Elevated thyroid-stimulating hormone is associated with poor sleep: a cross-sectional and longitudinal study

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Abstract

Purpose

Poor sleep and the accompanying TSH (Thyroid Stimulating Hormone) elevation are not uncommon since TSH secretion is controlled by the circadian rhythm. However, the true relationship between poor sleep and TSH elevation is unclear, and hence we aimed to elucidate this association by cross-sectional and longitudinal studies.

Methods

Participants with isolated elevated and normal TSH concentration were recruited, and the Pittsburgh Sleep Quality Index (PQSI) was used to assess sleep status. The patients with isolated TSH elevation were followed up longitudinally, and TSH levels were remeasured when sleep status improved.

Results

The proportion of poor sleep and occasional poor sleep among subjects with isolated TSH elevation was significantly higher than that in subjects with normal TSH (70.24% vs. 49.58%, $p = 0.001$; 9.52% vs. 1.68%, $p = 0.006$), and the ratio of good sleep was obviously decreased in subjects with isolated TSH elevation than normal TSH (20.24% vs. 48.74%, $p < 0.001$). Patients with isolated TSH elevation had significantly higher PSQI scores in the subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency dimensions than subjects with normal TSH (all $p < 0.05$). In the follow-up study, among patients with isolated TSH elevation at baseline, the ratio of TSH normalization in patients who slept better was significantly higher than that in patients who still slept poorly (85.42% vs. 6.45%, $p < 0.001$).

Conclusion

This study revealed isolated elevated TSH concentrations tends to normalize when sleep status improves, and we recommend that clinicians inquire about sleep status thoroughly and reexamine thyroid hormone levels when sleep status improves.

Introduction

Subclinical hypothyroidism (SCH), defined as persistent TSH elevation with normal free thyroxine (FT4), is mostly caused by chronic autoimmune thyroid disease, and it affects 5%-10% of subjects in the general population [1-3]. In addition, SCH occurs more frequently in elderly individuals and obese individuals because the TSH concentration is increased with increased age and body mass index (BMI) [4-5]. However, occasional TSH elevation is quite common in clinical practice, and the patients are often neither elderly nor obese. There is a lack of substantiating evidence for mild thyroid gland failure or a consensus

on effective drug treatments, and the outcomes of levothyroxine (LT4) therapy are variable for these patients [6]. Hence, we speculated that other factors induce TSH elevation and need further investigation.

It is well known that the hypothalamic-pituitary-thyroid axis is controlled by the circadian rhythm, and TSH secretion gradually rises in the early evening and decreases in the mid-afternoon [7-9]. Sleep plays essential roles in the regulation of pituitary TSH secretion [10-11], while the number of patients complaining of sleep disorders is increasing rapidly. The prevalence of insomnia has increased to 26.6%–33.9% in China [13-14]. Our previous study found that patients with sleep disorders have higher TSH levels than the general population, and the TSH levels were significantly higher in subjects who slept less than 3 hours per night than in those who slept more than 6 hours per night [15]. Moreover, we found that the ratio of isolated TSH elevation was increased when night-sleep was restricted, and elevated TSH levels could return to be normal when night-sleep was recovered [16]. Similarly, Adem Aydin and his colleagues reported that TSH levels increase significantly after sleep deprivation (SD) in healthy subjects [17]. These results raise questions about whether the cases of isolated TSH elevation detected in the clinic are associated with sleep disorders.

Based on the literature, we speculated that sleep disorders might be associated with increased TSH levels and that increased TSH levels may normalize in response to improving sleep status. In this study, we assessed the sleep status of subjects with isolated TSH elevation. We longitudinally followed these subjects and remeasured their TSH level when their sleep status had improved. We aimed to investigate the true relationship between isolated TSH elevation and sleep disorders.

Materials And Methods

Participants

We conducted this cross-sectional and longitudinal study in West China Hospital from November 2015 to February 2017. Our study recruited euthyroidism participants, defined by normal serum FT3 and FT4 concentration, with isolated TSH elevation from the Physical Examination Center. The inclusion criteria were patients aged 18 to 65 with a body mass index (BMI) of 18-24 kg/m^2. The exclusion criteria were as follows: individuals with previous or current thyroid disorders; individuals with a history of neck surgery; individuals with a history of ^{131}I treatment or radiotherapy; individuals with decreased serum iron and ferritin; individuals suffering from diabetes mellitus, renal insufficiency, or any other systemic severe disease or chronic wasting disease; individuals taking amiodarone or lithium; individuals with emotional or mental abnormalities; and pregnant or lactating women or those who were less than one year postpartum.

Additionally, euthyroidism subjects, similarly defined by normal serum FT3 and FT4 concentration, with normal TSH concentration were recruited into the study as controls and screened with the same inclusion and exclusion criteria mentioned above.

All participants provided written informed consent for participation, and the Biomedical Ethics Committee approved this study at West China Hospital, Sichuan University, China (5101070022002).

Procedures

First, for the cross-sectional survey, experienced staff conducted face-to-face interviews to evaluate sleep status with all subjects who met the inclusion and exclusion criteria in the clinical department. In addition, individualized sleep instruction was given to subjects with poor sleep, e.g., to maintain a sleep duration of more than 7 hours per night, to fall asleep before 23:00, to fall asleep before 23:00, to consult a sleep specialist or to exercise appropriately. Then, all of the patients with isolated TSH elevation were longitudinally followed-up 4 to 24 weeks at the clinic, and the serum levels of their thyroid hormones were remeasured when participants were sleeping better than before (at least 4 weeks later since the first measurement).

We used the Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality [12]. The PSQI is a seven-item (sleep duration, sleep efficiency, sleep latency, sleep disturbance, daytime dysfunction, frequency of sleep medications, and subjective sleep quality) questionnaire with scores ranging between 0 and 21. Higher scores indicate worse sleep. A PSQI global score greater than 5 indicates 'poor sleep,' with a sensitivity of 89.6% and a specificity of 86.5%. The Chinese version of the PSQI has good reliability and validity in patients and the general population [13-14,18].

In this study, subjects were divided into Group A if the PSQI score was six or higher and into Group B if the PSQI score was less than six. Moreover, we divided Group B into two sub-groups. Group B-1 included participants who reported good sleep and occasional poor sleep in the last 4 weeks, and Group B-2 included participants who reported persistent good sleep all of the time. Sleep time was also assessed in this study.

In further analysis, when subjects with positive TPO-Ab were excluded, Group C concluded patients with PSQI score not less than six, and Group D with PSQI score less than six. Similarly, Group D-1 included participants who reported good sleep and occasional poor sleep in the last 4 weeks, and Group D-2 included participants who reported persistent good sleep all of the time.

Measurements

All fasting blood samples were collected between 07:00 am to 09:00 am. Serum levels of TSH, free triiodothyronine (FT3), FT4, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibodies (TgAb) were examined by an electrochemiluminescence immunoassay (Roche Kit). In this cross-sectional study, we examined the TSH, FT3, FT4, TPOAb, and TgAb concentrations, and TSH, FT3, and FT4 were analysed in a longitudinal study. The normal hormone reference ranges were as follows: TSH 0.27-4.2 mU/L, FT3 3.60-7.50 pmol/L, FT4 12.0-22.0 pmol/L, TPOAb <34 IU/ml, and Tg-Ab <50 IU/ml.

Isolated TSH elevation was defined as TSH >4.2 mU/L, with FT3 and FT4 within the normal reference laboratory ranges. Normal TSH was defined as TSH 0.27-4.2 mU/L, with FT3 and FT4 within the normal

reference laboratory ranges.

As previously reported, chronic autoimmune thyroid disease was diagnosed if the serum TPOAb titre was 2-fold greater than the upper limit of the reference range [19]. Therefore, in this study, we diagnosed chronic autoimmune thyroid disease when TPOAb was >68 IU/ml.

Statistical Analysis

Data processing was performed with SPSS version 21.0. Clinical and laboratory values are reported as the mean±SD and the percentage and median when appropriate. We used Independent-Samples T Test, Paired-Samples T Test, rank-sum test Chi-square test and Fisher's exact test,to compare quantitative and qualitative variables between the groups, respectively. A p-value of <0.05 was considered to indicate statistical significance.

Results

Participant demographic characteristics

A total of 287 individuals, 96 males and 191 females, were included in this study, and the ratio of isolated TSH elevation was 58.54% (168/287). No obvious difference was found in the ratio of isolated TSH elevation between males and females (59.35% vs. 58.12%, p=0.838). As shown in Table 1, we further divided all 287 subjects into isolated TSH elevation group and normal TSH group, and similarly there was no significant difference in sex between the two groups (p>0.05, Table 1). Nevertheless, no statistically significant differences in FT3 or FT4 were observed between the two groups, as shown in Table 1.

Sleep status and PSQI scores

As shown in Figure 1, the proportions of patients with poor sleep (Group A), good sleep with occasional poor sleep (Group B-1), and persistent good sleep (Group B-2) were 70.24% (118/168), 9.52% (16/168), and 20.24% (34/168), respectively, among patients with isolated TSH elevation and 49.58% (59/119), 1.68% (2/119), and 48.74% (58/119), respectively, among subjects with normal TSH. A significantly higher ratio of poor sleep and good sleep with occasional poor sleep was observed among patients with isolated TSH elevation than normal TSH (70.24% vs. 49.58%, p=0.001; 9.52% vs. 1.68%, p=0.006).

Compared with subjects with normal TSH, patients with isolated TSH elevation had higher scores for multiple PSQI components. We observed significant differences in the PSQI scores of subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency between the two groups (all p<0.05, Table 2). However, no significant differences were observed in the other three PSQI component scores of sleep disturbance, need for sleep medications, and daytime dysfunction (all p>0.05, Table 2). The incidence of a later sleep time was significantly higher among patients with isolated TSH elevations than normal TSH (p=0.003, Table 2).

Sleep status and PSQI scores of non-autoimmune thyroiditis subjects

Excluding individuals with chronic autoimmune thyroiditis, the baseline characteristics were not significantly different between the two groups (Table 3, all $p>0.05$), and there was a higher ratio of poor sleep among patients with isolated TSH elevation than normal TSH [Figure 1, 67.88% (93/137) vs. 50.43% (58/115), $p=0.007$; 9.49% (13/137) vs. 1.74% (2/115), $p=0.014$].

Similarly, when excluding individuals with chronic autoimmune thyroiditis, patients with isolated TSH elevation had higher scores for multiple PSQI components, including subjective sleep quality, sleep latency, sleep duration, and habitual sleep efficiency, than subjects with normal TSH. No significant differences in the other three PSQI component scores, namely, sleep disturbance, need for sleep medications, or daytime dysfunction, were found between the two groups (all $p>0.05$, Table 4). Additionally, the late sleep time incidence was significantly higher among patients with isolated TSH elevation than normal TSH ($p=0.003$, Table 4).

Follow-up study of patients with isolated TSH elevation

A total of 105 patients, 79 in Group A, 14 in Group B-1, and 12 in Group B-2, were reexamined for thyroid hormone levels until Feb. 13, 2017 (Figure 2).

A total of 48 subjects in Group A slept better than before, and the remaining 31 participants still slept poorly (22 of whom had slept poorly for more than one year). As shown in Table 5 and Figure 2, the concentration of TSH, the proportion of different TSH decline, and the ratio of TSH normalization among the patients who slept better was significantly higher than that among those who still slept poorly (all $p<0.05$, Table 5 and Figure 2).

A total of 12 subjects in Group B-1 had normal TSH levels when their sleep had improved.

In Group B-2, five patients experienced good sleep but had late sleep times (beyond 00:30). When they fell asleep before 23:00, 4 of the five subjects were reexamined, and normal TSH levels were found.

The follow-up study of non-autoimmune thyroiditis patients with isolated TSH elevations

A total of 79 non-autoimmune thyroiditis patients, 58 in Group C, 11 in Group D-1, and 9 in Group D-2, were reexamined for thyroid hormone levels until Feb. 13, 2017.

A total of 39 patients in Group C slept better than they had previously, and the remaining 19 subjects still slept poorly (22 of whom had slept poorly for more than one year). The ratio of TSH normalization among patients who slept better was significantly higher than that among those who still slept poorly (89.74% vs. 5.26%, $p<0.05$).

All of the patients in Group D-1 had normal TSH levels after their sleep improved.

In Group D-2, five patients experienced good sleep but had late sleep times (beyond 00:30). When they fell asleep before 23:00, 4 of the five subjects were reexamined, and normal TSH levels were found.

Discussion

This study revealed that 70.24% of patients with isolated TSH elevation tended to experience poor sleep in the preceding month, and this proportion of poor sleep was much higher than the 33%-45% in the general population found by previous surveys [14,20]. Although no studies have investigated the prevalence or incidence of sleep disorders among patients with isolated TSH elevation, our study indicated that poor sleep is much more prevalent and apparent in patients with isolated TSH elevation than in the general population. Moreover we excluded patients with positive TPO-Ab, the characteristic antibody of chronic autoimmune thyroiditis to eliminate the effect of TPO-Ab on thyroid function, and the the result was similar, with a higher proportion of poor sleep in subjects with isolated TSH elevation than in subjects with normal TSH concentration.

Because sleep exerts direct inhibitory influences on pituitary TSH secretion [10], the association between sleep disorders and TSH elevation may be independent of chronic autoimmune thyroiditis. Lan Xia et al. observed that the serum TSH level was significantly higher in individuals with primary insomnia than in healthy controls and was positively related to PSQI scores in primary insomnia [11]. In obstructive sleep apnoea (OSA) patients, the proportion with high TSH levels and normal T4 levels was significantly increased compared with that in non-OSA patients (11.1% vs. 4%), and T4 treatment did not change the severity of OSA [21]. OSA patients had lower sleep duration and sleep quality, which correlated with TSH concentration [22-24]. It may be reasonable to speculate that serum TSH elevation is associated with short sleep duration or sleep disorders in OSA patients. The findings of our study were consistent with those of the OSA patients who experienced unsatisfactory night sleep. Therefore, we speculated that an elevated TSH concentration might normalize after improving sleep status.

Hence, we longitudinally followed subjects with isolated TSH elevations, and their serum level of thyroid hormones was remeasured. The results showed that 85.4% of patients with poor sleep had normal TSH when their sleep status improved, while merely 6.5% had normal TSH levels among subjects who experienced poor sleep persistently at both baseline and follow-up. Tae Hyuk Kim and his colleagues reported that 57.9% of subjects with elevated TSH and normal FT4 levels reverted to euthyroidism without any interventions during a median of 36 months of follow-up [23]. Another study reported that a total of 62.1% of outpatients with elevated serum TSH levels (>5.5 to ≤10 mIU/L) had normal TSH levels during a 5-year follow-up without the need for thyroid-specific medications [25]. Moreover, when excluding patients with positive TPO-Ab, the risk factor of thyroid dysfunction, the proportion of TSH normalization was 89.74% when sleeping improved, which was significantly higher than that among those with persistent poor sleep. The higher proportion in our results than for the spontaneous normalization of TSH in those two studies indicated that poor sleep may be an aetiology of TSH elevation, and isolated TSH elevation is independent of presence of TPO-Ab in subjects with poor sleep. In addition, we found that most of the subjects with occasional poor sleep or late sleep times had normalized TSH concentrations if they could sleep better or fell asleep before 23:00; however, elevated TSH levels were unlikely to normalize in subjects with persistent poor sleep, especially in those who had slept poorly for more than one year. The duration of poor sleep status might also affect TSH normalization.

Currently, few studies have investigated the physiopathologic mechanism linking sleep and hypothalamic-pituitary-adrenal (HPA) axis function. TSH secretion is regulated by the negative feedback inhibition of T3 and T4 levels and the positive feedback stimulation of TRH. However, increasing evidence has shown that the underlying system is far more complicated than previously thought [26]. Thyroid hormones assume a dual role in homeostatic regulation, acting as controlling and controlled elements. Sleep participates in these feedback control processes, including dopamine (DA) release [27-28]. However, the particular mechanism underlying the association between sleep and the HPT axis requires regulation and warrants investigation in further studies.

Conclusion

The current study found that poor sleep was prevalent and apparent in subjects with isolated TSH elevation independent of chronic autoimmune thyroiditis and further revealed that elevated TSH levels might normalize when sleep status improves. Poor sleep status, including late sleep time, may be associated with TSH elevation. Therefore, in the clinic, physicians are encouraged to carefully inquire into patients' sleep histories rather than immediately making an SCH diagnosis or prescribing levothyroxine treatment. It is appropriate to reexamine blood thyroid hormone levels when sleep duration and sleep quality improve. However, our study has some limitations. First, sleep status, assessed by the PSQI, may be relatively subjective, and in future studies, more objective assessments, such as polysomnography, may be recommended. Second, this study was an observational survey, and the effect of poor sleep on TSH concentration needs a large-scale prospective cohort study with larger-scale samples for confirmation.

Declarations

We declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Author contributions

Yuerong Yan and Jiaqi Li contributed equally to this manuscript. Yuerong Yan performed the project, analysed the data, and wrote the manuscript. Jiaqi Li helped analyse the data and wrote the manuscript. Weiwei Zhang, Hui Liu, Leilei Zhu, and Zhen Xiao helped collect the data. Huairong Tang and Youjuan Wang helped design the project. Yerong Yu conceived and designed the project and revised the manuscript.

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There is nothing to declare.

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Table

Table 1. Demographic characteristics among all participants

	Isolated TSH elevation n=168	Normal TSH n=119	p
Age (y)	40.65±11.15	40.36±10.49	0.826
Sex			0.899
Male [%(n)]	33.93%(57)	32.77%(39)	
female[%(n)]	66.07%(111)	67.23%(80)	
TSH (mU/L)	6.063±2.138	2.389±0.838	0.000
FT3 (pmol/L)	4.94±0.60	4.87±0.51	0.321
FT4 (pmol/L)	16.12±1.96	16.21±1.83	0.670
TgAb			0.000
positive[%(n)]	23.21%(39)	6.72%(8)	
negative[%(n)]	76.79%(129)	93.28%(111)	
Chronic autoimmune thyroiditis			0.000
yes[%(n)]	18.45%(31)	3.36%(4)	
no[%(n)]	81.55%(137)	96.64%(115)	

TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TgAb: thyroglobulin antibodies.

Table 2. Comparison of sleep status and PSQI component scores

	Isolated TSH elevation (n=168)	Normal TSH (n=119)	p
p status			<0.001
ɔr sleep [%(n)]	70.24%(118)	49.58%(59)	
ɔd sleep [%(n)]	29.76%(50)	50.42%(60)	
jective sleep quality			<0.001
y good [%(n)]	5.95%(10)	17.65%(21)	
·ly good [%(n)]	40.48%(68)	57.98%(69)	
·ly bad [%(n)]	50.00%(84)	21.85%(26)	
y bad [%(n)]	3.57%(6)	2.52%(3)	
p latency			<0.001
5 min [%(n)]	17.86%(30)	59.66%(71)	
-30 min [%(n)]	49.40%(83)	31.09%(37)	
-60 min [%(n)]	23.81%(40)	6.72%(8)	
0 min [%(n)]	8.93%(15)	2.52%(3)	
p duration			<0.001
h [%(n)]	10.71%(18)	5.04%(6)	
ı-5 h 59 min [%(n)]	30.95%(52)	5.04%(6)	
ı-6 h 59 min [%(n)]	36.90%(62)	59.66%(71)	
h [%(n)]	21.43%(36)	30.25%(36)	
roximate sleep time			0.003
ore 11:00 pm [%(n)]	15.48%(26)	31.09%(37)	
00 pm-12:00 pm [%(n)]	38.10%(64)	36.97%(44)	
00 beyond [%(n)]	46.43%(78)	31.93%(38)	

PSQI: the Pittsburgh Sleep Quality Index

Table 3. Demographic characteristics among nonchronic autoimmune thyroiditis subjects

	Isolated TSH elevation (TPOAb-) n=137	Normal TSH (TPOAb-) n=115	p
	40.88±10.62	40.19±10.53	0.605
[%(n)]	36.50%(50)	33.04%(38)	
ıle [%(n)]	63.50%(87)	66.96%(77)	
mU/L)	5.993±2.024	2.402±0.836	<0.001
)mol/L)	4.97±0.58	4.89±0.51	0.228
)mol/L)	16.20±1.96	16.22±1.84	0.953
			0.063
ive [%(n)]	10.95%(15)	4.35%(5)	
ıtive [%(n)]	89.05%(122)	95.65%(110)	

TSH: thyroid stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibody.

Table 4. Comparison of sleep status among nonchronic autoimmune thyroiditis subjects

	Isolated TSH elevation (TPOAb-) n=137	Normal TSH (TPOAb-) n=115	p
ɔ status			0.007
r sleep [%(n)]	67.88%(93)	50.43%(58)	
d sleep [%(n)]	32.12%(44)	49.57%(57)	
ective sleep quality			<0.001
/ good [%(n)]	6.57%(9)	17.39%(20)	
y good [%(n)]	43.07%(59)	58.26%(67)	
y bad [%(n)]	47.45%(65)	21.74%(25)	
/ bad [%(n)]	2.92%(4)	2.61%(3)	
ɔ latency			<0.001
5 min [%(n)]	9.49%(13)	21.74%(25)	
30 min [%(n)]	45.26%(62)	46.96%(54)	
60 min [%(n)]	21.90%(30)	25.22%(29)	
0 min [%(n)]	23.36%(32)	6.09%(7)	
ɔ duration			<0.001
h [%(n)]	10.95%(15)	5.22%(6)	
-5 h 59 min [%(n)]	32.85%(45)	5.22%(6)	
-6 h 59 min [%(n)]	35.04%(48)	59.13%(68)	
h [%(n)]	21.17%(29)	30.43%(35)	
oximate sleep time			0.003
ɔre 11:00 pm [%(n)]	16.06%(22)	32.17%(37)	
00 pm-12:00 am [%(n)]	35.04%(48)	36.52%(42)	
ɛr 12:00 am [%(n)]	48.91%(67)	31.30%(36)	

PSQI: the Pittsburgh Sleep Quality Index; TPOAb: thyroid peroxidase antibody.

Table 5. Comparison of TSH level and ratio of TSH decline between subjects slept better and still slept poor

	Slept better (n=48)	Still slept poor (n=31)	p
Age	37.31±1.64	41.84±1.79	0.066
Sex			0.359
Male	22.92%(11)	32.26%(10)	
female	77.08%(37)	67.74%(21)	
TSH level (baseline, M±SD)	6.303±0.319	6.725±0.525	0.495
Ratio of different TSH elevation [baseline, %(n)]			
TSH≥10.000mU/L	8.33%(4)	9.68%(3)	0.569
4.200≤TSH<10.000mU/L	91.67%(44)	90.32%(28)	
TSH level (follow-up, M±SD)	3.530±0.209	6.146±0.335	<0.001
Ratio of different TSH concentration [follow-up, %(n)]			
TSH≥10.000mU/L	2.08%(1)	3.23%(1)	<0.001
4.200≤TSH<10.000mU/L	12.5%(6)	90.32%(28)	
2.500≤TSH<4.200mU/L	70.83%(34)	3.23%(1)	
TSH<2.500mU/L	14.58%(7)	3.23%(1)	
Ratio of TSH decline [baseline vs. follow-up, %(n)]	100.00%(48)	48.38%(15)	<0.001
Ratio of TSH normalization [baseline vs. follow-up, %(n)]	85.42%(41)	6.45%(2)	<0.001

Figures

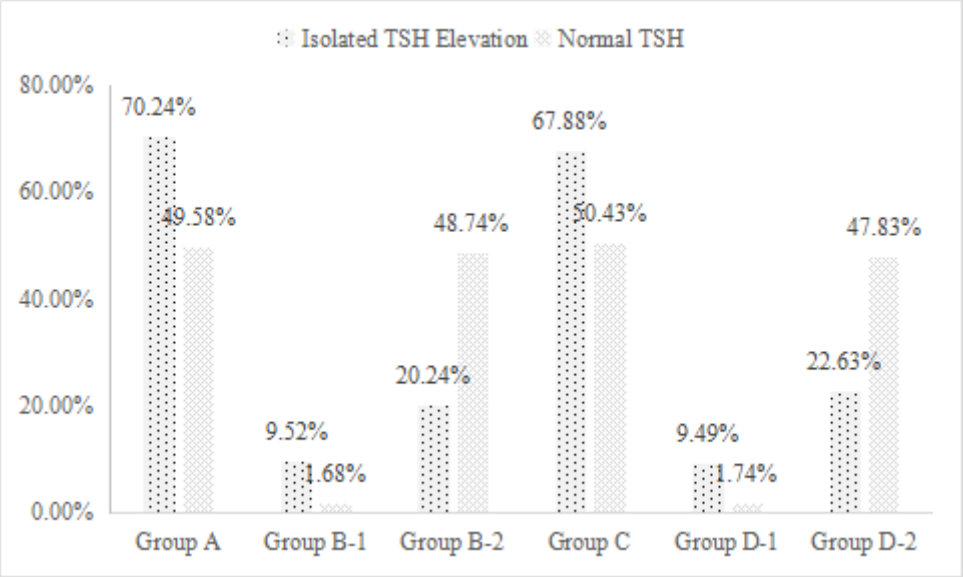

Figure 1

The proportions of patients with different sleep statuses among subjects with isolated TSH elevations and those with normal TSH concentration. Group A: poor sleep; Group B-1: good sleep but occasional poor sleep; Group B-2: persistent good sleep. Group C (negative TPO-Ab): poor sleep; Group D-1 (negative TPO-Ab): good sleep but occasional poor sleep; Group D-2 (negative TPO-Ab): persistent good sleep.

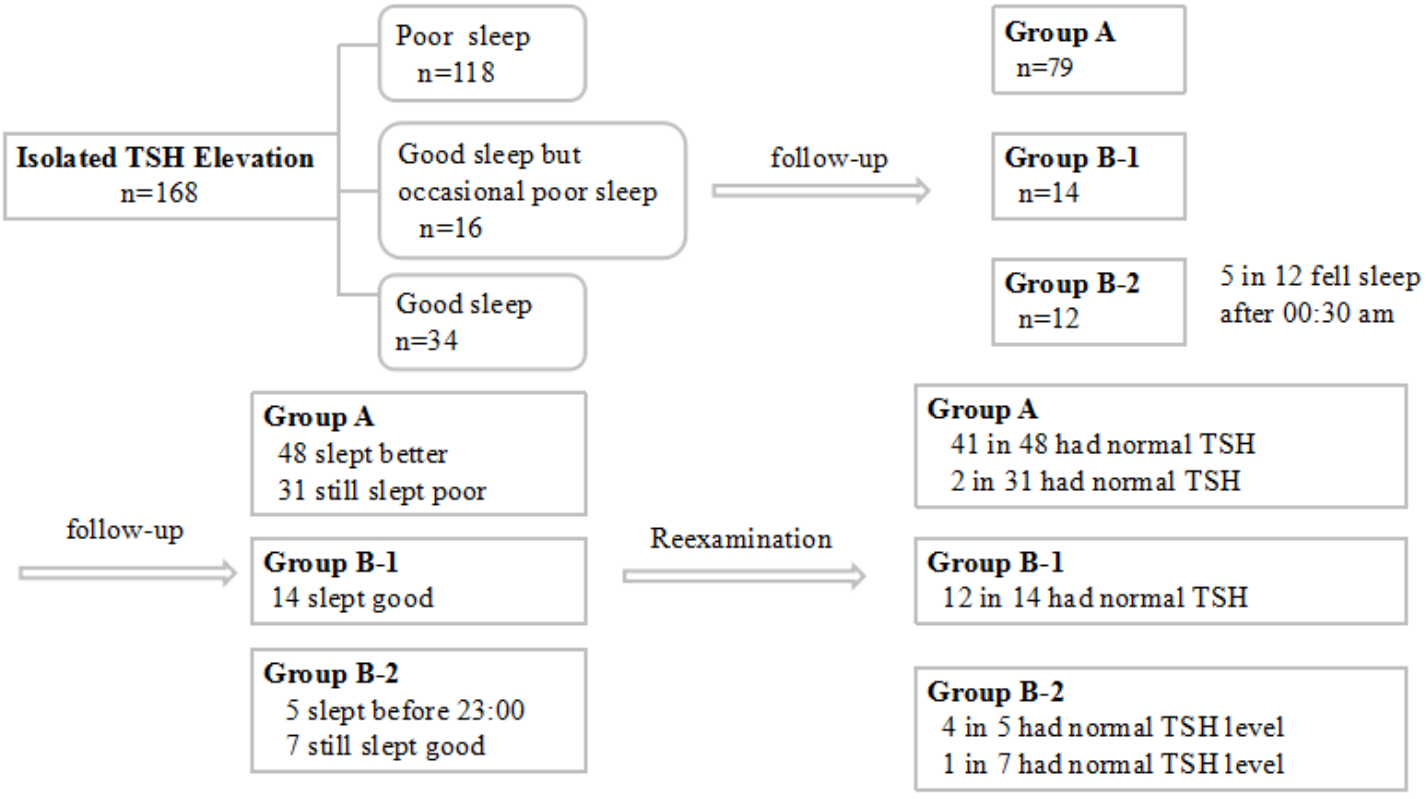

Figure 2

Flow chart of the follow-up of the subjects with isolated TSH elevation. Group A: poor sleep; Group B-1: good sleep but occasional poor sleep; Group B-2: persistent good sleep.