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Clinical Research Article

A Randomized Clinical Trial Comparing 2 Levothyroxine Regimens During Ramadan Fasting in Thyroidectomized Patients

Ali S. Alzahrani,[1] Noha Mukhtar,[1] Zahrah Alhammad,[1] Lulu Alobaid,[1] Abdulrhman Jaber Hakami,[1] Osamah Alsagheir,[1] Gamal Mohamed,[2] Maha Hameed,[3] and Abdulraof Almahfouz[1]

[1]Department of Medicine, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia
[2]Department of Epidemiology, Biostatistics and Scientific Computing, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia
[3]Clinical Trial Unit, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia

Correspondence: Ali S. Alzahrani, MD, Department of Medicine (MBC-46), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Email: aliz@kfshrc.edu.sa.

Abstract

Context: For Muslim patients on levothyroxine (L-T4) therapy, the best approach for L-T4 intake during Ramadan fasting remains unclear.

Objective: We compared 2 practical approaches for L-T4 intake during Ramadan.

Methods: We randomly assigned 69 patients (21 males, 48 females, median age 44 years) with differentiated thyroid cancer (DTC) who underwent thyroidectomy in the past and are on stable LT4 doses to 2 arms. Arm A (33 patients) ingested their pre-Ramadan L-T4 dose at the evening meal and ate immediately. Arm B (36 patients) increased their pre-Ramadan dose by 25 µg if their regular L-T4 dose was ≤150 µg/day or by 50 µg if their pre-Ramadan dose was >150 µg/day and ate immediately.

Results: At the beginning of Ramadan (baseline), the median thyrotropin (TSH) level and the numbers of patients in euthyroidism, subclinical hyperthyroidism (Shyper), or subclinical hypothyroidism (Shypo) were comparable between the 2 arms ($P = .69$ and $P = .65$, respectively). At the end of Ramadan, in arm A there were 17 (51.5%), 3 (9.1%), and 13 (39.4%) patients in euthyroidism, Shyper, and Shypo compared with 17 (47.2%), 14 (38.9%), and 5 (13.9%) patients, respectively, in arm B ($P = .005$). The mean ± SD TSH levels in arms A and B at the end of Ramadan were 5.6 ± 6.0 mU/L and 1.67 ± 2.6 mU/L, respectively ($P = .0001$).

Conclusion: No overt thyroid dysfunction developed but there were more cases of Shypo in arm A and Shyper in arm B. Arm B achieved desirable levels of TSH (normal or slightly suppressed) in 86% of cases and might be a preferable approach, especially for patients who need TSH suppression (eg, DTC).

Key Words: fasting, Ramadan, hypothyroidism, L-thyroxine, therapy

Abbreviations: DTC, differentiated thyroid cancer; FT4, free thyroxine; L-T4, levothyroxine; Shyper, subclinical hyperthyroidism; Shypo, subclinical hypothyroidism; TFT, thyroid function test; TSH, thyrotropin.

Ramadan fasting is one of the main duties in Islam that is practiced by millions of Muslims around the world. Fasting people abstain from eating or drinking anything by mouth including medications from dawn to sunset every day for 1 month. Fasting time on average is about 12 to 14 hours per day, although this varies depending on latitude and the season. At sunset, the first meal, called Iftar, is taken after a long day of fasting. Another meal, called Sahour, is usually taken just before commencing fasting of the next day at dawn, usually between 4 and 5 AM, but also depends on location and season. During the night between Iftar and Sahour, individuals are allowed to freely eat and drink. Fasting induces significant metabolic and physiological changes, including an increase in urea and uric acid, probably due to dehydration, an increase in high-density lipoprotein and apoprotein A1, and a decrease in low-density lipoprotein [1, 2]. It is also associated with circadian changes in body temperature, cortisol, melatonin, insulin, leptin, ghrelin, growth hormone, prolactin, sex hormones, and adiponectin [2-4].

Hypothyroidism is common, ranging between 0.2% and 1% in iodine-sufficient areas and 0.3% and 10.95% in iodine-deficient regions of the world [5-7]. The causes are many but the 2 most common causes are chronic autoimmune thyroiditis (Hashimoto thyroiditis) and thyroidectomy for different reasons [5-7]. Management is with levothyroxine (L-T4) replacement therapy [8]. L-T4 has a long half-life of about 7.5 days and is usually prescribed once per day on an empty stomach and to avoid food or drinks for at least 1 hour [8, 9]. The bioavailability of oral L-T4 is high, reaching about 85% to 90% [10]. Absorption is fast, occurring within about 1 hour after ingestion of the dose [10]. However, many factors may interfere with L-T4 absorption. These include food [11, 12],

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drugs such as calcium and iron tablets, sucralfate, proton pump inhibitors, and bile acid sequestrants [12, 13]. Other drugs modify L-T4 metabolism or protein binding and include anticonvulsants, aspirin, and furosemide, among others [14].

One of the issues that faces patients taking L-T4 during Ramadan fasting is the timing of the dose. While it is usually recommended that patients take L-T4 on an empty stomach and wait for about 1 hour before eating or drinking [8], it is not practical for fasting people to wait another hour after a long day of fasting. Different recommendations have been given, but none has been critically examined, and most of the previous studies were of retrospective nature, had low patient numbers, and/or chose complex L-T4 regimens [13, 15-25]. Therefore, we undertook this clinical trial to compare 2 practical approaches for L-T4 intake during Ramadan. Both of them do not entail waiting at the evening meal (Iftar).

Patients and Methods

This study was carried out at King Faisal Specialist Hospital & Research Centre (KFSHRC), Riyadh, Saudi Arabia, during the month of Ramadan 2023 (23 March-22 April 2023). The study was approved by the Office of Research Affairs and Ethical Committee of the KFSHRC (study # 2231063). Informed consents were obtained from the participants. Our primary objective was to compare 2 practical approaches for taking L-T4 during Ramadan fasting in maintaining euthyroidism in athyrotic patients who have hypothyroidism and are on stable doses of L-T4 replacement/suppressive therapy. Therefore, we randomized a cohort of patients with thyroid cancer who had total thyroidectomy and were taking L-T4 therapy for at least 6 months to 1 of 2 arms. Patients in arm A were instructed to take the pre-Ramadan L-T4 dose at the evening meal (Itfar) and eat immediately. Patients in arm B were asked to increase their pre-Ramadan dose by 25 µg if their regular L-T4 dose was ≤150 µg/day or by 50 µg if their pre-Ramadan dose was >150 µg/day and eat immediately (Fig. 1). To avoid complex calculations for patients, the increase in the L-T4 dose was empirically based on the previous L-T4 requirement.

Patients

We randomized patients ≥18 years old who underwent total thyroidectomy for thyroid cancer with or without radioactive iodine ablation at least 6 months before this study and were on stable doses of L-T4. We excluded (1) patients with severely abnormal thyroid function tests (TFTs) at the screening phase 4 to 6 weeks before Ramadan (thyrotropin [TSH] >10 mU/L [normal range 0.4-4.2 mU/L], free thyroxine [FT4] >30 pmol/L, and/or FT4 <8 pmol/L, [normal range 12-22 pmol/L]); (2) patients with progressive biochemically incomplete or structurally incomplete status at the time of randomization; (3) pregnant or lactating women; (4) patients with Hashimoto thyroiditis (since their remaining thyroid gland might still be partially functional); (5) patients with partial thyroidectomy only (since residual thyroid tissue is functional); (6) patients on drugs that interfere with thyroxine absorption, metabolism, or excretion; (7) patients who have malabsorption diseases such as celiac disease or short bowel syndrome; (8) patients who underwent any bariatric surgery; and (9) patients with significant comorbidities that may interfere with thyroxine dosing, absorption, or metabolism. This last group includes patients with stage II and above renal impairment, liver cirrhosis, congestive heart failure, chronic anemia (thalassemia, sickle cell anemia), connective tissue diseases, and those with active infections.

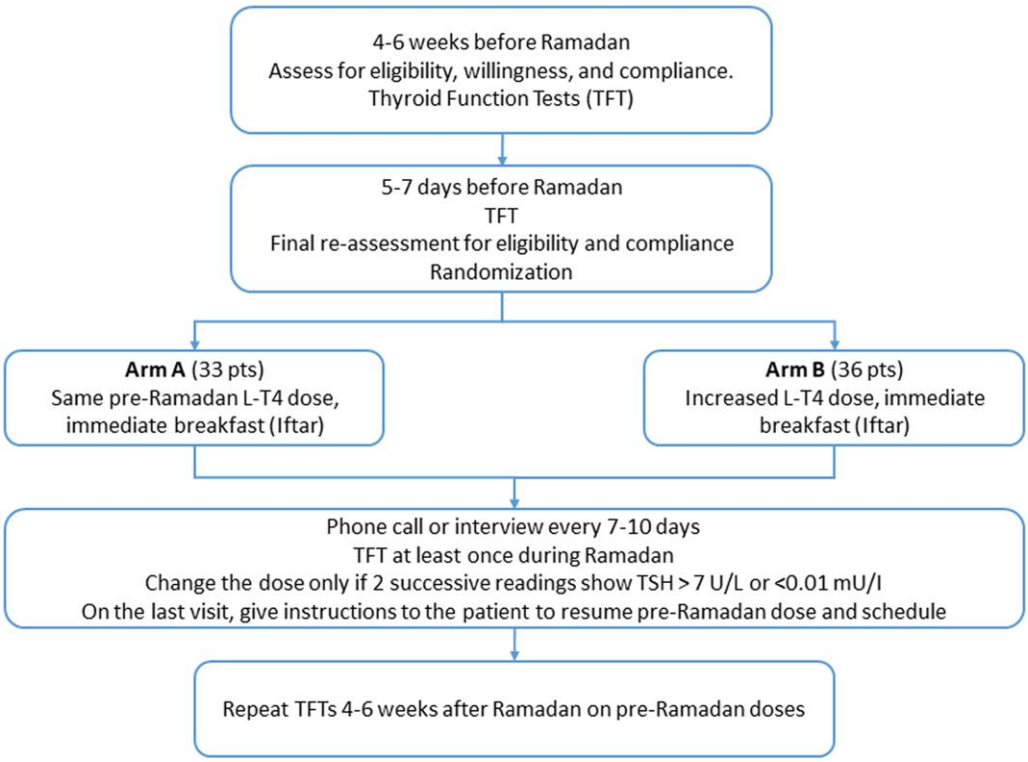

Figure 1. Flowchart of the study protocol.

Randomization

The needed sample size of the whole cohort was calculated to be 70 subjects (see statistical methods). We screened 90 patients and excluded 19 cases for various reasons including refusal to participate (11 patients), on interfering drugs (3 patients), or TFTs were significantly abnormal before Ramadan (5 patients). The remaining 71 patients were randomized to 1 of 2 arms (arm A or B). Two patients withdrew from the study after randomization, 1 from each arm. The remaining 69 patients (33 in arm A and 36 in arm B) completed this study (Fig. 1). After obtaining informed consent, patients were randomized using the random number generator of Stata software. To avoid unbalanced assignment of patients to treatment groups, we used the block randomization method. In this scheme, patients were grouped into several blocks of equal sizes according to their chronological entry time. The study was designed such that balance in the number of patients assigned to each treatment arm will be achieved at the end of each block of 10 patients.

Interventions

The flowchart of the study is shown in Fig. 1.

1. **Pre-Ramadan preparation:** Patients were interviewed 4 to 6 weeks before Ramadan to assess their eligibility and willingness to participate after a clear explanation of the protocol. TFTs that included TSH, FT4, and triiodothyronine were obtained to ensure euthyroidism or mild thyroid dysfunction (TSH <10 mU/L and FT4 <30 pmol/L and >8 pmol/L). If euthyroid, they were advised to be compliant with their current dose. If not, the dose was adjusted. Patients underwent TFTs and were interviewed again 5 to 7 days before Ramadan to ensure full understanding of the protocol and for randomization to either arm of the study.
2. **During Ramadan (study time):** The patients were contacted every 7 to 10 days to ensure compliance, answer patients' questions, and do TFTs. They were contacted or interviewed after each TFT to ensure compliance and to adjust the L-T4 dose if necessary. When TFT showed abnormalities (TSH outside the normal range), another set of TFTs was obtained within 2 days to confirm the changes in TFTs. if confirmed, the L-T4 dose was adjusted only if there were significant abnormalities (TSH >7 or <0.01 mU/L, repeated twice for confirmation within 2-3 days). TFTs were repeated during Ramadan as a precautionary measure to avoid severe changes in thyroid function and to interfere early if necessary.
3. **Post Ramadan:** TFTs were obtained at the end of Ramadan. L-T4 doses were adjusted if needed and the patients were instructed to resume their pretrial therapy schedule. For most patients, TFTs were also repeated 4 to 6 weeks after Ramadan.

Statistical Methods

We chose a repeated-measures design since it is powerful because using each subject as his or her own control reduces subject to subject variability. Initial TSH levels from a study by Al-Qahtani et al [15] were used to calculate the sample size. For treatment arms A and B, the baseline average TSH levels were assumed to be 1.8 mU/L in each group. We assumed that the variance of TSH will be 1.3 for the 2 groups at each of the TFT measurements, and that the correlation between the repeated measurements is 0.7. Using these parameters, the between-subject variance was calculated to be 0.1275 and the calculated total sample size to achieve a power of 80% was 70 subjects using a balanced design. The calculation and the statistical analysis were performed using Stata version 18. (Stata Statistical Software; StataCorp. 2023, College Station, TX).

Numerical values were expressed as mean ± SD or median (range) and were analyzed using a t test when normally distributed or Wilcoxon rank sum test when skewed. Categorical values were expressed as numbers, proportions, and percentages and analyzed using Fisher exact and chi-square tests. Statistical significance was set at $P = .05$.

Results

Patients

We randomized 71 patients who were eligible for inclusion in the study to arms A or B. Two patients withdrew from the study after randomization, 1 from each arm. The remaining 69 patients (33 in arm A and 36 in arm B) completed this study. These 69 patients with thyroid cancer (21 males, 48 females, with a median age of 44 years, range 21-75) had total thyroidectomy and were on stable L-T4 doses. The initial clinical, pathological, and laboratory characteristics of the 2 groups were comparable (Table 1).

Table 1. Clinical and laboratory characteristics of the 2 groups (arm A and arm B) of 69 thyroidectomized patients with thyroid cancer

Characteristic	Arm A[a] (n = 33)	Arm B[b] (n = 36)	*P* value
Age (mean ± SD) years	42.6 ± 11.3	47.2 ± 10.9	.09
Sex (female: male)	22:11	26:10	.81
BMI (kg/m^2)	30.4 ± 6	31.2 ± 6.5	.60
Thyroid cancer type (n)			
Papillary thyroid cancer	28	31	.52
Follicular thyroid cancer	1	2	
Oncocytic thyroid cancer	0	1	
Medullary thyroid cancer	4	2	
Current thyroid cancer status (n)			
Excellent response	18	22	.83
Indeterminate response	6	6	
Biochemically incomplete	5	3	
Structurally incomplete	4	5	
L-T4 dose before Ramadan (μg/day), mean ± SD	141.8 ± 28.7	137.1 ± 42.5	.59
TSH before Ramadan (mU/L) mean ± SD	1.94 ± 2.0	2.37 ± 3.7	.69
No. of patients with other comorbidities (DM, HTN, dyslipidemia, others)	10/33	14/36	.45

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; LT-4, levothyroxine; TSH, thyrotropin.
[a]Arm A: continued on the same LT-4 dose before the fasting month and broke their fasting immediately.
[b]Arm B: similar to arm A, but the LT-4 dose was increased by 25 μg if their pre-Ramadan dose was ≤150 μg/day and by 50 μg if the L-thyroxine daily dose was >150 μg daily

Comparison of the Primary Outcome of Arm A with Arm B

The primary objective of this study was to assess the effect of the 2 interventions in L-T4 dosing on thyroid status and TFTs at the end of Ramadan. At baseline (5-7 days before Ramadan), TFTs showed in arm A (total 33 patients), 20 (60.6%), 8 (24.2%), and 5 (15.2%) patients were euthyroid, subclinically hyperthyroid, or subclinically hypothyroid, respectively while in arm B (total 36 patients), the corresponding numbers were 18 (50%), 12 (33.3%), and 6 (16.7%) patients, respectively ($P = .65$ between the 2 arms). The mean ± SD TSH levels in arms A and B were 1.94 ± 2.0 mU/L and 2.37 ± 3.7 mU/L, respectively ($P = .69$) (Table 2). At the end of Ramadan (median duration between baseline and end of Ramadan TFTs 28 days); in arm A, 17 (51.5%) patients were euthyroid, 3 patients were subclinically hyperthyroid (9.1%), and 13 (39.4%) patients were subclinically hypothyroid. In arm B, 17 (47.2%) patients were euthyroid, 14 patients were subclinically hyperthyroid (38.9%), and 5 (13.9%) patients were subclinically hypothyroid ($P = .005$) (Fig. 2 and Table 2). The mean ± SD TSH levels in arms A and B at the end of Ramadan were 5.6 ± 6.0 mU/L and 1.67 ± 2.6 mU/L, respectively ($P = .0001$) (Table 2).

During the whole month of fasting, 9 patients needed adjustment of their L-T4 dose with all of them needing extra doses (when TSH >7 mU/L in 2 consecutive TFTs within 2 days). This L-T4 dose increase (25-37.5 µg increase in dose) was needed more in arm A (7/33, 21%) than in arm B (2/36, 5%) but did not reach statistical significance ($P = .08$).

Changes in Thyroid Function Over Time

To detect changes in thyroid unction early, TFTs were measured at 5 times points in this study, 4 to 6 weeks before Ramadan, 5 to 7 days before Ramadan, mid-Ramadan, 5 to 7 days within the end of Ramadan, and 4 to 6 weeks after Ramadan. The changes in TSH within each arm and between the 2 arms are shown in Table 3. The changes in thyroid status (euthyroid, subclinical hyperthyroidism, or subclinical hypothyroidism) at different time points are shown in Fig. 3. In arm A, compared with baseline values, there were significant changes in TSH at mid-Ramadan, end of Ramadan, and 4 to 6 weeks after Ramadan (Table 4). This was not the case in arm B, in which TSH values were not different at different time points (Table 4). TSH tended to decrease during Ramadan in arm B and to increase in arm A and these changes reached statistical

Table 2. Thyroid status and thyrotropin (TSH) levels before (baseline) and at the end of Ramadan fasting (post-intervention) in the 2 comparison groups (arm A and arm B)

	Arm A n (%)			Arm B n (%)		
Thyroid status	**Beginning of Ramadan**	**End of Ramadan**	***P* value**	**Beginning of Ramadan**	**End of Ramadan**	***P* value**
Euthyroid	20 (60.6)	17 (51.5)	0.2	18 (50.0)	17 (47.2)	.001
Subclinical hyperthyroidism	8 (24.2)	3 (9.1)		12 (33.3)	14 (38.9)	
Subclinical hypothyroidism	5 (15.2)	13 (39.4)		6 (16.7)	5 (13.9)	
TSH (mean ± SD) mU/L	1.94 ± 2.0	5.6 ± 6.0	0.001	2.37 ± 3.7	1.67 ± 2.6	.19

P values refer to the comparison of pre-Ramadan status with post-Ramadan status within each arm

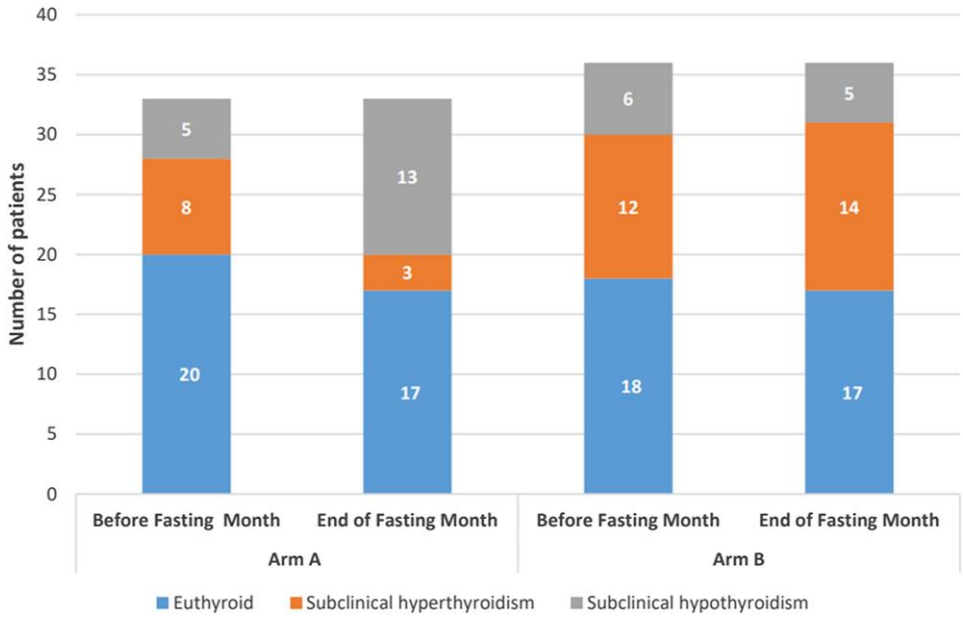

Figure 2. Changes in thyroid status from baseline (beginning of Ramadan) to after the intervention (end of Ramadan) in the 2 randomly assigned arms A and B. Arm A: no change in L-T4 dose and eating immediately after L-T4 intake; and arm B: increasing the dose and eating immediately after the L-T4 intake.

significance between the 2 arms at mid-Ramadan, end of Ramadan, and 4 to 6 weeks after Ramadan (Table 3). Thyroid status also showed a corresponding tendency toward euthyroidism or subclinical hyperthyroidism in arm B compared with a tendency toward subclinical hypothyroidism in arm A at the last 3 time points (mid-Ramadan, end of Ramadan, and 4-6 weeks after Ramadan). However, no overt hyperthyroidism or hypothyroidism was observed (Fig. 3). The changes per patient are shown in Table 5. In arm A, 15/33 (45.5%) patients remained in their pre-Ramadan status while the other 18 patients had different status. In arm B, 21/36 (58.3%) patients maintained their pre-Ramadan status while 15 patients changed their status. The difference between the 2 arms in the number of patients who maintained their thyroid status throughout Ramadan was not statistically different ($P = .28$)

Discussion

In this randomized clinical trial, we compared 2 regimens of L-T4 replacement in athyrotic patients who fasted during the month of Ramadan. In arm A, patients used their pre-Ramadan doses and ate immediately at Iftar. Arm B was similar to arm A but with an upward adjustment of the L-T4 dose. The 2 therapeutic approaches resulted in similar euthyroid rates at the end of Ramadan with maintenance of euthyroidism in about 50% of patients. However, there were more cases of subclinical hypothyroidism in arm A and subclinical hyperthyroidism in arm B. Patients in arm B (increasing L-T4 dose) achieved desirable levels of TSH (normal or slightly suppressed) in the majority of cases (86%) and might be a preferable approach, especially for patients who need TSH to remain in the low to suppressed levels (eg, differentiated thyroid cancer). Importantly, none of the patients in the 2 arms developed overt thyroid dysfunction. The results confirm the previously known negative effect of food intake on L-T4 absorption [12] even over a relatively short time (1 month) but also provide a method for dose adjustment that may allow patients to eat immediately at the time of evening meal (Iftar) during Ramadan without the need for abstinence of food and drinks for additional time after a prolonged period

Table 3. Comparison of thyrotropin (TSH) levels in the 2 arms at different time points of measurements

	Arm A		Arm B		
TSH measurements	**No.**	**Mean (SD)**	**No.**	**Mean (SD)**	**P**
TSH1 (4-6 weeks before Ramadan)	29	2.2 (2.4)	33	1.4 (1.5)	.26
TSH2 (3-5 days before Ramadan)	33	1.9 (2.0)	36	2.4 (3.7)	.70
TSH3 (mid-Ramadan)	33	5.3 (6.4)	33	3.9 (12)	.005
TSH4 (end of Ramadan)	33	5.6 (6.0)	36	1.7 (2.6)	.0001
TSH5 (4-6 weeks after Ramadan)	25	5.7 (10.8)	31	1.2 (1.3)	.01

TSH levels were compared using a 2-sample Wilcoxon rank-sum (Mann–Whitney) test.

Table 4. Wilcoxon signed-rank test *P* values for testing changes in thyrotropin (TSH) measurements over time within each arm of therapy

		Within arm B				
		TSH1	**TSH2**	**TSH3**	**TSH4**	**TSH5**
Within arm A	TSH1		.9704	.7208	.7163	.9916
	TSH2	.7011		.5872	.4103	.1628
	TSH3	**.0019**	**.0004**		.2849	.5942
	TSH4	**.0024**	**.0002**	.6745		.3993
	TSH5	.1808	.2021	.2387	.1162	

The off-diagonal is a comparison within arm B and below diagonal is the comparison within arm A. While no significant differences occurred in TSH in arm B, significant changes (in bold) in TSH occurred between TSH1 (4-6 weeks before Ramadan) TSH3 (mid-Ramadan), and TSH4 (end of Ramadan). Similarly, significant changes occurred between TSH2 (beginning of Ramadan) and TSH3 and TSH4 within arm A

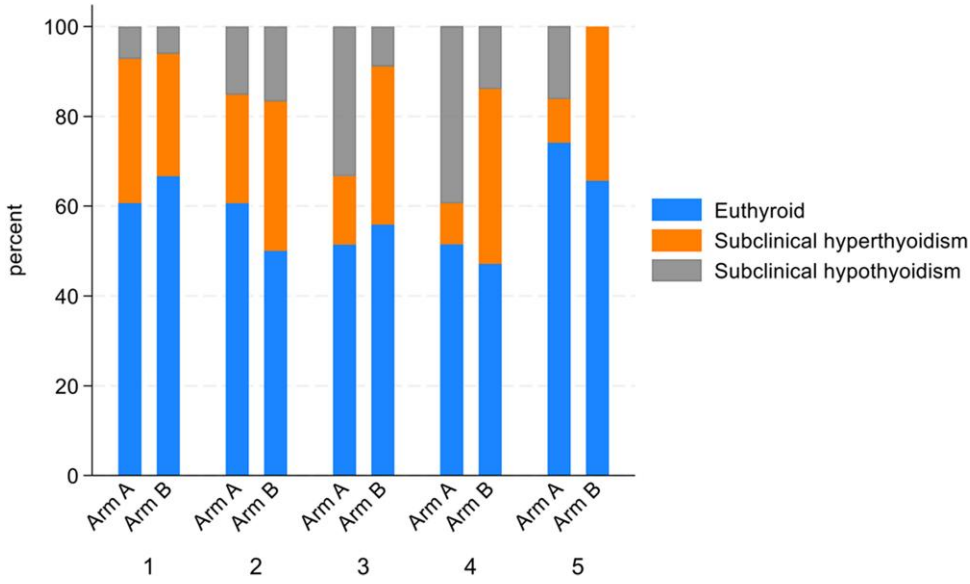

Figure 3. Changes in thyroid status over time. The times include (1) 4 to 6 weeks before Ramadan; (2) 5 to 7 days before Ramadan (baseline); (3) mid-Ramadan; (4) end of Ramadan, (5) 4 to 6 weeks after Ramadan.

Table 5. Changes in thyroid status between pre-Ramadan and the end of Ramadan in arm A and arm B

		End of Ramadan			
		SHyper	Euthyroid	SHypo	Total
Pre-Ramadan					
Arm A	SHyper	**10**	2	8	20
	Euthyroid	6	**1**	1	8
	SHypo	1	0	**4**	5
	Total	17	3	13	33
Arm B	SHyper	**10**	7	1	18
	Euthyroid	5	**7**	0	12
	SHypo	2	0	**4**	6
	Total	17	14	5	36

Arm A: In 15/33 patients (45.5%), thyroid status was maintained at the end of Ramadan to similar pre-Ramadan status (bolded numbers), and 20/33 patients (60.6%) achieved desirable thyroid status (euthyroid or subclinical hyperthyroidism since patients had differentiated thyroid cancer).
Arm B: 21/36 patients (58.3%) maintained their thyroid status at the end of Ramadan to the same status at the beginning of Ramadan (bolded numbers) and 31/36 patients (86%) achieved desirable thyroid status at the end of Ramadan (euthyroid or subclinically hyperthyroid since patients had DTC).
Abbreviations: SHyper, subclinical hyperthyroidism; SHypo, subclinical hypothyroidism

of fasting. It also shows the safety of both approaches without inducing overt thyroid dysfunction. An interesting observation is that the changes in thyroid dysfunction in the 2 arms persisted in some patients for 4 to 6 weeks after Ramadan, although all patients went back to their pre-Ramadan L-T4 doses and schedule. This might be due to the relative tissue levels of thyroid hormones that lingered behind the plasma levels. In other words, the concept of tissue hypothyroxinemia and hyperthyroxinemia is a possible explanation for this observation [26].

Many retrospective studies reported on L-T4 therapy during Ramadan in patients with hypothyroidism [16, 19, 21, 22, 24, 25]. El-Kaissi et al retrospectively analyzed a sample of 112 patients on L-T4 therapy for hypothyroidism [19]. They compared TSH within 3 months before Ramadan with TSH levels within 2 months after Ramadan. They found TSH after Ramadan to be significantly higher than pre-Ramadan levels. In a recent large retrospective observational study that included 481 patients on L-T4 therapy for hypothyroidism, TFTs within 3 months before Ramadan were compared with TFTs 1 to 2 weeks (PR1) and 3 months after Ramadan (PR2) [16]. TSH significantly increased from before Ramadan (a median of 2.0 [0.8-3.7] μIU/mL to 2.9 [1.4-5.6] μIU/mL at PR1; $P < 0.001$). This was accompanied by a fall in FT4 and free triiodothyronine at PR1 ($P < .001$) [16]. Our study supports these previous observations in that patients in arm A who were kept on the same pre-Ramadan doses and ate immediately tended to drift to the hypothyroid side with increasing TSH and more patients developing subclinical hypothyroidism.

A few randomized studies were carried out, but they have some shortcomings making their conclusion questionable. Dabbous et al ran an open-label, randomized prospective trial in which 50 patients with hypothyroidism took L-T4 at Iftar and waited for 30 minutes before breaking their fasting, and 46 patients with hypothyroidism took their L-T4 30 minutes before Sahour [17]. TSH increased in both groups compared with baseline levels at the beginning of Ramadan but there were no differences in TSH levels between the 2 groups at the end of Ramadan. However, only 41.6% and 35.7% of patients in the 2 groups were compliant with the instructions of when to take L-T4 [17]. In our study, we have taken extra steps to ensure compliance by contacting patients every 7 to 10 days and obtaining TFTs at least once during Ramadan.

In another randomized prospective trial, patients with hypothyroidism on stable L-T4 were randomized to 3 groups: group 1 (50 patients) to take L-T4 at Iftar and wait for 30 minutes before eating; group 2 (46 patients) to take L-T4 at least 3 hours after Iftar; and group 3 (52 patients) to take L-T4 30 minutes before Sahour [18]. The results suggested that group 1 (taking L-T4 before Iftar and waiting 30 minutes before eating) was associated with the slightest changes in TSH compared with the other 2 groups [18]. In contrast to this trial, which entails waiting for at least 30 minutes after taking L-T4 at Iftar, the approaches we tested in our study focused on practicality and convenience for the patients, since waiting further after a long day of fasting is a significant burden on patients.

In a recent randomized controlled trial in patients with prior total thyroidectomy, 48 patients with hypothyroidism received L-T4. They waited for 30 minutes after Iftar (group A), 47 patients ingested their L-T4 dose 3 hours after Iftar (group B), and 47 patients ingested their L-T4 dose 1 hour before Sahour (group C) [15]. Significant numbers of patients dropped out, with final numbers of 31, 34, and 22 in the 3 groups, respectively. TSH and FT4 were measured 2 weeks before and 2 weeks after Ramadan [15]. Group A had no significant changes in TSH while groups B and C both had significant increases in post-Ramadan TSH compared with pre-Ramadan [15]. Similar to all previous trials, practicality is lacking in this trial and our study suggests that this waiting time could be avoided with a minor increase in the daily dose of L-T4 during Ramadan.

The studies discussed above are either of low-level evidence or suffer from some design issues. The retrospective studies are primarily of small convenience samples reporting unmonitored observations. For that reason, the results are heterogeneous. Although 3 randomized trials have been reported, all of them suffer from shortcomings, including infrequent measurements of TFTs, no monitoring and reinforcement of the L-T4 dosing schedule to patients, and significant dropouts. Their results are significantly different, pointing to some issues in their design and conduction, resulting in heterogeneous and inconsistent results. Therefore, the question of when and how to prescribe L-T4 during Ramadan remains unanswered. The current trial avoided some of the flaws of the previous ones. We chose a homogeneous group of patients from our routinely followed patients with thyroid cancer to avoid the endogenous contribution of the remaining thyroid tissue in patients who did not have thyroidectomy (eg, Hashimoto thyroiditis) or only partial thyroidectomy. We also implemented frequent monitoring of TFTs, regular communications with the patients, and reinforcement of compliance with the dose schedule. Certain weaknesses are worth highlighting. Not all patients were completely euthyroid at the beginning of Ramadan. However, none had severely abnormal thyroid function abnormalities. Patients who were not euthyroid were mostly subclinically hyperthyroid as part of their thyroid cancer management protocol and some were subclinically hypothyroid. This spectrum of thyroid function reflects real-life situations and may lend strength to the study. This study was also conducted in athyrotic patients with thyroid cancer and its results may not be generalizable to the general population of patients with hypothyroidism, the majority of whom have Hashimoto

thyroiditis. However, we aimed to decrease the heterogeneity of patients included and avoid any endogenous contribution from remaining thyroid tissue in patients with Hashimoto thyroiditis and patients who had partial thyroid surgery. Another weakness in this study is the nonavailability in most patients of weight changes at the end of Ramadan because of Ramadan fasting. This could have an impact on the L-T4 dose. However, changes in weight during Ramadan are usually minimal [27]. In a meta-analysis that included more than 7000 participants, the median weight loss by the end of Ramadan was only −1.12 kg (95% CI −1.89 to −0.36) [27]. This weight loss is unlikely to be of clinical importance for the L-T4 dose. Finally, there was no formal assessment of the quality of life improvement with these regimens, although the majority of patients reported more satisfaction than the L-T4 intake methods they were following in previous years.

In conclusion, we tested 2 practical approaches of L-T4 therapy for hypothyroidism during Ramadan fasting that allow patients to take L-T4 and eat immediately. None of these approaches resulted in clinically significant changes in thyroid function and were mostly associated with euthyroidism or mild subclinical thyroid dysfunction. The second approach with an increase in the daily L-T4 dose by 25 to 50 µg (depending on the pre-Ramadan dose) during Ramadan and eating immediately at Iftar seems to be more optimal and practical for patients with hypothyroidism, especially those who need TSH to be on the low side or slightly suppressed, such as patients with differentiated thyroid cancer. However, further studies with larger samples are needed to support this conclusion.

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Disclosures

All authors have no conflict of interest or disclosures related to the work described in this article.

Data Availability

Original data generated and analyzed during this study are included in this published article.

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