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REVIEW ARTICLE

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Thyroid Hormones and Their Role in Male Infertility: A Comprehensive Review

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Abstract

Thyroid hormones are pivotal regulators of various physiological processes, including reproductive function. While the impact of thyroid dysfunction on female fertility has been extensively studied, its association with male infertility has gained increasing recognition. This comprehensive review explores the role of thyroid hormones in male infertility, focusing on their effects on spermatogenesis, sperm quality, and reproductive outcomes. The review delves into the physiology of thyroid hormones, the presence of thyroid hormone receptors in the male reproductive system, and the influence of thyroid dysfunction on spermatogenesis and semen parameters. Additionally, it examines the molecular mechanisms underlying thyroid hormone action in the male reproductive system and discusses potential therapeutic strategies targeting thyroid hormone pathways to improve male fertility. Understanding the intricate relationship between thyroid hormones and male infertility is crucial for advancing diagnostic and therapeutic approaches in the management of male infertility associated with thyroid dysfunction.**(International Journal of Biomedicine. 2024;14(2):231-234.)**

Keywords: thyroid hormones • testes • spermatogenesis • male infertility

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Abbreviations

TSH, thyroid-stimulating hormone; **T4**, thyroxine; **T3**, triiodothyronine; **FT3**, free triiodothyronine; **FT4**, free thyroxine.

Introduction

Thyroid hormones, predominantly thyroxine (T4) and triiodothyronine (T3), serve as pivotal modulators of metabolic processes, growth, and developmental pathways. Beyond their well-established roles in maintaining metabolic homeostasis, thyroid hormones exert profound effects on various physiological processes, including reproduction.[1] Within the repertoire of thyroid gland-secreted hormones, T4 stands as the predominant form, undergoing conversion into the bioactive hormone T3 facilitated by deiodinase enzymes.[2]

In clinical contexts, hyperthyroidism manifests with elevated levels of thyroid hormones, augmenting basal metabolic rate and oxygen consumption. Left untreated, hyperthyroidism fosters heightened production of reactive oxygen species, inducing oxidative damage and lipid peroxidation in biomembranes, while also triggering free radical generation within mitochondria.[3,4]

Furthermore, hyperthyroidism is recognized to instigate pro-oxidant mechanisms within tissues, including heightened nitric oxide synthase activity and pro-inflammatory reactions. In individuals with hyperthyroidism, T3 prompts a significant elevation—up to 80-fold—in serum levels of TNF-α, IL-10, and NF-κB activation. These effects are notably observed subsequent to the mobilization and activation of testicular interstitial macrophages.[1,5,6]

Changes in thyroid function are linked to disruptions in sexual functions and compromised fertility in both humans and rats. The testes, characterized by high levels of polyunsaturated fatty acids and limited antioxidant defenses, are particularly susceptible to peroxidative damage, compared

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to other organs.[4,5] In their study, Dahmani-Said et al.[2] observed that rats administered thyroxine exhibited symptoms of hyperthyroidism, including alterations in the seminiferous tubules and the testicular interstitium.

Notably, the observed disturbance in the testicular oxidant-antioxidant equilibrium caused by hyperthyroidism could lead to substantial DNA damage and apoptosis within the testes, potentially exacerbating testicular complications. A notable inverse relationship has been documented between the extent of oxidative DNA damage in sperm and the overall sperm count. Additionally, caspase-3, B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein (BAX) have been identified as potential regulators of germ cell apoptosis in the rat testis.[7] Caspases are a family of cysteine proteases pivotal in the regulation of apoptosis and inflammation. Upon receiving pro-apoptotic signals, they become activated, initiating a cascade of proteolytic cleavage of cellular proteins, ultimately culminating in cell death. Caspase-3, in particular, serves as a critical mediator in apoptosis, with its activation occurring through both extrinsic and intrinsic signaling pathways during the execution phase of programmed cell death.[8] Furthermore, the Bcl-2 family comprises numerous members, encompassing both pro-apoptotic (*Bax*, *Bak*) and anti-apoptotic (*Bcl-2*, *Bcl-XL*, *Mcl-1*) genes. Primarily, the Bcl-2 protein is involved in the mitochondrial apoptosis pathway, known as the Bcl-2-regulated pathway.[9]

Antithyroid medications persist as the primary therapeutic approach for managing hyperthyroidism and regulating thyroid function preoperatively. The antithyroid thioamide medication carbimazole stands as a cornerstone treatment for Graves' disease globally and is applicable in the management of other etiologies of hyperthyroidism, such as toxic nodular goiter.[10]

While the impact of thyroid dysfunction on female fertility has been extensively studied, its influence on male reproductive health has garnered increasing attention in recent years. This introduction sets the stage for a comprehensive review aimed at elucidating the role of thyroid hormones in male infertility. It highlights the importance of understanding the interplay between thyroid function and male reproductive physiology, emphasizing the need for a deeper exploration of this relationship to improve diagnostic and therapeutic strategies for male infertility associated with thyroid dysfunction.

Thyroid Hormones and Spermatogenesis

Thyroid Hormone Physiology

Thyroid hormones, namely T4 and T3, are produced and released by the thyroid gland under the influence of thyroid-stimulating hormone (TSH) secreted by the pituitary gland. T4 represents the primary hormone discharged by the thyroid gland, while T3, possessing greater biological activity, is derived from T4 via enzymatic conversion in peripheral tissues.[11] The synthesis and release of thyroid hormones are tightly regulated by feedback mechanisms involving the hypothalamus, pituitary gland, and thyroid gland. TSH from the pituitary gland prompts the thyroid gland to generate and release T4 and T3 in response to fluctuating levels of circulating thyroid hormones. These hormones exert widespread effects on various tissues and organs throughout the body, regulating metabolic rate, energy expenditure, heart rate, and body temperature.[11,12]

Thyroid Hormone Receptors in the Male Reproductive System

Thyroid hormone receptors are protein entities present in the cellular milieu of the male reproductive system, comprising Sertoli cells, Leydig cells, and germ cells within the testes.[13] These receptors hold pivotal significance in orchestrating the impact of thyroid hormones on spermatogenesis and male fertility. Upon interaction with thyroid hormones, thyroid hormone receptors undergo translocation to the nucleus, where they modulate the expression of target genes implicated in cellular proliferation, differentiation, and apoptosis.[14] Within the testes, thyroid hormone receptors exert influence over a spectrum of processes crucial for spermatogenesis. These include the development and maturation of germ cells, the synthesis of androgen-binding protein within Sertoli cells, and the production of testosterone by Leydig cells. The presence of thyroid hormone receptors underscores the pivotal role of thyroid hormones in coordinating the complex mechanisms governing male reproductive function.[13,14] The hormones T3 and T4 modulate testicular function via genomic and nongenomic pathways. Genomic effects occur upon T3 binding to thyroid hormone receptor within the nuclei of Sertoli and Leydig cells, triggering gene transcription and protein synthesis.[15] Thyroid hormone receptor isoforms, particularly TRα1, play a significant role in regulating germ cell development and Sertoli cell proliferation. T3 also acts on Leydig cells, stimulating steroidogenesis acutely but inhibiting it chronically, and stops Sertoli cell proliferation.[16] Nongenomic effects involve T3 and T4 binding to nonnuclear receptors on the spermatozoon, stimulating cyclic adenosine monophosphate (cAMP) synthesis and, thereby, sperm motility. Recent studies demonstrate that T4 rapidly increases sperm motility and improves the recovery of motile sperm for insemination.[17,18] Other iodothyronines, such as rT3 and T2, may also act through nongenomic mechanisms. Thyroid hormones regulate the redox status of the testis through antioxidant systems such as glutathione peroxidase, which is crucial for sperm motility and antiapoptotic action.[1] Selenium, an essential micronutrient incorporated into glutathione peroxidase and iodothyronine deiodinases, plays a vital role in thyroid homeostasis and sperm motility. Additionally, thyroid hormones modulate the expression of antioxidant systems in the testis. Alterations in thyroid function can affect spermatogenesis and semen quality.[19]

Effects of Thyroid Dysfunction on Spermatogenesis

Thyroid dysfunction, characterized by hypo- or hyperthyroidism, can disrupt normal spermatogenesis and impair male fertility. Hypothyroidism, characterized by insufficient thyroid hormone levels, may lead to reduced sperm production, impaired sperm motility, and altered sperm morphology. In rats administered antithyroid drugs, there is a decrease in seminal volume, arrest of spermatogenesis, and a reduction in the number and diameter of seminal tubules, accompanied by diminished weight of the testes and accessory glands compared

to euthyroid controls.[20] Progressive sperm motility, along with sperm transit time through the epididymis and epididymal secretory activity, are likewise impacted. Additionally, persistent hypothyroidism in rats leads to decreased testicular germ cells and live sperm count, potentially due to increased oxidative stress and reduced antioxidant systems.[21] In newborn mice treated with propylthiouracil, oxidative stress reduces the expression of glucose transporter proteins in Sertoli and Leydig cells, leading to diminished testicular glucose levels and increased apoptosis of germ cells. Additionally, oxidative stress diminishes the expression of connexin 43, a protein involved in regulating germ cell proliferation and apoptosis within the seminiferous epithelium.[22] In humans, teratozoospermia is the most prevalent semen abnormality observed in individuals with hypothyroidism, showing a negative correlation with serum T4 levels. Furthermore, altered sperm motility, reduced accessory gland secretory activity, and decreased ejaculate volume are also documented. Notably, semen abnormalities associated with hypothyroidism are reversible upon restoration of euthyroid status.[23] Conversely, hyperthyroidism, marked by excessive thyroid hormone levels, can also negatively impact spermatogenesis, resulting in decreased sperm quality and fertility. Hyperthyroidism in rodents leads to delayed spermatogenesis, maturation arrest, decreased seminiferous tubule diameters, impaired mitochondrial activity, and reduced lipid concentration.[21] It also affects antioxidant systems, with upregulated catalase and downregulated glutathione peroxidase.[20] In individuals with thyrotoxicosis, more than half experience asthenozoospermia, while approximately 40% manifest oligozoospermia and teratozoospermia, often accompanied by decreased semen volume.[24] Research indicates that hyperthyroid patients typically have lower sperm motility than euthyroid counterparts; however, semen parameters tend to normalize following treatment for hyperthyroidism.[25] A recent study observed significant differences in seminal vesicle volume changes before and after ejaculation between hyperthyroid and hypothyroid patients. Seminal vesicle volume, emptying, and fructose concentration positively correlated with serum FT3 levels. Moreover, there was a positive association between FT3, FT4, and ejaculate volume.[26] Thyroid dysfunction may disrupt germ cell development, impair sperm maturation processes, and induce changes in testicular morphology, contributing to male infertility.[20,26]

Future Directions: An overview of the research gaps is shown in Table 1.

Limitations

The literature presents three main limitations in the existing studies. First, the criteria for diagnosing semen abnormalities varied across studies. Second, many studies included cohorts from infertile couples, complicating the interpretation of results as these men may have had low semen quality due to factors unrelated to thyroid dysfunction. Third, the studies conducted so far often had small cohorts, which reduced their statistical power.

Conclusion

This review highlights the intricate interplay between thyroid hormones and male infertility, emphasizing the importance of thyroid function in spermatogenesis, sperm quality, and reproductive outcomes. Understanding the role of thyroid hormones in male fertility may pave the way for novel diagnostic and therapeutic approaches to address male infertility associated with thyroid dysfunction.

Table 1.

Overview of the research gaps and proposed future research directions in the field of thyroid dysfunction and reproduction. [1, 20, 26]

Research focus	Existing gaps	Proposed research directions
Thyroid dysfunction and male infertility	Lack of comprehensive understanding of causal mechanisms underlying the association between thyroid dysfunction and male infertility	Conduct prospective studies elucidating causal mechanisms between thyroid dysfunction and male infertility.
	Limited longitudinal investigations examining the long-term impact of thyroid hormone levels on reproductive outcomes	Undertake longitudinal investigations examining the impact of thyroid hormone levels on spermatogenesis, sperm quality, and fertility.
	Insufficient clinical trials evaluating the efficacy of thyroid hormone modulation in improving fertility outcomes in men	Design well-controlled clinical trials assessing the efficacy of thyroid hormone modulation in improving fertility outcomes.
	Limited evidence on the effects of thyroid hormone replacement therapy on sperm parameters and reproductive hormone levels	Evaluate the effects of thyroid hormone replacement therapy on sperm parameters, reproductive hormone levels, and pregnancy rates.
	Scarcity of research exploring the potential role of novel therapeutic targets in male fertility	Explore the potential role of novel therapeutic targets targeting thyroid hormone pathways in male fertility.
	Inadequate assessment of the safety and efficacy of thyroid hormone analogs and receptor modulators	Investigate the safety and efficacy of thyroid hormone analogs, receptor modulators, or pharmacological agents in improving fertility.
	Lack of optimized diagnostic and therapeutic strategies for improving reproductive outcomes in affected individuals	Foster research endeavors to optimize diagnostic and therapeutic strategies for improving reproductive outcomes in affected individuals.

Additional investigation is necessary to explore the impact of hyperthyroidism or hypothyroidism on nontraditional sperm parameters and the potential influence of subclinical thyroid dysfunction on male fertility.

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Competing Interests

The authors declare that they have no competing interests.

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