

## Thyroid Disorders and Semen Quality

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### ABSTRACT

Thyroid hormones and their impacts on male reproduction have been reported in numerous studies in past few decades. They are the crucial players in the regulation of male gonadal developments and reproductive functions. An excess or deficit of thyroid hormones not only alter the testicular functions but also interrupts neuroendocrine axis through the crosstalk between hypothalamic-pituitary-thyroid (HPT) axis and hypothalamic-pituitary-gonadal (HPG) axis. These changes result in decreased testosterone level and altered seminal plasma components which affect semen quality. The reports on the direct effects of thyroid disorders on semen quality are scanty. Thus, this review scrutinizes the available literature and aims to elucidate (a) the normal thyroidal regulations of semen parameters, (b) effects of hypothyroidism on semen quality (c) effects of hyperthyroidism on semen quality, and (d) the possible mechanism of action of thyroid dysfunctions on the alterations of semen quality. This review also highlights the limitations of the studies carried out so far and accentuates the necessity of large-scale human studies and animal studies specifically focusing on the molecular events of thyroid disorder-induced alterations in semen quality.

**Keywords:** Hypothyroidism, Hyperthyroidism, Semen quality, Sperm count, Sperm motility.

### INTRODUCTION

Thyroid hormones have adopted multivariate mechanisms to influence male reproductive functioning and have keenly been investigated since past several years, to aid proper understanding of the relation between the thyroid hormones and male infertility<sup>1-3</sup>. Over the past few decades, a worldwide declining trend in semen quality has been reported which is an alarming revelation of deterioration of male reproductive health<sup>4-10</sup>. This threatening trend in semen quality has drawn the attention of reproductive research arena in order to scrutinize the underlying causes

to bring about effective therapeutic and preventive measures. Although extensive research is still needed to unveil all the factors contributing to this global decline in semen quality, several key environmental and lifestyle factors have been identified in this aspect<sup>11-16</sup>. All these factors disrupt the normal endocrine milieu including the normal thyroid hormone profile<sup>7, 11, 13</sup> which is reportedly a vital endogenous factor influencing semen quality, and its variations are associated with alterations in the later even inducing male infertility<sup>17</sup>.

There have been detailed investigations concerning the general role of thyroid hormone in



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the regulation of male reproductive functioning<sup>2, 18</sup>, but studies revealing the relationship between thyroid disorders with that of altered state in semen quality are barely available<sup>19</sup>. Hence, this review aims to present a concise concept of, (a) normal thyroid function in the regulation of semen parameters, (b) hypothyroidism and semen quality (c) hyperthyroidism and semen quality, and the (d) possible mechanism of action of thyroid dysfunction on alterations of semen quality.

#### **Normal thyroid function and semen quality**

Thyroid hormones basically regulate semen quality by altering serum testosterone level<sup>20</sup>. The other mechanisms of thyroid hormones in the regulation of semen quality are mediated by the regulation of the seminal plasma components (calcium, fructose, magnesium, zinc etc.). By maintaining these components thyroid hormones regulate different seminal properties, like sperm motility, viability, and semen volume. Moreover, sufficient amount of testosterone promotes spermatogenesis and maintains sperm count<sup>21</sup>. Testosterone, together with the seminal components, also regulates semen parameters like sperm motility and sperm morphology<sup>18</sup>. Thyroid hormones evidently modulate the hypothalamic-pituitary-gonadal (HPG) axis through the crosstalk between HPG and hypothalamic-pituitary-thyroid (HPT) axis. It may also directly act either individually or in combination with follicular stimulating hormone (FSH) and/or luteinizing hormone (LH) on male reproductive tissues to exert their modulatory actions upon the gonadal development, testosterone synthesis, and spermatogenesis thereby accentuating the semen quality<sup>22</sup>.

Thyroid hormones, 3,5,3'-triiodothyronine (T3) and 3,5,3',5'-tetraiodothyronine or thyroxine (T4) may adopt genomic and nongenomic mechanisms to lay their effects upon semen quality<sup>2</sup>. In various vital male reproductive cells (germ cells, Leydig cells, and Sertoli cells), specific thyroid hormone membrane transporters have been detected such as organic anion-transporting polypeptides (OATP)-F in the Leydig cells transports T4 and reverse T3 (3',5',3-triiodothyronine, rT3) with high affinity<sup>23</sup>. Also, three novel OATP members have been designated as gonad-specific transporters (GSTs) in the rat (GST-1 and GST-2) and human testis<sup>24</sup>. In rat Sertoli

cells, Leydig cells and spermatogonia, GST-1 and GST-2 are shown to be highly expressed, both of which transport T4 and T3 in these cells. Moreover, two novel splice variants of OATP3A1-V1, OATPs, and OATP3A1-V2 were found to be expressed in Sertoli cells and testicular germ cells respectively<sup>25</sup>. In adult testicular cells both D1 and D2 are present. Their relative levels of activity indicate that D2 is the predominant activating enzyme in this organ. It is noteworthy that the highest level of D2 expression might play a major role in the intracellular conversion of T4 to T3<sup>26</sup>.

Thyroid hormone receptors are found in various compartments of the testis. Thyroid hormones can bind to specific nuclear thyroid hormone receptor (TR) (family of ligand-dependent transcription factors) in the Sertoli cells and Leydig cells, thereafter binding to the Thyroid Hormone Responsive Elements (TRE) to regulate gene transcription and protein synthesis<sup>2</sup>. Two genes reportedly encode this receptor, namely, c-erb A $\beta$  and c-erb A $\alpha$ . The c-erb A $\alpha$  gene encodes three different protein receptors,  $\alpha$ 1,  $\alpha$ 2 and  $\alpha$ 3 through alternative splicing, while the c-erb A $\alpha$  gene codes for  $\beta$ 1 and  $\beta$ 2 receptors<sup>27</sup>. In human Sertoli cells, expression of only the TR $\alpha$ 1 and TR $\alpha$ 2 isoforms have been documented, expression of TR $\alpha$ 2 being higher at all the stages of human development and the TR $\alpha$ 2/TR $\alpha$ 1 ratio elevates progressively in the Sertoli cells from fetal to adult life. Moreover, thyroid hormone receptors on germ cells suggest that there is a significant role of thyroid hormones in maintaining the survival and growth of different germ cells population. These receptors are also being detected on different stages of developing germ cells. TR $\beta$ 1 appears in the intermediate type spermatogonia while expression of TR $\alpha$  has been observed in type B spermatogonia<sup>18</sup>.

Binding of T3 to T3 receptors on Sertoli cells modulates the secretion and synthesis of Androgen Binding Protein (ABP), activins and inhibins. Thus T3 regulates testosterone secretion via influencing the HPG axis through inhibins and activins and also locally by altering ABP concentration<sup>28</sup>. In Sertoli cells, expression of certain genes and proteins determine its maturational status. Immature Sertoli cells exclusively express anti-Mullerian hormones (AMH), aromatase, neural cell adhesion molecule

(NCAM) whereas; in mature Sertoli cells, the characteristic markers of the androgen receptor (AR) are p27Kip1 and p21Cip1<sup>29</sup>. Expressions of immature Sertoli cell markers are suppressed by T3, including AMH, NCAM, and aromatase. Thyroid hormones induce Leydig cell development and also steroidogenesis. Hardy *et al.*, (1993) have demonstrated that in propylthiouracil (PTU) treated hypothyroid rats, the Leydig cell number is significantly increased as compared with euthyroid controls<sup>30</sup>. Thyroid hormones also positively affect Leydig cell steroidogenesis. T3 induces *de novo* synthesis of a 52 KDa soluble protein, which stimulates androgen production, testosterone synthesis within the Leydig cells<sup>31-33</sup>.

Thyroid hormones also help to maintain the redox status of the testis by regulating the balance between Reactive Oxygen Species (ROS) and antioxidant capacity<sup>34</sup>.

Thyroid hormones can also affect the semen parameters through the non-genomic mechanism which includes binding to nonnuclear receptors placed in the cytoplasmic membrane, cytoplasm, mitochondria, and cytoskeleton of the spermatozoon, inducing cAMP synthesis and Ca<sup>2+</sup> release and enhancing sperm motility<sup>35</sup>. T4 reportedly augments flagellar movements of spermatozoa and also the number of mature sperm recovered by swim-up. This is also evident from the study where a significantly greater quantity of motile sperm was obtained as compared to the samples that received pentoxifylline treatment (cAMP phosphodiesterase inhibitor) in order to perform intrauterine insemination<sup>35</sup>. Other iodothyronines (3,5 diiodothyronine or T2, rT3) through the nongenomic mechanisms bind to cytoskeleton or mitochondria to modulate semen parameters<sup>35</sup>.

The available studies suggest that normal putative thyroid activity seems vital for maintaining semen quality via genomic or non-genomic mechanisms, either locally acting on Sertoli cells, Leydig cells or germ cells or by affecting crosstalk between the classical endocrine axes, HPT axis, and hypothalamic-pituitary-testicular axis. Further deep insights are required to obtain clearer knowledge about these mechanisms.

## **Hyperthyroidism and semen quality**

### ***Human studies***

Hyperthyroidism is a condition of increased total thyroxine (T4) levels which has been associated with an increase in sex hormone binding globulin (SHBG) in circulation and decrease in the metabolic clearance rate of testosterone<sup>36, 37</sup>. In hyperthyroid males, bioavailable testosterone was found to be subnormal<sup>38</sup> with an elevated circulating estradiol (E2). It can result in gynecomastia<sup>38</sup>, decreased libido<sup>39</sup> and erectile dysfunction<sup>40</sup>. Studies have also reported that LH and FSH responses to GnRH administration are exaggerated in hyperthyroid males<sup>41, 42</sup>. Altered reproductive hormone levels affect sperm production and maturation, thus altering semen quality.

*The correlation between hyperthyroidism and semen quality has been reported only in few clinical studies. Clyde et al.*, investigating in three hyperthyroid male patients, found that out of the three patients, two had marked oligozoospermia with decreased motility while in the third patient they found a borderline low sperm count along with a decrease in sperm motility<sup>43</sup>. Kidd *et al.* had investigated among five hyperthyroid patients and reported reduced sperm counts (less than 40×10<sup>6</sup>/ml) in all the patients<sup>37</sup>. Hudson and Edwards (1992) studied the spermogram of 16 hyperthyroid males and observed reduced sperm density. They have also reported that the sperm motility in these patients was significantly reduced as compared to the euthyroid males<sup>44</sup>. Abalovich *et al.* studied the effect of hyperthyroidism on spermatogenesis in 21 patients. Nine patients (43%) were found to have low total sperm counts, 18 (86%) were observed with motility defects, and 13 (62%) were presented with progressive motility abnormalities<sup>38</sup>. Later, Krassas *et al.* in a prospective study, investigated the semen parameters in 23 hyperthyroid males and compared the results with 15 healthy euthyroid controls. They performed semen analysis both before and after five months of the restoration of euthyroidism that is achieved by treatment of methimazole (MMI) alone in 14 patients, or MMI plus radioiodine (R-131) in nine patients. Total fructose, Mg and Zn concentrations were also measured in the seminal plasma of 16 patients. But their concentrations were found unaltered in both patients, both before and

Table 1: Hyperthyroidism and hypothyroidism and their effects on semen parameters

Study	Sample (s)	Semen parameters
Hyperthyroidism		
Clyde <i>et al.</i> (1976)	3	All the patients had decreased sperm motility, two out of three had severe and one had borderline oligozoospermia.
Kidd <i>et al.</i> (1979)	5	All had sperm counts of less than $40 \times 10^6$ /ml
Hudson and Edwards (1992)	16	Sperm densities were found to be low but not different from controls, sperm motility was significantly lower in hyperthyroid patients.
Abalovich <i>et al.</i> (1999)	21	Nine patients had decreased sperm counts, a total of 18 patients had decreased sperm motility.
Krassas <i>et al.</i> (2002)	23	Mean sperm densities were low but did not differ from controls, sperm motility significantly lower in hyperthyroid patients.
Lotti <i>et al.</i> (2016)	163	Seminal vesicle emptying, semen volume and fructose concentration, correlated positively with serum free T3 levels
Vaghela <i>et al.</i> (2016)	351	Semen volume, sperm viability decreased significantly; percentage of immotile sperm increased; no sperm head or tail abnormality was found, mid-piece abnormalities were recorded
Hypothyroidism		
Griboff (1962)	5	Sperm count was normal, sperm motility had decreased in two patients.
Krassas <i>et al.</i> (2008)	25	Morphology was the only sperm parameter significantly affected, motility was also affected, but differences with samples from normal males were not statistically significant.
Vaghela <i>et al.</i> (2016)	351	Semen volume, sperm motility, sperm viability decreased significantly; no sperm head abnormality was found, mid-piece and tail abnormalities were recorded

after reaching the euthyroid condition, and values did not correlate with the semen parameters or with the pre-treatment level of thyroid hormones. The results of semen parameters had indicated unaltered semen volume in patients but the mean sperm density was reduced than that of controls, however, this difference was not statically significant<sup>45</sup>. A similar change was recorded for sperm morphology, however, in hyperthyroid men, the mean sperm motility was found decreased than the controls (mean±SE 28±8% vs. 57±7%, P<0.01). They have concluded that sperm morphology did not change after the treatment of hyperthyroidism. However, improvements in sperm motility and the density was recorded<sup>45</sup>.

In humans, the excess of circulating thyroid hormones that are found during thyrotoxicosis reported to result in asthenozoospermia in more than half of patients. Oligo- and teratozoospermia are found in about 40% of patients. These abnormalities frequently associated with a reduced semen volume (hypoposia)<sup>38, 41</sup>. In a recent study on 163 men referred to an infertility clinic, the rate of subclinical or overt hyperthyroidism was 3.7% or nil<sup>46</sup>. Hyperthyroid patients showed a greater difference in seminal vesicles volume before and after ejaculation compared to hypothyroid patients, which represented 7.4%. This difference, together with seminal vesicle emptying, semen volume and fructose concentration, correlated positively with serum free T3 levels<sup>46</sup> (Table 1).

#### **Animal studies**

Studies on animals correlating hyperthyroidism and semen quality are scanty. Hyperthyroid rats show a delay in spermatogenesis<sup>47</sup>, a decrease in seminiferous tubules diameters<sup>48</sup>, and an impairment of the mitochondrial activity<sup>49</sup>. Choudhury demonstrated in the murine model that hyperthyroidism positively regulated catalase, but negatively glutathione peroxidase<sup>50</sup>. Alterations in the redox status of testicular germ cells, Sertoli cells, and Leydig cells may affect the quality of semen.

#### **Hypothyroidism and semen quality**

Hypothyroidism is a clinical condition characterized by decreased circulating T3 and T4 levels. This condition has also reported being associated with a decrease in serum testosterone level<sup>51, 52</sup>. Thus it is related to erectile dysfunction,

delayed ejaculation, hypoactive sexual desire and decreased semen quality<sup>53</sup>. There are several studies that reported the correlation between hypothyroidism and male infertility<sup>20, 43, 52</sup> but the direct effects of hypothyroidism on semen quality have not been well documented<sup>41</sup>.

#### **Human studies**

Though hypothyroidism is less prevalent in men compared to women<sup>54, 55</sup>, it can be caused due to the chronic exposure of endocrine disruptors<sup>56, 57</sup>. In hypothyroid men, the concentration of SHBG and serum free testosterone usually remain normal or lower than euthyroid men<sup>54, 55</sup>. But the response of LH to GnRH, in the hypothalamic-pituitary-testicular axis, in hypothyroid males is not clear<sup>54</sup>. Plasma testosterone levels in hypothyroid men have been reported to return to normal after T4 therapy<sup>53</sup>.

In some studies, it has been reported that subclinical hypothyroidism does not to have any impact on sperm density, morphology and motility<sup>58</sup>. It has not been found to cause seminal alterations that are sufficient to cause infertility in men, but short term post-pubertal hypothyroidism might decrease semen volume<sup>52, 59</sup>. Altered sperm motility, the altered secretory activity of the accessory glands, and low ejaculate volume has been also reported<sup>54, 55</sup>. In a study, Griboff examined five patients, aged between 30 and 64 years, with primary hypothyroidism and he had found that they all had normal sperm counts, but sperm motility had decreased in two patients<sup>60</sup>. De la Balze *et al.* by investigating six hypothyroid males, aged between 17 and 59 years, reported that in five patients', thyroid insufficiency occurred before the onset of puberty and in one patient it occurred during childhood. All these patients had shown the features of hypogonadotropic hypogonadism. Testicular biopsy of all patients had revealed histological abnormalities. It was concluded that severe and prolonged thyroid insufficiency occurring early in life resulted in the moderate failure of pituitary gonadotropin secretion and abnormal testicular biopsies<sup>61</sup>. Wortsman *et al.*, in their study, with eight hypothyroid male patients, aged between 37 and 77 years, reported that all these patients had hypogonadism, out of these five were hypergonadotropic and the remaining three were hypogonadotropic. In four patients' serum testosterone and SHBG concentrations were found to be less than normal<sup>51</sup>. Later, Corrales Hernandez

and Miralles Garcia investigated spermatogenesis in ten patients who had a history of hypothyroidism and was treated with T4. In these patients, hypothyroidism was induced by stopping or by decreasing the dose of T4 over at least one spermatogenic cycle. It is observed that there was a decrease in seminal volume, and progressive forward motility compared to the controls. During euthyroid state, induction of hypothyroidism did not lead to seminal changes as compared with the same patients<sup>52</sup>. Therefore, it appears, short-term post-pubertal hypothyroidism does not cause sufficient seminal alterations to impair male fertility. Jaya Kumar *et al.* investigated the reproductive and endocrine functions of eight male patients with primary hypothyroidism. They conducted the investigation during the hypothyroid state and after the euthyroid state was achieved with T4 substitution therapy. The authors found low serum testosterone, low SHBG, subnormal testosterone responses to hCG and high mean gonadotropin levels. In five out of eight patients, semen analysis was performed but these data were not reported. However, the authors claimed there was some improvement in sperm count and its motility<sup>59</sup>. In prospective controlled study Krassas *et al.* investigated the effects of hypothyroidism on male spermatogenesis. They have performed semen analysis and have measured teratozoospermia index, fructose, and acid phosphate concentrations both before and after the treatment with T4 in 25 hypothyroid. They have noticed that hypothyroidism had adverse effects on male spermatogenesis, though the sperm morphology was the only parameter that was affected significantly, sperm motility was also affected but the differences were not statically significant<sup>62</sup>.

#### **Animal studies**

In rats, whose thyroid have been blocked with antithyroidal drugs show an arrest of spermatogenesis with a decrease in of seminiferous tubular diameter, and a decrease in seminal volume, testicular, epididymal and prostate weight, compared with euthyroid rats<sup>32,48,50,63</sup>. Progressive sperm motility, sperm transit time through the epididymis and epididymal secretory activity are also affected<sup>64,65</sup>. Hypothyroidism is also reported to reduce in acrosome integrity and mitochondrial activity of sperm<sup>64</sup>. Furthermore, the number of testicular germ cells decrease in persistent hypothyroidism but not in those with transient hypothyroidism,

while the number of live sperms is reduced both in transient and persistent hypothyroidism<sup>66</sup>. This reduction in sperm vitality may result from increased oxidative stress and reduced antioxidant capacity<sup>66</sup>. Very recently, Sarkar and Singh have shown that oxidative stress reduces the expression of glucose transporter 3 (GLUT3) in Sertoli cells and GLUT8 in Leydig cells in propylthiouracil-treated newborn mice, with a consequent decrease in testicular glucose levels and increased apoptosis of germ cells. Furthermore, oxidative stress downregulates the expression of connexin-43, a gap junctional protein in the seminiferous epithelium that regulates proliferation and apoptosis of germ cells<sup>63</sup>. Since thyroid hormones promote Sertoli cells differentiation and inhibit their proliferation, lower concentrations of thyroid hormones after birth, such as in rats with congenital hypothyroidism, lead to an extension of the Sertoli cells proliferative period, delaying their differentiation, and resulting in an increase of testicular weight and sperm production<sup>47, 67</sup>.

#### **Mechanism of action**

In hyperthyroidism, increased T4 levels, altered LH and FSH responsiveness, disrupt the endocrine regulation upon development and functioning of male reproductive tissues and germ cells resulting in distortions in tissues such as the reduced diameter of seminiferous tubule and impaired or delayed spermatogenesis. These, in turn, negatively affect sperm count and semen volume. Altered redox status of the testis, Sertoli cells and Leydig cells in hyperthyroidism, such as decreased glutathione peroxidase activities, also affect the quality of semen. Sperm motility may also be hindered in hyperthyroidism via impairment of mitochondrial activities in spermatozoa. Thus, reduced sperm count, vitality, and motility ultimately suggest a decline in semen quality owing to hyperthyroidism.

In hypothyroidism, decreased circulating T3 and T4 levels, reduced SHBG concentrations, decreased serum testosterone level adversely affect spermatogenesis. Prolonged thyroid insufficiency early in life result in moderate failure of pituitary gonadotropin secretion and hence impair gonadal growth and functions resulting in abnormal testicular histology, the altered secretory activity of the accessory glands, erectile dysfunction, delayed ejaculation, hypoactive sexual desire and decreased

semen quality in terms of sperm count, motility and low ejaculate volume. Hypothyroidism is also characterized by a decrease in seminiferous tubular diameter and reduction in testicular, epididymal and prostate weight thus affecting sperm development, progressive sperm motility, sperm transit time through the epididymis. Reduction in sperm vitality may result from increased oxidative stress and reduced antioxidant capacity in reduced thyroid hormone actions.

### CONCLUSION

This review summarizes the normal thyroid hormone regulation of semen quality, provides an update on human and animal studies

on thyroid disorders and altered semen quality and also elucidates the possible mechanism of hypothyroidism and hyperthyroidism-induced alterations in semen quality. This review also intends to highlight the necessity of large-scale cohort studies using human subjects, as the available reports used only limited number of subjects, which confines to obtain a valid conclusion. Animal studies are also required to find out the proper molecular events occur during thyroidal disorders leading to altered semen quality.

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