Thyroid dysfunction and semen quality

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Abstract
Thyroid hormones act on testis in multiple ways and exert their effect on different cell types, including Leydig and Sertoli cells, and germ cells. An excess or deficit of thyroid hormones results in alterations of testis function, including semen abnormalities. More frequently, hyperthyroidism has been associated with reduced semen volume and reduced sperm density, motility, and morphology, whereas hypothyroidism is associated with reduced sperm morphology. Therefore, thyroid function tests should be part of the diagnostic workup of the infertile man. This article is aimed at (1) elucidating how hyperthyroidism and hypothyroidism lead to a reduction in semen quality, briefly reviewing the current literature on murine models and humans, and (2) pinpointing the limitations of the studies carried out so far and identifying new perspectives for future research.

Keywords
male infertility, semen quality, thyroid hormones

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Introduction
The relationship between thyroid and testis has been adequately studied only in the past decades. Particularly, a number of papers have focused on the effects of thyroid hormone on testicular development and function1 and on the relationship between altered thyroid status and infertility.2,3

3,5,3′-triiodothyronine (T3) and thyroxine (T4) regulate testis functioning by genomic and non-genomic effects.2 Genomic effects result from the binding of T3 to its cognate receptor (thyroid hormone receptor, TR) in the nucleus of Sertoli and Leydig cells, where upon binding to the thyroid hormone response elements the hormone–receptor complex activates gene transcription and protein synthesis1,4 (Figure 1). Two genes (TRα and TRβ) encode five isoforms that are obtained by alternate splicing (TRα1, TRα2, TRα3, TRβ1, and TRβ2). TRα2 and TRα3 are devoid of the hormone-binding domain and have been shown to compete with T3 for the binding of the thyroid hormone response element (TRE), suppressing transcription.4 Particularly, TRα1 is the predominant isoform in germ cells (from intermediate spermatogonia to pachytene spermatocyte) and in Sertoli cells, whose development is regulated also by TRβ1 and TRβ2.4 T3 acts on nongerm cells by regulating their proliferation and differentiation1,2 (Figure 1). Particularly, T3 has a double action on Leydig cell, in that in rats it acutely stimulates luteinizing hormone (LH)-mediated steroidogenesis, but chronically inhibits it.3,4 T3 stops Sertoli cell proliferation, determining their number at puberty,5 and alters the attachment between them and gonocytes by inhibiting the expression of the neural cell adhesion molecule5 (Figure 1).

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Nongenomic effects of thyroid hormones result from their binding to nonnuclear receptors sited in the cytoplasmic membrane, cytoplasm, cytoskeleton, and mitochondria of the spermatozoon, enhancing cyclic adenosine monophosphate (cAMP) synthesis and Ca^{2+} release and ultimately sperm motility.\(^2,6\) Recently, T4 was demonstrated to rapidly increase flagellar movements of spermatozoa (hypermotility) and consequently to increase the number of spermatozoa recovered by swim-up.\(^6\) All the samples studied (100%) achieved the 5 million threshold of motile sperm for the intrauterine insemination, compared to the 60% of samples treated with pentoxifylline, an inhibitor of cAMP phosphodiesterase.\(^6\) Other than T3 and T4, in the literature, other iodothyronines have been reported to act through nongenomic mechanisms by binding to cytoskeleton (3,5′,3′-triiodothyronine, rT3) or mitochondria (T2),\(^7\) but their effects on spermatozoa have never been investigated so far.

Finally, thyroid hormones regulate the redox status of testis that relies on a number of antioxidant systems.\(^2\) The most abundant mitochondrial protein in the sperm midpiece is glutathione peroxidase (GPx), which includes a family of selenium-containing proteins.\(^8\) Selenium is a micronutrient that is fundamental for thyroid homeostasis, as it is incorporated in iodothyronine deiodinases, another class of selenium-containing proteins, which catalyzes conversion of T4 to T3.\(^9\) In the testis, GPx has both antioxidant action (when sited in the cytoplasm) and antiapoptotic action (when sited in the mitochondrial capsule).\(^9\) Notably, supplementation of selenium-deficient men resulted in the improvement of sperm motility other than improvement in thyroid autoimmunity.\(^8\) Other antioxidant systems in the testis include superoxide dismutase, γ-glutamyl transferase, catalase, glutathione-S-transferase, cytochrome C, melatonin, vitamin C, vitamin E, and zinc.\(^2\) Interestingly, the expression of γ-glutamyl transferase and catalase is enhanced by thyroid hormones, while that of GPx and cytochrome C is regulated negatively.\(^10,11\)

Given these data, it is not difficult to imagine that an altered thyroid function affects spermatogenesis and therefore semen quality.\(^3,4\) Most of the studies mentioned in this article have been carried out in mice/rats and subsequently in humans.

In this article, we will interchangeably use the terms “hyperthyroidism” or “thyrotoxicosis” to identify thyroid hormone excess.

### Hyperthyroidism

Hyperthyroid rats show a delay in spermatogenesis with maturation arrest, no pachytene spermatocytes, a decrease in seminiferous tubule diameters, an impairment of the mitochondrial activity, and a reduction in lipid concentration.\(^11\) Hyperthyroid rodents have also an alteration of antioxidant systems as catalase is upregulated while GPx is downregulated.\(^10\) In another animal model, the ram, levothyroxine administration causes a reduction in sperm motility and testis weight.\(^12\)

In humans, the excess of circulating thyroid hormones during thyrotoxicosis results in asthenozoospermia in more than half of the patients.\(^13\) Oligozoospermia and teratozoospermia are found in about 40% of thyrotoxic patients. These abnormalities frequently associate with a reduced semen volume (hypoposia).\(^13\) Thus, reduced sperm density, motility, and morphology together with an overall decrease in semen volume are the main semen alterations of thyrotoxic male patients.\(^3\)

Hudson and Edwards\(^{14}\) reported, first, a lower progressive forward motility in 16 adult men with thyrotoxicosis due to Graves’ disease compared with 21 euthyroid controls. Subsequently, Abalovich et al.\(^{13}\) reported asthenozoospermia, oligozoospermia, and teratozoospermia in 85.7%, 42.9%, and 19%, respectively. Krassas et al.\(^{15}\) found that hyperthyroid patients have a lower sperm motility compared to euthyroid controls (mean ± SEM, 28 ± 8% vs 57 ± 7%, \( P < 0.01\)). Notably, semen parameters reverted to normality in the majority of cases.
upon treatment of hyperthyroidism. In a recent study on 163 men referred to an infertility clinic, the rate of subclinical or overt hyperthyroidism was 3.7% or nil. Hyperthyroid patients showed a greater difference in seminal vesicle volume before and after ejaculation compared to hypothyroid patients, which represented 7.4%. Seminal vesicle volume and emptying and fructose concentration correlated positively with serum FT3 levels. In contrast with the previous studies, Lotti et al. found also a positive correlation between FT3, FT4, and ejaculate volume.

**Hypothyroidism**

Sperm abnormalities associated with hypothyroidism are partly similar to those reported in hyperthyroidism. Rats whose thyroid have been blocked with antithyroid drugs show a decrease in seminal volume with an arrest of spermatogenesis and a decrease in the number and diameter of seminal tubules. A concomitant reduction in testis and accessory gland weight compared with euthyroid controls is observed. Progressive sperm motility, sperm transit time through the epididymis, and epididymal secretory activity are also affected. Furthermore, the number of testicular germ cells is decreased in rats with persistent hypothyroidism but not in those with transient hypothyroidism, while the number of live sperms is reduced both in rats with transient and persistent hypothyroidism. This reduction in sperm vitality may result from unbalance between the increased oxidative stress, given, for instance, by lipid peroxidation, and the reduced antioxidant systems, such as catalase and superoxide dismutase. Very recently, Sarkar and Singh have shown that oxidative stress reduces the expression of glucose transporter 3 (GLUT3) in Sertoli cells and glucose transporter 8 (GLUT8) in Leydig cells in propylthiouracil-dosed newborn mice, with a consequent decrease in testicular glucose levels and increased apoptosis of germ cells. Furthermore, oxidative stress down regulates the expression of connexin 43, a gap junctional protein in the seminiferous epithelium that regulates proliferation and apoptosis of germ cells. Since thyroid hormones promote Sertoli cell differentiation and inhibit their proliferation, lower concentrations of thyroid hormones after birth, such as in rats affected by congenital hypothyroidism, lead to the extension of the Sertoli cell proliferative period, delaying their differentiation and resulting in increase of testis weight and sperm production.

In humans, the most frequent semen abnormality in patients with hypothyroidism is teratozoospermia. Indeed, teratozoospermia index, namely, the number of morphology alterations per spermatozoosperm, correlates negatively with serum T4 levels. Altered sperm motility, altered secretory activity of the accessory glands, and low ejaculate volume have been also reported. Similar to hyperthyroidism, semen alterations during hypothyroidism are reversible and mostly disappear upon achieving euthyroidism.

**Discussion**

Overall, thyroid dysfunction leads to multiple alterations of semen quality that include reduced volume, sperm density, sperm motility, and sperm morphology. Particularly, concerning conventional parameters of the seminal fluid, hyperthyroidism causes hypospermia, oligozoospermia, asthenozoospermia, and teratozoospermia, whereas hypothyroidism is associated more frequently with teratozoospermia. The mechanism whereby thyroid hormone excess or deficiency affects semen quality is poorly understood in humans. It may result from a direct effect on sperm cell, as well as from an effect on nongerm cells (Figure 2). In thyrotoxic rats, sperm mitochondrial activity is reduced and antioxidant defense is altered. Spermatogenesis is also delayed. In addition, neonatal Sertoli cell proliferative period is shortened under hyperthyroid conditions. On the contrary, thyroid hormone deficiency reduces sperm vitality and delays sperm transit through the epididymis. Furthermore, both hyperthyroidism and hypothyroidism are associated with altered macroscopic characteristics of seminal fluid such as reduced volume because of reduced secretory activity of accessory glands (Figure 2).

To the best of our knowledge, only one recent study focused on biofunctional nonconventional sperm parameters in rats. In this study, the authors found that hypothyroidism causes a reduction in acrosome integrity and mitochondrial activity, while it increases plasma membrane integrity. Instead, hyperthyroidism decreases mitochondrial activity and increases plasma membrane integrity. Regarding humans, no study to date has addressed
nonconventional sperm parameters during either the hyperthyroid or hypothyroid state.

Only one recent study has focused on fertility in men with subclinical thyroid dysfunction,16 but the small number of patients investigated prevents from drawing firm conclusions.

Limitations of the studies in literature are three. First, criteria used to diagnose semen abnormalities were frequently different from study to study. Second, in several studies, cohorts included men from infertile couples, namely, patients with low semen quality for reasons other than thyroid dysfunction. Third, studies performed so far have enrolled small cohorts of patients, hence lowering their statistical power.

In conclusion, although the screening of thyroid function is not recommended to date as part of the diagnostic workup of the infertile male, it might be reconsidered in light of the physiopathological background, provided that the evidence is further confirmed by multicentric studies on larger and homogeneous cohorts. Indeed, both hyperthyroidism and hypothyroidism are common in the general population, with a prevalence of 1% and at least 6%, respectively.

Further research is needed to investigate (1) whether hyperthyroidism or hypothyroidism affects nonconventional sperm parameters (2) whether subclinical thyroid dysfunction influences male fertility.

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Figure 2. Effects of thyroid dysfunction on seminal characteristics in rodents and in humans.
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