

Pharmacokinetics of Levothyroxine and Factors Influencing Its Therapeutic Efficacy in Hypothyroidism: A Comprehensive Review

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Abstract

Levothyroxine (LT4) remains the standard therapy for hypothyroidism due to its effectiveness in restoring normal thyroid hormone levels and improving physiological functions. However, its pharmacokinetic profile exhibits considerable variability, which may influence therapeutic outcomes in clinical practice. This review aims to comprehensively evaluate the pharmacokinetics of levothyroxine, including its absorption, distribution, metabolism, and elimination, along with factors affecting its therapeutic efficacy. A structured literature search was conducted using electronic databases, focusing on studies related to levothyroxine pharmacokinetics, drug interactions, and clinical outcomes. Evidence suggests that levothyroxine is primarily absorbed in the small intestine, with bioavailability ranging from 60–80%, and is significantly influenced by gastric pH, food intake, and concomitant medications such as proton pump inhibitors. Differences in absorption and metabolic processes may lead to inadequate therapeutic outcomes even when proper dosing protocols are followed. Additionally, levothyroxine therapy plays a crucial role in improving metabolic, cardiovascular, and neuropsychological functions in patients with hypothyroidism. Understanding the pharmacokinetic variability and patient-specific factors is essential for optimizing levothyroxine therapy. Individualized dosing strategies, proper patient counselling, and monitoring of thyroid function are critical to achieving consistent euthyroid status. Future research should focus on improving drug formulations and personalized therapeutic approaches to enhance treatment outcomes.

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Received Date: May 08, 2026

Accepted Date: May 11, 2026

Published Date: May 12, 2026

Citation: Mohd. Farhan, Nalini Kanta Sahoo, Alex Martin, Rajesh Nath, Asad Jamal Ansari, Ebadurrahman, Saurabh Kumar Chauhan. Pharmacokinetics of Levothyroxine and Factors Influencing Its Therapeutic Efficacy in Hypothyroidism: A Comprehensive Review. Research & Reviews: A Journal of Drug Formulation, Development and Production. 2026; 13(2): 27–33p.

Keywords: Levothyroxine, pharmacokinetics, hypothyroidism, bioavailability, drug interactions, thyroid hormones

INTRODUCTION

The principal diseases of the human thyroid gland are goiter (diffuse or nodular), hyperthyroidism, hypothyroidism, autoimmune thyroiditis, and neoplasm [1]. The thyroiditis types of cause inflammation of thyroid tissue and can release preformed hormone from the colloid space, causing thyro-toxicosis, which is transient and followed by recovery or development of hypothyroidism. In acute and subacute thyroiditis, thyroid tenderness and neck pain are often present. On the other hand, silent thyroiditis is devoid of the local symptoms [2].

In the USA and Canada, the extrapolated prevalences are 5,873,108 and 650,157, respectively. In Austria and Belgium, the prevalences are 163,495 and

206,965, respectively. In Bosnia and Macedonia, the prevalences are 8,152 and 40,801, respectively. For China and India, the prevalences are 25,976,952 and 21,301,412, respectively, while in Egypt and Iran they are 1,522,348 and 1,350,064, respectively. South Africa has a prevalence of 888,969 [3]. Global yearly occurrence rates for Hashimoto's thyroiditis are approximated at 0.3–1.5 instances per 1000 individuals, while Graves' disease affects roughly 5 per 10,000 people [4].

Human autoimmune thyroid disorders encompass primarily Graves' disease (GD) and Hashimoto's thyroiditis (HT), representing the predominant etiologies of thyroid dysfunction and nonendemic goiter [4]. These pathological states emerge through intricate interplay between environmental and hereditary elements [5] and demonstrate self-reactivity toward thyroidal antigens, manifesting as distinct inflammatory or antireceptor autoimmune pathologies [6, 7]. Key AITD susceptibility loci that have been identified and studied include the HLA-DR genetic region, along with non-MHC genetic variants such as CTLA-4, CD40, PTPN22, thyroglobulin, and TSH receptor genes [8]. Principal environmental precipitants of AITD encompass iodine exposure, pharmaceutical agents, infectious processes, tobacco use, psychological stress, and hereditary AITD susceptibility, contributing to emerging hypothetical pathways through which gene-environment interactions may precipitate thyroidal autoimmune responses [9].

The first pathological features of autoimmune thyroiditis were described in 1912 [10] when patients with goiter exhibited diffuse lymphocyte infiltration, atrophy of follicular cells, presence of granulated thyrocytes (oncocyctic cells or Hurtle's cells), and fibrosis in the histological pictures of their thyroid tissues [10]. Hashimoto's thyroiditis represents an autoimmune condition targeting thyroidal antigens and constitutes the predominant etiology of hypothyroidism [11]. Annual occurrence ranges from 0.3 to 1.5 per 1000 individuals, with female predominance of 4 to 10-fold compared to males [8, 11, 12]. This condition demonstrates higher prevalence in regions with elevated dietary iodized salt consumption, while tobacco use elevates risk [8]. Goitrous presentation may occur, though thyroidal atrophy represents the more frequent finding. Hashimoto's thyroiditis correlates with additional endocrinopathies within polyglandular autoimmune syndromes (Addison's disease, type 1 diabetes mellitus, and hypogonadism) [8]. Diagnostic confirmation relies on clinical manifestations, elevated TSH levels, reduced thyroid hormone concentrations, and detectable antithyroid peroxidase antibodies (anti-TPO) [13].

Thyroidal hormones serve essential physiological functions, necessitating therapeutic intervention when deficient. Levothyroxine represents the standard treatment for thyroid hormone insufficiency. Following a concise examination of thyroidal hormone physiology, this discussion will emphasize current understanding of levothyroxine pharmacokinetics (PKs) and describe variables influencing its pharmacokinetic profile. The thyroidal gland governs synthesis, storage, and secretion of metabolic hormones, including iodinated thyroxine (T4) and triiodothyroxine (T3).

These hormones are essential for regulating numerous metabolic pathways and are critical for normal developmental processes. They participate in thermogenic, cardiovascular, and metabolic functions. These hormones presumably exert their influence through activation of gene transcription involving messenger RNA and protein synthesis. This occurs through cellular nuclear entry and binding to DNA-associated thyroidal receptors, which modulate transcriptional activity [14, 15].

LT4 functions primarily as a T3 precursor within target tissues through deiodinase enzyme activity, as previously described [5]. Consequently, this section will encompass information regarding hypothyroidism's impact on major organ systems, along with the therapeutic benefits of LT4 treatment. Table 1 summarizes these effects of LT4 replacement therapy on significant physiological and metabolic functions in hypothyroid patients.

Table 1. Effects of hypothyroidism and impact of LT4 replacement therapy.

Physiological process	Effect of hypothyroidism	Effect of LT4 replacement therapy
Energy Expenditure	Reduced resting energy expenditure and metabolic rate.	Restores energy expenditure and normal metabolic activity.
Lipid Profile	Dyslipidaemia due to ↓ hepatic LDL receptors; ↑ total and LDL cholesterol.	Reduces total cholesterol, LDL levels, and intrahepatic lipid content.
Glucose Metabolism	Overt: may reduce IGT; Subclinical: ↑ insulin resistance, ↑ diabetes risk.	Improves insulin sensitivity and glucose tolerance.
Inflammation	Increased systemic inflammatory markers.	Decreases systemic inflammation.
Coagulation	Overt: hypocoagulable (like VWS); Subclinical: procoagulant tendency.	Improves fibrinolysis and normalizes coagulation markers.
Brain (Mood/Affect)	Altered mood, depression, cognitive changes.	Improves mood and reduces depressive symptoms.
Adipose Tissue	Modest ↑ weight; ↓ brown fat activation.	Reverses weight gain (minimal effect on body composition).
Cardiovascular System	Reduced cardiac contractility, ↑ BP, worsens cardiac disease.	Improves cardiac structure and function.
Bone Health	Reduced bone turnover; risk of low bone density.	Excess LT4 may cause bone loss; requires careful monitoring.
Kidney Function	↓ Glomerular filtration rate (GFR).	Improves GFR; may reduce uric acid and albumin excretion.
Quality of Life (QoL)	Fatigue, reduced health-related QoL.	Variable improvement; depends on accurate diagnosis.

INDICATION AND DOSAGE

Levothyroxine represents a synthetically produced T4 hormone that exhibits biochemical and physiological properties identical to its naturally occurring counterpart, prescribed in cases where endogenous hormone production is insufficient [16]. The oral delivery of levothyroxine is, therefore, recommended for managing acquired primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) forms of hypothyroidism [17]. Additionally, this medication finds application in treating euthyroid goiters encompassing thyroid nodules, subacute or chronic lymphocytic thyroiditis, multinodular goiter, or in thyroid cancer patients following thyroidectomy, serving as a supplementary treatment to surgical intervention and radioiodine therapy. For typical adults below 50 years of age, the standard levothyroxine sodium dosage approximates 1.7 mcg/kg/day, corresponding to roughly 100–125 mcg daily. Elderly patients or those presenting with cardiac conditions may necessitate reduced levothyroxine quantities, with dosage adjustments implemented at 4–6-week intervals. Newborns, infants, and adolescents demonstrate requirements exceeding 1.7 mcg/kg/day. The recently published recommendations from the American Association of Clinical Endocrinologists and American Thyroid Association task force addressing adult hypothyroidism encompass therapeutic recommendations alongside diagnostic considerations [18].

ABSORPTION AND BIOAVAILABILITY

The primary site of levothyroxine absorption occurs within the small bowel, particularly across the duodenum, jejunum, and ileum, with minimal gastric uptake. Therefore, individuals who have undergone intestinal resection procedures resulting in shortened small bowel length demonstrate diminished absorption capacity and necessitate elevated levothyroxine dosing. Peak plasma concentrations (Tmax) are reached at roughly 2 hours in euthyroid individuals, whereas this parameter extends to approximately 3 hours in those with hypothyroidism. Concurrent food intake further prolongs Tmax [19, 20].

In euthyroid subjects, levothyroxine demonstrates bioavailability ranging from 60–80%. This parameter may be marginally elevated in both hypothyroid and hyperthyroid populations, though it

decreases with food consumption from 79% during fasting states to 64% when administered with meals for a 100-mcg dose [21, 22].

Gastric acidity appears to modulate levothyroxine absorption. Centanni and colleagues established that euthyroid patients with nontoxic multinodular goitre who had compromised gastric acid production or were receiving omeprazole therapy required increased dosing to achieve adequate TSH suppression. Correspondingly, Schmich's research demonstrated that prolonged lansoprazole administration in hypothyroid individuals necessitated higher levothyroxine doses to achieve target TSH concentrations [23, 24].

VOLUME OF DISTRIBUTION

Levothyroxine exhibits a restricted distribution volume, documented as 11.6 litres in euthyroid subjects and 14.7 L in individuals with primary hypothyroidism [25]. This corresponds roughly to the body's extracellular fluid compartment.

METABOLISM

While T4 undergoes various metabolic pathways, the predominant route involves deiodination processes mediated by deiodinase enzymes. Iodine removal from the outer ring's carbon 5 position converts T4 to T3 [26, 27], positioning T4 as a precursor hormone to T3 [28–30]. Inner ring deiodination can alternatively occur, producing biologically inactive reverse T3 (rT3). Approximately equal proportions of deiodinated T4 yield rT3 and T3. Subsequently, both T3 and rT3 undergo further degradation to diiodothyronine (T2), iodothyronamine (T1), and their reverse counterparts [30, 31].

ELIMINATION

T4 demonstrates a daily turnover rate of roughly 10%, while T3 exhibits 50–70% turnover, with marginally accelerated rates in healthy individuals versus those with primary hypothyroidism. This corresponds to T4 half-lives of 7.5 days in hypothyroid patients and 6.2 days in euthyroid persons, whereas T3 half-lives approximate 1.4 and 1.0 days for hypothyroid and euthyroid subjects, respectively. T4 clearance rates were comparable between groups at 0.056 and 0.054 L/h for hypothyroid and euthyroid populations, respectively. These findings align with previously reported values in hypothyroid patients (0.0385 L/h/70 kg) and healthy controls (0.053 to 0.064 L/h) [32–35].

METHODOLOGY

This examination aimed to synthesize and analytically assess the pharmacokinetic properties of levothyroxine alongside variables that impact its therapeutic effectiveness in hypothyroid conditions. A systematic literature exploration was executed utilizing electronic repositories such as PubMed, Scopus, and Google Scholar. The investigation encompassed publications spanning 2000 to 2025, with special focus on contemporary research from the preceding 5–10 years.

The search methodology incorporated keyword combinations including “levothyroxine,” “pharmacokinetics,” “absorption,” “bioavailability,” “hypothyroidism,” “drug interactions,” and “thyroid hormone metabolism.” Boolean operators (AND, OR) were employed to enhance search precision and optimize retrieval accuracy.

Selection parameters encompassed peer-reviewed primary research publications, clinical investigations, systematic analyses, and meta-analyses in English that examined pharmacokinetic characteristics, clinical applications, or determinants influencing levothyroxine treatment. Studies focusing on drug–drug interactions, food interactions, gastrointestinal influences, and patient-specific variables affecting levothyroxine absorption and metabolism were also included. Exclusion criteria included non-English publications, case reports, conference abstracts, duplicate studies, and articles lacking sufficient methodological detail or relevance to the review objectives.

The titles and abstracts of identified articles underwent relevance assessment, subsequently followed by comprehensive full-text review of qualifying investigations. Relevant data were extracted and

synthesized qualitatively to provide a comprehensive overview of levothyroxine pharmacokinetics and its clinical implications. Where appropriate, findings were compared across studies to identify consistencies, variations, and gaps in the existing literature.

Although this review follows a structured approach to literature selection and analysis, it is primarily a narrative synthesis and does not involve quantitative meta-analysis. The reporting of this review was guided, where applicable, by principles outlined in PRISMA [36] to ensure transparency and clarity.

DISCUSSION

The pharmacokinetic profile of levothyroxine demonstrates significant variability, primarily influenced by factors affecting its gastrointestinal absorption and metabolism. In clinical practice, impaired absorption remains one of the most important causes of suboptimal therapeutic response, particularly in patients presenting with persistent hypothyroid symptoms despite adequate dosing. Recent evidence highlights that gastric pH plays a critical role in levothyroxine dissolution, and concomitant use of proton pump inhibitors (PPIs) can significantly reduce its bioavailability by increasing gastric pH. A 2023 clinical study reported that PPI therapy leads to a measurable elevation in serum thyroid-stimulating hormone (TSH) levels in levothyroxine-treated patients, indicating reduced drug absorption and efficacy. Similarly, recent reviews have emphasized that not only PPIs, but also dietary factors, calcium, iron supplements, and gastrointestinal disorders contribute to fluctuations in levothyroxine absorption and therapeutic outcomes [37]. These findings underline the importance of individualized dosing strategies, patient counselling regarding administration conditions (fasting state), and consideration of alternative formulations, such as liquid or soft gel preparations, in patients with absorption-related issues. Therefore, optimizing levothyroxine therapy requires a comprehensive understanding of both pharmacokinetic variability and patient-specific factors to achieve consistent euthyroid status.

CONCLUSION

Levothyroxine remains the cornerstone of therapy for hypothyroidism due to its efficacy, safety, and ability to restore normal physiological function. However, its pharmacokinetic profile is characterized by considerable variability, particularly in terms of absorption and bioavailability. Factors – such as gastric pH, food intake, concomitant medications, and gastrointestinal disorders – significantly influence its therapeutic effectiveness. Understanding these variables is essential for optimizing treatment outcomes and avoiding suboptimal response or dose adjustments.

Moreover, while levothyroxine effectively normalizes biochemical parameters and improves clinical symptoms in most patients, individualized therapy is often required to achieve consistent euthyroid status. Careful dose titration, patient education regarding proper administration (especially fasting conditions), and monitoring of thyroid function tests are critical components of successful management. Emerging approaches, including alternative formulations and personalized dosing strategies, may further enhance therapeutic outcomes in patients with absorption-related challenges.

To summarize, a thorough comprehension of levothyroxine pharmacokinetic properties and the variables affecting its distribution is essential for healthcare practitioners to guarantee optimal and secure hypothyroidism treatment. Subsequent investigations should emphasize the advancement of pharmaceutical delivery mechanisms and the enhancement of personalized therapeutic strategies to address current constraints and improve patient well-being.

Competing Interests

Author states no conflict of interest.

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