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Thyroid Dysfunction: In Connection with PCOS

Mariya Anwaar and Qaiser Jabeen

Abstract

As the prevalence of endocrine dysfunction is increasing and is associated with many complications including polycystic ovary syndrome (PCOS) which, itself is a risk factor of thyroid dysfunction. Although the causality of this association is uncertain, the two conditions share a bidirectional relationship. Both syndromes share certain common characteristics, risk factors and pathophysiological abnormalities, which can be managed by lifestyle changes as well as pharmacological treatment. Polycystic appearing ovaries are a clinical feature of hypothyroidism as well as hyperthyroidism in a few case studies. Adiposity, evidence of deranged autoimmunity, increased insulin resistance and disturbed leptin levels are present in both the disease states, seeming to play a complex role in connecting these two disorders. Major endocrine pathways including hypothalamic-pituitary-thyroid axis (HPTA) and HP-gonadal axis are involved in parallel relationship of PCOS and thyroid dysfunction. This chapter helps to explore all the dimensions of the relationship between PCOS and thyroid dysfunction.

Keywords: thyroid dysfunction, hypothyroidism, hyperthyroidism, PCOS, HPTA

1. Introduction

Thyroid dysfunction as well as polycystic ovary syndrome (PCOS) are very common endocrine disorders among the general population. Although, thyroid dysfunction and PCOS have completely different etiopathogenesis, but have various common features. In primary hypothyroidism, an increased ovarian volume and cystic changes in ovaries have been reported. It is also increasingly recognized that thyroid dysfunction is more common in females with PCOS as compared to the healthy individuals [1, 2]. This is may be due to some common considerations as well as pathophysiological connection between PCOS and thyroid disorders leading an individual towards both the disorders. Considering the high prevalence of Hashimoto's thyroiditis (HT) and the high prevalence of PCOS in women in the reproductive period, the emphasis will lie on the possible etiological and clinical connections between HT and PCOS.

2. Endocrine system

The endocrine system is a network of glands that produce and secrete hormones to regulate many physiological processes [3]. The endocrine system is comprised of

hypothalamus, pituitary gland, pancreas, adrenal gland, ovaries, testes, pineal gland, thyroid gland, parathyroid gland and thymus gland [4]. These glands communicate with each other through different pathways called axis. Major endocrine pathways include hypothalamic-pituitary-thyroid axis (HPTA), hypothalamic-pituitary-gonadal axis, hypothalamic-pituitary-adrenal-axis, renin-angiotensin-aldosterone axis and hypothalamic-pituitary-adipose axis [5]. Endocrine glands are also closely linked with stress system, gut microbial flora and immune system [6].

2.1 Endocrine feedback system

Hormones are required for maintaining homeostasis and optimum body functions. Adequate secretion of hormones is ensured through biological feedback system that aims to provide hormones in a specific physiological range. Feedback system, is combination of several axis, that regulates endocrine and neural responses after any external or internal stimuli [7]. There are two types of feedback systems; positive feedback mechanism and negative feedback mechanism. Thyroid hormones exert both positive and negative feedback mechanism, which controls the release of both thyrotropin-releasing hormone (TRH) from hypothalamus and thyroid stimulating hormone (TSH) from anterior pituitary gland [8].

2.2 Endocrine dysfunction

Endocrine dysfunction is characterized by abnormal production and secretion of hormones from particular glands. Endocrine dysfunction can be categorized into following types; endocrine hyposecretion (deficiency of hormones), endocrine hypersecretion (excess of hormones), altered tissue response (hormone insensitivity irrespective of circulating hormone) and endocrine tumors [3, 9].

3. Thyroid gland

The thyroid gland is, morphologically, a butterfly-shaped organ, located anterior to the trachea, just inferior to the larynx. It is flanked by wing-shaped left and right lobes and the medial region called isthmus [3, 10]. The thyroid gland produces thyroid hormones, mainly triiodothyronine (T_3) and thyroxine (T_4). Multiple thyroid hormone receptor isoforms, derived from two distinct genes, mediate the action of thyroid hormones. The thyroid hormone receptors belong to a nuclear receptor superfamily. Thyroid hormone receptors bind to specific thyroid hormone-responsive sequences in promoters of target genes by regulating transcription. However, hypothalamic-pituitary-thyroid axis regulates thyroid hormones [7, 11].

3.1 Hypothalamic-pituitary-thyroid (HPT) axis

The hypothalamic-pituitary-thyroid axis is the part of neuroendocrine system consisting of hypothalamus, pituitary gland and thyroid gland. The hypothalamus is directly connected to the pituitary gland [12]. Hypothalamus secretes TRH which stimulates pituitary gland to produce and secrete TSH. TSH then acts on thyroid gland to produce and secrete thyroxine (T_4) and triiodothyronine (T_3). T_4 is converted into T_3 by deiodination controlled by various hormones like TSH, vasopressin and catecholamines in the peripheral organs (liver, adipose tissues, glia

and skeletal muscles). T_4 and T_3 control the secretion of TRH and TSH by negative feedback mechanism to maintain normal levels of the hormones of HPT axis into the blood stream. Reduced levels of circulating TH result in increased TRH and TSH production and vice versa [13].

3.2 Thyroid dysfunction

Thyroid disease is very common worldwide affecting 5–15% of general population. Women are 3–4 times more susceptible to experience any type of thyroid disease. Thyroid dysfunction can be due to overproduction or under production of thyroid hormones. Thyroid disorders can lead to enlargement of thyroid gland as well as thyroid cancer. Abnormal production of thyroid hormones can lead to following pathological conditions; hypothyroidism (under production of thyroid hormones) and hyperthyroidism (overproduction of thyroid hormones) [3, 14]. There are a few drugs, classically associated with thyroid dysfunction, including lithium, amiodarone, interferon alfa, interleukin-2 and tyrosine kinase inhibitors [15].

3.2.1 Hypothyroidism

Hypothyroidism is described as the thyroid gland's inability to produce enough thyroid hormone to meet the body's metabolic demands. Hypertension, dyslipidemia, cognitive impairment, infertility and neuromuscular dysfunction are associated with untreated hypothyroidism. Hypothyroidism is more prevalent in women than men and increases with age. Primary thyroid gland failure or insufficient gland stimulation by the hypothalamus or pituitary gland may lead to hypothyroidism. Primary gland failure can be resulted from congenital abnormalities, iodine deficiency, autoimmune destruction (Hashimoto disease) and infiltrative diseases. Iatrogenic hypothyroidism occurs after radioiodine therapy, thyroid surgery and neck irradiation. Disorders generally associated with transient hypothyroidism include postpartum thyroiditis, silent thyroiditis, subacute thyroiditis and thyroiditis associated with thyroid stimulating hormone (TSH) and receptor-blocking antibodies. Basic causes of hypothyroidism are generally found with other manifestations of hypothalamic or pituitary dysfunction, and, are characterized by decreased levels of TSH relative to inadequate thyroid hormone.

3.2.2 Hyperthyroidism

Hyperthyroidism is defined as “the excessive production and secretion of thyroid hormones from the thyroid gland” and is characterized by weight loss, tachycardia, palpitation, arrhythmia, tremor, nervousness, irritability, anxiety, heat intolerance, sweating, increased thirst and appetite, fatigue, hyperdefecation, diffused goiter, warm and moist skin and disturbances in menstrual cycle [14, 16]. Hyperthyroidism can be caused by graves' disease, painless thyroiditis or postpartum thyroiditis, painful subacute thyroiditis, toxic multinodular goiter or toxic adenoma and exogenous thyroid hormone excess [3]. Menstrual disturbances are common in hyperthyroidism. Thyrotoxicosis may cause delay in sexual maturation and onset of menstrual cycle, oligomenorrhea, polymenorrhea and increased concentrations of sex hormone binding globulin (SHBG). Progesterone (P_4) and follicle-stimulating hormone (FSH) significantly increase and, luteinizing hormone (LH) as well as estradiol (E_2) significantly decrease in hyperthyroidism [17].

4. Ovary

Ovaries are the female pelvic reproductive organs that house the ova and are also responsible for the production of sex hormones. Ovaries are paired organs located on both sides of the uterus within the broad ligament beneath the uterine (fallopian) tubes. The ovary within the ovarian fossa is a space that is bound by the external iliac vessels, obliterated umbilical artery and the ureter. The ovaries house and release ova or eggs, needed for reproduction. A female has approximately 1–2 million eggs at the time of birth but only 300 of these eggs will become mature and released for fertilization [18].

4.1 Polycystic ovary syndrome (PCOS)

PCOS is the common endocrine disorder among females. It is estimated that 6–10% of women are affected by PCOS in reproductive years of their life. 1 out of 10 women experiences its symptoms in her fertile age. The multifaceted nature of PCOS makes it difficult to define. This clinically heterogenous endocrine syndrome is infertility to gynecologist, hirsutism to a dermatologist, menstrual irregularity to a physician and pseudo-Cushing's disease to an internist. Considering all the the symptoms collectively, it can be defined by hyperandrogenism, oligomenorrhea and multiple cystic follicles in ovaries. Disturbed pulsatile release of GnRH leads to excessive LH, contributing to hyperandrogenism and polycystic morphology. Genetic and epigenetic reasons of these changes have also been investigated [19, 20].

4.2 Hypothalamic-pituitary-ovarian (HPO) axis

Reproductive activity is regulated by the hypothalamic-pituitary-ovarian (HPO) axis which secretes hormones necessary for reproduction. HPO is comprised of three main components. Hypothalamus is located at the base of the brain, just above the brainstem. Along with homeostasis, the hypothalamus also secretes certain hormones, including gonadotropin-releasing hormone (GnRH). Pituitary gland is located below the hypothalamus, in the base of the skull. This gland secretes a variety of hormones, including luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to GnRH. Ovaries are located in the woman's pelvis, and secrete estrogen and progesterone [21].

5. PCOS and hypothalamic-pituitary-thyroid axis

HPO axis and HPT axis are physiologically related. Thyroid receptors in ovaries control female reproductive functions and estrogen affects HPT axis. This link designates subclinical hypothyroidism as a determinant of PCOS. The high prevalence of hypothyroidism among PCOS patients also indicates a strong relation. Thyroid levels are more frequently disturbed in PCOS patients and are more commonly associated with anovulation. Insulin resistance is also a common feature of both the diseases. Incidence of subclinical hypothyroidism among PCOS women augments insulin resistance and hyperandrogenism [22, 23].

6. Prevalence

The autoimmune thyroid disease (AITD) is found more prevalent in females with PCOS than the females without PCOS. Many systematic prospective studies

were carried out to observe the levels of thyroglobulin (Tg) antibodies and thyroid peroxidase (TPO), distinctive for hashimoto thyroiditis (HT) in females with PCOS. It was observed that TPO and Tg levels were elevated in PCOS patients than the healthy females. Moreover, in thyroid ultrasound, hypoechoic pattern which is typical of Hashimoto thyroiditis (HT) was also found more prevalent in PCOS patients. Increased level of thyroid antibodies and hypoechoic thyroid ultrasound pattern revealed the prevalence of HT in PCOS patients and found to be increased by three-fold when compared with controls [24, 25]. In Asia, recently cross-sectional studies, revealed higher prevalence of TPO-positive autoimmune thyroiditis with increased mean TSH levels, increased prevalence of goiter and frequently a hypoechoic thyroid ultrasound pattern in patients with PCOS aged between 13 and 45 years, than in control [1, 26, 27]. Recent meta-analysis included most of the studies, which confirmed higher prevalence of AITD, higher TSH levels and positive TPO and TG antibodies in PCOS patients than in controls [28].

The possibility of having Graves' disease along with PCOS could be higher. In this regard, no broad epidemiological data was found as of recently with the exception of the case reports [1, 2, 29].

In girls of age 13–18 years with HT, a study showed highly significant prevalence of PCOS than in girls without HT, who were negative for TPO antibodies [30]. From the majority of studies, this can be concluded that HT and PCOS frequently occur together.

7. Etiology and pathogenesis

The etiology of HT is complicated and involves mainly genetic along with gender-associated and environmental factors like iodine supply, drugs, chemicals and infections [31]. Similarly, genetic, ovarian-related as well as other hormonal and metabolic factors such as hyperinsulinemia were supposed to involve in the etiology of PCOS [32].

Genetic susceptibility for HT has been confirmed by family and twin studies [33, 34]. Similarly, genetic susceptibility and familial aggregation were also found in PCOS patients [35, 36]. Various susceptibility genes have already been proposed for HT as well as PCOS [37, 38]. Although, a common genetic background still has not been established. Polymorphism of susceptibility genes in HT may influence the occurrence and characteristics of PCOS. Such possible connections will be discussed in more detail. Furthermore, HT is the most prevalent autoimmune disorder [37]. Possible role of autoimmune phenomena in the etiology of PCOS has been suggested [30, 39]. Therefore, supposed genetic and causal factors related to autoimmunity in both the disorders will be explained along with the role of polymorphism of susceptibility genes, alter growth factor beta (TGF β), regulatory T cells (Tregs), the thymus and variations of sex hormones.

7.1 Susceptibility and candidate genes

In HT, family and twin studies recognized strong genetic susceptibility. The risk of developing HT is increased by 32 and 21 fold in children and siblings of patients with HT respectively, where females were more prone to be affected than males [33]. Various genes are said to be associated with the disease occurrence, progression and severity such as human leukocyte antigen (HLA-DR), cytotoxic

T-lymphocyte-associated protein 4 (CTLA4), CD40, interleukin 2 receptor, protein tyrosine phosphatase 22 (PTPN22), alpha (IL2RA), vitamin D receptor (VDR) and thyroid-specific gene thyroglobulin (Tg) [31, 40, 41].

Familial clustering is well established in PCOS. An increased prevalence of PCOS has been documented in first-degree relatives of females with PCOS [38, 42, 43]. Several candidate genes have been studied for PCOS, such as those coding for fibrillin 3 (FBN3), insulin (INS), INS receptor substrate 1, transcription factor 7-like 2, calpain 10, the fat mass and obesity associated protein [44, 45], sex hormone binding globulin (SHBG) [38] and VDR [46]. Recently, in an Asian as well as European population, the DENND1A gene, which encodes a protein participating in the endosomal membrane transport, was recognized by genome-wide association studies (GWAS) as a true PCOS susceptibility gene [47, 48]. However, the found results of a large number of candidate gene studies were mostly inconclusive.

7.2 Genetic polymorphism

FBN3 gene polymorphisms may play a role in the etiology of PCOS and HT by influencing the activity of TGF, which is regulated by FBNs. The FBN3 gene, like FBN1 and FBN2, is likely to encode FBNs, which are microfibril networks in the extracellular matrix that provide binding opportunities for TGF sequestration [49, 50]. Polymorphisms in the FBN3 gene, which impact the activity of TGF, which is regulated by FBNs, may play a role in the etiology of PCOS and HT. FBN3 is likely to encode FBNs, which are a component of extracellular matrix microfibril networks that provide binding opportunities for TGF sequestration, similar to FBN1 and FBN2 [47, 50–52]. Activins, inhibins, and anti-Mullerian hormone, all members of the TGF superfamily, are thought to play a role in the etiology of PCOS. However, genome wide association studies (GWAS) have found no members of the TGF signaling pathway to be among the top signals for PCOS. Changes in TGF have been linked to the etiology of PCOS in terms of prenatal origins, metabolic abnormalities, and reproductive abnormalities [50]. FBN3 is abundant in fetal organs, including the ovaries [53, 54]. FBN3 expression in the stromal compartments of fetal ovaries disappears after the first trimester. As a result, FBN3 has an effect on the activity of TGF, which is involved in the regulation of stromal formation and function throughout fetal development, confirming notions about PCOS having a fetal origin [54]. Recent genetic studies have also reported that polymorphism of the FBN3 gene has been shown to be associated with the levels of TGF β . Allele 8 (A8) of D19S884, a dinucleotide repeat polymorphism in intron 55 of the fibrillin-3 gene, is linked to polycystic ovary syndrome [55]. Similarly, in HT, lower levels of serum TGF β 1 were found when compared with healthy controls. Moreover, levels of serum TGF β 1 did not increase after treatment with levothyroxine (l-T₄), indicating the interrelation between TGF β 1 and HT [56]. TGF stimulates the production of the transcription factor forkhead box P3 (FOXP3) and the creation of Tregs in the establishment of immunological tolerance, and it works as a fundamental regulator of immune tolerance by promoting suppressive Tregs and blocking T cell differentiation [31, 57].

As a result, TGF could play a role in the development of autoimmune diseases like HT. Given this context, it's possible that PCOS women with allele 8 of the D19S884 gene in the FBN3 gene, and hence lower TGF1 levels, are more likely to develop HT than PCOS women without allele 8, but this has yet to be researched.

There has recently been evidence of a link between the three prime untranslated region (3'-UTR) mutation rs1038426 of the gonadotropin-releasing hormone receptor

(GnRHR) and INS production in PCOS, as well as a link between serum TSH, serum INS levels, and INS sensitivity. This could point to a significant role for GnRHR genetic variants in INS secretion and INS resistance in PCOS, as well as a link to thyroid function [58].

Finally, the CYP1B1 gene, which codes for an enzyme that converts E2 to 4-hydroxyestradiol, is linked to PCOS. The CYP1B1 L432V (rs1056836) polymorphism was linked to serum thyroxine (T₄), free T₃ (fT₃), and free T₄ (fT₄) levels [59]. This discovery could point to a third genetic relationship between thyroid function and PCOS.

7.3 Thymus

The importance of the thymus gland in immune system modulation and autoimmune development is well understood. Two processes permit the maintenance of self-tolerance and prevention of autoimmunity; the central immunological tolerance, which is enabled by the thymic deletion of autoreactive T cells during fetal development, and peripheral immune tolerance, in which Tregs play the key role [37, 60]. These cells are attained from the thymus as well as peripheral T cells. Tregs suppress the immune system and prevent an overabundance of immunological responses [61]. As previously established, lower TGF1 levels in the blood have been linked to HT [56].

In animal models, estrogen-induced immunological disruption has been demonstrated to play a role in the development of PCOS. Anovulation and follicular cysts were generated in female mice when estrogen was given before 10 days of age, when the thymus was in the latter stages of development [62]. The effect of estrogen on the thymus was investigated in estrogen-injected female mice with intact thymus, had follicular cysts in their ovaries; however, no cysts were found in mice who were thymectomized before estrogen injections and then reconstituted with adult thymocytes. Ovulation occurred and follicular cysts did not arise when estrogen was unable to exert influence upon the thymus during its development when adult thymic cells were given later. In addition, estrogen-injected animals with an intact thymus had a lower number of thymocytes than controls. The absence of Tregs due to an estrogen-affected thymus was thought to be a needed for the production of estrogen-induced cysts, supporting the autoimmune etiology of PCOS [63]. Similarly, the highest prevalence of infertility was seen in women prenatally exposed to diethylstilbestrol (DES), a strong synthetic estrogen that was given in the United States from 1940 to 1971, when they were exposed to DES from 9 to 12 gestational weeks [64]. This is also the period during which the thymus develops at its most rapidly [65]. A higher frequency of autoimmune disorders has been found in DES-exposed women [66]. Phytoestrogens, which are found in flax seeds and soy bean products, may expose modern pregnant women to higher doses of estrogen. In addition to estrogens, adrenal steroids like corticosterone have been demonstrated to reduce thymic weight and number, resulting in anovulation and the production of ovarian cysts in mice [67].

To summarize, different variables such as excessive estrogen levels or severe stress with increased adrenal hormones may be responsible for changes in the fetal thymus, resulting in changes in immunological tolerance and the occurrence of HT and PCOS in predisposed individuals in adulthood.

7.4 Sex hormones

The sex hormones play an important role as females are significantly more often affected by autoimmune disorders than males. Autoimmune disease autoimmune

affects 5% of the world's population and 78% of those affects women [68]. A doubled chromosome X and a low androgen-to-estrogen ratio were thought to play a role in the etiology of autoimmune disorders even in Klinefelter's syndrome [69]. The onset of autoimmune disorders in women is earlier than in males, and it frequently correlates with elevated levels of the female hormone progesterone [68]. As a result, when comparing pre-pubertal children with chronic autoimmune thyroiditis to pubertal adolescents or adults, the female-to-male ratio was shown to be considerably lower in pre-pubertal children with chronic autoimmune thyroiditis [70]. Similarly, estrogen usage was linked negatively with the presence of TPO antibodies [71]. During the menstrual cycle, higher levels of estrogens during the follicular phase and lower levels of estrogens during menstruation and luteal phase, lead to a shift from Th1 to Th2 mediated immunity, respectively [72]. As a result, throughout the typical menstrual cycle, levels of the Th2 cytokine interleukin 6 (IL6) were adversely linked with progesterone levels in young women. IL6 levels were lowest during the luteal phase and highest during the follicular phase [73]. The activation of FOXP3 and the generation of Tregs was inhibited by IL6 [62]. On the other hand estrogens have been shown to promote Treg development [72].

As a result, it was observed that the number of Tregs decreases during the luteal phase and increases during the late follicular phase [74]. Pregnancy causes several changes in the immune system in order to tolerate the fetus, the most notable of which is a shift from Th1 to Th2 cytokine profile [75, 76]. This is most likely due to Treg expansion generated by estrogen, which suppresses both Th1 and Th2 immune responses, while the latter are less vulnerable to Tregs and thus prevail. After delivery, a decrease in Tregs alters the cytokine profile from Th2 to Th1, causing autoimmunity to exacerbate or worsen [76]. A connection between the number of deliveries and the risk of AITD was found in a few retrospective studies [77, 78].

Sex hormones regulate in vitro and in vivo immune system [79]. Estrogens have been linked to a hyperactivity of T cells and a hypoactivity of B cells in animal studies [80]. The generation of autoantibodies was higher in female mice than in male mice [81]. Estrogens have been shown to decrease T suppressor cell function, enhance B cell activity, boost the release of the Th2 cytokine IL6, and shift the immune response to Th2 and antibody generation [38, 68]. In comparison to men, women have a greater CD4+/CD8+ ratio, higher CD4+ levels, and more antibodies [75]. Androgens suppress most immune system components, increase the activity of T suppressor cells, and increase the Th1 response and CD8+ cell activation [74, 82]. Progesterone inhibits macrophage growth, IL6 generation, and peripheral antibody production [82]. Oscillations in progesterone levels during pregnancy and the ovulatory cycle are thought to be linked to reversible immune system alterations [83].

Women with PCOS have lower progesterone and higher testosterone levels than women without PCOS [2]. Menstrual irregularity in women suffering from PCOS and several anovulatory cycles may have no or very low progesterone, resulting in an elevated estrogen-to-progesterone ratio for long duration. As a result, their vulnerability to autoimmune diseases may increase because of a stimulating effect of estrogens on the immune system [39, 49]. On the other hand, autoimmune disease could be prevented by androgens. However, their impact on the immune system and levels in PCOS are unlikely to be sufficient to avoid autoimmunity. As a result, an imbalance in progesterone, estrogen, and androgens may contribute to the development of HT. Taking this idea into account, as well as the three PCOS phenotypes that have been postulated [84], the increased prevalence of HT would be expected in women with

PCOS and chronic anovulation as well as without hyperandrogenism, followed by classic PCOS with hyperandrogenism and anovulation, while the decreased incidence would be supposed to expect in ovulatory PCOS with hyperandrogenism. However, this hypothesis is yet to be confirmed.

8. Conclusions

Almost unanimously, prevalence studies report on a frequent joint appearance of PCOS and HT in women within the reproductive age. Therefore, the above discussion, may conclude that thyroid disorders and PCOS are undoubtedly associated with each other, with respect to their etiology, pathogenesis and clinical consequences. However, this chapter provides scientific ground to further investigate the connection between thyroid dysfunction and PCOS.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

AITD	autoimmune thyroid disease
CTLA	cytotoxic T-lymphocyte-associated protein
E	estradiol
FBN	fibrillin
FSH	follicle stimulating hormone
GnRH	gonadotropin releasing hormone
GWAS	genome wide association studies
HPOA	hypothalamic-pituitary-ovarian axis
HPTA	hypothalamic-pituitary-thyroid axis
HT	Hashimoto's thyroiditis
HLA	human leukocyte antigen
IL	interleukin
IL2RA	interleukin 2 receptor alpha
INS	insulin
LH	luteinizing hormone
PCOS	polycystic ovary syndrome
PTPN	protein tyrosine phosphate non-receptor
P	progesterone
SBGH	sex hormone binding globulin
Tg	thyroglobulin
TGFβ	growth factor beta
Th	T helper cell
TH	thyroid hormone
TPO	thyroid peroxidase
TRN	thyrotropin releasing hormone
Tregs	regulatory T cells
TSH	thyroid stimulating hormone

T ₃	triiodothyronine
T ₄	thyroxine
UTR	untranslated region
VDR	vitamin D receptor

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