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# Thyroid disease-related sleep disorders and its diagnostic and therapeutic recommendations: A literature review

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## Highlights

- Complains of sleepless and tinnitus are common in sleep clinics, which is a different type of sleep disorder. In this article, we first summarize this disorder, which is defined as thyroid disease-related sleep disorder (TSD), and propose to categorize it as insomnia secondary to a somatic disorder.
- We have attempted to provide some preliminary diagnostic and therapeutic recommendations for TSD.
- In the treatment of TSD, we suggest relying on the theory of integrating Chinese and Western medicine, emphasizing holistic diagnosis and treatment, and precise medication.

## Abstract

As perioperative medicine evolves, more hospitals are offering comfort sleep clinics. Thyroid disorders (e.g., hypothyroidism, hyperthyroidism, and thyroid cancer) affect the peripheral circadian clock. Elevated serum thyroid-stimulating hormone levels have been found to associate with the incidence of thyroid cancer in humans, but the relationship between circadian disruption and thyroid disease requires further investigation. Malignant transformation of thyroid nodules is characterized by disruption of the expression of biological clock genes. Sleep clinics often see patients complaining of sleepiness and tinnitus. These patients often have comorbid thyroid disorders and are therefore highly susceptible to misdiagnosis or underdiagnosis. In this article, we first summarize this category of disorders, which we propose to classify as insomnia secondary to somatic disease and define as thyroid disease-related sleep disorder (TSD). The primary and common clinical complaints of TSD patients are different types of sleep disorders. In addition, we attempt to provide some preliminary diagnostic and therapeutic recommendations for TSD in the hope that it may assist healthcare professionals in the early diagnosis and management of this disorder.

**Keywords**: Thyroid disease, sleep disorders, definition, diagnose and treatment, traditional Chinese medicine

## I. Introduction

As more patients undergo surgery, the prevention of perioperative neurocognitive deficits has become a priority for patients, families, and perioperative research. As perioperative medicine evolves, more hospitals are offering comfort sleep clinics. Sleep and hypothalamic-pituitary-thyroid (HPT) axis are closely related and mutually interact with each other. Sleep quality and duration can significantly affect thyroid stimulating hormone (TSH) rhythms, which in turn cause a variety of endocrine and metabolic changes [1, 2]. Decreased sleep quality and duration can lead to decreased TSH secretion and concomitant

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sympathetic activation, which in turn increases thyroxine (T4) secretion. HPT axis activity can influence sleep quality and duration. Some studies have shown that changes in thyroid structure and function can also alter biological circadian rhythms, but the exact mechanisms are unknown [1-4].

It is well known that the HPT axis is controlled by the circadian rhythm system and plays a dominant role in the central pacemaker in the suprachiasmatic nucleus as well as in the sleep-wake cycle [3]. Thyroid disorders, such as hypothyroidism, hyperthyroidism and thyroid cancer, affect the peripheral biological clock. Thus, thyroid function and the biological clock are interrelated [4]. Generalized disruption of the endocrine system is thought to be one of the important mechanisms mediating the adverse effects of circadian dysregulation [2]. Although several studies have shown that elevated serum TSH levels are associated with the incidence of thyroid cancer in humans, the relationship between circadian disruption and thyroid cancer requires further investigation [4-6]. In contrast, disruption of oncogenes can cause dysregulation of the biological clock, and disruption of biological clock gene expression has been reported during malignant transformation of thyroid nodules [4, 5]. Since this type of sleep disorder is often overlooked and misdiagnosed, its analysis and generalization is of unique significance in the early diagnosis of thyroid nodules, especially thyroid cancer [5].

Thyroid disease-related sleep disorders (TSD), a type of secondary insomnia, is a group of somatic sleep disorders associated with thyroid disease in which sleep disturbance is the primary complaint. Patients are often first seen in sleep clinics with insidious clinical features of primary thyroid disease and a specific clinical presentation. Previously, this condition was not well understood, and affected patients often have a delayed diagnosis, which causes patient distress and exacerbates physician-patient conflicts. Therefore, in this article, we defined this clinical syndrome and provide some preliminary diagnostic and therapeutic recommendations to help health care professionals diagnose and treat this disease.

## II. Thyroid Disorders and Sleep Disorders

### The reciprocal relationship between sleep and the thyroid axis under normal circumstances

#### *Physiology of the HPT axis*

Thyrotropin-releasing hormone (TRH) is the central hub of the HPT axis. The circadian rhythm affects the function of the suprachiasmatic nucleus and the pineal gland to promote the secretion of TRH from the median eminence, which in turn acts on thyrotropin in the anterior pituitary and stimulates the secretion of TSH, triggering the secretion of T4 and triiodothyronine (T3). Then, the downstream signaling molecules of T4 and T3 negatively feedback to regulate TRH and TSH, thus maintaining the physiological function of the HPT axis [5, 6] (**Figure 1**).

#### *Sleep stages and architecture*

Based on sleep architecture and electroencephalogram, human physiological sleep is divided into rapid eye movement (REM) and non-rapid eye movement (NREM) [4-8]. NREM can be further divided into three distinct stages, N1, N2, and N3 [9]. REM and NREM occur alternately with an interval of 90-120 minutes each [10, 11].

#### *Biological clocks, sleep and thyroid hormone secretion*

Circadian rhythm is a natural, internal process that regulates the sleep-wake cycle and repeats approximately every 24 hours. Other physiological changes that occur according to circadian rhythms include heart rate and various cellular processes, such as oxidative stress, cellular metabolism, immune and inflammatory responses, regulation of endocrine function, and autophagy [12-14]. The supraoptic nucleus and the pineal gland are thought to be the regulatory centers for circadian rhythms. When light stimulation is received, the production of melatonin in the pineal gland is suppressed, thereby keeping people awake. Conversely, melatonin is produced, and people becomes tired [15, 16] (**Figure 1**).

Numerous studies have shown that in normal humans, the secretion of thyroid hormones (TRH, TSH, free triiodothyronine (FT3) and free thyroxine (FT4), etc.) regulated by the HPT axis has obvious circadian rhythm characteristics [17, 18]. Among them, TSH fluctuates most significantly during the day and night, making TSH the most studied target.

Studies have shown that under normal sleep conditions, TSH secretion begins to increase in the evening until it reaches its highest concentration at 2-3 a.m. and then starts to decrease [17]. The disruption of the normal sleep schedule may affect the circadian rhythm of TSH and thyroid hormone secretion. Studies exhibited

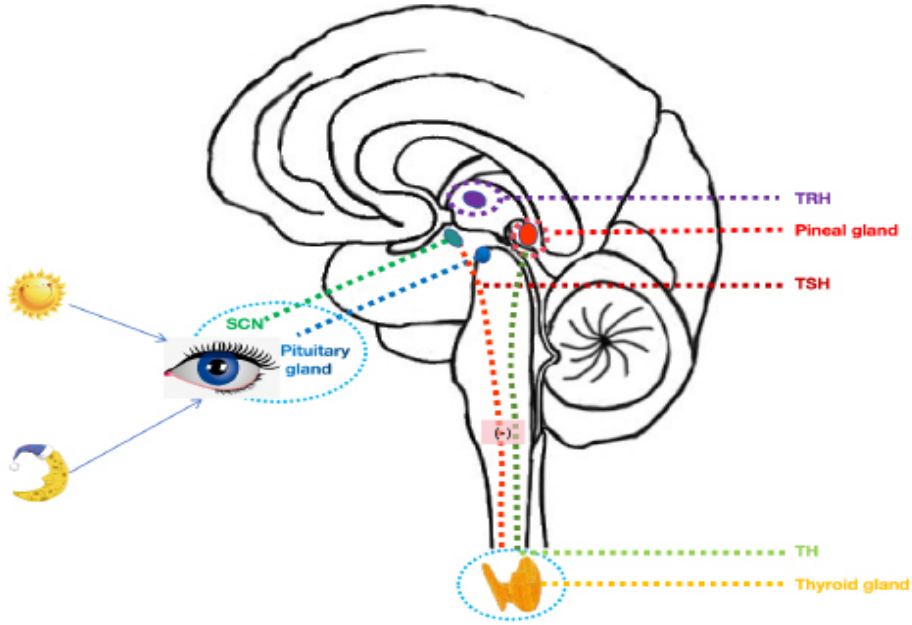


**Figure 1. Schematic diagram of circadian rhythm regulation of HPT axis.** HPT, hypothalamic-pituitary-thyroid; SCN, suprachiasmatic nucleus; TRH, thyrotropin-releasing hormone; TSH, thyrotropin; TH, thyroid hormone.

that blood levels of TSH hormone showed significant circadian fluctuations, and the peak of TSH hormone secretion tended to occur at night [17, 19].

In addition, there was a strong correlation between the circadian profile of blood FT3 and TSH. There is also a significant correlation between circadian fluctuations in blood FT3 and TSH fluctuations. Ninety minutes after the peak TSH fluctuation, there was also a peak secretion of FT3, and the amplitude of circadian fluctuations of FT4 was lower [17-20].

Sleep inhibits TSH release and can reduce diurnal TSH fluctuations, which in turn affects HPT axis hormone secretion [21-23]. Additional sleep after sleep deprivation can significantly inhibit TSH secretion. The existence of a regulatory effect of sleep on the HPT axis has been further demonstrated [24-26].

TSH release is inhibited during sleep, which is related to the sleep-wake cycle and sleep architecture, and the amplitude of TSH oscillations is not affected by gender, body mass index (BMI), or age. However, the onset of the nocturnal TSH surge is significantly delayed with increasing BMI but advanced with increasing age [23].
In patients with normal thyroid function or subclinical hypothyroidism associated with somnolence, levothyroxine tablets may improve somnolence. In replacement therapy for hypothyroid patients, excessive levothyroxine tablets or incorrect administration may cause insomnia along with symptoms of euphoria such as sweating, headache, restlessness, agitation, palpitations, and diarrhea [27, 28].

T4 and T3 enter the cell membrane via a carrier-mediated adenosine triphosphate-dependent transport process [29, 30]. Much of the T4 is deiodinated to the T3 form, which interacts with the thyroid hormone receptor and binds to the X-like receptor of vitamin A and the thyroid hormone responsive element of the gene. This action either upregulates or downregulates the transcription of genes that lead to the formation of proteins contributing to the cellular response to thyroid hormone [31].

Sleep restriction or sleep deprivation can significantly increase blood thyroid hormone levels, adenosine triphosphate (ATP) concentrations, and neuronal excitability. ATP can act as an excitatory neurotransmitter alone or can enhance HPT axis-sleep interactions [27, 32, 33].

Dopamine (DA) is a neurotransmitter associated with a variety of functions in the body and can regulate a number of different physiological activities. DA has a regulatory effect on sleep: too little DA secretion can lead to too much sleep, while too much DA secretion can lead to too little sleep due to hyperexcitability. Also, DA can inhibit the body's secretion of TSH and thyroid hormones and plays a role in preventing thyroid nodules [34, 35].

***Sleep alterations and their effect on thyroid hormone secretion***

Sleep restriction has previously been shown to differentially alter HPT axis activity. In sleep-restricted subjects, the nocturnal blood TSH is decreased while blood FT4 is increasing, and this persists during the sleep restriction period and is reversed when sleep is restored [36, 37].

Another study confirmed that TSH changes in sleep-restricted subjects were not affected by light stimulation, suggesting that the effect of sleep restriction on HPT axis is independent of mechanisms affecting the circadian rhythm of sleep. Scientists speculate that the mechanism may be through altered sympathetic tone activity, which in turn leads to altered TSH activity [38, 39].

Reduced sleep has been shown to increase sympathetic activity and interfere with HPT axis activity, resulting in decreased TSH and increased T4 [24, 36]. The study by Kessler et al. suggests that the duration of sleep deprivation affects the secretion pattern of thyroid hormones in HPT axis [38]. Compared to unrestricted sleep, sleep deprivation leads to lower blood TSH and FT4 in adult women [38]. The above changes were less pronounced in male subjects, suggesting gender differences in the above effects.

In order to maintain the metabolic needs of the brain, the reduced thyroid hormone increases the body's catabolism, which is used to maintain alertness and stress resistance.

### *Interaction between sleep and HPT axis*

The endocrine homeostasis maintained by HPT axis under physiological conditions is closely linked to sleep. Sleep and HPT axis interact to regulate energy and metabolic homeostasis, and alterations in one can lead to dysregulation in the other [5]. Therefore, it is of great value to characterize the mechanisms and clinical manifestations of the interdependence between sleep and the HPT axis.

### *TSH influences the quality and architecture of sleep*

Sleep quality has been shown to influence the circadian rhythm of TSH and thyroid hormone secretion. Short-term sleep restriction significantly reduces the amplitude of nocturnal TSH secretion and may regulate active thyroid hormone secretion by increasing sympathetic tone [24-26]. Conversely, TSH and active thyroid hormones influence sleep quality and sleep architecture. For example, low TSH levels allow for slow-wave sleep and maintenance of normal sleep architecture, whereas insufficient or excessive secretion of active thyroid hormones adversely affects sleep quality and quantity [25, 26, 39].

### *The role of thyroid hormones in sleep deprivation (SD)*

SD is a distressing as it induces a sense of malaise and impairs overall functioning in the affected individual. However, in some cases, SD may be critical to an individual's survival, because it can lead to a dramatic increase in thyroid hormone activity, which is a central mechanism of SD. This condition prompts the pituitary gland to release more thyrotropic hormone, leading to an initial dramatic surge in the HPT axis [40, 41].

Due to the close interconnection between the autonomic nervous system and the HPT axis, prolonged SD leads to sympathetic activation, elevated TSH, and the duration of abnormal wake exceeds the duration of sleep [36, 38]. As a compensatory response to SD, the increase in thyroid hormone activity further enhances purinergic neurotransmission, which increases synaptic transmission by activating a mitochondria-dependent increase in ATP [36, 40, 41].

## Hypothyroidism and sleep disorders

### *Non-rapid Eye Movement*

In hypothyroid patients, T4 insufficiency is now considered to be the main cause of fatigue and sleepiness. Total sleep time is not significantly altered in hypothyroid patients but is mainly characterized by decreased non-rapid eye movement 1 (N1) and non-rapid eye movement 2 (N2) as well as non-rapid eye movement 3 (N3) and REM, suggesting poor sleep quality [42, 43]. Another study suggested that hypothyroidism may lead to a reduction in the number of awakenings and slow-wave sleep (SWS) through a mechanism related to disturbances in thyroid hormone, TSH, and TRH secretion [44-47].

Because hypothyroidism is often associated with obstructive sleep apnea (OSA) syndrome, it may trigger or exacerbate pre-existing airway obstruction and respiratory sleep apnea. Compared to OSA patients with normal thyroid function, patients complicated with hypothyroidism have increased adverse markers of OSA (Epworth scale, sleep oxygen saturation <90%, hypoventilation index, etc.) [48]. Mechanisms include blunted response to hypercapnia and hypoxia, deposition of airway mucin exacerbat-

ing upper airway narrowing, retrosternal goitre inducing positional dyspnea, increased BMI, and altered respiratory muscle activity [49-51].

In patients with subclinical hypothyroidism, low thyroid hormone can lead to increased sleep latency, decreased sleep duration, and decreased sleep satisfaction, along with anxiety, impatience, and muscle and joint pain [47, 52].

### *Hypothyroidism, OSA and sleep disorders*

In a population-based clinical study of OSA, the prevalence of OSA was 24% in adult men and 9% in women [53]. After adjusting for demographic characteristics (BMI, alcohol consumption, smoking, etc.), Thavaraputta et al. confirmed a significant association between hypothyroidism and OSA. Another study confirmed that obese patients without sleep disorders often have hypothyroidism [54, 55].

The above studies suggest that hypothyroidism may lead to OSA, and the specific mechanism may be similar to the pathogenesis of OSA [56]. In addition, T4 replacement therapy has previously been shown to improve sleepiness and fatigue in OSA patients [57]. Thyroid hormone therapy may partially ameliorate apneic episodes and hypoxemia, thus improving sleep structure and duration [58]. However, there is no conclusive evidence regarding hypothyroidism and the pathogenesis of OSA. Thyroid hormones do not predict the degree of airway obstruction in OSA [59-61].

In a clinical study of 271 patients, researchers evaluated the correlation between OSA and thyroid hormone levels. Among patients diagnosed with OSA, 0.4% had combined hypothyroidism; in patients previously diagnosed without OSA, 1.4% had combined hypothyroidism; in patients newly diagnosed with OSA, 11.1% had combined hypothyroidism; in newly diagnosed patients without OSA, 4% had combined hypothyroidism [51]. The above results suggest that patients with OSA are more likely to have hypothyroidism. However, the degree of hypothyroidism does not appear to predict the degree of airway obstruction.

### *Hypothyroidism treatment and sleep disorders*

#### *Thyroid function replacement therapy and sleep disorders*

Sleep-disordered breathing is common in patients with primary hypothyroidism. In patients with idiopathic narcolepsy, patients with combined subclinical hypothyroidism have shortened sleep latency and prolonged total sleep time, but normal NREM/REM scores.

T4 therapy reversed the SD in 10/12 patients, and the mechanism may be related to improved upper airway stenosis [62]. In addition, levothyroxine relieves excessive daytime sleepiness, anxiety, and insomnia due to hypothyroidism [63-65].

#### *Effect of continuous positive airway pressure (CPAP) treatment on serum thyroid hormone levels*

Changes in serum thyroid hormone levels before and after CPAP treatment have been studied previously. Patients with OSA were found to have altered baseline thyroid hormone levels. In these patients, CPAP attenuated the changes in FT3 and TSH seen in patients with non-thyroid disease syndromes. The mechanism may be related to CPAP's capacity to reduce hypoxemia and inflammatory responses. In contrast, CPAP treatment did not have these effects in patients with normal baseline hormone levels [66-68]. In the future, it is necessary to select patients with consistent baseline hormone levels for further in-depth study.

#### *Effect of thyroidectomy on the airway of patients with OSA*

High BMI with narrow upper airway stenosis is an important predisposing factor for OSA. As the disease progresses, mucopolysaccharides are deposited along the oropharyngeal structures, causing thickening of the pharyngeal wall and pharyngeal dilator muscles, further exacerbating airway narrowing.

Untreated hypothyroidism is thought to exacerbate upper airway narrowing by depositing mucopolysaccharides along the oropharyngeal structures, which can lead to thickening of the pharyngeal wall and hypovolemic myopathy of the pharyngeal dilator muscles. In addition, retrosternal goiters may directly compress the trachea and worsen dyspnea [61, 69, 70]. A meta-analysis found that the symptoms of airway obstruction was alleviated in patients with OSA who underwent thyroidectomy, especially positional dyspnea [71, 72].

## Hyperthyroidism and sleep disorders

Elevated circulating T4 is commonly associated with thyroid hyperstimulation, thyroid nodules with abnormal function, increased or excessively decreased T4 uptake, and pituitary tumors with excessive TSH secretion. It is well known

that hyperthyroidism and thyrotoxicosis can lead to sleep disturbances, usually thought to be related to thyroid-induced hyperarousal [73-75].

In hyperthyroidism, immunoglobulins are overactivated by T4, followed by clinical symptoms such as sleep disturbance, prolonged sleep latency, difficulty in maintaining sleep, compensatory daytime somnolence, changes in appetite, abnormal bowel movements, increased anxiety, and increased tremor. Sleep disturbance is an important hallmark of hyperthyroidism, and the degree of TSH, T3, and T4 abnormalities is closely related to the severity of sleep disturbance [76, 77]. In several clinical studies, patients with hyperthyroidism developed hypodynamic sleep, mainly characterized by decreased sleep duration and SWS [78-81]. Kraemer et al. found that excess T4 can increase REM density and body motor function in thyrotoxicosis patients, and Sridhar et al. found that thyrotoxicosis can lead to decreased sleep efficiency and duration, as well as a significant increased sleep latency [76, 82]. These are consistent with other studies which reported that endogenous hyperthyroidism led to sleep disturbances [82-84].

### *Hyperthyroidism treatment and sleep disorders*

Excessive use of iodine-containing tablets can cause symptoms similar to hyperthyroidism, such as insomnia and heart palpitations, and insomnia may improve when drug suspension [85, 86]. Studies have confirmed that growth hormone and SWS are closely related. Hyperthyroidism can inhibit the release of growth hormone and reduce the duration of SWS, which can be reversed by propylthiouracil [87]. Patients undergoing radioiodine ablation therapy often complain of sleep disturbance, especially older patients [88].

In a study of Graves Disease (GD) recurrence after discontinuation of antithyroid medication, investigators found that the recurrence rate in patients with comorbid insomnia was three times higher than in patients without insomnia. In similar studies in children, children with GD recurrences were more likely to have reduced sleep duration than control children. Prolonged sleep duration may improve the prognosis of children with GD [89, 90]. However, the above studies only examined sleep duration and did not investigate the effect of sleep quality on GD relapse.

## Thyroid nodules, thyroid cancer, and sleep disorders

Gene expression in the thyroid gland is now thought to be associated with altered circadian patterns. Thyroid diseases such as hypothyroidism, hyperthyroidism, and thyroid cancer can affect the peripheral biological clock. In addition, genes affecting circadian rhythms have been identified in other tumors such as leukemia, breast cancer, endometrial cancer, and colorectal cancer [91-98].

Most thyroid nodules are benign, and only about 5% develop into thyroid cancer. Patients with benign nodules have less psychological distress and sleep disturbance than those with thyroid nodules suspected to be cancerous [5]. It has been reported that elevated serum TSH level is associated with the incidence of thyroid cancer in humans, but the relationship between circadian disruption and thyroid cancer requires further investigation [4]. Changes in the expression of biological clock genes have been reported during the malignant transformation of thyroid nodules [92]. Pharmacological modulation of biological clock mechanisms may provide new strategies for the treatment of thyroid malignancies. Symptoms such as nausea and vomiting, insomnia, and anorexia were improved in patients with differentiated thyroid cancer after one month of radioactive iodine treatment [97].

Alterations in circadian genomics are an area of great scientific interest from the standpoint of carcinogenesis and possible therapeutic approaches. An in-depth understanding of circadian rhythm dynamics in patients with thyroid malignancies may aid in their early diagnosis and provide insights into the effects of thyroid cancer on sleep [86, 98]. Mannic et al. found that the expression level of Bmal1 was upregulated in tissue samples of follicular thyroid cancer (FTC) and papillary thyroid cancer (PTC) compared to normal thyroid and benign nodules, whereas the expression level of Cry2 was downregulated in FTC and PTC [92]. Human thyroid cells derived from normal thyroid tissue showed expression of the brain and muscle arnt-like 1 (BMAL1) gene. BMAL1 protein can form a heterodimer with clock circadian regulator (CLCOK) protein and participate in the regulation of cellular rhythmic changes.

Thyroid cells derived from FTC and PTC exhibited clock transcript oscillations similar to those from normal thyroid tissue and benign nodules (except Per2 alterations in PTC), whereas cells derived from poorly differentiated thyroid carcinoma exhibited markedly altered circadian

oscillations. The characterization of altered thyroid clock mechanisms during malignant transformation of thyroid nodules contributes to the understanding of the link between the biological clock and oncogenic transformation. In addition, it helps to improve the preoperative diagnosis of thyroid nodules [92].

## Hypothyroidism and restless legs syndrome (RLS)

### *RLS and thyroid function*

The prevalence of RLS is approximately 0.1-15% in the normal population. At night or at rest, patients with RLS experience discomfort in the lower extremities, accompanied by irresistible leg movements [99-101]. Patients with RLS are often comorbid with sleep disorders and anxiety and depression [102, 103]. RLS is classified into idiopathic and secondary types. Secondary RLS is common in pregnancy women and patients with multiple sclerosis, Parkinson's disease, anemia, iron deficiency, and chronic renal failure [104, 105]. MEIS1 is currently considered a susceptibility gene for RLS [106-108]. Although the pathogenesis of RLS is still unclear, RLS has been shown to be closely related to DA and iron deficiency in the nervous system [101, 108].

A growing number of studies have confirmed that the dopaminergic system is related to the HPT axis [34, 109-112]. DA decreases thyroid hormone and thyroid-stimulating hormone (TSH) and increases TRH release over time [35]. In animal studies of RLS, nigrostriatal 18F-dopa uptake was found to be reduced and presynaptic DA was decreased [112, 113]. These findings facilitate a detailed study of the mechanisms by which DA dysfunction promotes the pathogenesis of RLS. In idiopathic RLS cadavers, DA 2 receptors were found to be reduced compared to controls, and the degree of reduction was correlated with the severity of RLS [114]. It has been shown that exogenous supplementation with DA or DA agonists can reduce the symptoms of RLS, further confirming that DA dysfunction exists in RLS patients [115].

### *Thyroid hormone axis and hypothyroidism with iron and DA systems*

Previous studies have confirmed that either iron deficiency or anemia is highly associated with the development of RLS and hypothyroidism [116]. In contrast, after iron supplementation, patients had increased T4 and decreased TSH. It has also been suggested that there is an interaction between thyroid function and the iron metabolism system [116-118]. A clinical study in pregnant women found that pregnant women with comorbid RLS were more likely to develop hypothyroidism [119-123]. The mechanisms underlying the relationship between iron metabolism and thyroid hormones are unclear, and it is currently believed that TRH upregulates total iron-binding protein in the pituitary gland [124, 125]. Neuropathological studies have found iron and ferritin deficiencies in the striatum and ventral midbrain nucleus in patients with RLS, along with DA overload [126-128]. Neuroimaging and cerebrospinal fluid biochemical analyses suggest that iron deficiency is prevalent in the brain of RLS patients [129, 130].

### *TRH, black cortisol system, and RLS*

Pro-opiomelanocortin (POMC) neurons originating in the arcuate nucleus of the hypothalamus can send excitatory neuronal projections to TRH neurons in the paraventricular nucleus [131]. Hypothalamic POMC neurons can produce melanocortin (MC), and there is a marked circadian regularity in blood MC levels, which may have a regulatory effect on sleep architecture [132-139]. When MC was injected into rodents, the animals exhibited RLS-like clinical features and nociceptive sensitization [140, 141].

DA can inhibit α-melanocyte activity in MC, which is a possible mechanism by which dopaminergic drugs lead to stereotyped responses [137-141]. In mice with high expression of alpha-melanocyte-stimulating hormone, impaired negative feedback can increase hypothalamic TRH mRNA and blood thyroid hormone [131, 139, 141]. Similar changes are present in patients with hypothyroidism combined with RLS. POMC is seen in the anterior pituitary, pituitary mesenchymal cells, and the hypothalamus [142-144].

## Thyroid disease, tinnitus, and sleep disorders

Tinnitus is a phantom sound, such as buzzing and hissing, in the ear or inside the skull that patients experience in the absence of an external sound source, which may last for a period of time. Patients may experience tinnitus symptoms after a long period of insomnia, and some patients may experience tinnitus symptoms first before it leading to insomnia. A study found that in the tinnitus group, the incidence of insomnia is 28.1% in men and 36.1% in women [145].

### *Hyperthyroidism with tinnitus and insomnia*

A cohort study found that the risk of combined

tinnitus in patients with hyperthyroidism was 1.38 times higher than that in patients without hyperthyroid (95% CI=1.27-1.50) [145, 146]. In addition, dizziness, insomnia, anxiety and/or hearing loss may be risk factors for combined tinnitus in hyperthyroidism [145, 146]. The above studies suggest an association between thyroid function and tinnitus, but the mechanism by which thyrotoxicosis causing tinnitus is unknown. In addition to T4 affecting cochlear maturation, other mechanisms include potassium channels, Na+/K+ ion gradient across the vessel wall, and thyroid hormone-sympathetic adrenal system interaction [146]. The next step should be to observe whether tinnitus appears to improve after treatment of hyperthyroidism.

*Hypothyroidism with tinnitus and insomnia*

Tinnitus was also found to be associated with hypothyroidism. After correcting confounding factors such as age, sex, and economic status, the overall incidence of tinnitus was significantly higher in hypothyroid patients than in non-hypothyroid patients (9.49/1,000 vs. 6.03/1,000 annually) [147].

The mechanisms by which hypothyroidism causing tinnitus include altered sympathoadrenal activity due to thyroid status, altered cochlear blood flow, and thyroid hormones affecting neuronal maturation [147-150]. In animal models of congenital hypothyroidism, the auditory system develops abnormally [151, 152]. Childhood hypothyroidism also causes hearing loss in children [153].

**Sleep disorder and hypothyroidism in pregnancy**

Hypothyroidism in pregnancy is one of the most common endocrine disorders in pregnancy. The causes of hypothyroidism in pregnancy may be related to the high basal metabolism of pregnant women, relative thyroid insufficiency, increased consumption of thyroid-stimulating hormones, specific iodine leakage, dilution of thyroid hormones in the blood, increased iodine consumption, and decreased T4 stores [154-157].

A study reported that 64.0% of pregnant women with normal thyroid function had one or more symptoms resembling hypothyroidism, with the most common comorbid symptoms being insomnia and drowsiness (30.3%), followed by fatigue (20.3%) [158]. In addition, sleep disturbances in some hypothyroid pregnant women may be associated with psychoneurological abnormalities due to hypothyroidism [159].

**Thyroid function changes induced by immunotherapy**

Abnormal thyroid function is more common in patients undergoing tumor immunotherapy. Thyrotoxicity or hyperthyroidism usually occurs first, with 80% eventually progressing to hypothyroidism [160, 161]. Increased doses and drug combinations may lead to a higher incidence and earlier onset of immune-related adverse events. Therefore, it is particularly important to study immunotherapy-associated hypothyroidism.

Immunotherapy-associated hypothyroidism usually has insidious symptoms, and adverse effects are usually grade 2 or milder, with very few serious adverse effects [162]. In these patients, fatigue, tiredness, hoarseness, drowsiness, and dry skin are the most common clinical manifestations. Therefore, if these patients present with fatigue and drowsiness that cannot be explained by other causes, it is important to consider whether they have immunotherapy-associated hypothyroidism and to treat it as soon as possible. It is currently believed that the mechanisms may include: 1) over-activation or destruction of the autoimmune system, leading to some destruction of normal thyroid cells [160-167]; 2) elevation of inflammatory factors such as IL-17; 3) elevation of autoantibody levels (TSH, anti-thyroglobulin antibodies (TGAb), etc.), reduction of immune tolerance, or reduction of immune tolerance [59-61, 168]; and 4) genetic factors, e.g., the single nucleotide polymorphisms of CTLA-4 in Asians may confer a greater susceptibility to thyroiditis, which in turn may lead to hypothyroidism [62].

**Other drugs affecting T4 concentration**

Following non-pharmacological (SD, 12-hour fasting, 14-day calorie-restricted diet) and pharmacological (ethanol, haloperidol, clozapine, etc.) treatments, more pronounced changes in 5'D-II activity and thyroid hormone concentrations were observed in up to 10 regions of the rat brain, suggesting that iodothyronine metabolism in the central nervous system may be mediated by other pathways of iodothyronine metabolism in the CNS [168]. The above suggests that 5'D-II activity and thyroid hormone concentrations in the CNS are highly sensitive to a variety of events that may cause changes in neuronal activity. In an animal study of thyroid hormone stimulation of central cholinergic neuronal function, the latency to betaine-induced REM showed a moderately significant negative correlation with free T4 index [169].

## Recognition and research progress of Chinese medicine on thyroid-related insomnia

According to Chinese medicine theory, the locus of insomnia mainly lies in heart and closely related to liver (gall bladder), spleen (stomach) and kidneys. The etiology and pathogenesis of insomnia mainly include the imbalance of yin and yang, disturbance of qi and blood, the disharmony between ying and wei, and the disturbance of the heart by evil-qi [170, 171].

### *"Ying" disease*

Although there is no concept of thyroid nodules in Chinese medicine, from the point of clinical symptoms and etiology of thyroid nodules, it is very similar to the internal disease "Ying" in Chinese medicine which believes that the formation of "Ying" disease is due to the factors such as internal injuries to emotions and feelings, improper diet, as well as physical factors.

According to Traditional Chinese Medicine (TCM), qi stagnation, phlegm condensation, and blood stasis are the basic pathological changes of "Ying" disease [172]. The appearance of thyroid nodules is related to the malfunction of the liver, spleen, and kidney, and the core mechanism is stagnation of liver qi and spleen dysfunction. When joy and anger are out of order, the seven emotions are disrupted, causing stagnation in the human body's emotions and feelings, leading to qi imbalance. This marks the onset of generalized qi stagnation, progressing subsequently to phlegm stagnation and blood stasis, ultimately contributing to the development of thyroid nodules. In the later stages of "Ying" disease, the weakening of the liver, spleen and kidney, and the imbalance of qi, blood, yin and yang are the main pathogenic mechanisms [173-175].

### *Relevance of "Ying" disease, depression and insomnia*

The heart is the organ similar to the monarch and is responsible for spirit and mental activity. Patients with "Ying" disease are often disturbed by blood stasis and phlegm opacity. In the early stage, they are often accompanied by fire-heat, which affects the physiological function of the heart, thus disturbing the heart and mind, manifesting symptoms such as palpitations, tachycardia, dizziness, and insomnia.

The Liver meridian of Foot Jueyin starts from the big toe, goes up into the calf, through the diaphragm and then enters the lower forehead, i.e., the neck and throat, after traveling along the trachea. Patients with "Ying" disease have blood and phlegm stagnation in the Liver meridian, which affects the operation of qi and blood in the Liver meridian, resulting in hyperactivity of "Liver" yang and "Liver" qi stagnation. Since the liver stores blood and the blood shelters the soul, when the liver meridian is disturbed, it is difficult for the soul to be at peace, so patients with "Ying" disease often manifest depression, chest distention and tightness, irritability and insomnia [176-178]. Therefore, it is of great significance to actively utilize TCM to improve the mental status of such patients [179, 180].

### *Knowledge and research progress of Chinese medicine on insomnia and wasting due to thyroid disease*

Hyperthyroidism is a type of disease mainly characterized by the enlargement of nodules on both sides of the laryngeal nodes in the front of the neck, caused by the interaction of qi stagnation, blood stasis, and phlegm coagulation as demonstrated in TCM theroy [181, 182].

The initial onset of insomnia and wasting due to thyroid disease is accompanied by excessive internal heat, and the long duration of the internal heat will inevitabley harm Yin and body fluids. The location of the lesions mainly includes heart, liver and kidneys. Ancient medical practitioners keenly recognized the close relationship between emotions and thyroid disease, and believed that emotional disorders resulted imbalance of qi and blood is its pathological basis, and the treatment focuses on nourishing the heart and liver, revitalizing blood, or psychotherapy. Due to the leading knowledge about the pathogenicity of emotional disease, TCM has accumulated a wealth of experience in the use of medicines in the course of development, and has unique advantages and efficacy in the treatment of psychiatric symptoms associated with hyperthyroidism, such as insomnia and anxiety [183, 184].

### *Progress in the study of Chinese medicine syndromes of autoimmune thyroiditis*

Autoimmune thyroiditis is a common clinical organ-specific immune disease, of which Hashimoto's thyroiditis (HT) is the most common [185, 186].

Yang et al. data-mined 77 research papers on HT evidence in Chinese medicine and obtained a total of 17 typical symptoms. The top 8 signs with the highest frequency were spleen-kidney yang deficiency, qi stagnation and phlegm con-

gestion, qi and yin deficiency, phlegm and stasis entanglement, liver depression and qi stagnation, phlegm congestion and blood stasis, qi stagnation and blood stasis, and yin deficiency and fire exuberance [187, 188]. The decomposition of these signs yielded eight pathognomonic elements, namely qi stagnation, phlegm congestion, excessive internal heat, blood stasis, dampness obstruction, yin deficiency, qi deficiency, and yang deficiency.

In addition, the information of the four described TCM diagnoses of HT were clustered, analyzed and summarized to correspond to four types of evidence: spleen and kidney yang deficiency, yin deficiency and fire exuberance, qi stagnation and phlegm condensation, and phlegm and stasis association. It is believed that emotional disturbances are the main causative factors for the development of HT. Long-term worry, depression or irritation can lead to liver stagnation and spleen deficiency, impaired qi and blood circulation, as well as abnormal fluid transport, resulting in the development of thyroid diseases.

## III. Diagnosis and treatment of TSD

### Definition and classification of TSD

#### *Definition*

TSD is characterized by fatigue and weakness, frequent and persistent difficulty in falling asleep and/or maintaining sleep, resulting in a feeling of dissatisfaction with sleep. TSD may be accompanied by sleepiness, weakness upon awakening or impairment of other systemic functions. Sleep disturbances may be resolved after treatment of thyroid diseases.

#### *Proposed classification*

According to the International Classification of Sleep Disorders (ICSD-3), we first categorized TSD into chronic TSD, short-term TSD, and other types of TSD [189, 190]. Other types of TSD should be considered if the patient does not meet the criteria for chronic and/or short-term TSD, and the diagnosis must be made with caution. Unlike chronic TSD, the diagnosis of transient TSD does not require a duration of ≥3 months and a frequency of ≥3 episodes/week.

### Diagnosis and differential diagnosis

#### *Diagnosis of TSD*

a. Sleep disorder characterized by frequent and persistent sleepiness, difficulty in falling asleep and/or difficulty in staying asleep, resulting in an unsatisfactory sleep experience.
b. Sleep disorders are closely related with the development of thyroid disease.
c. Sleep disorders can be cured or alleviated after treatment of thyroid disease.
d. Polysomnography shows abnormal sleep architecture along with (or without) structural or functional abnormalities of the thyroid gland; sleep architecture improves after treatment of thyroid disease.

#### *Differential diagnosis*

The following differential diagnoses must be considered in TSD:

a. Primary sleep-disordered breathing.
b. Sleep disorders caused by somatic diseases, including neurological, cardiovascular, respiratory, digestive, genitourinary, musculoskeletal, and other sleep disorders.
c. Sleep disorders related to psychiatric disorders.
d. Sleep disorders associated with thyroid medications, including psychoactive substances/drugs such as antidepressants, central nervous system stimulants, cardiovascular drugs, narcotic analgesics, and asthma medications.
e. Sleep disorders caused by formaldehyde, alcohol and tobacco. These drugs, alone or in combination, can cause sleep disturbances.

### Principles of TSD treatment

Our proposed treatment principles include:

a. Treating thyroid precursors;
b. Increasing effective sleep time and/or improve sleep quality;
c. Improving daytime functional impairments associated with sleep disturbances;
d. Reducing or eliminating the risk of conversion of short-term sleep disturbances to chronic sleep disorder;
e. Reducing the risk of sleep disorder-related somatic disorders or comorbid psychiatric disorders;
f. Providing individualized, comprehensive, and evidence-based treatments such as herbal medicine, acupuncture, massage, and aerobic exercise;
g. Adopting comfort anesthesia diagnostic and treatment techniques according to the type of primary thyroid disorder and the type of sleep disorder;
h. Improving psycho-behavioral problems associated with insomnia;
i. Avoiding the adverse effects of medications or therapeutic interventions.

## IV. Summary and Prospects

With the increasingly fierce social competition and the accelerated pace of life and work, sleep disorders have become common and frequent clinical diseases, among which insomnia is the most common sleep disorder. However, the nomenclature, diagnostic criteria, classification criteria and efficacy evaluation criteria of TSD are still unclear, which greatly affects the determination of efficacy and further in-depth research. Therefore, it is urgent to clarify their definition and pathogenesis, and establish unified diagnostic, classification, and efficacy evaluation criteria.

The holistic view is one of the fundamental features of anesthesia therapeutics in the new century [191]. The HPT axis and sleep disorders are closely related and mutually interact with each other. Improvement in the function of the HPT axis is accompanied by the improvement of sleep quality. In addition, anesthetic approach for the treatment of sleep disorders has a palliative effect on HPT axis disorders. In the treatment of TSD, it is recommended to rely on the theories that integrate western and Chinese medicine, emphasizing holistic diagnosis and treatment, as well as precise medicine.

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