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Thyroid, spermatogenesis, and male infertility

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TABLE OF CONTENTS

1. ABSTRACT

Since the identification of thyroid hormone receptors on the testes, thyroid has been suggested to have a significant impact on the male reproductive tract, spermatogenesis, and male fertility. Several research articles on the role of thyroid in spermatogenesis or male infertility have been published in the last three decades. We conducted an exhaustive literature search was conducted in order to create an up-to-date review of literature. This review aims to discuss the impact of thyroid on testicular development, spermatogenesis, hypo- or hyper- thyroidism and male infertility, and the management of thyroid related abnormal semen profile. The literature revealed that thyroid significantly impacts testicular development and that abnormal thyroid profile affects semen quality and male fertility by compromising testicular size, sperm motility and ejaculate volume. A clear link exists between thyroid hormones, testicular development and spermatogenesis. Thyroid disease negatively affects spermatogenesis and consequently may cause male infertility. In such cases, infertility is reversible, but more studies need to be conducted, especially in post-pubertal males to cement the current findings.

2. INTRODUCTION

To better understand how the body operates and performs its vital processes, one must consider the very fundamental principles of the body's communication system. Hormones are one of the principal factors in intercellular and inter-organ communication. We have several endocrine glands producing chemical messengers to participate in various physiological functions, and the thyroid gland holds a central place in controlling the physiology of human body. The thyroid hormones are widely considered to be indispensible to the human body. Thyroid stimulating hormone (TSH) is secreted by the pituitary gland and stimulates the thyroid gland to secrete two different thyroid hormones: tri-iodo-L-thyronine (T3 or triiodothyronine) and tetra-iodo-L-thyronine (T4 or thyroxine). The thyroid hormones are crucial for normal functioning because of their control over body's basal metabolic rate, as well as growth, development, and differentiation of many cells/organs in the body (1). Given diverse roles of thyroid in the human body, it would be interesting to explore if thyroid affects testes, and consequently the process of spermatogenesis.

The process of spermatogenesis is generally divided into three distinct stages: (i) mitosis of spermatogonia (ii) meiosis to make haploid germ cells, and (iii) maturation of spermatids to spermatozoa (2). A defect in even a single step may disrupt the process of spermatogenesis, resulting in the production of defective or underdeveloped spermatozoa (2). Likewise, spermatogenesis is hormonally controlled by the gonadotropin releasing hormone (GnRH), which in turn stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), affecting the growth of the Sertoli and Leydig cells (3). However, since spermatogenesis occurs in close proximity with the Sertoli cells, it is suspected that the thyroid hormone receptors recently identified on the Sertoli cells, could be responsible for initiating sperm development (reviewed in 2). Until recently it was believed that thyroid hormones had no effect on the male reproductive tract. In the last two decades, researchers have identified thyroid hormone receptors (TRs) directly on cells within the testes, indicating that thyroid hormones greatly affect growth and development of the testes (1). It is thought that TRs are located on the Sertoli cells of the testes, and it is believed that T3 binds directly to these receptors (4).

Since the testes are the site of spermatogenesis, and male germ cell development is largely dependent on the nurturing processes of the Sertoli cells, research is now actively being pursued to further understand primary effects that thyroid hormones have on sperm production. Thus, the knowledge regarding the effects of thyroid disease, such as hyperthyroidism and hypothyroidism, on spermatogenesis and overall male infertility has advanced considerably. The amount of primordial germ cells formed during fetal life and their growth after birth determines the ultimate sperm production (2). Therefore, if the thyroid hormone is responsible for proper germ cell development, thyroid hormone fluctuation may impair testes growth, spermatogenesis, and ultimately fertility in the adult male (2).

The literature suggests that the first indication of the impact of the thyroid hormones on spermatogenesis and male reproduction was uncovered about three to four decades ago. However, the number of studies over this time period has been relatively less and a comprehensive review exploring the link between thyroid and infertility has not been recently updated. Therefore, we undertook this review of literature to highlight the current state of research suggesting that hypothyroidism and hyperthyroidism can not only affect the testes, but spermatogenesis as well, leading to another probable cause of pre-testicular male infertility. An exhaustive literature search was performed in 'PubMed', 'Ovid', and 'ScienceDirect' using the keywords 'male infertility' and 'thyroid' 'male infertility and thyroid' 'hypothyroidism and male infertility' 'hyperthyroidism and male infertility'. All the studies discussing role of thyroid in testes development, spermatogenesis and male infertility were considered for inclusion in the literature review, and the most relevant and scientifically significant studies were included accordingly.

3. THYROID, HUMAN PHYSIOLOGY AND MALE REPRODUCTION

As previously stated, the thyroid gland synthesizes two different hormones: T3 and T4. The epithelial cells of the thyroid are responsible for uptake of iodide for hormone production. The iodide undergoes a set of reactions with the amino acid tyrosine to result in T4 and T3. T4 is formed in greater amounts than T3. However, T3 is far more biologically active, as thyroid hormone receptors (TRs) have a much greater affinity for it compared to T4 (5). Thus, approximately 80% of the T4 formed by the thyroid gland undergoes a conversion process to T3 (6). This occurs in organs such as liver and kidneys and is done through the action of the enzymes named types 1 and 2 deiodinases (D1 and D2) (5). D2 is more efficient of the two enzymes and is the principal source of extrathyroid T3, generating about two-thirds of it (7). The ratio of T3 produced by D2 and D1 seems to be dramatically decreased in patients with hyperthyroidism (7). It is interesting to note that D1 is mainly seen on the plasma membrane of cells while D2 is primarily located in the endoplasmic reticulum (7). It is believed that the T3 synthesized by D2 enzyme would result in easier access for the T3 to enter the nucleus to affect local transcription since the endoplasmic reticulum is closer to it than the plasma membrane (8). In humans, about only 20% of the T3 used on a daily basis is produced by thyroid gland directly. The other 80% or 40 nmols of daily T3 made is derived from the conversion of T4 as previously discussed (7).

Thyroid hormone generation is controlled by an extensive negative feedback system. The thyroid gland is a part of the hypothalamus-pituitary-thyroid (HPT) axis. Thyroid-stimulating hormone (TSH) is secreted by the anterior pituitary. TSH binds to TSH receptor on the thyroid epithelial cells to signal the thyroid gland to secrete T4 and T3. Thyrotropin-releasing hormone (TRH) from the hypothalamus binds to its receptors at the pituitary and controls the release of TSH. Thus, high TRH levels would result in elevated TSH concentrations, leading to stimulated activity of the thyroid gland in producing T4 and T3. The thyroid hormones have a negative feedback loop on this system, inhibiting the production of TRH and TSH at their respective sites of production, as the serum concentrations of the thyroid hormones increase (Figure 1). Other factors can also affect this regulatory mechanism. For example, exposure to a cold environment elevates TRH levels, which leads to greater thyroid hormone production (9).

The binding interaction between thyroid hormone and TR mediates the effects of T3, the bioactive form of the thyroid hormone. TR is encoded by two different genes, *C-erbAalpha* and *C-erbAbeta* which are located in humans on chromosome 17 and 3, respectively. These encode for TR*alpha* and TR*beta,* respectively. Since alternative splicing can result in more variants, several isoforms of TRs exisit including *TRalpha*1, *TRalpha*2, *TRbeta*1, and *TRbeta*2. In general, the primary purpose of

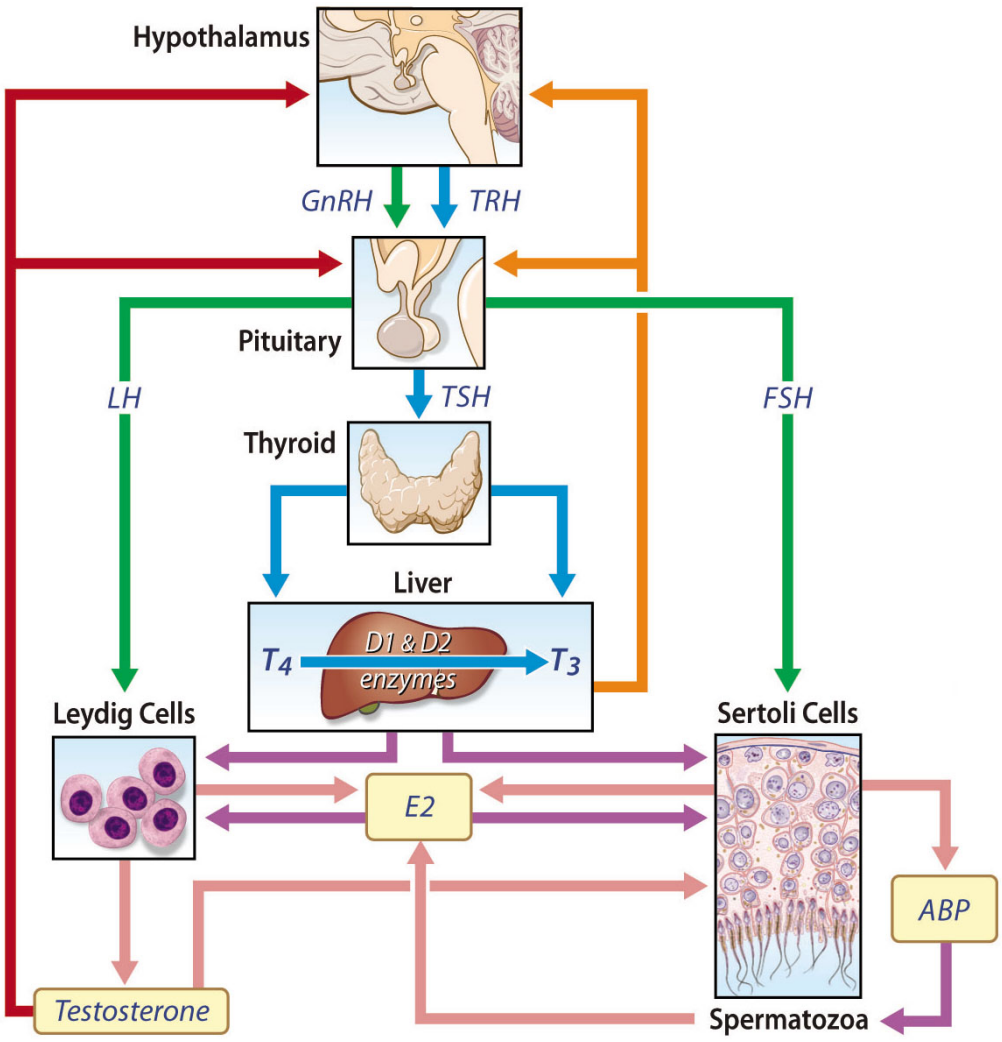

Figure 1. Summary of the role of thyroid in testicular development and spermatogenesis and possible interaction between hypothalamus pituitary gonadal (HPG) and hypothalamus pituitary thyroid (HPT) axis: All arrows denote the production of a molecule or action on a specific tissue/organ. The HPG axis is coded by green (stimulatory) and red (inhibitory) arrows. The HPT axis is encoded by blue (stimulatory) and orange (inhibitory) arrows. Purple denotes an unclear/proposed mechanism or role. Pink denotes production or stimulatory action that is not part of HPG or HPT axis.

TRs is to act as transcription factors to modulate gene expression via DNA response elements. The T3 response elements (TREs) are small, repetitive stretches of DNA. It should be noted that TRs may bind to TREs constitutively regardless of the presence of a ligand. TRs bind as monomers, homodimers, or heterodimers; heterodimers have the highest affinity for TRs and are believed to be the major functional form (10). TRs form heterodimer complexes with a retinoid X receptor. Unliganded TRs usually have a negative effect on transcription levels. When the thyroid hormone binds to TR, it elicits a conformational change in the TR, leading to activation of transcription of the gene(s) of relevance (11). The multiple sub-classes of TRs may imply that they participate in diverse functions.

Before the establishment of the importance of thyroid receptors, it was widely accepted that LH, FSH, and tesosterone regulate spermatogenesis. It is established beyond a doubt that testosterone is essential for successful completion of spermatogenesis. Without it, the conversion of round spermatids to spermatoza is impaired (12). It should be noted that FSH plays an important role in this conversion, as well as differentiation of spermatogonia into spermatocytes (13). Thus, these hormones must act through the Sertoli cells, which are responsible for nurturing the germ cells. Testosterone is produced by Leydig cells which receive the signal by the anterior pituitary. The anterior pituitary gland is responsible for synthesis of the gonadotropins, LH and FSH. The production of these two hormones is stimulated by gonadotropin releasing hormone (GnRH) released by the hypothalamus. This pathway is collectively known as the hypothalamus-pituitary-gonadal axis (HPG axis). Like the HPT axis, there is a negative feedback mechanism in which

the testosterone produced in the testes inhibits production of GnRH and LH and FSH. It is now evident that the two axes may interact with each other to influence their own effects on the testes.

Though the effects of LH, FSH, and testosterone on the testes were understood, it was previously believed that the testes was unresponsive to thyroid hormones. Numerous studies demonstrating the presence of T3 receptors on the testes and its effect on spermatogenesis have now dispelled this belief (as reviewed in 1,5,6). TRs were specifically localized onto the Sertoli cells a decade back (14, 15). However, there is evidence backing the argument that other cell types in the testes have TRs (16, 17). The data supports the theory that *TR-alpha* isoform is exclusively expressed in human testes (14). However, in animal experiments, TR-*beta* expression has been detected in the testes (15,16, 17). Despite all this controversy, it is generally accepted that *TRalpha* is more prevalent than *TRbeta*. Nonetheless, the relationship between thyroid and spermatogenesis remains somewhat hazy. Higher free T4 levels have also been associated with greater sperm concentration and a reduced occurrance of having <50% sperm motility (18). However, T4 levels must be controlled because hyperthyoridism, which could lead to thyrotoxicosis, may compromise sperm motility (19). Hypothyroidism has been linked to abnormalities in sperm morphology which normalizes after euthyroidism is restored (19). There have been contradictory reports disputing how thyroid hormone acts on Leydig and Sertoli cells. A study conducted by Manna *et al* stated that an acute T3 addition appeared to increase LH receptors and steroidogenesis of Leydig cells, but chronic treatment led to a significant decrease in these levels (20). These time-length dependent trends with T3 addition also hold true for expression of steroidogenic acute regulatory protein (StAR) which is involved in a rate-determining step of steroidogenesis, suggesting a regulatory role of T3 (21). The effects of T3 on StAR appear to act through a mechanism involving steroidogenic factor 1 (SF-1) regulation (22). T3 has also been seen to directly stimulate basal testosterone generation which could be the result of its action on Leydig cells (23).

The effect of T3 on Leydig cell steroidogensesis appears to be through Sertoli cell paracrine factors or gonadotropins (reviewed in 24). Thyroid hormones seem to impact testes maturation by inhibiting proliferation of Sertoli cells while stimulating differentiation (25). It has been shown that regular amounts of germ cell production in adults is related to the Sertoli cell population size; therefore, the perinatal stage in which this population is accumulated is crucial for normal adult spermatogenesis (26). Sertoli cells undergo two main steps to reach full functionality: proliferation and maturation/differentiation. The proliferation period, in which the Sertoli cell count rises, occurs during the neonatal and peripubertal stages of life in humans (reviewed in 27). These cells at this point are immature, and do not have all the capabilites needed to ensure proper nourishment of developing germ cells. Once puberty begins, the Sertoli cells stop proliferating and adjacent Sertoli cells form tight junctions which leads to formation of the blood-testes barrier (27). Germ cells are then cut off from nutrients except through the interaction with Sertoli cells. It is not certain whether this cessation of proliferation occurs abruptly or through a step-wise mechanism. Laboratory trials have indicated that T3 is an important factor in the overall process of Sertoli cell maturation. T3 results in an increase in $p27^{Kip1}$ and $p21^{Cip1}$, which are cyclin-dependent kinase inhibitors (CDKIs) (28). CDKIs negatively modulate the cell cycle at the critical G1 checkpoint. Therefore, elevated levels of these two CDKIs likely play a vital role in ending the proliferation stage, and this may be a point of interfernece in thyroid disease. Another molecule affected by T3 is neural cell adhesion molecule (NCAM), which helps form the tight junctions of Sertoli cells. T3 downregulates the expression of NCAM and decreases the likelihood of spermatogonia to bind to Sertoli cells (29). However, the reasons for this remain to be explained. It is probable that other intermediary molecules involved in termination of Sertoli cell proliferation exist as well. Higher TR expression in the Sertoli cells has been seen to decrease after the proliferative stage, suggesting that the sensitivity of these cells to T3 is lowered after this step (17). Although not certain, it is believed that maturation of Sertoli cells occurs through multiple steps (reviewed in 27).

Thyroid also appears to impact the level of estrogens, which is now known to affect spermatogenesis. This may result in a marked increase in 2-hydroxyestrogens and a decrease in 16alpha-hydroxyestrogens (30). This flucuation in males suffering from hyperthyroidism may manifest in the form of gynecomastia, decreased libido and spider angiomas (30). Likewise, Aromatase expression has been seen in Sertoli, Leydig, and even germ cells with expression being maximum in the Leydig cells of adult rat (31, 32). Aromatase is an enzyme involved in estrogen synthesis. Aromatase expression has been found to be downregulated by T3 treatment in Sertoli cells (33). Estrogen receptors have been found on both Leydig and Sertoli cells, but the exact function of estradiol (E2) in spermatogenesis remains unclear (34). On one hand, E2 has been linked to improved sperm migration, and lack of estrogen receptor has been demonstrated to cause infertility and defects in sperm function due to abnormality in the epididymis (35, 36). However , many other sources have shown that estradiol administration in males can lead to impaired spermatogenesis or infertility (37, 38, 39). It has been shown in adult rat that estrogens modulate Leydig cell development negatively by inhibiting the precursor for cell replication, and this is believed to affect testosterone production due to the lowered number of Leydig cells (reviewed in 40). Currently, it is believed that T3 plays a direct role in down-regulating estrogen receptors and up-regulating androgen receptors (AR) in the developing Sertoli cells (41). Particularly, an important note is that estradiol levels are significantly decreased in hypothyroid rat which could potentially explain the observation of reduced germ cells in them (42). This information supports previous data suggesting that T3 hormone indirectly plays a crucial role in testicular development, especially in proliferation and development of the Sertoli cells. Thus, both Sertoli and Leydig cells seem to play a part in

mediating the effect of thyroid hormone on testes, although there is still lack of consensus on how each occurs.

Serum sex hormone binding globulin (SHBG) and androgen binding protein (ABP) levels are also influenced by thyroid hormones. SHBG and ABP have same amino acid sequence, as they are encoded by the same SHBG gene but have different post-translational modifications and are synthesized at different locations. SHBG is produced by the liver and ABP is made by Sertoli cells (43). It is thought that testicular ABP is secreted in both seminiferous tubules and blood (44). Both serve as transport carriers for testosterone and E2. Many investigators refer to SHBG and ABP collectively as SHBG/ABP. ABP is believed to be involved in maintenance of the androgen environment necessary for germ cell differation and maturation (reviewed in 45). Age has been linked to a decrease in SHBG; adult animals have significantly lower levels than prepubertal ones (42). T3 is a potent inducer of SHBG synthesis and can be considered a biological marker of thyroid hormone action (46). In hypothyroid rats, SHBG levels are noticeably reduced while elevated levels are seen in thyrotoxicosis (47). T3 administration decreases ABP production in Sertoli cells (48). The cells of 28-day old hyperthyroid rats demonstrated a decrease in ABP production (49). However, conflicting data from JN Rao *et al* revealed significantly lower ABP mRNA levels in hypothyroid, pre-pubertal rats, but not in similar adult rats (50). Likewise, TR alpha mRNA levels were significantly increased in hypothyroid rats at day 21 and were suppressed in hyperthyroid rats; however, no significant changes were detected in euthyroid animals (50). The thyroid hormone has been suggested to possess a regulatory function in the pre-pubertal rat essential for post-natal Sertoli cell maturation (49). Thus, ABP expression in Sertoli cells is controlled by thyroid hormone, but it is unknown exactly how. In addition, the differential effects of T3 on SHBG and ABP remain to be elucidated. SHBG/ABP isoform transcripts have been seen in testicular germ cells and SHBG/ABP accumulates in the acrosome of sperm (51). The reason behind this is currently unknown. However, sperm SHBG concentrations are low in fertile men and high in those with varicocele (52). Sperm SHBG/ABP isoform levels correlate with age and sperm motility (52). Interestingly, E2 has been shown to increase SHBG secretion (53). Therefore, it is possible that one way of thyroid hormone action on spermatogenesis is via regulating the synthesis of SHBG.

Thyroid hormones have also been discovered to have an effect on the balance between reactive oxygen species (ROS) and antioxidants within testes. ROS are reduced forms of oxygen and their respective molecules, and are considered to be free radicals that are chemically reactive (54). Oxidative stress, which is overproduction of ROS with respect to antioxidants, has been strongly associated with sperm abnormalities and male infertility. ROS has detrimental effects on the sperm plasma membrane as well as the nuclear DNA, all of which negatively affect the spermatoza's chance of causing a succesful pregnancy (55). Also, decreased sperm motility has been associated with increased levels of ROS (56). Lipid peroxidation is an indicator of oxidative stress, along with protein carbonyl content (57). Some of the antioxidant defense molecules at the human body's disposal include catalase, superoxide dismutase, reduced glutathione, and glutathione peroxidase. After drug-induced hypothyroidism in adult rats, oxidative stress markers such as protein carbonyl content have been observed to increase while superoxide dismutase and catalase activity fell (57). Catalase activity was elevated but the protein carbonyl levels unexpectedly continued to increase after T3 treatment (57). This suggests a complex mechanism of T3 action on oxidant-antioxidant balance. The study supported the evidence from Choudhury *et al* 2003 regarding increased oxidative stress following thyroid hormone treatment of the hypothyroid rats. Higher thiobarbituric acid (TBARS), which is a marker of lipid peroxidation, was observed after persistent hypothyroidism, as well as augmented superoxide dismutase and catalase activity (58). This finding regarding the catalase activity contradicts the findings by Choudhury *et al* 2003. However, in transient hypothyroidism, lower lipid peroxidation was noticed, implying that there are differences in transient and long-term hypothyroidism (58). In hyperthyroid rats, lipid peroxidation, reduced glutathione, glutathione peroxidase, and catalase activity levels all increased (60). T3 treatment in hyperthyroid rats led to greater oxidative stress, as seen by elevated TBARS concentrations (60). Thus, alterations of thyroid hormone levels could correlate with oxidative stress within the adult testes, although it is not completely clear how. More evidence must be accumulated before any consensus could be built.

As the human male ages, many physiological changes take place within the body, including the thyroid gland and hormones. Generally, TSH and free T3 levels decrease, while free T4 levels tend to remain stable, and the inactive form of the T3 metabolite seems to increase (reviewed in 61). Hypothyroidism increases to about 5% of males over 60 years of age, and they tend to present with atypical symptoms or no symptoms at all (61). The frequency of hyperthyroidism in males over 60 year of age increases to 0.5-3% (61). It is well known that sperm count and fertility decrease with age. Though there is no concrete evidence, altered thyroid activity could be one of the several possible reasons associated with decreased fertility with age. Age related changes in the thyroid activity could also affect ROS level which is a well known factor affecting fertility.

4. THYROID DISEASE, SPERMATOGENESIS AND MALE FERTILITY

Thyroid disease is classified into two categories: hypothyroidism and hyperthyroidism. The symptoms of hypothyroidism often include palmer yellowing, dry skin, coarse hair, slurred speech, slowed mental activity, weight gain and an increased sensitivity to cold temperature (62). In neo-natal and pre-pubertal humans, symptoms are more subtle and consist of behavior problems, weight gain with slowed physical growth, and a delayed onset of puberty, appearing younger than their actual age (63). Likewise, severe hypothyroidism can even cause the thyroid to

protrude from the neck, and cause weight gain from anywhere from 10 to 20 pounds (64). Common signs of hyperthyroidism include fatigue, weight loss, irritability, muscle weakness and palpitations according (65). Similarly, hyperthyroidism can be attributed to serious conditions such as an irregular heartbeat and or congestive heart failure (64). Therefore, it is clearly known that too great of an increase or decrease in the thyroid hormone levels has detrimental effects on human body. Likewise, since the identification of thyroid receptors on the male testes, it has been increasingly questioned how thyroid diseases affect testicular development, spermatogenesis, and overall male fertility. Thus, a closer look at how hypothyroidism and hyperthyroidism affect spermatogenesis will help determine the connection between thyroid disease and male infertility.

4.1. Hypothyroidism

Hypothyroidism is very rare in males with an occurrence rate of only 0.1% in the general population (reviewed in 30). Nevertheless, for men who suffer from hypothyroidism, it is essential to understand how the disease affects their fertility and spermatogenic process. Hypothyroidism may result in a reduction in SHBG and ABP, and lead to a decrease LH, FSH, and total serum testosterone levels (reviewed in 30). Likewise, hypothyroidism negatively affects male fertility in an indirect manner by increasing body weight and thus slowing down the metabolism. Thus, this creates a potentially great body mass index (BMI), which has been associated with sub-fertility in men due to negative correlation between BMI and testosterone level and SHBG (66). As previously discussed, both SHBG and testosterone are essential for proper spermatogenesis and male fertility. Generally, as a result of hypothyroidism, the Leydig and Sertoli cells are less stimulated to differentiate into mature cells, thus negatively affecting spermatogenesis (67). This enlarges the testes in pre-pubertal males, and if the condition persists, extensive damage could be done to the adult testes (68). Likewise, this could lead to a decrease in the number of mature, viable, and functional cells for spermatogenesis later in life. Thus in patients with hypothyroidism that developed the disease as an infant or adolescent, increased testicular size is observed along with a significant drop in mature germ cells within the seminiferous tubules, as reviewed by Wagner *et al* (5). In fact, Sertoli cells have been shown to proliferate so much during the pre-pubertal years that it results in an increase of 157% in the adult testes of hypothyroid patients (5). The disrupted cellular communication that can be attributable to hypothyroidism causes extensive proliferation of testes size and is the direct result of increased levels of T3 activated receptors in the Sertoli cells (1). The prolonged proliferation of the Sertoli cells could provide the missing link in how hypothyroidism leads to spermatogenetic dysfunction. It must be remembered that there is a direct link between the number of mature Sertoli cells in the adult testes and a male's fertility status due to the fact that spermatogonia are physically nurtured into mature spermatozoa by the Sertoli cells (1). Therefore, a decrease in the number of mature Sertoli cells equates to lesser number of mature sperm. Similarly, in rats that suffered from transient neonatal hypothyroidism, Leydig cell number was increased in adulthood. (1). It is interesting to note that transient hypothyroidism (birth - 30 days) induced with 0.05% propylthiouracil (PTU) via drinking water was reported to decrea0se germ cell numbers in Wistar rats. Even though this study was conducted with a relatively low dose of PTU, it is still significant due to the fact that it highlights the detrimental effects transient hypothyroidism has on testicular development (58). Further looking at this topic, Cooke *et al* found that PTU exposure in the first postnatal week eventually increases testes weight and sperm production (59). Thus, a contradiction in the literature exists regarding the effects of transient hypothyroidism on testicular development and overall male fertility.

Overall our review of the literature focusing on thyroid and male infertility has shown that hypothyroidism indeed negatively affects testicular development and spermatogenesis during the fetal and neo-natal, and pre-pubertal years, respectively (69). However, the effects are reversible and can be treated. If not treated at birth neonates suffering congenital hypothyroidism may develop cretinism, a syndrome that is characterized by severe metabolic disruptions that lead to growth retardation and even mental handicaps (70). It is not exactly known why this period is the most devastating for testicular development, spermatogenesis and overall fertility, but it can be hypothesized to be due to the fact that the Sertoli and Leydig cells during this period are in proliferation stage of their respective developments. Thus, if proliferation is prolonged and differentiation is delayed, the effects on spermatogenesis are passed on to the adult male, posing one possible rationale for male infertility. Four studies in particular examined the changes described above in hypothyroid patients/animal models, as well as examining several different seminal parameters. All concluded that hypothyroidism adversely affects testicular development and spermatogenesis.

In the first study, J. J Corrales Hernandez *et al* (1990) looked at the seminal parameters of ten (10) patients, aged between 17-70 years, who suffered from primary hypothyroidism (71). The study took both blood and semen samples from the participants and analyzed both samples using a series of tests. The overall results indicated a decrease in ejaculate volume and a decrease in progressive forward motility of the spermatozoa (Table 1). Thus, there appears to be significant adverse impact on semen quality due to hypothyroidism. However, when the patients returned to a euthyroid state after treatment, no seminal abnormalities were found and spermatogenesis was not disturbed. The authors concluded that hypothyroidism may significantly affect semen quality but the changes could be treated post-pubertal to restore fertility (71).

A second study was performed by Maran *et al* (2002) on neonatal Wistar Rats from 1 to 60 days postpartum (42). The neonatal rats were partitioned into six subgroups according to age, and were sacrificed according to the time frame of each subgroup. Blood plasma was collected and the testes and other reproductive organs were

Table 1. List of the studies conducted to understand the role of thyroid in spermatogenesis and male infertility

Study Name	Reference	Subjects	Observations	Conclusions	Treatment, type of	Outcome
Hypothyroidism, spermatogenesis and male fertility						
Primary Hypothyroidism and Human Spermatogenesis	71	10 Human Males	• Adverse impact on semen quality • Decrease in ejaculate volume • Decreased sperm motility	• May adversely affect semen quality in post-pubertal men, but fertility restored with treatment	Yes, Thyroxine	Seminal abnormalities were reversed with treatment
Mechanism underlying transient gestational-onset hypothyroidism-induced impairment of posttesticular sperm maturation in adult rats.	69	Wistar Rats	• Gestational rats exposed to a hypothyroid environment had decreased epididymal tissue • 50-66% decrease in these rats to mate as adults • Decrease in androgen receptors (AR) • Decrease in forward sperm motility	• Emphasizes the importance of euthyroid state and the essential role it plays in normal reproductive development in pre-natal, neo-natal, and pre-pubertal stages of life development.	No	-
Adverse effects of neonatal hypothyroidism on Wistar rat spermatogenesis.	42	Wistar Rats	• Decrease in testicular weight • Smaller seminiferous tubules • Only a single layer of germ cells present	• Thought that thyroid hormone in hypothyroidism interferes with the Sertoli cell function, thus hurting spermatogenesis • Thus, hypothyroidism does have an adverse affect on spermatogenesis and the underlying reason may have to do with testosterone and SHBG levels	No	-
Hypothyroidism Has an Adverse Effect on Human Spermatogenesis: A Prospective, Controlled Study	25	35 Human Males	• Abnormal morphology • Decreased motility	• Motility reversed with treatment, but no affect on morphology • Hypothyroidism adversely effects spermatogenesis, but can be improved, if not corrected, with treatment	Yes, Levothyroxine	Did not affect morphology but did improve motility after treatment
Hyperthyroidism, spermatogenesis and male fertility						
Elevated plasma testosterone and gonadotropin levels in infertile males with hyperthyroidism.	74	3 Human Males	• Decreased sperm counts • Decreased sperm motility	• Infertility is more common than previously though and is possibly correlated to T, LH and FSH levels • Increased TeBG binding and increase in testosterone and E2	Yes, propylthiouracil (dosage vaired for patient)	Seminal Abnormalities reversed with medical hyperthyroid treatment
Testicular function in hyperthyroidism.	75	16 Human Males	• Decreased sperm motility • Decreased sperm density • Abnormalities in HPG axis	• Thyroid hormone may indirectly affect spermatogenesis through its effects on sex steroid productions • Overall, abnormalities in seminal parameters, sex steroid levels, and gonadotropin levels were all noted.	Yes, Radioiodine & Propranolol-nine men became euthyroid, the other seven became hypothyroid before being retested	All seminal and hormonal abnormalities returned to normal in euthryoid state
Male reproductive function in relation with thyroid alterations	30	23 Human Males	• Decreased sperm motility	• Recovered with treatment • Hyperthyroidism contributes to abnormal seminal parameters, but are easily reversed with conventional thyroid treatment	Yes, Methimazole or 1plus Methimazole	All seminal parameters normalized except sperm count and morphology with treatment
Dietary-Induced Hyperthyroidism Marginally Affects Neonatal Testicular Development	73	Wistar Rats	• Profuse Leydig cell proliferation by day 35 of rat's life	• Mild increase in thyroid hormone did not cause significant testicular damage but initially delayed Leydig cell development • Could lead to problems in future with spermatogenesis	No	-

isolated and weighed. The results of the study showed that testicular weight decreased as the neonatal rats aged as compared to the control, analogously age paired group, and the hypothyroid rats had much smaller seminiferous tubule diameters as compared to the control group. Most significantly, the hypothyroid rats only had a single layer of

germ cells by day 60 whereas in the control rats, seminal lumen was already filled with spermatozoa. Though the precise process of spermatogenesis in not fully understood at the biochemical level, it is thought that hypothyroidism ultimately interferes with Sertoli cell function, and thereby disrupts spermatogenesis. Overall, the study claimed that hypothyroidism adversely affects spermatogenesis, germ cell differentiation, and that the underlying explanation for thyroid's effect on spermatogenesis is related to testosterone levels and secretion of SHBG (42). This study clearly highlights the negative effects hypothyroidism can have on the neonate.

Another study highlighting similar findings was conducted by Krassas *et al* (2008) on 35 male patients aged between 18-65 years that were clinically diagnosed with hypothyroidism in Panagia General Hospital in Thessalalonki, Greece (72). Semen samples were collected from male individuals in their hypothyroid state followed by treatment. Upon treatment, semen analysis on fresh samples was continued for an additional 6-9 months. Semen samples were analyzed using biomarkers, and the most significant finding was abnormal sperm morphology. A decrease in sperm motility was also observed, but the results were insignificant. Motility returned to a normal state upon treatment, but morphology remained abnormal. The authors concluded that hypothyroidism negatively affects human spermatogenesis and that the disease can be treated in order to improve semen quality (72).

Finally, a recent pivotal trial was performed on Wistar rats by Anbalagan *et al* (69). The authors carefully observed the effects of transient gestational hypothyroidism on male rat fertility in adult life. Hypothyroidism was induced by addition of methimazole (MMI 0.05%) to the drinking water of pregnant rats during certain fetal development and differentiation phases of male reproductive tract. The results revealed that when these rats reached adulthood, they experienced a 50%-66% reduction in successful mating, a decrease in epididymal tissue levels of sialic acid, glycerylphosphorylcholine (GPC), and carnitine. The study also indicated a decrease in 5-alpha reductase 1 mRNA expression in all regions of the epididymis, and a significant decrease in androgen receptor expression in cauda epididymis in the experimental group. Though the adult rats with neonatal-onset hypothyroidism had increased sperm production, decreased motility pointed to a pre-testicular cause of infertility, as supported by the results stated above. It is thought that the epididymis is impaired by a decrease in AR and 5alpha-Reductase activity. Thus, this study emphasizes importance of the euthyroid state in normal reproductive development in the prenatal, neonatal and pre-pubertal periods to ensure fertility as an adult (69).

Overall, it appears that hypothyroidism adversely affects semen quality; particularly the size of seminiferous tubule and sperm motility, but the changes could be treated pre-pubertal or post-pubertal. However, only a few significant studies have been conducted, none of which is on a large scale, and more studies need to be undertaken before we could reach to some sound conclusion regarding the effects of hypothyroidism on spermatogenesis and overall semen quality. The promising aspect of the effect of hypothyroidism on spermatogenesis is that many, if not all, of the abnormal and negative semen parameters are corrected when the patient is treated for hypothyroidism and returns to the euthyroid state (1). However, much controversy surrounds regarding the effect hypothyroidism has on the post-pubertal male testes and accordingly spermatogenesis and male infertility. This confusion largely stems from the fact that very few research studies have been conducted on this issue due to lack of participants, ethical issues, and the simple fact that the results themselves are conflicting. Further studies need to be undertaken with particular attention concerning treatment undertaken before and after puberty, and determining if the two have any significant difference in the outcome.

4.2. Hyperthyroidism

Hyperthyroidism is associated with an increase in SHBG levels, increased bound testosterone, along with decreased free testosterone in blood due to the fact that most of the testosterone is bound to binding molecules (reviewed in 72). According to the review of literature by Krassas *et al*, it appears that hyperthyroidism has a detrimental effect on spermatogenesis and may cause infertility (30). Hyperthyroidism primarily influences the metabolism of androgens and estrogens. Hyperthyroidism is associated with an increased production of 5alpha-metabolites, and an increase in the conversion of androgens to estrogens (30). Likewise, it has been noted that there is an increase in the secretion of estrogen metabolites, all of which lead to elevated estrogen bioactivity that tends to be clinically present in males suffering from hyperthyroidism (30). Similarly, there is a direct effect of thyroid hormone on gonadotropin sensitivity to GnRH, possibly leading to a disruption in the metabolic pathway of the production of LH and FSH (30). Thus, estrogen biosynthesis and abnormal gonadotropin levels are postulated to lead to erectile and spermatogenetic dysfunctions in men diagnosed with hyperthyroidism (72).

Besides the consequences hyperthyroidism has on the molecular level, it also has several effects on cellular level in the testes. The primary disturbance is that hyperthyroidism provokes premature cessation of Sertoli cell proliferation (5). It is estimated that hyperthyroid patients have 50% less differentiated Sertoli cells than euthyroid patients (73). Thus, there are fewer mature Sertoli cells, which lead to decreased testicular size as well as decreased sperm production due to inadequate number of Sertoli cells to nurture developing germ cells (5). Similarly, Leydig cells proliferation is stimulated in males suffering from hyperthyroidism, increasing the total number of Leydig cells in the adult testes by at least 70% (73). This is thought to be a consequence of the T4's ability to inhibit androgen receptors, increasing testosterone level, ultimately signaling the HPG to secrete more gondaotropins (73). It is interesting to note that both hypothyroidism and hyperthyroidism appear to cause a prolonged period of Leydig cell proliferation, and the reason behind this correlation is unknown. It may,

however, have to do with the fluctuating levels of testosterone which a male with thyroid disease is always subject to. The explanation behind exactly why hyperthyroidism causes such differences in testicular development and seminal parameters appears to depend on the concentration of testosterone. When there is an increase in plasma testosterone levels, there is a causal increase in the binding of testosterone to SHBG (74). The associated decrease in free testosterone sends a signal to the pituitary gland to secrete more gonadotropins (74). Such an increase in gonadotropins, especially LH could also play a role in promoting Leydig cell proliferation in an attempt by the body to produce more testosterone.

The effects of hyperthyroidism on testicular development, spermatogenesis, and male infertility have been subject to a small number of studies. However, all of the studies seem to conclude that hyperthyroidism adversely effects spermatogenesis, presenting yet another pre-testicular cause for male infertility. The first study conducted by Clyde *et al* (1976) provided some very early and critical information about hyperthyroidism's effect on spermatogenesis in human (74). Clyde *et al* looked at three individual cases with hyperthyroidism and infertility. Hormone levels were measured and recorded, and the overall results revealed that all three patients had low sperm count as well as decreased sperm motility (Table 1). However, such abnormalities were corrected when the patient was treated for his thyroid disease. Clyde *et al* concluded that male infertility is more common than previously thought in males with hyperthyroidism, possibly in correlation to the elevated levels of testosterone, LH and FSH (74).

Another study performed by Hudson and Edwards (1992) focused on the spermograms of 16 thyrotoxic human males between 17-46 years of age all suffering from Grave's disease (75). All 16 males had abnormalities in the HPG axis concerning hormone levels, a decrease in sperm density, and a significant impairment in forward sperm motility. The authors proposed that the thyroid hormone affected spermatogenesis indirectly by altering the levels of sex steroids and gondaotropins secreted. However, all seminal and hormonal abnormalities were corrected when the patients returned to a euthyroid state upon treatment. In conclusion, Hudson and Edwards proposed that hyperthyroidism indirectly affects spermatogenesis, but can be reversed with typical treatments for hyperthyroidism (75).

Another study some years later was conducted by Krassas (2002) and provided statistically significant data (30). The study focused on 23 human male individuals with hyperthyroidism and 15 healthy male individuals as control subjects. Semen samples were initially analyzed before treatment, and were re examined up to five months after euthyroidism was maintained. The pre-treatment results showed a significant decrease in sperm motility but it was noted that motility appeared to recover with treatment. The authors proposed that hyperthyroidism definitely contributes to abnormal seminal parameters that can be easily corrected with conventional thyroid treatment (30).

Recently, Rijntjes *et al* (2008) studied the effects of hyperthyroidism in rats by giving them T4 in their diet (73). This ensured that the rats were gradually exposed to increased levels of T4, as would happen in human body over time, rather than a sudden increase in T4 levels that is unlikely to naturally occur. The main focus of this study was to see how the Leydig cells responded to increased level of T4. In the experiment, Leydig cell proliferation was profuse, and was believed to be caused by the ability of T4 to inhibit androgen receptors. Overall, the authors concluded based on their study as well as review of literature that a mild increase in the thyroid hormone did not cause significant testicular damage, but it delayed Leydig cell development, which could be linked to abnormalities in spermatogenesis later in life (73).

5. MANAGEMENT OF THYROID ASSOCIATED MALE INFERTILITY

Though the studies conducted on thyroid disease thus far indicate that both hypothyroidism and hyperthyroidism have a detrimental effect on spermatogenesis and consequently male fertility, the silver lining is that both medical conditions can be easily and readily treated with traditional thyroid treatment. Concerning the studies on hypothyroidism, the Hernandez *et al* and the Krassas *et al* looked at thyroid disease and male infertility in regards to treatment. Hernandez *et al* treated post-pubertal males afflicted with hypothyroidism with thyroxine, and when the patients returned to a euthyroid state; all seminal parameters that previously constituted poor semen quality were reversed, thus restoring fertility (71). Similarly, the study performed by Krassas *et al* demonstrated that treatment with levothyroxine, a synthetic form of T4, in post-pubertal males reversed poor sperm motility, but did not reverse abnormal morphology (25). Concerning hyperthyroidism, three studies outlined the effects of hyperthyroidism on overall male fertility and looked at the possibility of treatment. Clyde *et al* treated three post-pubertal men with PTU and showed improved semen quality and that abnormal seminal parameters were reversed (74). A second study by Hudson and Edwards showed that all seminal and hormonal abnormalities were corrected in post-pubertal male patients suffering from hyperthyroidism when they returned to a euthyroid state after being treated with radioiodine and/or propranol (75). However, it is important to note that seven patients did become hypothyroid before semen quality could again be tested and analyzed (75). Lastly, Krassas *et al* concluded that all seminal parameters except sperm count and motility normalized after treatment with methimazole or 1- plus methimazole in the 23 post-pubertal male individuals afflicted with hyperthyroidism (30). Therefore, it can be reasonably concluded that treatment of thyroid disease in effect resolves any associated fertility problems. Therefore, men diagnosed with thyroid disease are recommended to have a semen analyses performed upon their diagnosis to examine any adverse effect on semen quality so that restoration of

fertility and thyroid hormone levels can be documented accordingly. Nevertheless, the literature of both hypothyroidism and hyperthyroidism lack the sheer number of studies that analyze the treatment aspects of thyroid disease and associated male infertility. In addition, there is no consensus as to when the treatment should start in order to optimally help the patient. To the best of our knowledge, only a few studies have elaborated on the treatment aspects. As mentioned above, both hypothyroid and hyperthyroid patients are able to reverse negative effects on semen quality and seminal parameters with appropriate treatment and a return to the euthyroid state.

6. CONCLUSION AND FUTURE DIRECTIONS

Given that research over several decades has identified the presence of thyroid receptors on testes and particularly on the cells known to participate in spermatogenesis, it should not be surprising that thyroid affects male reproductive health. It appears that the thyroid hormone is crucial in proper development of the testes, especially in pre-pubertal boys. In the last two decades, increasing amounts of research efforts have been dedicated to looking into thyroid's effect on male fertility. Thyroid diseases such as hypothyroidism and hyperthyroidism do indeed have an effect on testicular development, and current research has indicated that abnormal thyroid profile may lead to a pre-testicular cause of abnormal spermatogenesis and male infertility. What is more interesting is that both hypo- and hyper- thyroidism affect fertility by similar means, i.e. primarily decreasing sperm motility. While it is clear that there is some definite connection between thyroid and spermatogenesis, much contradiction still surrounds the thyroid's effects on the post-pubertal male. Nevertheless, more studies need to be done concerning both hypothyroidism and hyperthyroidism, especially in post-pubertal men in order to truly and comprehensively understand the disease process.

It remains to be explored how exactly thyroid impacts testicular development and spermatogenesis. The thyroid could impact spermatogenesis directly, indirectly, or by a combination of the two. Concerning the indirect effects, it seems likely that HPT and HPG axis cross communicates with each other and that thyroid hormone levels may affect the levels of gonadotropins. Though there is no concrete evidence of such a complex interaction, alterations in the gondaotropins levels in the individuals with abnormal thyroid profile indicates a link between the two axes. Thyroid also appears to impact the level of estrogens, which is known to affect spermatogenesis. The direct effects of thyroid hormone on testes and spermatogenesis could be mediated by thryroid receptors on the Sertoli cells which are very crucial for spermatogenesis. As discussed above, thyroid hormones seem to impact testes maturation by inhibiting the proliferation of Sertoli cells while stimulating differentiation (25). At present, it is believed that T3 plays an essential role in down-regulating estrogen receptors and up-regulating androgen receptors in the developing Sertoli cells (41). It is possible that the action of thyroid hormone is crucial for maintenance of appropriate ratio of Sertoli versus germ cells to maintain optimal spermatogenesis. However, the field is open to further research and much remains to understand about the impact of thyroid on testes development and spermatogenesis, particularly the molecular connection between them.

A lack of research exists concerning thyroid, spermatogenesis and male infertility, further enhancing the contradictions that are present. To the best of our knowledge, most of the studies to date have analyzed semen quality in individuals/animal models with thyroid disease. One limitation of such studies is that we need to identify suitable subjects, and complete a semen profile on them. Comprehensive and large scale studies are difficult to perform since thyroid disease, in addition to affecting spermatogenesis, has serious effects on metabolism and general health. This predicament presents both a clinical and ethical challenge to the researcher. Therefore, animal studies are the key to understand the relationship between abnormal thyroid profile and infertility. Studies on animal models with compromised thyroid action early in life, pre-pubertal stage, and post- pubertal stage especially need to be undertaken to identify the affects thyroid could have on testes and spermatogenesis during different developmental phases. If the molecular connection between thyroid disease and male infertility could be deciphered, then those men that present with the signs and symptoms of hypothyroidism or hyperthyroidism could be easily screened and treated immediately. This would prevent the patient from going through infertility treatments, and the patient can be saved from further physical discomfort and emotional hardship.

Another important aspect that seeks attention at present is the management of hypothyroidism or hyperthyroidism. Five out of eight studies on hypothyroidism and hyperthyroidism have indicated that it is possible to restore fertility once the patient is treated to return to euthyroid state. Studies looking at the treatment before and after puberty could help determine appropriate age of treatment such that the fertility of the patient is not compromised. Animal models of both hypo- and hyper-thyroidism are available to study the treatment aspects. The only issue that needs to be addressed is the identification of testicular/semen marker to follow the treatment. The establishment of an appropriate model of treatment would help conduct more studies on the subject and really understand how to better manage abnormal thyroid profile to restore not only normal physiology but also normal fertility.

In conclusion, thyroid definitely impacts testes development, spermatogenesis and male fertility such that abnormal thyroid profile could affect semen quality and may lead to infertility. However, further research and testing is needed to understand how thyroid affects testicular development and spermatogenesis which could help unravel the molecular connection between thyroid, spermatogenesis and male infertility, and provide optimal testing and treatment to the patients in a timely and cost-effective manner.

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