ORIGINAL INVESTIGATION

Effects of Evening vs Morning Levothyroxine Intake

A Randomized Double-blind Crossover Trial

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Background: Levothyroxine sodium is widely prescribed to treat primary hypothyroidism. There is consensus that levothyroxine should be taken in the morning on an empty stomach. A pilot study showed that levothyroxine intake at bedtime significantly decreased thyrotropin levels and increased free thyroxine and total triiodothyronine levels. To date, no large randomized trial investigating the best time of levothyroxine intake, including quality-of-life evaluation, has been performed.

Methods: To ascertain if levothyroxine intake at bedtime instead of in the morning improves thyroid hormone levels, a randomized double-blind crossover trial was performed between April 1, 2007, and November 30, 2008, among 105 consecutive patients with primary hypothyroidism at Maasstad Hospital Rotterdam in the Netherlands. Patients were instructed during 6 months to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Primary outcome measures were thyroid hormone levels; secondary outcome measures were creatinine and lipid levels, body mass index, heart rate, and quality of life.

Results: Ninety patients completed the trial and were available for analysis. Compared with morning intake, direct treatment effects when levothyroxine was taken at bedtime were a decrease in thyrotropin level of 1.25 mIU/L (95% confidence interval [CI], 0.60-1.89 mIU/L; $P < .001$), an increase in free thyroxine level of 0.07 ng/dL (0.02-0.13 ng/dL; $P = .01$), and an increase in total triiodothyronine level of 6.5 ng/dL (0.9-12.1 ng/dL; $P = .02$) (to convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; and total triiodothyronine level to nanomoles per liter, multiply by 0.0154). Secondary outcomes, including quality-of-life questionnaires (36-Item Short Form Health Survey, Hospital Anxiety and Depression Scale, 20-Item Multidimensional Fatigue Inventory, and a symptoms questionnaire), showed no significant changes between morning vs bedtime intake of levothyroxine.

Conclusions: Levothyroxine taken at bedtime significantly improved thyroid hormone levels. Quality-of-life variables and plasma lipid levels showed no significant changes with bedtime vs morning intake. Clinicians should consider prescribing levothyroxine intake at bedtime.

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BECAUSE THE PREVALENCE OF primary hypothyroidism is high among the general population,[1,2] levothyroxine sodium is one of the most prescribed medications. Absorption of levothyroxine is approximately 70% to 80% and occurs in the small bowel.[3] There is consensus that levothyroxine should be taken before breakfast to prevent interference of its intestinal uptake by food or other medications.[4-10] In our clinics, we observed several patients whose thyroid hormone levels improved markedly after changing the scheduled intake of levothyroxine to bedtime. A pilot study[11] confirmed this observation among 11 patients. The mean (SD) plasma thyrotropin level significantly decreased from 5.1 (0.9) to 1.2 (0.3) mIU/L (to convert thyrotropin level to micrograms per liter, multiply by 1.0), and free thyroxine (FT_4) and triiodothyronine (T_3) levels increased when levothyroxine was taken at bedtime. The circadian pattern of thyrotropin rhythm remained intact, which was important regarding the time of blood sampling for thyrotropin levels to monitor levothyroxine therapy.

Accordingly, we conducted a randomized double-blind crossover trial to confirm whether levothyroxine taken at bed-

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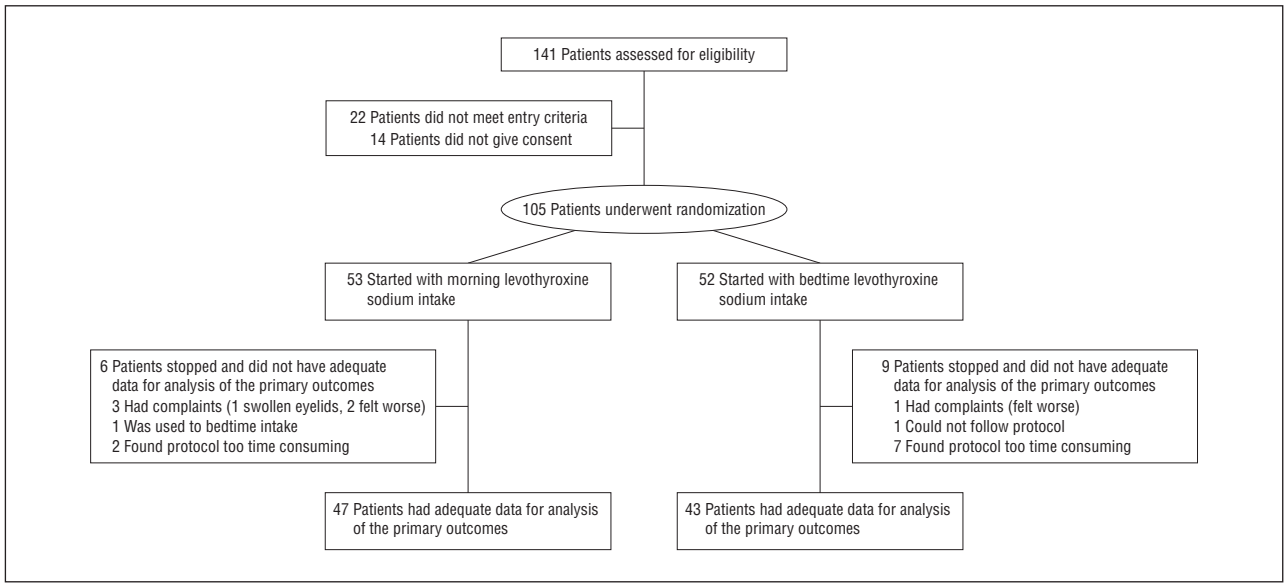

Figure 1. Flowchart of the study, showing disposition of patients from screening to study completion. Consecutive patients with primary hypothyroidism who visited our clinics were assessed for study eligibility. Study exclusion criteria were gastrointestinal disorder, thyroid carcinoma, and pregnancy.

time leads to lower thyrotropin and higher FT_4 and T_3 levels. Hypothyroidism can have major effects on health and quality of life (QOL), as it is associated with fatigue, weight gain, cold intolerance, depression, neuromuscular symptoms, diastolic dysfunction, and impairment of renal function.[12-15] It is also associated with risk factors for cardiovascular disease, such as hyperlipidemia, hyperhomocystinemia, and arterial hypertension, notably in the case of insufficient thyroid hormone supplementation.[16,17]

The primary objective of this study was to determine whether a change occurred in thyrotropin and thyroid hormone levels when levothyroxine was taken at bedtime vs in the morning. We further investigated whether a bedtime regimen would affect creatinine and lipid levels, body mass index, heart rate, and QOL.

METHODS

STUDY PARTICIPANTS

A randomized double-blind crossover trial was performed among consecutive patients with primary hypothyroidism who visited our clinics. The patients had to be 18 years or older and have been on a stable levothyroxine regimen for at least 6 months. Patients with a gastrointestinal tract disorder, those with thyroid carcinoma, and those who were pregnant were excluded from the study. Also excluded were patients who were taking medication known to interfere with the uptake of levothyroxine.[4,7-10] The medical ethics committee of the Maasstad Hospital Rotterdam in the Netherlands approved the study protocol, and written informed consent was obtained from each patient.

RANDOMIZATION AND TREATMENT

After informed consent had been obtained, patients were randomized to start the study period with 1 capsule of levothyroxine in the morning (and 1 capsule of placebo at bedtime) or with 1 capsule of levothyroxine at bedtime (and 1 capsule of placebo in the morning). After 3 months, patients were switched from levothyroxine in the morning to placebo and vice versa for another 3 months. Double-blind study medication was provided by the hospital pharmacy, which performed the randomization. Commercial levothyroxine sodium tablets (Thyrax Duotab, 0.100 mg; Organon, Oss, the Netherlands) were used and were reformulated as capsules with lactose monohydrate as the single excipient (in compliance with Good Manufacturing Practice guidelines, annex 13, manufacture of investigational medicinal products). Every patient received study capsules containing a similar dose of levothyroxine as before entry into the trial. Placebo and levothyroxine capsules were visually identical. Patients were instructed by a research nurse to take the morning capsule on an empty stomach half an hour before breakfast and the bedtime capsule at night just before going to bed.

DATA COLLECTION, FOLLOW-UP, AND COMPLIANCE

At baseline and every 6 weeks, patients were seen in our clinics by a research nurse. At these visits, blood samples were obtained to determine plasma thyrotropin, FT_4, T_3, creatinine, and lipid levels, and blood pressure, heart rate, and body weight were measured. The remaining capsules in the containers were counted to check for compliance. Quality-of-life questionnaires were completed by patients at baseline, at 3 months, and at the end of the study.

BLOOD SAMPLING

Blood samples were drawn on the morning of the planned visit to the research nurse. Capsules were not withheld on the day of blood sampling. Serum thyrotropin levels (reference range, 0.4-4.0 mIU/L) were measured by immunometric assay (Immulite 2000; DPC Nederland, Breda, the Netherlands), with a detection limit of 0.002 mIU/L. Levels of FT_4 (reference range, 10.0-24.0 pmol/L; equivalent to 0.78-1.86 ng/dL) and T_3 (reference range, 1.23-2.80 nmol/L; equivalent to approximately 80-182 ng/dL) were measured by competitive immunoassay (Immulite 2000). Creatinine and lipid levels were also measured (Dimension RxL; Dade Behring, Deerfield, Illinois).

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Table 1. Baseline Characteristics of 90 Patients With Adequate Data for Analysis of the Primary Outcomes

Characteristic	Morning Levothyroxine Sodium Intake First (n=47)	Bedtime Levothyroxine Sodium Intake First (n=43)
Age, mean (SD), y	48 (11)	48 (13)
Male sex, No.	13	7
Body mass index, median (range)[a]	29.1 (20.0-40.1)	27.9 (19.8-41.0)
Etiology of hypothyroidism, No.		
Hashimoto disease	26	26
Sodium iodide I 131	17	17
Thyroidectomy	3	0
Neck radiation therapy	1	0
Duration of hypothyroidism, median (range), y	3.0 (0.5-25.0)	2.0 (0.5-21.0)
Levothyroxine dosage, median (range), μg	125 (50-200)	100 (50-250)
Thyrotropin level, mean (SD), mIU/L	1.5 (1.7)	3.3 (3.0)
Free thyroxine level, mean (SD), ng/dL	1.58 (0.26)	1.50 (0.27)
Triiodothyronine level, mean (SD), ng/dL	132.9 (30.7)	122.0 (38.1)
Patients who used other medications, No.	26	25

SI conversion factors: To convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; total triiodothyronine level to nanomoles per liter, multiply by 0.0154.

[a]Calculated as weight in kilograms divided by height in meters squared.

QUALITY OF LIFE AND PATIENT PREFERENCE

Three QOL questionnaires (36-Item Short Form Health Survey, Hospital Anxiety and Depression Scale, and 20-Item Multidimensional Fatigue Inventory) and a specific questionnaire about symptoms of hypothyroidism and hyperthyroidism were completed by patients at baseline, at 3 months, and at the end of the study. Patients completed the questionnaires under the supervision of a research nurse. The 36-Item Short Form Health Survey is a general QOL questionnaire that comprises 8 scales.[18] The Hospital Anxiety and Depression Scale consists of 14 items pertaining to anxiety and depression.[19] The 20-Item Multidimensional Fatigue Inventory measures 5 different dimensions of fatigue.[20] The specific questionnaire for thyroid symptoms assesses 14 symptoms of hypothyroidism and 6 symptoms of hyperthyroidism.[21] At the end of the trial before the randomization code was broken, patients were asked during which period of the trial they had felt better. After the trial ended, patients were free to choose at what time of day they preferred to continue taking levothyroxine, in the morning or at bedtime. One year after the trial, we asked every patient at what time he or she was taking the levothyroxine tablet.

STATISTICAL ANALYSIS

The primary end point was a change in thyroid hormone variables (thyrotropin, FT_4, and total T_3 [TT_3] levels) between 12 weeks of morning levothyroxine intake and 12 weeks of bedtime levothyroxine intake. Secondary end points were changes in QOL (measured by 3 questionnaires), thyroid symptom score, body mass index, heart rate, and serum lipid and creatinine levels.

The direct treatment effect among all variables was measured by performing an independent-samples *t* test between the differences of week 12 and week 24 in the first group (started with morning levothyroxine) and the second group (started with bedtime levothyroxine).[22] The presence of a carryover effect from one period to the other was measured by performing an independent-samples *t* test on the sum of the variables at 12 and 24 weeks in each patient. All *P* values were 2-sided and were not adjusted for multiple testing. All calculations were performed using commercially available statistical software (SPSS 17.0 for Windows; SPSS Inc, Chicago, Illinois).

To calculate the sample size, we assumed that a difference in thyrotropin level of 1.0 mIU/L between morning and bedtime ingestion of levothyroxine would be clinically relevant. From previous results in a pilot study, we calculated that the standard deviation of the difference between morning and bedtime administration would be between 2.5 and 3.0 mIU/L. Based on these calculations, a sample size of 75 patients would give at least 80% power to detect a significant difference of 1 mIU/L between morning and bedtime administration.

RESULTS

STUDY PARTICIPANTS AND TREATMENT

Between April 1, 2007, and November 30, 2008, a total of 141 consecutive patients with primary hypothyroidism were assessed for study eligibility. Ultimately, 105 patients met the inclusion criteria and gave written informed consent. Reasons for exclusion were current use of interfering medication (n=11), history of thyroid carcinoma (n=3), unusual dosage of levothyroxine (n=6), treatment for breast cancer (n=1), and Addison disease (n=1). Fifteen randomized patients withdrew their consent shortly after enrollment in the trial and had baseline data only. The baseline characteristics of these patients did not differ from those of patients who completed the trial. Data for the entire 24 weeks were available for 90 patients (86%) who enrolled in the trial, 47 of whom started with levothyroxine intake in the morning and placebo at bedtime and 43 of whom started with levothyroxine intake at bedtime and placebo in the morning (**Figure 1**).

Baseline characteristics of the 2 groups are given in **Table 1**. There were differences between the 2 groups in the proportions of male patients, levothyroxine dosages, and thyrotropin levels. On average, patients missed a mean (SD) of 1.3 (6.0) capsules in the morning and 1.9 (10.1) capsules in the evening during 24 weeks of the trial (*P*=.54). Because there were no severe symptoms related to hypothyroidism or hyperthyroidism, no patient required a change in levothyroxine dosage during the trial.

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Table 2. Laboratory Results and Measurements After 12 and 24 Weeks of Morning vs Bedtime Levothyroxine Sodium Intake in the 2 Randomized Study Groups

	Mean (SD)					
	Morning Levothyroxine Sodium Intake First (n=47)			Bedtime Levothyroxine Sodium Intake First (n=43)		
Variable	Baseline	12 wk	24 wk	Baseline	12 wk	24 wk
Thyrotropin level, mIU/L	1.52 (1.71)	2.66 (2.53)	1.74 (2.43)	3.31 (3.01)	2.36 (2.55)	3.86 (4.02)
Free thyroxine level, ng/dL	1.58 (0.26)	1.48 (0.24)	1.59 (0.33)	1.50 (0.27)	1.54 (0.28)	1.51 (0.20)
Total triiodothyronine level, ng/dL	132.9 (30.7)	121.2 (28.1)	127.0 (31.6)	122.0 (38.1)	128.4 (30.6)	121.9 (36.3)
Creatinine level, mg/dL	0.76 (0.17)	0.77 (0.21)	0.74 (0.16)	0.75 (0.28)	0.74 (0.26)	0.74 (0.29)
Total cholesterol level, mg/dL	194.3 (38.5)	197.1 (38.1)	191.3 (38.3)	201.2 (44.7)	198.9 (46.6)	199.0 (43.2)
Body mass index[a]	29.5 (5.4)	29.7 (5.6)	29.7 (5.6)	28.7 (4.6)	28.8 (4.6)	29.1 (4.8)
Heart rate, beats/min	75.0 (11.5)	79.0 (12.3)	79.0 (13.0)	77.0 (11.6)	78.0 (11.7)	77.0 (11.0)

	Difference			
Variable	Morning Levothyroxine Sodium Intake First	Bedtime Levothyroxine Sodium Intake First	Direct Treatment Effect (95% Confidence Interval)	*P* Value
Thyrotropin level, mIU/L	–0.92 (2.08)	1.57 (3.87)	1.25 (0.60 to 1.89)	<.001
Free thyroxine level, ng/dL	0.11 (0.27)	–0.04 (0.25)	–0.07 (–0.13 to –0.02)	.01
Total triiodothyronine level, ng/dL	5.80 (26.20)	–7.13 (26.30)	–6.46 (–12.10 to –0.90)	.02
Creatinine level, mg/dL	–0.03 (0.10)	0.00 (0.10)	0.020 (–0.001 to 0.037)	.13
Total cholesterol level, mg/dL	–5.75 (26.70)	0.57 (19.70)	3.16 (–1.90 to 8.20)	.22
Body mass index[a]	0.01 (0.80)	0.28 (0.60)	0.13 (–0.02 to 0.29)	.09
Heart rate, beats/min	0.93 (12.70)	–1.07 (8.90)	–1.00 (–3.40 to 1.40)	.40

SI conversion factors: To convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; total triiodothyronine level to nanomoles per liter, multiply by 0.0154; creatinine level to micromoles per liter, multiply by 88.4; cholesterol level to millimoles per liter, multiply by 0.0259.

[a] Calculated as weight in kilograms divided by height in meters squared.

PRIMARY OUTCOMES

Results of the primary outcomes are summarized in **Table 2** and in **Figure 2**. Among the group that received morning levothyroxine first, the mean (SD) thyrotropin level decreased from 2.66 (2.53) mIU/L at 12 weeks to 1.74 (2.43) mIU/L at 24 weeks. In contrast, among the group that received bedtime levothyroxine first, the mean (SD) thyrotropin level increased from 2.36 (2.55) mIU/L at 12 weeks to 3.86 (4.02) mIU/L at 24 weeks. When overall changes were compared between the 2 groups, bedtime levothyroxine intake was found to have a direct treatment effect, with a decrease in thyrotropin level of 1.25 mIU/L (95% confidence interval [CI], 0.60-1.89 mIU/L; $P<.001$) relative to morning levothyroxine intake.

The mean (SD) FT_4 level in the group that received morning levothyroxine first increased from 1.48 (0.24) ng/dL at 12 weeks to 1.59 (0.33) ng/dL at 24 weeks. In the group that received bedtime levothyroxine first, the mean (SD) FT_4 level decreased from 1.54 (0.28) ng/dL at 12 weeks to 1.51 (0.20) ng/dL at 24 weeks. Therefore, bedtime levothyroxine intake resulted in a direct treatment effect, with an increase in FT_4 level of 0.07 ng/dL (95% CI, 0.02-0.13; $P=.01$) relative to morning levothyroxine intake.

Changes in TT_3 levels were similar to changes in FT_4 levels. In the group that received morning levothyroxine first, the mean (SD) TT_3 level increased from 121.2 (28.1) ng/dL to 127.0 (31.6) ng/dL. In the group that received bedtime levothyroxine first, the mean (SD) TT_3 level decreased from 128.4 (30.6) ng/dL to 121.9 (36.3) ng/dL. In this case, the direct treatment effect of bedtime levothyroxine was an increase in TT_3 level of 6.5 ng/dL (95% CI, 9.0-12.10 ng/dL; $P=.02$). No first-order carryover effect was found for thyrotropin, FT_4, or TT_3 levels.

SECONDARY OUTCOMES

There were no differences between the 2 study groups in serum creatinine or lipid levels, blood pressure, body mass index, or heart rate. These results are summarized in Table 2.

The 36-Item Short Form Health Survey, Hospital Anxiety and Depression Scale, and 20-Item Multidimensional Fatigue Inventory showed no differences in subscale or total scores between the periods of morning vs bedtime intake of levothyroxine (**Table 3**). Hypothyroidism symptoms were unchanged between the 2 periods, despite improved thyroid hormone profiles, nor was there a difference in hyperthyroidism symptoms.

PATIENT PREFERENCE

When asked at the end of the trial (before the randomization code was broken), 34 of 90 patients said that they felt better during the period of morning intake of levothyroxine, 31 patients preferred the period of bedtime intake, and 25 patients indicated no preference. At 1 year

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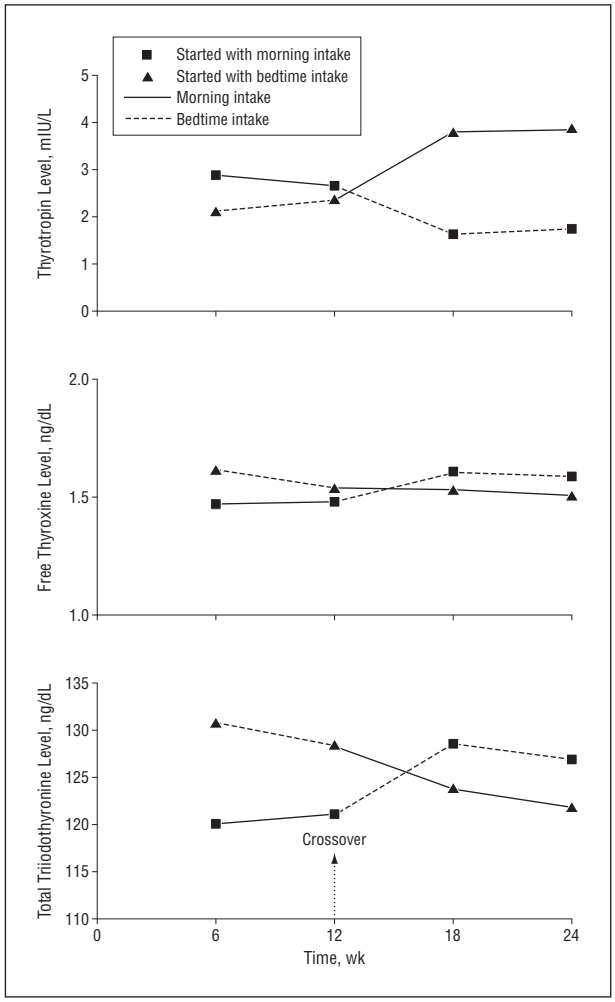

Figure 2. Thyroid hormone levels after 6 and 12 weeks of morning or bedtime intake of levothyroxine sodium. To convert thyrotropin level to micrograms per liter, multiply by 1.0; free thyroxine level to picomoles per liter, multiply by 12.871; and total triiodothyronine level to nanomoles per liter, multiply by 0.0154.

after completion of the trial, more than half of the patients still preferred bedtime intake of levothyroxine.

COMMENT

We performed this large, randomized, double-blind crossover trial among 90 patients to address whether levothyroxine taken at bedtime instead of in the morning improves thyroid hormone levels. The primary outcomes show a decrease in thyrotropin level of 1.25 mIU/L and an increase in FT_4 and TT_3 levels when levothyroxine is taken at bedtime. Despite the change in thyroid hormone levels, the patient QOL did not differ. Bedtime levothyroxine intake could be more convenient for patients, as they do not have to postpone breakfast. After our study was completed, more than half of the patients decided to continue with bedtime intake of levothyroxine.

How can the bioavailability effects of levothyroxine be explained? An interval of 30 minutes between taking levothyroxine and eating breakfast may be too short to prevent interference with gastrointestinal absorption of levothyroxine. Moreover, many patients drink coffee in the morning, often instead of eating breakfast,[6] or may take other medications that interfere with levothyroxine absorption. In contrast, most patients in our study stated that they had eaten no food or snacks for several hours before bedtime, this being their usual routine. Bowel motility is slower at night, resulting in more prolonged exposure of levothyroxine to the intestinal wall and, consequently, in better bioavailability.[23] Furthermore, basal gastric acid secretion is highest in the late evening and is lowest in the morning.[24] An acidic environment promotes the absorption of levothyroxine.[25] These circadian differences in gastrointestinal function could be a pathophysiological explanation for our findings.

Thyroid hormone level changes did not translate into QOL changes. There are various explanations for this observation. Patients with hypothyroidism taking adequate doses of levothyroxine (ie, those whose thyrotropin level is in the reference range) can still have significant impairment in psychological well-being and cognitive function compared with control subjects.[26,27] This could be related to their knowing that they have a chronic illness or are overweight. Weight gain and inability to lose weight are known to occur in patients with treated hypothyroidism and hyperthyroidism.[28,29] In our study, body mass index was high in both study groups. A trial investigating T_3 supplementation showed that improved QOL was limited to a subgroup of patients with suppressed thyrotropin levels who had lost weight.[30] Based on the results of population studies,[2,28] it has been suggested that the treatment goal in patients with hypothyroidism should be a thyrotropin level of 1.0 mIU/L or lower. In contrast, plasma thyroid hormone levels may not be representative of thyroid hormone levels at the tissue level (eg, in the brain); therefore, they would be unrelated to QOL.[31,32] Finally, newly discovered thyroid hormone metabolites such as thyronamine that are not replaced by levothyroxine could influence QOL[33]; furthermore, the presence of an autoimmune disorder (eg, Hashimoto disease) may have an effect on the brain and on QOL independent of thyroid hormone supplementation.[34]

Primary outcomes of this study are consistent with results of an earlier pilot study.[11] Two other studies on the timing of levothyroxine intake have been published. In a retrospective medical record review of 15 nursing home residents, Elliott[35] observed a nonsignificant decrease in thyrotropin levels when levothyroxine intake was switched from after breakfast to midnight. The findings in that nonrandomized trial confirm the results of our study. A 3-period crossover design study[36] showed higher thyrotropin levels when levothyroxine was taken at bedtime instead of before breakfast, but there was no change in FT_4 or TT_3 levels, as in our study. The exclusion criteria for that study were extensive, and only 19% of eligible patients were agreeable to participation. The study also included patients with thyroid cancer, whose thyrotropin levels were maintained at lower levels than those of the rest of the population. Therefore, we believe that the findings in that study extend the generalizability of our study results to the treatment of primary hypothyroidism. Lower thyrotropin levels associated with levothyroxine intake before breakfast vs at bedtime intake in

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Table 3. Quality of Life and Symptoms After 12 and 24 Weeks of Morning vs Bedtime Levothyroxine Sodium Intake in the 2 Randomized Study Groups

	Score, Mean (SD)					
	Morning Levothyroxine Sodium Intake First			Bedtime Levothyroxine Sodium Intake First		
Variable	Baseline	12 wk	24 wk	Baseline	12 wk	24 wk
36-Item Short Form Health Survey						
Physical functioning	62.7 (20.2)	64.5 (19.6)	62.7 (20.9)	65.2 (17.9)	67.4 (16.4)	66.5 (16.4)
Social functioning	72.3 (23.6)	71.5 (26.8)	70.9 (23.0)	65.8 (27.5)	73.0 (20.6)	71.2 (24.2)
Role limitations due to physical problems	55.9 (42.4)	63.0 (40.7)	59.2 (41.3)	65.6 (39.9)	57.9 (42.0)	67.9 (39.5)
Role limitations due to emotional problems	72.3 (41.3)	73.9 (37.1)	69.6 (39.0)	79.4 (35.3)	71.4 (36.5)	69.8 (40.4)
Mental health	70.3 (17.8)	69.6 (18.6)	68.3 (17.8)	65.2 (20.1)	63.7 (21.8)	66.0 (21.7)
Vitality	50.0 (23.7)	55.1 (21.2)	52.0 (22.9)	51.1 (20.0)	52.2 (20.2)	52.6 (20.4)
Pain	73.3 (26.2)	73.8 (25.3)	72.8 (23.5)	75.6 (26.7)	75.6 (28.7)	76.7 (28.0)
General health	53.8 (22.4)	56.5 (22.7)	56.6 (21.6)	56.7 (21.9)	59.3 (23.2)	58.8 (22.7)
Hospital Anxiety and Depression Scale						
Anxiety	6.3 (4.5)	6.5 (4.5)	5.9 (4.2)	7.0 (4.2)	7.1 (5.0)	7.2 (4.3)
Depression	5.0 (3.8)	4.8 (4.1)	4.4 (3.8)	5.8 (4.0)	5.0 (4.5)	5.6 (5.0)
20-Item Multidimensional Fatigue Inventory						
General fatigue	12.7 (5.3)	11.9 (4.9)	12.2 (5.0)	12.4 (5.1)	12.3 (5.1)	12.4 (5.5)
Physical fatigue	12.5 (5.4)	11.1 (4.9)	11.7 (4.8)	12.8 (4.5)	11.8 (4.7)	11.3 (4.6)
Reduced activity	10.8 (4.3)	10.5 (4.1)	10.7 (4.4)	11.1 (4.5)	11.2 (4.5)	11.2 (4.1)
Reduced motivation	9.6 (4.3)	9.7 (4.7)	9.9 (4.5)	10.8 (4.0)	10.7 (4.4)	10.7 (4.1)
Mental fatigue	9.8 (5.0)	10.4 (5.1)	10.0 (4.8)	11.0 (5.4)	11.0 (5.1)	10.4 (4.2)
Symptoms						
Hypothyroidism	29.8 (8.6)	27.2 (7.7)	28.7 (8.3)	31.5 (9.4)	29.2 (8.5)	29.6 (8.8)
Hyperthyroidism	11.5 (3.7)	11.0 (3.3)	10.8 (3.5)	12.5 (3.9)	12.1 (3.8)	12.0 (4.3)

	Difference			
Variable	Morning Levothyroxine Sodium Intake First	Bedtime Levothyroxine Sodium Intake First	Direct Treatment Effect (95% Confidence Interval)	*P* Value
36-Item Short Form Health Survey				
Physical functioning	−2.56 (13.43)	−0.83 (10.93)	0.86 (−1.26 to 3.50)	.52
Social functioning	−2.22 (23.43)	−1.74 (20.52)	0.24 (−4.44 to 4.92)	.92
Role limitations due to physical problems	−4.44 (38.54)	8.75 (35.15)	6.60 (−1.40 to 14.60)	.10
Role limitations due to emotional problems	−3.70 (43.36)	−0.79 (39.98)	1.46 (−7.46 to 10.37)	.75
Mental health	−1.28 (12.82)	2.67 (13.73)	1.97 (−0.83 to 4.77)	.16
Vitality	−3.09 (20.07)	0.35 (15.75)	1.72 (−2.09 to 5.52)	.37
Pain	−1.00 (19.09)	1.09 (20.19)	1.05 (−3.07 to 5.16)	.62
General health	−1.56 (15.48)	−0.73 (13.99)	0.41 (−2.77 to 3.59)	.80
Hospital Anxiety and Depression Scale				
Anxiety	−0.60 (2.53)	0.09 (2.93)	0.34 (−0.23 to 0.92)	.23
Depression	−0.45 (2.66)	0.55 (3.03)	0.50 (−0.10 to 1.10)	.10
20-Item Multidimensional Fatigue Inventory				
General fatigue	0.30 (4.13)	0.17 (3.77)	−0.07 (−0.91 to 0.77)	.88
Physical fatigue	0.55 (3.89)	−0.51 (3.82)	−0.53 (−1.34 to 0.28)	.19
Reduced activity	0.23 (3.44)	−0.10 (3.94)	−0.16 (−0.94 to 0.62)	.67
Reduced motivation	0.15 (3.75)	−0.05 (4.34)	−0.10 (−0.95 to 0.75)	.82
Mental fatigue	−0.34 (4.14)	−0.56 (3.91)	−0.11 (−0.96 to 0.74)	.80
Symptoms				
Hypothyroidism	1.45 (7.14)	0.42 (5.11)	−0.51 (−1.83 to 0.80)	.44
Hyperthyroidism	−0.15 (3.16)	−0.12 (2.80)	0.02 (−0.61 to 0.65)	.96

that study could be explained by the longer interval between levothyroxine intake and breakfast (60 minutes vs 30 minutes in our study). Also, most patients in our study stated that they had nothing to eat (or only a small snack) for several hours before bedtime, which differs across cultures. In all studies performed on the timing of levothyroxine ingestion, intake on an empty stomach seems to result in maximal absorption of levothyroxine. Our study shows that if this fasting regimen can be achieved at bedtime, then resulting thyroid hormone levels are better than those associated with levothyroxine intake 30 minutes before breakfast.

The crossover design of our study has the advantage that each patient served as his or her own control. Therefore, a statistical difference in thyrotropin values at baseline will not influence primary and secondary outcomes of the study. The study design has potential limitations, including order and sequence effects. We found no first-order carryover effect between the 2 periods, but we looked at no other order or sequence effects. It should

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also be noted that this was a single-site study in the Netherlands, where eating habits might be different from those in other countries or cultures.

Based on the results of our study, clinicians should inform patients with hypothyroidism that levothyroxine intake at bedtime is a good alternative to levothyroxine intake in the morning, provided that levothyroxine is taken on an empty stomach. For patients who do not attain normal thyrotropin or FT_4 levels with morning levothyroxine intake, a switch to bedtime is recommended. Recommendations on timing of levothyroxine intake and on uptake interference by food are found in few guidelines about the management of hypothyroidism.[37,38] Drug information resources and guidelines require revision in this respect.

In conclusion, bedtime intake of levothyroxine in our study significantly improved thyroid hormone levels. This may be explained by better gastrointestinal bioavailability at night or by less uptake interference by food or medications. As shown in this study, bedtime administration is more convenient for many patients. Clinicians should inform their patients about the possibility of taking levothyroxine at bedtime. A prolonged period of bedtime levothyroxine therapy may be required for a change in QOL to occur.

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