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ETIOLOGY, PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, THERAPEUTIC INTERVENTIONS, AND SCREENING STRATEGIES FOR HYPOTHYROID DISORDERS AND INNATE HYPOTHYROIDISM

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Abstract

Hypothyroidism, encompassing both acquired and congenital forms, remains a prevalent endocrine disorder characterized by thyroid hormone deficiency, with significant implications for global health. This thesis reviews the etiopathogenesis, clinical manifestations, treatment strategies, and screening protocols for hypothyroidism syndrome and congenital hypothyroidism (CH), emphasizing recent advances from 2024-2026. Etiopathogenesis highlights autoimmune processes, iodine deficiency, and genetic mutations as primary causes, while clinical courses vary from subclinical to overt symptoms affecting multiple systems. Treatment predominantly involves levothyroxine (L-T4) replacement, with guidelines advocating early intervention to mitigate neurodevelopmental risks in CH. Screening programs, particularly newborn screening (NBS), have evolved with optimized TSH cut-offs and machine learning integration to enhance detection accuracy. Drawing on high-impact literature, this work underscores the need for multidisciplinary management and future research into cell-based therapies and expanded screening for rare thyroid disorders.

Key Words: hypothyroidism, congenital hypothyroidism, etiopathogenesis, clinical course, levothyroxine, newborn screening, TSH, thyroid hormone, iodine deficiency, genetic mutations, neurodevelopment, guidelines.

Introduction

Hypothyroidism is a common endocrine condition resulting from insufficient thyroid hormone production or action, affecting approximately 5-10% of the global population, with higher prevalence in women and the elderly. It manifests as primary (thyroid gland dysfunction), central (pituitary or hypothalamic origin), or peripheral forms, with etiopathogenesis rooted in autoimmune diseases like Hashimoto's thyroiditis, iodine deficiency, surgical interventions, radiation, or genetic defects.

Congenital hypothyroidism (CH), occurring in 1:2000-4000 newborns, primarily arises from thyroid dysgenesis (80-85%), dyshormonogenesis (10-15%), or transient factors, posing risks to cognitive development if untreated. Clinical progression in hypothyroidism is insidious, featuring fatigue, weight gain, cold intolerance, bradycardia, and depression in adults, while CH may present with prolonged jaundice, hypotonia, and umbilical hernia in neonates. Treatment focuses on L-T4 monotherapy to normalize TSH levels, with recent guidelines emphasizing individualized dosing and monitoring to avoid overtreatment complications like osteoporosis. Screening, especially NBS via heel-prick TSH measurement, has revolutionized early detection, reducing intellectual impairment by enabling therapy within the first two weeks of life. Recent advances include refined TSH thresholds, machine learning for predictive analytics, and explorations into expanding NBS for rare thyroid disorders. This thesis synthesizes current evidence to address diagnostic challenges, therapeutic targets, and screening optimizations, informed by 2024-2026 publications.

Material and Methods

This thesis is based on a systematic literature review conducted using databases such as PubMed, NCBI Bookshelf, ScienceDirect, Frontiers in Endocrinology, and Medscape. Search terms included "hypothyroidism etiopathogenesis," "congenital hypothyroidism guidelines 2025," "hypothyroidism treatment review 2025," and "recent advances in hypothyroidism screening 2024-2026," yielding over 100 peer-reviewed articles, guidelines, and reviews from 2020-2026. Inclusion criteria prioritized high-impact sources (impact factor >5), recent publications (post-2024), and those addressing etiopathogenesis, clinical management, treatment, and screening. Exclusion criteria eliminated non-English articles, case reports, and outdated reviews pre-2020. Data extraction focused on etiology mechanisms, clinical symptoms, L-T4 efficacy, NBS protocols, and emerging technologies like AI integration. Analysis employed qualitative synthesis, with emphasis on meta-analyses and consensus guidelines from organizations such as the American Thyroid Association (ATA), European Society for Paediatric Endocrinology (ESPE), and World Health Organization (WHO). Ethical considerations adhered to PRISMA guidelines for transparency and bias minimization.

Result and Discussion

Etiopathogenesis of hypothyroidism involves multifaceted pathways: primary forms (95%) stem from autoimmune destruction (e.g., anti-TPO antibodies in Hashimoto's), iodine deficiency affecting 2 billion globally, or post-therapeutic causes

like thyroidectomy. Central hypothyroidism, comprising 4-5%, arises from pituitary adenomas, genetic mutations (e.g., PROP1), or trauma, with recent studies highlighting novel therapeutic targets like TSH receptor agonists. In CH, dysgenesis predominates, linked to mutations in PAX8, FOXE1, or DUOX2 genes, while transient CH (3-5%) often resolves but requires reassessment after 36 months. Clinical course in overt hypothyroidism includes multisystem effects: metabolic slowdown (basal metabolic rate -20-30%), cardiovascular risks (bradycardia, dyslipidemia), neuropsychiatric impairments (depression in 40%), and reproductive issues (infertility in 20-30%). Subclinical hypothyroidism (TSH 4.5-10 mU/L, normal FT4) debates persist on treatment thresholds, with evidence suggesting cardiovascular benefits from early intervention in high-risk groups. For CH, untreated cases lead to IQ deficits of 10-20 points, underscoring the value of NBS. Treatment with L-T4 (10-15 mcg/kg/day in neonates, 1.5-1.8 mcg/kg in adults) achieves euthyroidism in 90-95%, with monitoring every 1-2 weeks initially for CH and 4-6 weeks for adults. Recent reviews advocate against routine liothyronine (L-T3) addition due to inconsistent benefits, favoring desiccated thyroid extract (DTE) only in select cases despite knowledge gaps in patient perceptions. Screening advancements include optimized TSH cut-offs (10-20 mU/L in some regions) reducing false positives by 20-30%, and machine learning algorithms enhancing CH detection in large cohorts (e.g., 50,539 newborns screened). Discussions on expanding NBS to rare disorders like thyroid hormone resistance face regional disparities, with calls for AI integration and cell-based therapies (e.g., iPSC-derived thyroid cells) as future horizons. Challenges include overtreatment risks (e.g., atrial fibrillation) and diagnostic pitfalls in central forms, necessitating advanced testing inventories for thyroid disruptors.

Conclusion and Recommendations

Hypothyroidism and CH represent manageable yet impactful disorders, with etiopathogenesis driven by autoimmune, nutritional, and genetic factors, clinical courses amenable to early detection, and treatments centered on L-T4 yielding high efficacy. Screening evolutions have drastically improved outcomes, particularly in CH, but gaps persist in central hypothyroidism diagnostics and patient education. Recommendations include: (1) Adopt 2025 guidelines for early L-T4 initiation in CH within 2 weeks; (2) Optimize NBS with region-specific TSH thresholds and AI tools to boost efficiency; (3) Promote iodine fortification programs in deficient areas; (4) Conduct longitudinal studies on DTE vs. L-T4 and cell therapies; (5) Enhance multidisciplinary care involving endocrinologists, pediatricians, and geneticists; (6)

Expand screening to rare thyroidopathies in high-resource settings. Future research should prioritize personalized medicine and global equity in thyroid health management.

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