ. Triiodothyronine levels in athyreotic individuals during levothyroxine therapy. JAMA 2008; 299: 769–77 [PubMed: 18285588]

112.Werneck de Castro JP, Fonseca TL, Ueta CB, et al. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. J Clin Invest 2015; 125: 769–81. [PubMed: 25555216]

113.Escobar-Morreale HF, del Rey FE, Obregón MJ, de Escobar GM. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology 1996; 137: 2490–502. [PubMed: 8641203]

114.Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999; 340: 424–29. [PubMed: 9971866]

115.Nygaard B, Jensen EW, Kvetny J, Jarlov A, Faber J. Effect of combination therapy with thyroxine (T4) and 3,5,3 “-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. Eur J Endocrinol 2009; 161: 895–902. [PubMed: 19666698]

116. Walsh JP, Shiels L, Lim EM, et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab 2003; 88: 4543–50. [PubMed: 14557419]

117. Escobar-Morreale HF, Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med 2005; 142: 412–24. [PubMed: 15767619]

118.Appelhof BC, Fliers E, Wekking EM, et al. Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. J Clin Endocrinol Metab 2005; 90: 2666–74. [PubMed: 15705921]

119.Grozinsky-Glasberg S, Fraser A, Nahshoni E, Weizman A, Leibovici L. Thyroxine triiodothyronine combination therapy versus thyroxine monotherapy for clinical hypothyroidism:

meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2006; 91: 2592–99. [PubMed: 16670166]

120. Wiersinga WM. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Nat Rev Endocrinol 2014; 10: 164–74. [PubMed: 24419358]

121.McAninch EA, Bianco AC. New insights into the variable effectiveness of levothyroxine monotherapy for hypothyroidism. Lancet Diabetes Endocrinol 2015; 3: 756–58. [PubMed: 26362364]

122.McAninch EA, Jo S, Preite NZ, et al. Prevalent polymorphism in thyroid hormone-activating enzyme leaves a genetic fingerprint that underlies associated clinical syndromes. J Clin Endocrinol Metab 2015; 100: 920–33. [PubMed: 25569702]

123.Panicker V, Saravanan P, Vaidya B, et al. Common variation in the DIO2 gene predicts baseline psychological well-being and response to combination thyroxine plus triiodothyronine therapy in hypothyroid patient. J Clin Endocrinol Metab 2009; 94: 1623–29. [PubMed: 19190113]

124. Wouters HJ, van Loon HC, van der Klauw MM, et al. No effect of the Thr92Ala polymorphism of deiodinase-2 on thyroid hormone parameters, health-related quality of life, and cognitive functioning in a large population-based cohort study. Thyroid 2016; published online Oct 27 DOI:10.1089/thy.2016.0199.

125.Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of LT-4 + LT-3 in the treatment of hypothyroidism. Eur Thyroid J 2012; 1: 55–71. [PubMed: 24782999]

126.Chaker L, Korevaar TI, Medici M, et al. Thyroid function characteristics and determinants: the Rotterdam study. Thyroid 2016; 26: 1195–204. [PubMed: 27484151]

127.Boas M, Feldt-Rasmussen U, Main KM. Thyroid effects of endocrine disrupting chemicals. Mol Cell Endocrinol 2012; 355: 240–48. [PubMed: 21939731]

128.Rodondi N, den Elzen WPJ, Bauer DC, et al., for the Thyroid Studies Collaboration Study Group. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010; 304: 1365–74. [PubMed: 20858880]

129.Gencer B, Collet TH, Virgini V, et al., for the Thyroid Studies Collaboration Study Group. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 2012; 126: 1040–49. [PubMed: 22821943]

130.Chaker L, Baumgartner C, den Elzen WPJ, et al., for the Thyroid Studies Collaboration Study Group. Subclinical hypothyroidism and the risk of stroke events and fatal stroke: An individual participant data analysis. J Clin Endocrinol Metab 2015; 100: 2181–91. [PubMed: 25856213]

131.LeFevre ML, the U.S. Preventive Services Task Force. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015; 162: 641–50. [PubMed: 25798805]

17% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Bibliography
- Quoted Text

Match Groups

- **62** Not Cited or Quoted 11%
  Matches with neither in-text citation nor quotation marks
- **42** Missing Quotations 6%
  Matches that are still very similar to source material
- **0** Missing Citation 0%
  Matches that have quotation marks, but no in-text citation
- **0** Cited and Quoted 0%
  Matches with in-text citation present, but no quotation marks

Top Sources

13% Internet sources
12% Publications
15% Submitted works (Student Papers)

Integrity Flags

0 Integrity Flags for Review

Our system's algorithms look deeply at a document for any inconsistencies that would set it apart from a normal submission. If we notice something strange, we flag it for you to review.

A Flag is not necessarily an indicator of a problem. However, we'd recommend you focus your attention there for further review.

0% detected as AI

The percentage indicates the combined amount of likely AI-generated text as well as likely AI-generated text that was also likely AI-paraphrased.

Caution: Review required.

It is essential to understand the limitations of AI detection before making decisions about a student's work. We encourage you to learn more about Turnitin's AI detection capabilities before using the tool.

Detection Groups

- 0 AI-generated only 0%
  Likely AI-generated text from a large-language model.
- 0 AI-generated text that was AI-paraphrased 0%
  Likely AI-generated text that was likely revised using an AI-paraphrase tool or word spinner.

Disclaimer
Our AI writing assessment is designed to help educators identify text that might be prepared by a generative AI tool. Our AI writing assessment may not always be accurate (i.e., our AI models may produce either false positive results or false negative results), so it should not be used as the sole basis for adverse actions against a student. It takes further scrutiny and human judgment in conjunction with an organization's application of its specific academic policies to determine whether any academic misconduct has occurred.

Frequently Asked Questions

How should I interpret Turnitin's AI writing percentage and false positives?
The percentage shown in the AI writing report is the amount of qualifying text within the submission that Turnitin's AI writing detection model determines was either likely AI-generated text from a large-language model or likely AI-generated text that was likely revised using an AI paraphrase tool or word spinner.

False positives (incorrectly flagging human-written text as AI-generated) are a possibility in AI models.

AI detection scores under 20%, which we do not surface in new reports, have a higher likelihood of false positives. To reduce the likelihood of misinterpretation, no score or highlights are attributed and are indicated with an asterisk in the report (*%).

The AI writing percentage should not be the sole basis to determine whether misconduct has occurred. The reviewer/instructor should use the percentage as a means to start a formative conversation with their student and/or use it to examine the submitted assignment in accordance with their school's policies.

What does 'qualifying text' mean?
Our model only processes qualifying text in the form of long-form writing. Long-form writing means individual sentences contained in paragraphs that make up a longer piece of written work, such as an essay, a dissertation, or an article, etc. Qualifying text that has been determined to be likely AI-generated will be highlighted in cyan in the submission, and likely AI-generated and then likely AI-paraphrased will be highlighted purple.

Non-qualifying text, such as bullet points, annotated bibliographies, etc., will not be processed and can create disparity between the submission highlights and the percentage shown.