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ORIGINAL ARTICLE

Effects of evening *vs* morning thyroxine ingestion on serum thyroid hormone profiles in hypothyroid patients

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Summary

Objective Standard drug information resources recommend that L-thyroxine be taken half an hour before breakfast on an empty stomach, to prevent interference of its intestinal uptake by food or medication. We observed cases in which TSH levels improved markedly after changing the administration time of L-thyroxine to the late evening. We therefore conducted a pilot-study to investigate whether L-thyroxine administration at bedtime improves TSH and thyroid hormones, and whether the circadian rhythm of TSH remains intact.

Design Patients were studied on two occasions: on a stable regimen of morning thyroxine administration and two months after switching to night-time thyroxine using the same dose. On each occasion patients were admitted for 24 h and serial blood samples were obtained.

Patients We investigated 12 women treated with L-thyroxine because of primary hypothyroidism, who used no medication known to interfere with L-thyroxine uptake.

Measurements Patients were admitted to hospital and blood samples were obtained at hourly intervals for 24 h via an indwelling catheter. Following this first hospital admission, all women were asked to switch the administration time from morning to bedtime or vice versa. After 2 months they were readmitted for a 24-h period of hourly blood sampling. Blood samples were analysed for serum TSH (immunometric assay), FT4 and T3 (competitive immunoassay), T4 and rT3 (radioimmunoassay), serum TBG (immunometric assay) and total protein and albumin (colourimetric methods).

Results A significant difference in TSH and thyroid hormones was found after switching to bedtime administration of L-thyroxine. Twenty-four-hour average serum values amounted to (mean ± SD, morning *vs* bedtime ingestion): TSH, $5{\cdot}1 \pm 0{\cdot}9$ *vs* $1{\cdot}2 \pm 0{\cdot}3$ mU/l ($P < 0{\cdot}01$); FT4, $16{\cdot}7 \pm 1{\cdot}0$ *vs* $19{\cdot}3 \pm 0{\cdot}7$ pmol/l ($P < 0{\cdot}01$); T3, $1{\cdot}5 \pm 0{\cdot}05$ *vs* $1{\cdot}6 \pm 0{\cdot}1$ nmol/l ($P < 0{\cdot}01$). There was no significant change in T4, rT3, albumin and TBG serum levels, nor in the T3/rT3 ratio. The relative amplitude and time of the nocturnal TSH surge remained intact.

Conclusions L-thyroxine taken at bedtime by patients with primary hypothyroidism is associated with higher thyroid hormone concentrations and lower TSH concentrations compared to the same L-thyroxine dose taken in the morning. At the same time, the circadian TSH rhythm stays intact. Our findings are best explained by a better gastrointestinal uptake of L-thyroxine during the night.

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Introduction

Levothyroxine is currently one of the most prescribed medications.[1] For the widely used oral preparations, enteral absorption of L-thyroxine is approximately 70–80%.[2–4] The small bowel is the primary site of thyroid hormone absorption by a mechanism of translocation across the mucosa that remains unclear.[5] Interference with L-thyroxine absorption has been documented for cholestyramine resin, colestipol hydrochloride, sucralphate, iron sulphate, aluminium antacids, activated charcoal, raloxifen, food and herbal remedies.[2,6] Also, a fibre-enriched diet has been shown to have an adverse effect on the intestinal absorption of L-thyroxine.[7] Therefore, standard drug information resources, including manufacturers' prescribing information, recommend that L-thyroxine be taken on an empty stomach in the morning. Consequently, hypothyroid patients worldwide are advised to take L-thyroxine tablets in the morning half an hour before breakfast. However, whether intestinal absorption is better when the stomach is empty in the morning or at night has never been studied systematically. Recently, we observed several patients whose thyroid hormone profiles improved markedly after changing the administration time of L-thyroxine to bedtime. This prompted us to further study this phenomenon. The circadian variation of serum TSH in man is well-documented. The serum levels of TSH increase in the evening, reach a maximum near sleep onset and are followed by a progressive decrease during the night and low values during the day.[8–11] The percentage nocturnal rise of TSH is 71 ± 40% in healthy controls, and is maintained in euthyroid patients on levothyroxine therapy taken in the morning (63 ± 51%) and patients with mild hypothyroidism (54 ± 33%),[10] whereas in overt hypothyroidism this nocturnal surge disappears.

Changing the administration time of L-thyroxine to bedtime in patients with primary hypothyroidism might influence the nocturnal TSH surge and the circadian variation of serum TSH. In that case, taking one blood sample per day may not represent average hormone levels, as this single blood sample may be drawn at completely different points in the hormone cycles. Thyroid hormone deiodination by deiodinases type 1, 2 and 3, and other pathways of T4 metabolism could also be affected by altering the administration time of L-thyroxine. The aim of this pilot study was, to investigate the effect of changing the administration time of L-thyroxine from early morning to bedtime on thyroid hormone profiles, the circadian rhythm of TSH and thyroid hormones and thyroid hormone metabolism.

Patients and methods

Twelve women, aged 25–75 years (mean 48 years), taking L-thyroxine treatment for primary hypothyroidism, volunteered for this study. The mean dose of L-thyroxine (Thyrax, Organon) was 121 μg, the mean body weight 78 kg. None of the patients used medication known to interfere with L-thyroxine absorption, nor were they known to have gastro-intestinal disease. The cause of hypothyroidism was primary (auto-immune) hypothyroidism in eight subjects, previous radioiodine treatment given for Graves' disease in three subjects and thyroidectomy because of a nodular goitre in one. All subjects gave written consent and the protocol was approved by the local ethics committee. Patients were admitted to the hospital for 24 h on two separate days, with a two-month interval. On the first day all subjects were still taking L-thyroxine at their usual time (10 women in the morning, 2 women at bedtime). The former were used to taking L-thyroxine half an hour before breakfast, between 0600 h and 0700 h. Blood samples were obtained at hourly intervals for 24 h via an indwelling catheter, followed by rinsing with heparinized saline. Following this first hospital admission, all women were asked to switch the administration time from morning to bedtime at 2200 h (and vice versa from bedtime to morning between 0600 and 0700 h). After 2 months they were readmitted for a 24-h period of hourly blood sampling. During admission all subjects were ambulant during the day, meals were taken at standardized times (0730 h, 1230 h and 1730 h), and they were in bed from 2200 h to 0700 h. Blood samples were immediately centrifuged and stored at 4 °C. Within 12 h the plasma samples were divided in small aliquots and stored at –80 °C until analysis. Serum TSH (normal range 0·4–4·0 mU/l) was measured by immunometric assay (Immulite 2000, DPC Nederland, Breda, the Netherlands), with a detection limit of 0·002 mU/l. The interassay variation was 12·5, 4·6, 5·1, 4·5 and 6·4% at mean TSH values of 0·02, 1·3, 7·3, 19·0 and 39·0 mU/l, respectively. FT4 (normal range 10·0–24·0 pmol/l) and T3 (normal range 1·23–2·80 nmol/l) were measured by competitive immunoassay (Immulite 2000), T4 (normal range 58–128 nmol/l) and rT3 (normal range 0·14–0·34 nmol/l) by radioimmunoassay, serum TBG (normal range 12–38 mg/l) by immunometric assay (Immulite 2000), and total protein and albumin by colourimetric methods.

We asked all patients to fill out forms concerning symptoms of hypothyroidism and Quality of Life (QOL) during the periods of morning administration and bedtime administration. Firstly, a subjective symptom questionnaire which assessed 20 symptoms of hypothyroidism and/or hyperthyroidism (for example depression, weight gain, cold/heat intolerance, constipation, etc.) was obtained.[14] Patients scored these symptoms as not present (1 point), hardly present (2 points), present (3 points), or severely present (4 points). Secondly, a general QOL questionnaire (RAND-36)[15] was used to measure health related QOL according to eight subscales which are: physical functioning, role physical functioning, bodily pain, general health perception, role emotional functioning, emotional well-being, energy/fatigue and social functioning. The scale score ranged from 0 to 100 for every subscale, with a higher outcome meaning a better health status.

Statistical analysis

Statistical analysis was carried out using ANOVA, paired student *t*-tests and paired-samples *t*-test for the blood pressure and pulse frequency. Significance of diurnal variation (time dependency) of the different hormone curves was assessed using a one-way ANOVA with repeated measures. Only if ANOVA detected a significant effect of time, a cosinor analysis was performed on the data sets of individual patients, using the fundamental period (24 h). Curve fitting was performed using constrained nonlinear regression analysis (SPSS 11·0). Subsequently, only if the significance level of the fitted curve was less than 0·05, data were used to calculate circadian rhythm parameters.[12] Student's *t*-test (paired) were used to detect significant differences between the curves of the morning and evening treatment. For the ANOVA (paired) *t*-tests and the cosinor analysis, $P < 0{\cdot}05$ was considered to be a significant difference. In all cases, statistics and cosine analysis were performed on absolute values. Circular statistics were applied for the acrophase data, that is, Jupp's Phi and S for mean angle and angular standard deviation, Mardia–Watson–Wheeler χ^2-test for evaluation of acrophase differences between groups.[13] This was not a randomized double-blind study although hormone measurements and statistical analyses were performed without information about the time of L-thyroxine ingestion.

Results

Serum TSH levels decreased and FT4 and T3 levels increased remarkably and significantly after changing the time of L-thyroxine ingestion from morning to bedtime (Fig. 1). The results of 11 patients are given, as it was impossible to gain venous access in one subject. Table 1 shows all the 24-h mean values ± standard deviation (SD) for TSH, FT4, T3, T4, rT3, the T3/rT3 ratio, albumin and TBG during morning and bedtime thyroxine administration. When levothyroxine is taken in the morning there is an increase in serum FT4 after taking the tablet ($P < 0{\cdot}05$), which is not found after taking the tablet at bedtime, as is shown in Fig. 1c. Serum rT3 levels, the biologically inactive product of inner ring deiodination of T4, did not change significantly, and neither did TT4, with time of thyroxine digestion. The ratio of active *vs* inactive thyroid hormone (T3/rT3), a parameter which reflects thyroid hormone metabolism by outer ring *vs* inner ring deiodination did not differ between the morning or bedtime ingestion of levothyroxine. TSH decreased and FT4 rose in all patients

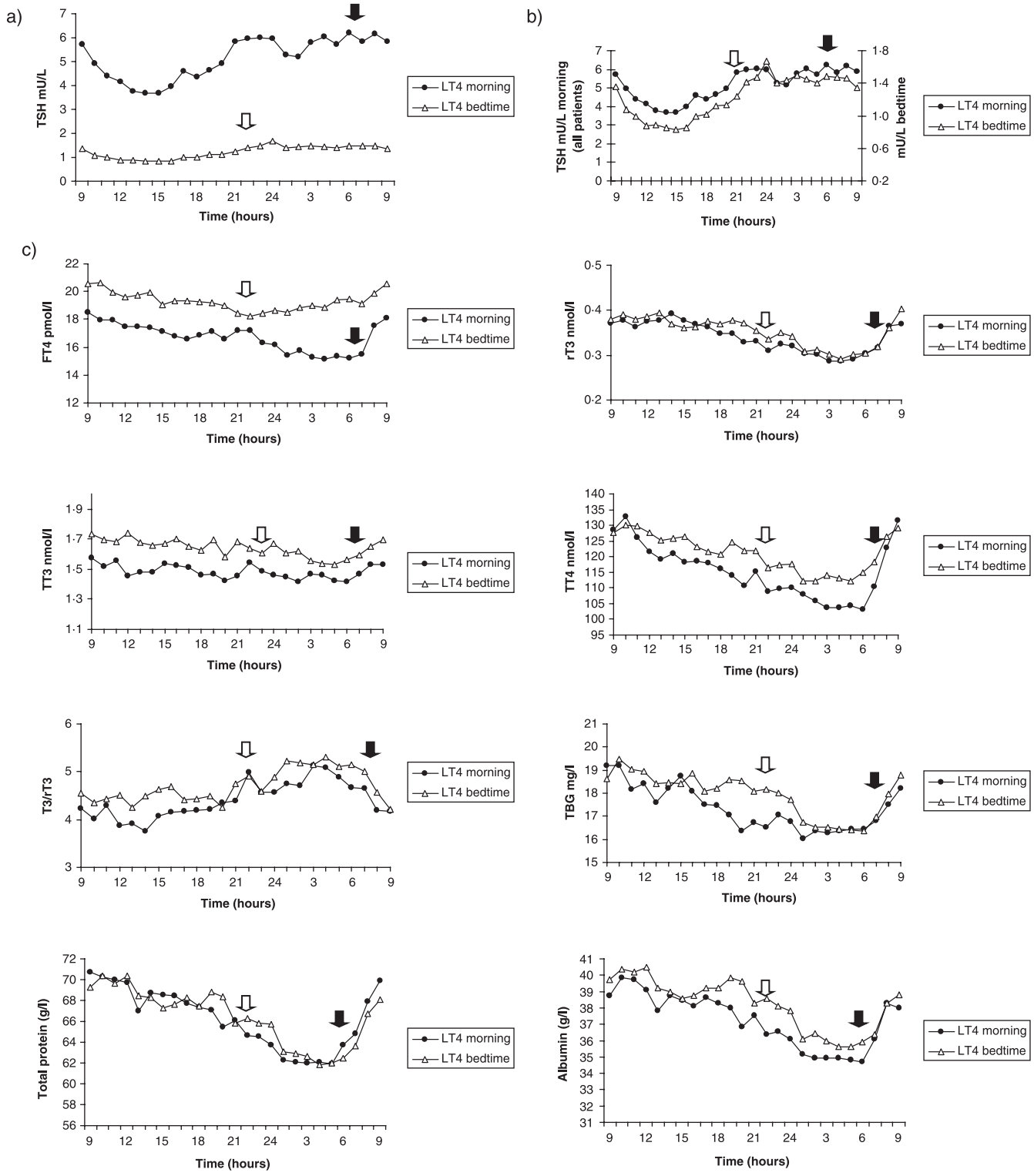

Fig. 1 Thyroid hormones and TSH during the morning administration of levothyroxine (●) and the bedtime administration of levothyroxine (Δ). Levothyroxine was taken at 0700 h (⬇) or at 2200 h (⇩). (a) Mean TSH serum levels of all patients over 24 h. On the same scale. (b) TSH levels on different scales (morning administration on the left axis, bedtime administration on the right axis) to show that the circadian rhythm of TSH remained intact during the morning and bedtime administration. (c) Mean FT4, TT3, rT3, TT4, TBG, total protein, albumin serum levels and the T3/rT3 ratio of all patients over 24 h.

Table 1. Difference in serum levels of thyroid hormones and their binding proteins, between the morning administration and bed time administration of levothyroxine. Data given as the 24 h mean hormonal values ± SD of all 11 patients

	TSH mU/l	FT4 pmol/l	TT3 nmol/l	TT4 nmol/l	rT3 nmol/l	TT3/rT3	Albumin g/l	TBG mg/l
LT4 morning	5·1 ± 0·9	16·7 ± 1·0	1·48 ± 0·05	115·3 ± 8·8	0·34 ± 0·03	4·40 ± 0·38	37·2 ± 1·6	17·3 ± 1·0
LT4 bedtime	1·2 ± 0·3	19·3 ± 0·7	1·64 ± 0·1	121·2 ± 6·0	0·35 ± 0·03	4·70 ± 0·34	38·2 ± 1·6	17·9 ± 1·0
P-value	< 0·01	< 0·01	< 0·01	ns	ns	ns	ns	ns

by changing thyroxine ingestion from early morning to bedtime and T3 levels rose in all but one subject. A decrease in TSH levels was observed irrespective of initial TSH levels. The 24-h mean TSH levels during both the morning and bedtime administration of levothyroxine are negatively correlated with the 24-h mean FT4 levels ($R = -0{\cdot}64$). The pattern of the circadian rhythm remained intact during the morning and bedtime administration of levothyroxine, and is almost identical (Fig. 1b). The ANOVA and cosinor analysis showed a significant effect of time on all parameters (Table 2) except for T3 (not shown). FT4, as well as T4, shows a significant difference between the morning administration and the bedtime administration in the 24-h mean values of the fitted curves, with higher values after the bedtime administration. In addition, bedtime administration slightly decreased the relative amplitude of their daily rhythms and phase-advanced the timing of their acrophase. Daily TSH rhythms were not affected by the timing of L-thyroxine intake. The mean blood pressure was 130/75 mmHg during the morning dosage and 127/77 mmHg during the bedtime dosage (ns) and mean pulse rate 68 beats/min and 65 beats/min, respectively (ns). The subjective symptom questionnaire showed no change in quality of life, with 41·5 ± 9·9 points during the morning administration of levothyroxine and 39·5 ± 12·2 points during the bedtime administration. The RAND-36 questionnaire was also analysed and among the 8 subscales, only the subscale bodily pain changed significantly in favour of the bedtime administration of levothyroxine ($P = 0{\cdot}016$).

Discussion

This study shows that thyroid hormone profiles improve strikingly after changing the time of ingestion of L-thyroxine from early in the morning, before breakfast, to late in the evening, at bedtime. This has important consequences for the millions of patients who take L-thyroxine daily. Taking levothyroxine at bedtime is also more practical for most patients, as it does not coincide with meal times. Switching to bedtime administration also proves to be safe and was well-tolerated. We carried out this pilot study to make sure that the time of L-thyroxine administration does not change the circadian rhythm of the serum TSH and iodothyronine levels that could result in a systematic error if a large, randomized and double-blind study of the effects of the time of L-thyroxine ingestion was to be analysed using a single time of blood collection. The marked improvement in T4 availability after changing the time of L-thyroxine ingestion from before breakfast to bedtime which is strongly suggested by this pilot study indeed needs to be confimed in a larger randomised trial. Although the study design seems to be unbalanced as 2 cases took T4 in the evening first and then switched to the morning dose, the results of the study were similar in both these 2 cases and in the 10 other cases and therefore confirm the overall study outcome.

There may be several explanations for our results. Firstly, breakfast may interfere with intestinal absorption of L-thyroxine, even if eaten half an hour after ingestion of the tablet. If patients take the tablet just before bedtime, it is usually hours since their last meal. Secondly, bowel motility is slower at night,[16] resulting in a more prolonged exposure of the L-thyroxine tablet to the intestinal wall and, consequently, in a better uptake. The mechanism of transport of L-thyroxine across the intestinal wall is unclear. Thus, it is not known whether this is an active or a passive process, and what factors influence this process. It is possible that this transport process plays a role in the difference in L-thyroxine uptake at different times of the day;[17,18] Thirdly, the production and activity of deiodinases (type 1, 2 and 3) is influenced by hyper- and hypo-thyroidism and certain drugs,[19,20] but also a circadian rhythm of the deiodinases has recently been demonstrated. Type 2 deiodinase for example has a circadian rhythm in the central nervous system.[21] Other inactivating pathways of T4 metabolism, such as glucuronidation and sulphation in liver and other tissues, may also vary during the day, and contribute to the greater bioavailability of thyroxine taken at night. However, one would expect changes in the serum T3/rT3 ratio and T4 patterns, if the metabolism of thyroid hormones is affected by changing the time of intake of levothyroxine, which was not observed.

The bioactivity of TSH also has a circadian variation, with less bioactive and differently glycosylated TSH molecules secreted during the night.[22] This has been used as an explanation for why thyroid hormones do not have a nocturnal rise after the TSH surge. Whether the bioactivity of TSH is influenced by changing the time of levothyroxine ingestion is unknown. Although we did not find a correlation between the circadian rhythms of TSH and FT4, we found, as expected, a negative correlation of the 24-h mean TSH levels with the 24-h mean FT4 levels. In our study the magnitude and time of the nocturnal TSH surge were the same during the morning and bedtime administration of L-thyroxine. Although FT4 and T4 showed a different timing in acrophase, this was not enough to influence the timing of the TSH acrophase. The important practical consequence of our findings, namely that the circadian rhythm of TSH does not change when switching the time of levothyroxine ingestion to bedtime, is that blood sampling for monitoring thyroid hormone replacement in patients taking L-thyroxine at bedtime need not be changed, i.e. can take place in the morning as is usually done. The circadian rhythm of the binding proteins TBG, total protein and albumin is explained by postural changes (with lower levels in supine position). Interestingly, we also found a circadian rhythm in FT4, T4 and rT3. In previous studies only rapid fluctuations of FT4 were

Table 2. Results of cosinor analysis for significance of diurnal variation

	Amplitude	R^2	Mesor	Acrophase	*n*
TSH					
A	39·2 ± 3·6	74 ± 4%	5·6 ± 2·5	02 : 20 ± 1 : 25	11
B	34·9 ± 2·6	71 ± 3%	1·3 ± 0·4	02 : 25 ± 1 : 28	10
n	10	10	10	10	
P-value	0·144	0·51	0·082	0·19	
FT4					
A	9·8 ± 1·1	51 ± 6%	17·0 ± 0·8	13 : 34 ± 1 : 15	9
B	5·9 ± 0·7	44 ± 6%	20·2 ± 1·0	10 : 23 ± 2 : 05	9
n	8	8	8	8	
P-value	**0·04**	0·71	**0·006**	**0·04**	
Total protein					
A	6·7 ± 0·6	63 ± 5%	66·2 ± 0·9	12 : 50 ± 1 : 28	11
B	5·9 ± 0·8	48 ± 6%	66·4 ± 0·9	13 : 31 ± 1 : 35	11
n	11	11	11	11	
P-value	0·299	**0·013**	0·72	0·22	
Albumin					
A	6·7 ± 0·6	62 ± 6%	37·5 ± 0·6	13 : 51 ± 1 : 32	11
B	5·4 ± 0·8	54 ± 6%	38·4 ± 0·7	13 : 59 ± 2 : 18	10
n	10	10	10	10	
P-value	0·073	0·232	0·186	0·50	
rT3					
A	15·5 ± 2·0	58 ± 5%	0·35 ± 0·04	13 : 26 ± 1 : 06	11
B	15·0 ± 0·8	52 ± 5%	0·35 ± 0·04	14 : 09 ± 1 : 53	10
n	10	10	10	10	
P-value	0·580	0·367	0·840	0·98	
TBG					
A	7·8 ± 1·4	42 ± 6%	18·0 ± 0·9	13 : 00 ± 1 : 15	11
B	9·3 ± 1·1	46 ± 6%	18·2 ± 1·1	14 : 47 ± 2 : 28	9
n	9	9	9	9	
P-value	0·419	0·623	0·829	0·12	
T4					
A	11·4 ± 1·0	64 ± 5%	110·7 ± 4·4	12 : 55 ± 0 : 28	10
B	7·4 ± 0·7	58 ± 5%	120·6 ± 6·0	11 : 47 ± 1 : 40	11
n	10	10	10	10	
P-value	**0·016**	0·373	0·051	**0·003**	

Only if ANOVA detected a significant effect of time, a cosinor analysis was performed on the data sets of individual patients (*n* = the number of patients showing a significant fit). Only if the significance level of the fitted curve was less than 0·05 data were used to calculate circadian rhythm parameters. The fitted function is defined by its mesor (rhythm-adjusted mean), amplitude (50% of the difference between the maximum and the minimum of the fitted curve, expressed as a percentage of the mesor), and acrophase (time of the maximum). R^2, goodness of fit; A, morning administration; B, bedtime administration. *P*-values indicate the result of the paired student *t*-test on the means of A and B. Significant differences are indicated in bold.

observed, without evidence of a circadian rhythm.[23] In conclusion, our study shows that taking L-thyroxine at bedtime significantly improves thyroid hormone profiles in patients with primary hypothyroidism, whereas the circadian rhythm of TSH remains intact. A large double-blinded randomised study will need to be performed to confirm our results.

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