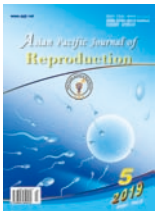

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Thyroid hormones in male reproduction and infertility

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ABSTRACT

Thyroid hormones have been well studied for its relevance to male reproduction in the last few decades. They are considered as essential regulators of male reproductive functions and play vital roles in male gonadal developments. Hyperthyroidism and hypothyroidism both affect testicular functions and influence neuroendocrine regulations over reproductive functions *via* the crosstalk between the hypothalamic-pituitary-thyroid axis and the hypothalamic-pituitary-gonadal axis. The alterations in the male reproductive hormonal milieu by thyroid hormones may lead to reduced testosterone levels and deterioration of semen quality. However, there are very few reports on the direct effects of thyroid disorders upon testicular functions and semen quality. This article aims to review the available literature to present a concise updated concept on the regulation of male reproductive functions by the thyroid hormones, and the possible mechanism by which thyroid dysfunctions affects testicular functions.

1. Introduction

Thyroid hormones may modulate male reproductive functions by various routes, which have been the research interests since the past several decades. However, the exact mechanism of how thyroid hormones associate with male infertility remains elusive[1]. A global declining trend in semen quality over the last decades presents an alarming revelation on male fecundity[2-6]. To unveil the underlying causatives for such declining pattern in male fertility parameters, the endocrine regulations of male reproduction have been set forth as one of the major research interests. Male subfertility or infertility involves multivariate causatives with innumerable environmental and lifestyle factors leading to endogenous modulations[7-11]. They may disrupt the physiological hormonal milieu, among which one of the most important is the thyroid hormone profile that carries out versatile functions[5,12] and also essentially determines normal male reproductive functions. The altered levels in thyroid hormones have deleterious impacts upon semen quality and male fertility[13].

The overall idea of thyroid hormone functions in the regulation of male reproduction can be contemplated through several studies[14,15]. However, the mechanisms of how altered thyroid profile affects male fertility parameters are the subjects that are less delved[16]. This article thereby aims to review and present a concise updated knowledge on the general functions of thyroid hormones in regulating male reproductive functions and the possible mechanism by which thyroid disorders lead to altered testicular functions and semen quality.

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2. Genomic and non-genomic effects of thyroid hormones on male reproduction

Mechanism of action of thyroid hormones is mainly fulfilled through transcriptional regulation. Thyroid hormone nuclear receptors were found to be expressed in fetal and adult Sertoli cells[17]. Binding of triiodothyronine (T3) to its receptors in testicular cells activates gene transcription and protein synthesis as well as Sertoli cells proliferation and differentiation[18,19]. The non-genomic effects may comprise binding of thyroid hormones to their nonnuclear receptors or to affect cell's structure, metabolic rate, and proliferation of cells. However, the differences between genomic and nongenomic actions of the hormone have not yet clearly understood[20]. It was demonstrated that binding to nonnuclear receptors enhances the synthesis of cyclic adenosine monophosphate, the releasing of calcium, and the improvement of sperm kinetics. It was reported that addition of thyroxine (T4) to semen samples significantly increased hypermotility within 20 minutes[21]. Also, other iodothyronines could have an unknown non-genomic effect on spermatozoa by binding to its cytoskeleton or mitochondria[20].

Furthermore, thyroid hormones were known to regulate redox status and involve antioxidant systems[22]. Increased oxidative stress, due to neonatal hypothyroidism, has impaired the testicular glucose homeostasis, which may affect germ cell survival and proliferation as well as expression of proliferating cell nuclear antigen[23]. In transient hypothyroidism, there is higher protein carbonylation with a reduction in levels of superoxide dismutase (SOD), catalase, glutathione reductase, and glutathione peroxidase. While in the persistent type, only SOD and catalase levels were increased[24].

3. Impact of hypothyroidism on semen parameters and sex hormones

Hypothyroidism is a pathological state of reduced circulating levels of T4 and T3 and increased thyroid stimulating hormone. Such decreased thyroid hormones have been reported to positively correlate with reduced serum testosterone level[25,26]. This condition is related to several male reproductive disorders, such as hypoactive sexual behavior, erectile dysfunctions, delayed ejaculation, and deteriorated semen quality[27]. Hypothyroidism and male infertility have been associated through different studies[26,28,29] but it is not yet clear how hypothyroidism may directly affect semen quality[30].

3.1. Human studies

Hypothyroidism in men is not as common as found in women[31,32], and its occurrence in men can be due to chronic exposure to various endocrine disruptors[33,34]. It has been reported that hypothyroidism may cause a slight reduction in the serum levels of sex hormone-binding globulin (SHBG) and free testosterone as compared to that in the euthyroid men[31,32]. The responsiveness of the gonadotropic cells of the anterior pituitary to gonadotropin-releasing hormone (GnRH) for the secretion of luteinizing hormone (LH) may get altered in hypothyroidism which leads to the altered hormonal milieu of the hypothalamic-pituitary-testicular axis[31]. It has been shown that T4 therapy could potentially result in an elevation of plasma testosterone level to normal in hypothyroid men[27].

Subclinical hypothyroidism in men has been shown to have insignificant impacts on semen quality in terms of sperm count, morphology and motility[35]. However, short-term post-pubertal hypothyroidism has been suggested to reduce semen volume[26,36], sperm motility and secretions by the accessory glands[31,32]. De la Balze *et al* demonstrated testicular histological abnormalities in six hypothyroid men with prepubertal/pubertal hypothyroidism. Through these observations it had been suggested that severe and prolonged hypothyroidism since childhood or puberty may lead to inhibition upon pituitary gonadotropins secretion that in turn may affect testicular morphology and functions[37]. Wortsman *et al* have found reduced levels of serum testosterone and concentrations of SHBG in most of the male subjects with hypothyroidism[25]. Corrales *et al* had also demonstrated that short-term post-pubertal hypothyroidism in men could not alter the testicular functions to the extent to deteriorate semen quality[26]. Jaya Kumar *et al* studied the male reproductive and endocrine functions in eight primary hypothyroid men. Their investigation proceeded from the hypothyroid state to the euthyroid state with T4 therapy. The study claimed some improvements in semen quality as the subjects achieved euthyroid state[36]. In a prospective controlled study, Krassas *et al* had also put forth that hypothyroidism impairs spermatogenesis, with alterations in sperm morphology and sperm motility[38].

3.2. Animal studies

Studies in rats demonstrated that hindering thyroid hormone secretions by antithyroidal drugs leads to spermatogenic arrest, reduction in seminiferous tubular diameter, seminal volume, weight of testicles, epididymis and prostate gland[39–42]. Hypothyroidism in rats has also been associated with impairment in progressive sperm motility, transit time of sperm through the epididymis and secretions of the accessory glands[43,44]. This condition also seems to affect sperm acrosome and mitochondrial functions[43]. Moreover, a significant decline in the number of viable testicular germ cells has been evident in rats with both transient and persistent hypothyroidism[24], which may attribute to reduced antioxidant capacity and induction of testicular oxidative stress[24,41]. As thyroid hormones are essential for regulation of Sertoli cells differentiation, reduced levels of thyroid hormones after birth in rodents with congenital hypothyroidism have been shown to result in unregulated Sertoli cells proliferation and delay in their differentiation. This resulted in an uncontrolled high testicular weight and unregulated sperm production[45,46].

3.3. Mechanism of action

Hypothyroidism characterized by reduced circulating levels of T3 and T4 may decrease SHBG concentrations and serum testosterone level, thereby impairing spermatogenesis. Thyroid insufficiency for a long period in childhood or puberty may lead to inhibition in pituitary gonadotropin secretions impeding gonadal growth, functions, secretory activities of the accessory glands, and may also induce erectile dysfunction, delayed ejaculation, lower libido and deteriorate semen quality. It also results in decreased seminiferous tubular diameter and net organ weight of testicles, epididymis and prostate gland thereby leading to impaired sperm development, sperm motility, and their transport through the epididymis. Sperm vitality may also get affected in conditions of hypothyroidism owing to the induction of testicular oxidative stress[47].

4. Impact of hyperthyroidism on semen parameters and sex hormones

4.1. Human studies

Hyperthyroidism, a state of elevated serum total T4 levels is related to enhanced circulation levels of SHBG and reduced metabolic clearance rate of serum testosterone[48,49]. Hyperthyroid men mainly suffer from subnormal levels of bioavailable testosterone[50] and an increase in circulating estradiol levels. These alterations in sex hormones may lead to gynecomastia[50], reduced libido[51] and occurrence of erectile dysfunction[52]. It is also evident that the LH and follicle-stimulating hormone responses are exaggerated towards the exogenous administration of GnRH in hyperthyroid men[30,53]. The changes in the reproductive hormones profile thereby affect testicular functions and alter semen quality.

There are very few clinical studies that have correlated hyperthyroidism with semen quality. Clyde *et al* had reported that out of three hyperthyroid male patients in a clinical study, two was detected with oligozoospermia with reduced sperm motility, while the third had reduced sperm count besides having decreased sperm motility[54]. Kidd *et al* had also shown decreased sperm counts ($<40 \times 10^6$/mL) in hyperthyroid men[49]. The clinical study by Hudson and Edwards in 1992 with 16 hyperthyroid men reported similar observations[55]. The study by Abalovich *et al* on the effect of hyperthyroidism on spermatogenesis in 21 male subjects showed that nine had reduced sperm counts, 18 had impaired sperm motility and 13 had defects in progressive sperm motility[50]. Krassas *et al* in a prospective study with 23 men had investigated semen parameters comparing the data with 15 euthyroid men used as control. They treated the hyperthyroid men with methimazole alone or in combination with radioiodine to render them euthyroid, while they performed semen analysis both pre- and post-treatment phases. The results showed slight reductions in mean sperm density, alterations in sperm morphology and significant reductions in mean sperm motility, as compared to controls[56]. They have demonstrated an improvement in sperm count and sperm motility after the tenure of treatment[56].

In humans, thyrotoxicosis which leads to an uncontrolled rise in levels of circulating thyroid hormones has been reported to be closely associated with asthenozoospermia, oligozoospermia and teratozoospermia. The conditions of excessive thyroid hormones in circulations lead to diminished semen volume (hypoposia)[30,50].

4.2. Animal studies

There is a deficit in animal research on the association of hyperthyroidism and semen quality. Based on the reports from few noteworthy studies, it may be suggested that hyperthyroidism in rats may be associated with delayed spermatogenesis[46], the reduced diameter of the seminiferous tubules[39], and impaired mitochondrial activity[57]. A study has demonstrated that hyperthyroidism in murine model upregulates catalase activities, and downregulates glutathione peroxidase activities[40].

4.3. Mechanism of action

Hyperthyroidism is characterized by increased circulating T4 levels, compromised responsiveness of LH and follicle-stimulating hormone, altered endocrine profile, all of which result in impaired testicular functions, morphology, reduced seminiferous tubule diameter, delayed spermatogenesis, stunted sperm development and reduced sperm motility[25]. These disruptions in male reproductive functions cause low sperm count and deteriorated semen quality in hyperthyroid men. Hyperthyroidism-induced changes in the redox status of the testis, in the Leydig cells, Sertoli cells and germ cells, as well as impaired sperm mitochondrial activities, severely affect sperm count, vitality, and motility, thereby deteriorating semen quality[47].

5. Thyroid disorders and male reproductive dysfunctions

5.1. Serum SHBG and androgen binding protein (ABP) levels

Altered thyroid status affects the liver and Sertoli cells production of both SHBG and ABP levels that transport testosterone. In thyrotoxicosis, SHBG, as well as testosterone, is increased due to the reduction in its metabolism[52]. However, ABP production by Sertoli cells was decreased in the culture medium following exgenous T3 administration[52].

5.2. Sexual dysfunction: libido and erectile dysfunction

Thyroid hormones, along with several other metabolic hormones, regulate the ejaculatory process. Thus, hypothyroidism has been recorded to be associated with delayed ejaculation. In contrast, premature ejaculation is related to hyperthyroidism[58]. In a multicenter trial to assess the prevalence of sexual dysfunctions in patients with thyroid disorders, hypoactive sexual desire, erectile dysfunction, and delayed ejaculation were recorded to be higher in hypothyroid patients (64.3%). The prevalence of premature ejaculation was higher in hyperthyroid patients (50.0%) than the hypothyroid counterparts (7.1%). Subsequent normalization of the thyroid hormone levels in hyperthyroid patients, premature ejaculation was declined to 15%, while delayed ejaculation was improved in half of the treated hypothyroid male patients[59]. In another survey that examined the effects of thyroid dysfunctions on male sexual health by using the Sexual Health Inventory for Males (SHIM), a significant difference was reported between patients and controls; 78.9% of patients with thyroid dysfunctions scored 21 or less (normal SHIM: 22-25) *versus* 33.8% of controls. However, following treatment, a significant increase in SHIM scores was noted in both hyperthyroid and hypothyroid patients (P<0.000 1). Also, a high prevalence of erectile dysfunction was noted in patients with hyperthyroid and hyperthyroid patients, compared to controls[60].

5.3. Spermatogenesis and semen parameters

Thyroid hormone is a major metabolic regulator of testicular development and function that could influence spermatogenesis[61]. Evidence from clinical and experimental studies in male rats/human revealed that thyroid disorders (either excess or deficient), as well as altered thyroid status, are associated with controversial effects on male reproductive physiology. For instance, transient hypothyroidism in neonatal rats was associated with enlargements in testicular size[62], hyperthyroid patients were noted to have lower sperm motility, asthenozoospermia, oligozoospermia and teratozoospermia, compared to the control groups with euthyroid state[40,63]. In addition, a recent study revealed a positive association of free T3 with ejaculate volume and seminal fructose levels[64].

Hypothyroid state could affect the sperm morphology and motility, and hence increase the incidence of teratozoospermia index. In patients with hypothyroidism, a significant difference was detected in semen parameters: sperm count, sperm motility and morphology as well as seminal vesicles longitudinal diameters.

Rodent models with induced hypothyroidism presented decreased sperm production, viable spermatozoa in the epididymis, and testicular germ cell count[24,43]. It also reduces gonadal androgen receptor expression[65,66], sperm motility, fertilizing capacity, and epididymal secretory activity. Additionally, it may affect the mitochondria such as alteration of mitochondrial lipid peroxidation[24], apoptotic changes in epididymal mitochondria[67], reduction in acrosome integrity and mitochondrial activity[43]. Moreover, an increase in the expression of thyroid hormones receptors (Thra1) and a decrease in the expression of deiodinases (Dio3) were associated with hypothyroidism, suggesting a critical metabolic role of thyroid hormones in spermatogenesis[43].

Rat models with hyperthyroidism also reflected a delayed spermatogenesis, maturational arrest, Leydig cell proliferation, reduction in the diameters of the seminiferous tubule, alteration in mitochondrial activity and antioxidant status. In addition, it increases the expression of monocarboxylate transporter 8 and plasma membrane integrity, solute carrier family 16 member 2[40,46,60,68,69].

6. Thyroid disorders and testicular oxidative stress

6.1. Hyperthyroidism and testicular oxidative stress

Hyperthyroidism seems to render the tissues more vulnerable to oxidative damages[70,71]. As thyroid hormones commonly invigorate physiological functions, it is quite inevitable that hyperthyroidism would overstimulate metabolic state, and upregulate excess free radical generation, resulting in oxidative damage and lipid peroxidation in different tissues[70,72]. Testis, having a substantial amount of unsaturated fatty acids, potent machineries to generate reactive oxygen species along with limited antioxidant capacity[73], possesses much higher susceptibility towards oxidative damage compared to other tissues[74].

Studies have reported that induction of hyperthyroidism using different thyroid hormone isomers could result in varying levels of oxidative stress. The testicular oxidative stress has been suggested to get highly elevated in hyperthyroidism as it is evident *via* increased malondialdehyde levels[75], increased thiobarbituric acid reactive substances, high levels of lipid hydroperoxide, protein carbonyl contents or hydrogen peroxide[70]. Alterations in antioxidant defense parameters such as increased testicular glutathione (GSH) contents had been observed in case of short-term *L*-thyroxine treatment to hypothyroid[75]. Treatment with T3 to hypothyroid rats for 3 days showed elevated oxidized glutathione disulfide, decreased in GSH contents, and thereby decreased ratio of reduced to oxidized glutathione in testis[76]. T3 treatment for 5 days showed an increase in testicular GSH contents in mitochondrial as well as post-mitochondrial fractions, along with an increase in testicular ascorbic acid content[70]. Both the mitochondrial and post-mitochondrial fractions exhibited higher 'reduced to oxidized' glutathione ratio in *L*-thyroxine or T3 induced hyperthyroidism[24,70].

Acute hyperthyroidism has been reported to be associated with decreased testicular SOD, while increased testicular catalase (CAT), glutathione peroxidase (GPx) and glucose-6-phosphate dehydrogenase activities[24,70]. It has been shown that in mitochondrial and post-mitochondrial fractions of testis, GPx is increased by many folds in response to *L*-thyroxine[77]. In case of

T3 treatment, seleno-independent GPx activity was demonstrated to be increase only in the testicular mitochondrial fraction[70]. These elevated levels of seleno-dependent and/or independent GPx as responses of hyperthyroidism induction by *L*-thyroxine[77] or T3[70], may be considered as an adaptive response for neutralizing the testicular toxic hydrogen peroxide effects. Such hyperthyroidism-induced alterations in the testicular antioxidant defense mechanisms and oxidative stress parameters affect male fertility in terms of decreased viable and total sperm counts[24,70].

6.2. Hypothyroidism and testicular oxidative stress

Hypothyroidism is also responsible for alterations in testicular redox status, oxidant generation and testicular antioxidant capacity owing to a hypo-metabolic state. Both persistent and transient hypothyroidism have been associated with changes in testicular antioxidant defense mechanism during gonadal development and maturation[73]. Hypothyroidism have been shown to modulate testicular oxidative stress parameters such as reduction in malondialdehyde levels[75] with elevated hydrogen peroxide, protein carbonyl contents, mitochondrial lipid peroxidase[78]. Protein carbonylation in mitochondrial membrane have also been used as a marker for oxidative damage in hypothyroid rat testis[77,79].

In hypothyroid rats, lower levels of testicular GSH have been documented[75]. Contrarily, in hypothyroidism, oxidized glutathione content was shown to be higher which results in decreased 'reduced to oxidized' glutathione ratio in testis[76]. It has been reported that persistent hypothyroidism disrupts the normal testicular redox status in immature rats[77]. Decreased SOD and CAT activities as well as increased GPx activity with reduced glutathione-S-transferase have been demonstrated in the testis of hypothyroid rats[40,76]. However, persistent hypothyroidism has been shown to elevate testicular SOD and CAT activities and reduce GPx and glutathione reductase activities[24]. Chronic hypothyroidism has also been shown to reduce both testicular seleno-dependent and independent GPx[77], which suggests that SOD and CAT are the key enzymes regulating of hypothyroidism-induced oxidative stress, not the GPx[73]. However, the reduced GPx levels affect the testosterone production in hypothyroid rats since the testosterone metabolism needs protection against peroxidation. Reduced serum levels of testosterone in turn impairs normal spermatogenesis leads to increased germ cell apoptosis, and thereby decreases testicular germ cell count and affects the semen quality[70,73,77,80]. Further effects of hypothyroidism in the testicular morphology essentially include the reduced diameter of seminiferous tubule[77]. Hypothyroidism-induced alterations in testicular physiology may be reflected in adulthood with reduced fertility as evidenced through deteriorated semen quality in terms of germ cell viability[70] and sperm counts[73].

7. Crosstalk of thyroid hormones with other hormones and growth factors in regulating male reproductive functions

7.1. Prolactin

The direct effect of physiological doses of prolactin on Sertoli cells was demonstrated to increase the synthesis of ABP, which plays a significant role in Sertoli cell proliferation and metabolism[81]. A study by Koivisto *et al* on the male Beagles reported a significant increase in prolactin level with a single intravenous injection of thyroxin in metoclopramide-induced short-term hyperprolactinemia. Of note, there were no changes in semen quality, LH, and testosterone levels[82]. However, markedly higher prolactin levels were demonstrated in hypothyroid patients in comparison with controls (P<0.001)[83].

7.2. Growth hormone

Increased levels of growth hormone and acromegaly could be associated with thyroid dysfunction. The prevalence of erectile dysfunction among 57 acromegalic subjects was 42.1% especially in a long disease duration[84].

7.3. Insulin-like growth factor (IGF)-1

By increasing the bioactivity of IGF3 *via* blocking IGF-binding proteins, T3 and IGF-3 were found to enhance proliferation and predominant differentiation of type A undifferentiated spermatogonia[85].

7.4. Leptin

Hypothyroidism is associated with weight gain and obesity[86]. Leptin is produced by the adipocytes and reported to have a central and peripheral effects on reproductive tissues. The expression of leptin receptors was observed in Leydig cells, prostate, and seminal vesicles, which influences male reproductive functions[87-89]. Leptin was found to inhibit testosterone in the testis[90,91]; however, it has an indirect effect that could regulate the GnRH function[92]. Hyperleptinemia induces cytokine signaling-3 expression, inhibits phosphorylated signal transducer, and activates the transcription-3 expression. This resulted in a decline in the weight and volume of the testicles as well as the diameter of the seminiferous tubules and the numbers of spermatocytes[93,94]. Also, there is an interaction between thyroid hormones and leptin; a positive correlation was recorded between thyroid stimulating hormone and leptin and body mass index[95]. In hypothyroid patients, serum leptin levels could be increased to overcome the gain of body weight caused by hypothyroidism[96].

8. Conclusions

This review article has critically and concisely presented an updated concept on general functions of thyroid hormones in the regulation of male reproductive functions. Based on available reports, it also has put forth probable mechanism by which thyroid disorders may affect testicular physiology, resulting in altered semen quality. In doing so, the regulations of the testicular redox status *via* thyroid hormones have also been elucidated. However, the review finds that there are several gaps in concept in the proper molecular events that associate thyroid hormonal milieu with altered semen quality, which seeks further research interventions.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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