A Comprehensive Review of the Beneficial and Adverse Effects of Levothyroxine Therapy in Health and Disease

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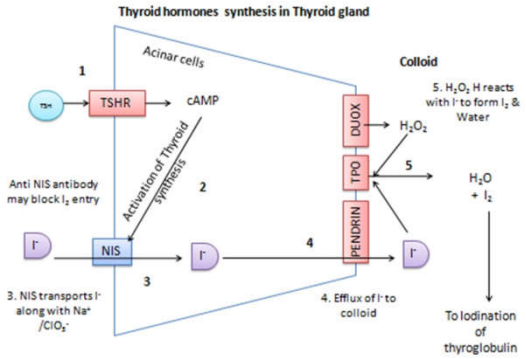
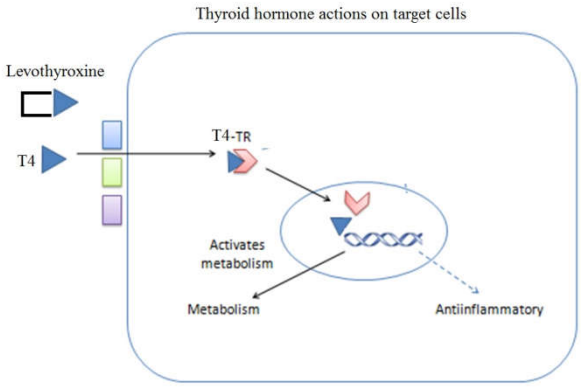
Abstract:

Levothyroxine is a synthetic form of the thyroid hormone used to treat hypothyroidism, a condition where the thyroid gland does not produce enough hormones. It helps normalize thyroid hormone levels, improving symptoms such as fatigue, weight gain, cold intolerance, and cognitive difficulties. Levothyroxine also supports metabolism, heart function, and mood. However, its use can lead to side effects, particularly if the dose is not properly adjusted. Common side effects of an overdose include increased heart rate, anxiety, and weight loss, while an underdose can result in fatigue, weight gain, and depression. Long-term use of high doses may also affect bone health and increase the risk of osteoporosis. Regular monitoring of thyroid hormone levels is essential to ensure the correct dosage, and interactions with other medications should be considered. Levothyroxine is generally safe when used appropriately but requires careful management to avoid complications.





Keywords: Levothyroxine, hypothyroidism, thyroid hormone, thyroid treatment, medication management.

INTRODUCTION:

Hypothyroidism is a common pathological condition characterized by a deficiency of thyroid hormones, disrupting the body's metabolic balance. The thyroid gland functions within a complex homeostatic system where thyrotropin, also known as thyroid-stimulating hormone (TSH), plays a regulatory role. While more stable thyroxine (T4) serves primarily as a precursor, triiodothyronine (T3) is the biologically active form that impacts numerous physiological processes and is regulated when produced in excess by negative feedback mechanism suppressing TSH (1). In hypothyroidism, this regulatory mechanism becomes dysfunctional, leading to reduced levels of T4 and T3, resulting in widespread metabolic disturbances. There are 3 types of hypothyroidism such as Primary, secondary and tertiary hypothyroidism (2). In primary hypothyroidism, the thyroid gland itself is impaired with elevated TSH levels but reduced levels of free thyroxine (T4). In contrast, secondary hypothyroidism, caused by pituitary or hypothalamic dysfunction, may present with low or normal TSH despite low T4 levels. Levothyroxine (LT4) is indeed the standard of care for managing hypothyroidism, which is a condition where the thyroid gland does not produce enough thyroid hormone. Levothyroxine (LT4), a synthetic version of the thyroid hormone is a preferred drug of choice due to its stability, long half-life, and effectiveness in maintaining proper hormone levels. Regular monitoring of thyroid-stimulating hormone (TSH) levels ensures the correct dosage for optimal management of treating overt hypothyroidism which relieves the symptoms associated with the condition (3–5). The prevalence of hypothyroidism is estimated to be 3–11% which varies depending on factors such as age, gender, and geographical location (6). Levothyroxine (LT4) works by increasing the levels of T4 and T3, in the bloodstream to regulate various metabolic processes, such as energy production, growth, and body temperature. Despite its efficacy, some patients report that they still experience symptoms of hypothyroidism, such as fatigue, weight gain, and depression, even while taking Levothyroxine (LT4). This has led to discussions about the potential for alternative treatments or adjunct therapies, but Levothyroxine (LT4) remains the gold standard due to its proven effectiveness and safety profile (7).

HYPOTHYROIDISM:

Hypothyroidism, a condition marked by thyroid hormone deficiency and higher TSH levels, may either be classified as overt hypothyroidism or subclinical hypothyroidism. The T4 level in the subclinical hypothyroidism is within the reference levels and in overt hypothyroidism the T4 falls below lower limit. On the other hand, primary hypothyroidism is a common disorder worldwide, with iodine deficiency and Hashimoto's thyroiditis being the principal causes. Iodine deficiency impairs thyroid hormone production, while Hashimoto’s thyroiditis involves autoimmune destruction of the thyroid gland. The prevalence of primary hypothyroidism is highest in populations with either high iodine intake or severe iodine deficiency, compared to those with

sufficient iodine status. In regions where iodine intake is excessive, such as through overuse of iodized salt, there is a risk of iodine-induced hypothyroidism. Excessive iodine can disrupt thyroid function by causing the gland to become less responsive or by triggering autoimmune reactions, particularly in genetically predisposed individuals. Conversely, in areas with severe iodine deficiency, the thyroid cannot produce adequate hormones, leading to hypothyroidism and goiter. Central hypothyroidism is a rare disorder caused by secondary hypothyroidism, which results from pathology of the pituitary gland that produce TSH, impairing thyroid hormone production. Incidence estimates for congenital central hypothyroidism ranges widely from 1:21,000 to 1:160,000 cases possibly due to differences in neonatal diagnostic screening strategies for thyroid disorders (8,9). Tertiary hypothyroidism is caused by pathology of the hypothalamus, leading to insufficient production of thyrotropin-releasing hormone (TRH). Tertiary hypothyroidism, which is caused by dysfunction of the hypothalamus leading to insufficient production of thyrotropin-releasing hormone (TRH), is a rare form of hypothyroidism. Its prevalence is not well-documented in large-scale studies, as it is less common compared to primary and secondary hypothyroidism. However, it is believed to account for a very small proportion of hypothyroid cases, with most estimates suggesting that it constitutes less than 1% of all hypothyroidism cases (1).

LEVOTHYROXINE AS A PRINCIPAL DRUG OF CHOICE FOR TREATEMENT OF HYPOTHYROIDISM

Levothyroxine, also known as L – thyroxine is a synthetic version of the thyroid hormone used to treat hypothyroidism by replenishing the hormone levels in the body (10). It was initially isolated from thyroid glands of pigs by Edward Calvin Kendall and later synthetic form came into use (11). It is commonly prescribed for thyroid hormone deficiency such as myxedema coma to restore normal metabolic function. Additionally, levothyroxine can be used to treat and prevent certain thyroid tumors by suppressing thyroid-stimulating hormone (TSH) production, which helps reduce tumor growth and recurrence. Levothyroxine can be taken orally or injected intravenously, depending on the patient's needs. With a half-life of 7.5 days, it takes time to accumulate in the body, and it typically reaches a steady level in the blood after about six weeks, during which it achieves its full therapeutic effect. (12)

MECHANISM OF ACTION OF LEVOTHYROXINE:

Thyroid hormones play a crucial role in physiological processes by modulating DNA transcription and protein synthesis. This binding forms a hormone-receptor complex that activates gene transcription, leading to the production of messenger RNA and the synthesis of cytoplasmic proteins. While both triiodothyronine (T3) and thyroxine (T4) contribute to thyroid hormone actions, triiodothyronine (T3) is predominantly responsible for these effects. Thyroxine enhances

oxygen consumption and heat production in body cells, stimulating metabolic activities. This includes increased carbohydrate utilization, elevated protein catabolism reflected in greater nitrogen excretion and enhanced fat oxidation, often resulting in weight loss. Major characteristics of levothyroxine Pharmacokinetics properties include absorption, distribution, metabolism, and excretion of levothyroxine. Oral levothyroxine absorption from the gastrointestinal tract ranges between 40% and 80%, with most of the dose absorbed in the jejunum and upper ileum (13). Levothyroxine tablets have a relative bioavailability of approximately 95-98% compared to an equivalent dose of oral levothyroxine sodium solution. Fasting enhances T4 absorption, while conditions like malabsorption syndromes, certain foods (e.g., soybeans), and dietary fiber reduce it. Absorption may also decline with age, and various drugs and foods can interfere with its uptake. Over 99% of thyroid hormones in circulation are bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA), each varying in their capacity and affinity for these hormones. The stronger binding affinity of TBG and TBPA for T4 accounts for its higher serum levels, slower metabolic clearance, and longer half-life compared to T3. Protein-bound thyroid hormones exist in dynamic equilibrium with a small fraction of free hormones, with only the unbound form being metabolically active. About 80% of circulating T3 is produced from peripheral T4 through monodeiodination. The liver is the main site of degradation for both T4 and T3, although T4 deiodination also occurs in other tissues, including the kidneys. Roughly 80% of the daily T4 dose is converted to equal amounts of T3 and reverse T3 (rT3). Both T3 and rT3 are further deiodinated into diiodothyronine. Additionally, thyroid hormones are metabolized through conjugation with glucuronides and sulfates, then excreted into the bile and gut, where they undergo enterohepatic recirculation. The kidneys are the primary organs responsible for the elimination of thyroid hormones. However, some conjugated hormones remain unchanged and pass into the colon, where they are excreted in the feces. Around 20% of T4 is eliminated via the stool, and urinary excretion of T4 declines with age (14,15).

BENEFICIAL ROLE OF LEVOTHYROXINE IN TREATING HYPOTHYROIDISM

Levothyroxine has some promising function while treating hypothyroidism. It helps in normalizaiton of metabolic function by restoring thyroxine and thereby normalizing metabolism. It helps in reducing symptoms such as weight gain, fatigue, cold intolerance and slow thinking or concentration (brain fog). Studies have found on improving energy levels, cardiovascular functions, cognitive imporovement, besides the regulation of the growth and neurological development among children and infants (16).

HEALTH RISKS ASSOCIATED WITH LEVOTHYROXINE THERAPY

While levothyroxine is generally well-tolerated when properly dosed, inappropriate dosing or sudden increases can lead to side effects. Some studies have found that excessing dosage of levothryoxine may cause symptoms of hyperthyroidism such as palpitations, anxiety, insomnia, weight loss, remors, sweating, heat intolerance and in some case diarrohoea. Chronic overuse oflevothyroxine may post threat of osteoporosis among postmenopausal women. Some studies have found cardiovascular risk, hair thinning or loss, allergic reaction that has been reported. Some medications such as antacids, calcium, iron supplements and antidepressants may potentially alter the absorption or effectiveness of levothyroxine (17,18).

CLINICAL INDICATIONS AND USAGE OF LEVOTHYROXINE IN HYPOTHYROID:

Levothyroxine is widely indicated for the treatment of hypothyroidism in both pediatric and adult patients. It is used as replacement therapy to restore normal thyroid hormone levels in cases of primary hypothyroidism (caused by thyroid gland dysfunction), secondary hypothyroidism (due to pituitary gland dysfunction), and tertiary hypothyroidism (resulting from hypothalamic dysfunction) (1,12). Levothyroxine is effective in addressing both congenital and acquired forms of these conditions, supporting normal growth and metabolic functions in pediatric patients and maintaining metabolic stability in adults(19,20).

CONCLUSION

Levothyroxine is the cornerstone treatment for hypothyroidism, as it effectively restores normal thyroid hormone levels in the body. By supplementing the deficient thyroid hormones (T4 and its active form, T3), levothyroxine helps regulate metabolism, energy levels, cardiovascular health, mood, and cognitive function, ultimately improving the quality of life for individuals with hypothyroidism. While levothyroxine is generally safe and well-tolerated, its dose must be carefully adjusted to avoid side effects associated with overtreatment, such as hyperthyroidism, bone loss, or cardiovascular risks. Regular monitoring of thyroid hormone levels (particularly TSH and T4) is crucial for ensuring proper dosing. With appropriate management, levothyroxine provides substantial benefits, including symptom relief and prevention of long-term complications associated with untreated hypothyroidism.

DISCLOSURES

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CONFLICT OF INTEREST

The authors do not report a potential conflict of interest.

AUTHOR CONTRIBUTIONS

VV involved in concepting, designing and supervising the manuscript. VI prepared the manuscript.

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