

Research Article

Effects of Supraphysiological Doses of Levothyroxine on Sleep in Healthy Subjects: A Prospective Polysomnography Study

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Disrupted sleep is prevalent in both mood and thyroid disorders. Given the emerging use of thyroid hormones in the treatment of mood disorders, we investigated the effects of supraphysiological doses of levothyroxine (L-T₄) on sleep. In an open-label design, 13 healthy subjects received up to 500 $\mu\text{g}/\text{day}$ for an eight-week period. A baseline night was polysomnographically recorded (PSG) followed by PSG under the maximum tolerated dose of L-T₄. All subjects developed hyperthyroxinemia. The heart rate and respiration rate increased significantly with treatment; a significant increase in body temperature was observed in men but not in women. Surprisingly, treatment with supraphysiological doses of L-T₄ did not cause significant effects on sleep architecture. However, the increase in body movements and REM density was close to reaching statistical significance. Here, we report on the sleep data, thyroid hormone levels, and physiological parameters during sleep. We conclude that experimentally induced hyperthyroidism does not profoundly change the sleep structure in healthy individuals underlining the good tolerability of treatment with supraphysiological doses of L-T₄ in patients with mood disorders.

1. Introduction

Neuropsychiatric manifestations occur often within the course of primary thyroid disorders [1]. The interrelation between psychiatric and thyroid disorders has been extensively studied in the past decades [1, 2] and is currently in the focus of modern brain imaging techniques [3]. In hypothyroid patients, thyroid hormone treatment reduced depressive symptoms and somatic complaints and restored the metabolic activity in brain areas that are integral to the regulation of mood and cognition [3]. In patients with primary mood disorders, treatment with thyroid hormones normalised hypoperfusion of specific brain regions associated with depression [4]. Clinical data have evidenced good efficacy of supraphysiological dosages of thyroid hormones in the treatment of unipolar and bipolar mood disorders.

High doses of up to 600 μg per day of L-T₄ were surprisingly well tolerated even over treatment periods of up to 51 months [5, 6], as indicated by cardiovascular monitoring, special questionnaires [7], and measurements of bone mineral density [6, 8].

Disrupted sleep is considered both a prominent symptom of mood disorders and a typical sign of thyrotoxicosis [9]. In the context of supraphysiological application of thyroid hormones in depressed patients, presumably leading to hyperthyroxinemia [10], investigation of sleep is consequently of particular interest. We, therefore, felt it was worth investigating the effects of supraphysiological doses of L-T₄ on sleep architecture by means of polysomnography.

Although it is well established that various hormones (e.g., growth hormone releasing hormone, corticotropin releasing hormone, and prolactin) modulate sleep-wake

activity, little is known about the effects and underlying mechanisms of changes in thyroid status on sleep [9]. Hypothyroidism, a clinical syndrome characterized by a deficient thyroidal production of thyroid hormone, has been observed to be accompanied by increased numbers of awakenings and a reduced amount of slow wave sleep (SWS) in humans and rats [11]. Patients with hypothyroidism may sleep for long periods during the day and, in severe cases, may lapse into stupor and even coma [12]. On the contrary insomnia is listed among the neuropsychiatric manifestations of thyrotoxicosis, the clinical syndrome of hypermetabolism that results from sustained increased serum concentrations of thyroid hormones [13]. Three studies of patients with clinical or subclinical hyperthyroidism reported sleep problems as a frequent complaint and sleep quality being subjectively rated as bad [14–16]. With respect to sleep architecture, the results of some studies are in agreement, while others contradict each other: Passouant and coworkers [17] observed an increased sleep latency, a reduced total sleep time, an increased REM density and REM duration as well as a reduction in slow wave sleep in eight patients with clinical hyperthyroidism. Kronfol et al. [18] observed a reduced sleep efficiency, low delta sleep, short REM latency, and a high REM density in one case of thyrotoxicosis. In contrast to this finding, Dunleavy et al. [19] reported a higher percentage of SWS during the hyperthyroid state as compared to the sleep structure, once the thyroid hormone levels had returned to normal in a study of four subjects. Kales and coworkers [20] studied six patients with clinically determined hypothyroidism and found normal REM parameters, sleep latencies, and sleep duration, but an increase in sleep stage 2 (S₂), and a reduction of SWS. The latter was reported to return to normal during hormone replacement therapy. The only finding that could be replicated was reduced SWS in nine patients with hypothyroidism Ruiz-Primo et al. [21]—rated according to the rules of Rechtschaffen and Kales [22]. However, it should be emphasized that all but one of these studies date back to a time when a commonly accepted and reliable system of sleep scoring was not yet available and thyroid dysfunction was diagnosed clinically. Only in the study by Kronfol et al. [18] were serum thyroid hormone levels determined.

Sleep disorders are of high medical and socioeconomic relevance [23–25]. Their adequate appraisal and treatment is essential. As polysomnography is time consuming and costly, effective preclinical diagnostic procedures are needed. Thus, knowledge as to which disorders can cause sleep disturbances and which diseases can present initially as a sleep disorder, are helpful in managing the patients and in reducing the costs of diagnostic procedures and treatment by improving the diagnostic rationale. The present study was part of a project that investigated differences in response to supra-physiological doses of levothyroxine between healthy individuals and patients with refractory depression [26]. In this study, we investigated the effects of high, supra-physiological doses of levothyroxine on sleep and other physiological parameters (electrocardiogram, heart rate, body temperature, and respiration rate) in healthy individuals. By inducing an experimental hyperthyroid state in healthy individuals, we

also expected to get a clear picture of the effects of hyperthyroidism on sleep.

2. Methods

This study was part of a series of trials to investigate the effects, tolerability, and safety of treatment with supra-physiological doses of L-T₄ in patients with refractory mood disorders and in healthy controls [7, 10, 26]. Written informed consent was obtained from all subjects. The study was approved by the local ethics committee. Subjects were reimbursed for participation.

2.1. Subjects. Thirteen healthy volunteers (6 female, 7 male; age range: 23–50 years, mean \pm SD: 36.2 \pm 8.8 years) participated. Inclusion or exclusion from the study was determined by a semistructured medical and psychiatric interview including a physical examination, an electrocardiogram (ECG), measurements of blood pressure, heart rate and body weight, a laboratory workup including red and white blood cell count, blood chemistry, basal TSH, serum thyroid hormones (total thyroxine [T₄], free T₄ [fT₄], total triiodothyronine [T₃], and free T₃ [fT₃]), and thyroid autoantibodies (thyroid peroxidase antibody, thyroglobulin antibody). The inclusion criteria were 18 to 50 years of age, euthyroid status, absence of any signs of medical illness, euthymic mood (as indicated by a score < 8 on the Hamilton rating scale for depression). The exclusion criteria were: past or current thyroid, medical or psychiatric disorder; substance abuse or dependency, pregnancy or lactation; and use of any medication or hormones, apart from oral contraception (for details, see Bauer et al. 2002 [10]).

2.2. Procedures. After an adaptation night and baseline PSG, the initial dose of 50 μ g/d of L-T₄ was administered as a single morning dose 15–30 minutes prior to breakfast. The dosage was increased by 50 μ g/d every three to seven days to achieve a dose of 500 μ g/d by day 42, maintaining that dose for another two weeks. The dosage of L-T₄ was not further increased if the subject experienced intolerable symptoms or wished to discontinue the study. In the latter case, if the subject agreed, the highest possible L-T₄ dosage was continued for a maximum of 14 days, and discontinued after carrying out the final examinations. If this was not possible, the final examinations were done immediately, hormone intake was discontinued immediately, and the sleep recording was performed the same night. This was the case for three subjects. For the remaining ten subjects, at the end of the 14 days period on the maximum dosage of L-T₄, all examinations were repeated. One whole night's sleep was recorded in the sleep laboratory, following the same protocol as mentioned below.

Subjects documented their medication intake, heart rate, and possible side effects every morning. At weekly visits, the *Thyroid Symptom List*, a 24-item clinician-administered instrument to rate signs and symptoms of thyrotoxicosis, was completed for each subject [10]. Safety evaluations regarding the laboratory and cardiovascular workup were performed

TABLE 1: Serum concentrations of thyroid hormones at baseline and during maximal dosage of levothyroxine (L-T4)¹.

Thyroid hormone (normal range)	Baseline		During T ₄ treatment		Δ^2		<i>P</i>
	Median	Quartile range	Median	Quartile range	Median	Quartile range	
T ₃ (0.8–1.6 $\mu\text{g/L}$)	1.3	1.2–1.4	2.3	2.0–2.9	1.2	0.8–1.4	.0005
T ₄ (45–125 $\mu\text{g/L}$)	89	76–91	197	169–224	108	88–136	.0002
fT ₃ (2.3–5.1 ng/L)	4.2	3.7–4.7	6.9	5.2–7.2	2.3	1.2–3.1	.0015
fT ₄ (7–19 ng/L)	10.8	9.2–12.2	45.8	32.6–53.6	37.5	21.7–41.5	.0002

¹For abbreviations see text.

² Δ refers to intraindividual differences.

weekly until the end of treatment. For safety reasons, thyroid function tests were monitored weekly. Compliance with medication was monitored by weekly measurement of TSH (thyroid stimulating hormone; usually suppressed at a L-T4 dose of $>200 \mu\text{g/d}$).

2.3. Polysomnographic Procedures. Before initiation of T₄ administration, two subsequent nights of sleep were recorded polysomnographically, including the registration of the following leads: vertical and horizontal electrooculogram (EOG), electroencephalogram (EEG) with 5 leads (C3-A2, C4-A1, C3-C4, Oz-A1, and Oz-A2), mental electromyogram (mEMG), and EMG of both anterior tibial muscles (tEMG) (PL-EEG, WALTER GRAPHTEC GmbH, Bad Oldesloe, Germany). Furthermore, nasal air flow, thorax movements, snoring, electrocardiogram (ECG), and rectal body temperature (W+W-Recorder Series 310; YSI Thermistorsonden, Serie 400) were recorded.

Sleep recordings were analysed visually according to the rules of Rechtschaffen and Kales [22]. To determine the heart rate and respiration rate during sleep, the night was divided in three thirds. For each of the sleep stages S2, SWS, and REM, ten artefact-free 30-second-epochs were identified in each third of the night. Within these selected epoques, R-spikes and breaths were manually counted. Body temperature was documented continuously by a rectal device. The body temperature was read every 15 minutes. The first pre-medication night was an adaptation night and, therefore, not used for analysis.

2.4. Statistical Analysis. To assess the effect of L-T4 on hormones of the hypothalamic-pituitary-thyroid (HPT) axis (T₃, fT₃, T₄, fT₄, and TSH), physiological parameters (core body temperature, heart and respiration rate) and a number of sleep parameters were taken into account. These were time in bed (TIB), sleep period time (SPT), total sleep time (TST), sleep efficiency (SEI: TST/TIB \times 100), number of changes of sleep stages (CSS), body movement index (BMI; number of larger body movements during TST), eye movement index (EM; number of rapid eye movements during REM = REM density), latencies to sleep stage 1 (L S1; time from lights off until the first occurrence of sleep stage 1), to sleep stage 2 (L S2; time from lights off until the first occurrence of sleep stage 2), to slow wave sleep (L SWS; time from lights off until the first occurrence of slow wave sleep), to rapid eye movement sleep (L REM; time from

falling asleep until the first occurrence of sleep stage REM), the amount of wakefulness (W), the duration of the sleep stages S1, S2, SWS, and REM, and movement time (MT). The individual differences between baseline levels and those under treatment were assessed by Wilcoxon's matched pairs signed ranks test. Although there was no reason to reject the hypothesis that the Δ -values were normally distributed as tested by Shapiro-Wilk test, the nonparametric Wilcoxon's matched pairs signed ranks test was chosen instead of the *t*-test for paired observations, since the sample size is small. All tests were performed with a double sided $P < .05$.

3. Results

During administration of L-T4 (mean \pm SD: $476 \pm 41 \mu\text{g/d}$), serum total thyroid hormone levels (T₃ and T₄) and free hormone levels (fT₃ and fT₄) increased significantly (all $P < .01$). Before administration of L-T4, basal TSH levels were within the normal range of 0.4–3.5 mU/L in all individuals. As expected from an intact negative feedback control of the HPT axis, the basal TSH values decreased significantly ($P < .05$) during L-T4 administration (Table 1). TSH was fully suppressed in all individuals including subjects that had to discontinue L-T4 intake early, as well as those that reached the highest dosage. Therefore, the data of all 13 subjects included in the study was able to be used for analysis of the sleep data.

The results presented in Table 2 demonstrate a statistically significant increase in heart rate and respiration rate during L-T4 intake. The data also show that this increase persists during the sleep stages S2, SWS, and REM. Furthermore, the data indicate that the known tendency of a slightly higher heart rate and respiration rate in REM sleep is preserved during L-T4 intake.

Data on nocturnal core body temperature were available for 11 subjects only, because two subjects did not tolerate the rectal measuring device. The mean values of body temperature tended to be slightly higher during L-T4 intake; however, the differences were not statistically significant (Table 3). The standard deviation calculated on the basis of measurements read every 15 minutes, which was used as an indicator of variability, did also not show a clear trend.

An intraindividual test (Wilcoxon's matched pairs signed ranks test) on homogeneity of the body temperature distributions revealed that, except for one female subject, the differences were statistically significant ($P < .05$). For seven of the ten subjects with statistically significant differences,

TABLE 2: Heart rate and respiration rate at baseline and during maximal dosage of levothyroxine (L-T4)¹.

Physiological parameter	Baseline		During T ₄ treatment		Median	Δ^2 Quartile range	P
	Median	Quartile range	Median	Quartile range			
Heart rate/beats per minute							
S2	64.4	55.1–72.7	81.4	75.1–87.2	18.9	12.5–20.8	.0002
SWS	66.8	56.6–75.6	83.3	75.8–87.1	18.6	11.5–20.6	.0012
REM	72.0	56.4–74.3	84.0	76.1–88.0	14.9	10.5–20.4	.0002
Respiration rate/per minute							
S2	15.3	14.2–17.0	17.4	16.4–19.7	2.0	1.6–2.9	.0010
SWS	15.3	14.5–17.4	17.2	16.2–20.3	1.6	1.1–3.0	.0005
REM	16.7	15.1–17.5	19.9	16.9–22.1	3.2	1.3–4.1	.0005

¹For abbreviations see text.

² Δ refers to intraindividual differences.

TABLE 3: Mean core body temperature at baseline and during maximal dosage of levothyroxine (L-T4).

Temperature	Baseline		During T ₄ treatment		Median	Δ^1 Quartile range	P
	Median	Quartile range	Median	Quartile range			
Both sexes <i>n</i> = 11							
Mean	36.48	36.38–36.85	36.65	36.56–36.91	0.11	–0.18–0.33	.4014
SD	0.14	0.11–0.17	0.12	0.10–0.21	–0.02	–0.03–0.06	.9658
Females <i>n</i> = 6							
Mean	36.77	36.44–36.87	36.64	36.56–36.91	–0.07	–0.40–0.18	.8750
SD	0.14	0.09–0.14	0.15	0.10–0.21	0.02	–0.03–0.07	.4375
Males <i>n</i> = 5							
Mean	36.45	35.38–36.48	36.69	36.57–36.78	0.24	0.11–0.33	.0625
SD	0.17	0.17–0.17	0.12	0.11–1.14	–0.02	–0.05–0.02	.4375

¹ Δ refers to intraindividual differences.

body temperature measured prior to medication was lower than during L-T4 treatment. The three subjects with a higher body temperature prior to L-T4 treatment were women. A representative example of the time course of core body temperature differences in males recorded before and during L-T4 intake is shown in Figure 1. In females, opposite trends were observed in different subjects; some showed a decrease in core body temperature during treatment, others an increase (see Figures 2(a) and 2(b)).

In seven out of the eleven subjects in whom core body temperature could be sampled, the nadir of body temperature was advanced during L-T4 intake by 15 minutes to 270 minutes. It was most pronounced in three of these subjects with an advance of 75, 150, and 270 minutes, respectively. In one subject, a delay of 120 minutes occurred. No shift was found in two subjects, while due to a dislocation of the measuring device during sleep, the nadir could not be determined in one further subject.

The descriptive data for the quantitative sleep data are shown in Table 4. The medians of the individual differences between the pre-T₄ treatment night and the night during L-T4 intake were close to zero for the entire group in the global sleep parameters TIB and SPT although there were marked differences in individual subjects, partly showing an increase partly a decrease. TST tended to be shorter during L-T4 intake, the median of the individual differences was

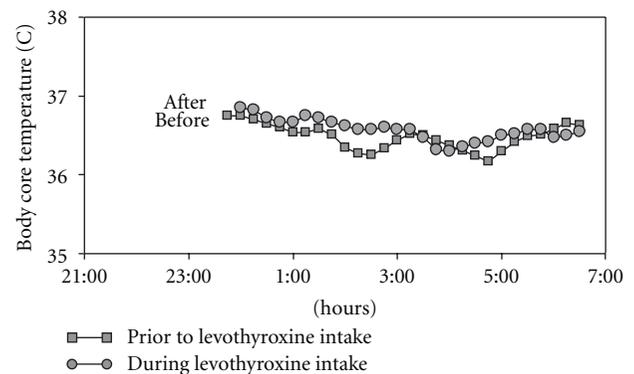


FIGURE 1: Time course of core body temperature in a male subject prior to (grey square) and during (grey circle) levothyroxine intake.

38 minutes. The SEI tended to be slightly reduced during L-T4 intake. Since two individuals showed a pronounced increase in their SEI with medication while nine subjects showed the expected decrease, the differences on average were statistically not significant. CSS did not change notably with L-T4.

Neither the sleep stage latencies nor their duration expressed as percentages revealed any systematic changes. Only two parameters showed a tendency in their variation, namely,

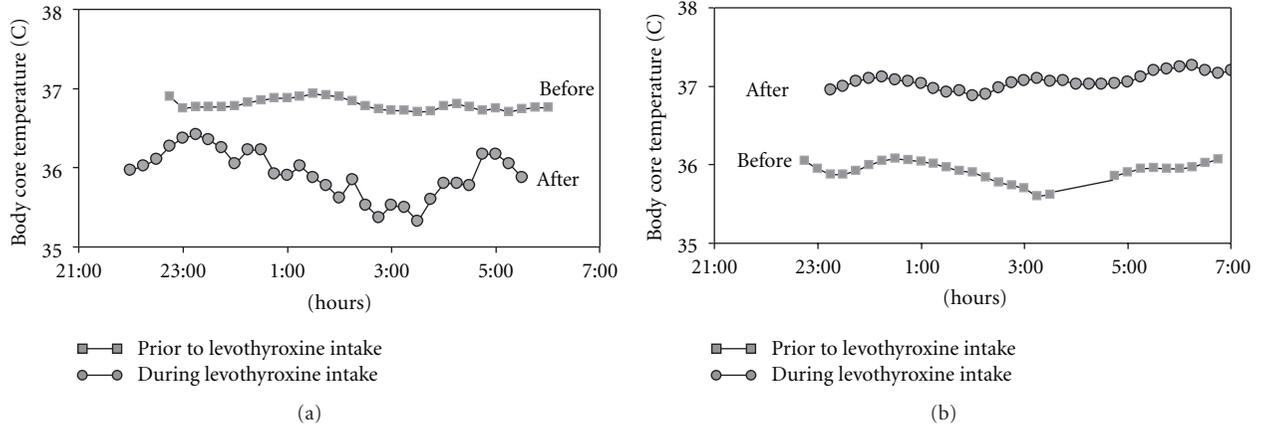


FIGURE 2: (a) Female subject with a higher core body temperature prior to levothyroxine intake (grey square) than during levothyroxine intake (grey circle). (b) Female subject with a lower core body temperature prior to levothyroxine intake (grey square) than during levothyroxine intake (grey circle).

TABLE 4: Sleep parameters at baseline and during maximal dosage of levothyroxine (L-T4)¹.

Sleep parameters	Baseline		During T ₄ treatment		Δ^2		P
	Median	Quartile range	Median	Quartile range	Median	Quartile range	
TIB (min)	415	404–477	411	405–471	1	–79–43	.6772
SPT (min)	405	378–472	401	382–440	–4	–72–39	.6848
TST (min)	384	357–399	378	341–386	–38	–61–29	.2439
SEI	89.5	86.0–95.9	90.4	86.0–92.8	–3.2	–9.3–7.2	.6484
CSS	150	141–185	157	144–180	–2	–14–17	.9324
BM	10.3	9.3–16.1	14.0	12.3–17.0	2.0	–0.4–4.5	.1272
EM	36.5	27.3–39.6	36.9	30.7–48.1	7.8	0.7–9.1	.0681
L S1	6.5	3.5–13.0	9.0	7.5–16.0	1.0	–4.0–7.0	.5295
L S2	10.5	5.0–22.5	11.0	9.0–21.5	0.0	–6.0–9.0	.6084
L S3	16.0	11.5–29.5	18.0	16.5–22.5	5.0	–5.5–10.5	.7354
L S4	23.5	14.0–39.5	23.5	19.0–28.5	4.5	–18.5–9.9	.9233
L REM	72.0	63.0–100.0	71.5	67.5–91.0	5.0	–9.0–20.5	.5417
W (%)	7.1	2.5–11.9	4.5	3.3–8.9	1.3	–8.4–6.4	.8394
S1 (%)	7.6	4.9–9.1	6.8	5.5–9.9	0.6	–2.8–1.2	1.0000
S2 (%)	48.4	40.0–51.6	48.5	37.9–51.8	–1.3	–5.8–1.9	.4548
SWS (%)	15.7	11.1–18.9	13.2	10.8–14.8	0.0	–6.2–4.3	.8394
REM (%)	20.1	16.4–22.7	21.5	17.2–23.9	0.0	–2.4–4.6	.7334
MT (%)	1.3	0.9–1.6	1.5	0.9–2.3	0.2	–0.2–1.1	.2104

¹For abbreviations see text.

² Δ refers to intraindividual differences.

BM and REM density. Both tended to be higher with L-T4. The latter almost reached statistical significance.

4. Discussion

To our knowledge, this is the first study to investigate the effects of supraphysiological doses of L-T4 on sleep by means of polysomnography. All subjects developed hyperthyroxinemia as indicated by significantly elevated serum free thyroxine levels, heart rate, and respiration rate, and by suppression of basal TSH during treatment with L-T4. These results were expected from treatment with supraphysiological doses of

L-T4 and are in line with those given in the pertinent literature [10]. It is also well established that increased serum levels of thyroid hormones may lead to an accelerated heart and respiration rate [27–29].

The main finding of this study is that 8 weeks of treatment with supraphysiological doses of L-T4 do not profoundly influence the sleep structure. This result was unexpected for two reasons: (1) patients with clinical hyperthyroidism frequently complain about sleep disturbances [30] and (2) previous studies have suggested a substantial role of the HPT system in sleep endocrine activity [31], and as evidenced in experimentally induced hypothyroid conditions

in rats [32, 33]. However, there are studies demonstrating no alterations in sleep characteristics in subjects with overt hyperthyroidism [34] and thyroxine-injected (euthyrot) rats [32, 35]. Furthermore, thyrotropin-releasing hormone (TRH) exerts only weak effects on the sleep patterns of healthy male volunteers [36]. Thus, it appears that normal thyroid hormones are necessary for sleep but that a further increase in thyroid hormone levels does not produce significant changes in the sleep architecture underlining the good tolerability of supraphysiological doses of L-T4 in the treatment of mood disorders. However, we would like to emphasize that this may be different in patients with clinical hyperthyroidism who may well suffer from sleep disruption which is caused by higher and longer-lasting thyroid hormone levels than those which are produced in an eight-week experimental study.

In the male subjects, a slight increase in core body temperature was observed consistently in all individuals. However, marked interindividual differences were present. In women, body temperature changes had opposite directions in different individuals. This might be due at least in part to the influences of the menstrual cycle, which was not controlled for. Thyroid hormones increase thermogenesis as a result of the stimulation of numerous metabolic pathways involved in the development and delivery of energy to the tissues [37]. As a result, high fever ($>40^{\circ}\text{C}$) is a cardinal manifestation of severe forms of thyrotoxicosis [38]. The advancement of the nadir of body temperature that was observed in most of the subjects might be due to the suppression of TSH. In undisturbed sleep, a decrease in TSH precedes the sleep phase [39]. Thus, it may be speculated that low/suppressed TSH levels could be responsible for inducing a phase advance state.

With respect to treatment efficacy in depressed patients with L-T4, it is of great interest that in the present study the effect of L-T4 was most pronounced on REM sleep. Although REM latency, which is delayed by a number of antidepressive drugs (e.g., tri- and tetracyclic drugs, MAO inhibitors) [40], did not change markedly, REM density increased. This could be another indicator for the suggested stimulation of the cholinergic system, which is involved in mood regulation, by L-T4 [41]. Because of the marked effects of the hyperthyroxinemic state that was induced in this study, neither the subjects nor the physicians could effectively be blinded. Further work to establish the effect of thyroid dysfunction on sleep has to be done.

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