

Twice or Thrice Weekly versus Daily Thyroxine in Hypothyroid Fasting Ramadan: A Pilot Study

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Abstract

Context: Hypothyroid patients require to take levothyroxine (L-T4) on an empty stomach, 60 min before next meal which is difficult to achieve while fasting Ramadan, on a daily basis. This pilot study aimed to assess the effect of twice or thrice weekly versus standard daily L-T4 dosing during Ramadan on adherence, post-Ramadan TSH, and thyroid status. **Methods and Materials:** The study included 2 groups; group 1 included 11 patients assigned to take L-T4 twice or thrice a week, and group 2 included 113 patients assigned to take L-T4 daily. Patients chose between three L-T4 regimens: regimen 1 – 60 min before Iftar; regimen 2 – 60 min before Suhor, on empty stomach for 3–4 h; regimen 3 – before the next fast, on empty stomach for 3–4 h. Thyroid status was assessed before and within 6 weeks after Ramadan. Only euthyroid patients were included. **Results:** No significant differences between the two groups regarding adherence, post-Ramadan TSH, or post-Ramadan thyroid status. 90.9% in group 1 and 88.5% in group 2 were adherent [$p = 1.000$]. Post-Ramadan TSH in group 1 was 1.9 ± 1.5 mIU/L, in group 2 was 2 ± 1.6 mIU/L [$p = 0.809$]. 81.8% in group 1 and 82.3% in group 2 were euthyroid post-Ramadan [$p = 0.209$]. **Conclusions:** In this pilot study, taking L-T4 twice or thrice weekly during Ramadan achieved similar adherence and metabolic control to standard daily L-T4, making it an easier option for hypothyroid patients wishing to fast Ramadan.

Keywords: Daily, levothyroxine, Ramadan, weekly

INTRODUCTION

Adherence is a major issue in levothyroxine (L-T4) treatment in hypothyroid patients. Adherence to L-T4 is a major determinant in achieving and maintaining target TSH.^[1] Nonadherence to L-T4 can be as high as 52% after one year of treatment in a database of more than half a million users of L-T4.^[2]

Nonadherence – among other factors – is due to having to take L-T4 daily, on empty stomach, 60 min before next meal or beverages.^[3,4] This is especially true in hypothyroid patients fasting Ramadan. Nonadherence to L-T4 during Ramadan can be as high as 75%.^[5]

Half-life of levothyroxine is 7 days for euthyroid, and up to 9 days for hypothyroid patients.^[3] Since T4 is a prohormone that is converted to the active T3 or the inactive reverse-T3 peripherally through deiodinases, an autoregulation of this conversion exists. Meaning that, if T4 is increased, preferential conversion to r-T3 occurs to prevent thyrotoxicosis, and if T4 is decreased, preferential conversion to T3 occurs to prevent

hypothyroidism.^[6,7] Based on these two facts, once, twice, or alternate day dosing of L-T4 has been tested in hypothyroid patients versus standard daily dosing.^[3,6-11]

Once weekly L-T4 was reported to be well tolerated and safe alternative to standard daily L-T4, with no adverse events reported in five studies using hyperthyroid symptom score and echocardiographic evaluation.^[3,6-9] One study reported better quality of life using once weekly versus daily L-T4.^[6] Although TSH showed a mild increase with once weekly dosing, it remained within normal range after 6 weeks of treatment.^[3,6] Overall, it was efficacious and safe alternative to daily L-T4.^[3,6-9]

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Submitted: 01-Jan-2022

Revised: 25-Jan-2022

Accepted: 22-Apr-2022

Published: 04-Aug-2022

Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/ijem.ijem_1_22

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How to cite this article: Elsherbiny TM. Twice or thrice weekly versus daily thyroxine in hypothyroid fasting Ramadan: A pilot study. Indian J Endocr Metab 2022;26:265-8.

Twice weekly L-T4 for 10 weeks and alternate day L-T4 for 3 months was also well tolerated, with no hyper- or hypothyroid symptoms, and TSH showed a slight increase but was maintained within normal range.^[10,11]

This is a pilot study aiming to report the effect of twice or thrice L-T4 during Ramadan, as an easier alternative, on adherence and thyroid status after Ramadan compared to standard daily dosing.

SUBJECTS AND METHODS

This was a prospective study including Muslim hypothyroid patients willing to fast Ramadan during the year 2020 attending endocrinology outpatient clinic, Alexandria faculty of medicine, Alexandria university, Egypt. All included patients were euthyroid, and stable on the same L-T4 dose for at least 3 months before the start of Ramadan. Exclusion criteria were thyroid cancer patients requiring suppressive therapy, central hypothyroidism, pregnancy, coronary heart disease, arrhythmia, chronic heart failure, liver cirrhosis, renal failure, acute medical, or surgical illness at the time of evaluation to avoid acute and chronic non-thyroidal illness syndromes. All patients were explained the nature and aim of the study and signed an informed written consent. The protocol of the study was approved by the ethical committee of Alexandria faculty of medicine [IRB number 12098].

Recruited patients were divided into two groups. Group 1 included 11 patients who were switched at the beginning of Ramadan from standard daily L-T4 to twice or thrice weekly dosing. Their weekly dose was divided equally into two or three doses, given at two or three successive fixed days of the week, Saturdays, Sundays, and Mondays. These days were chosen specifically to avoid family gatherings usually taking place at weekends, Thursdays, and Fridays.

Group 2 included 113 patients who continued to take L-T4 on standard daily basis. Patients from both groups were free to follow one of three L-T4 regimens during Ramadan, explained in detail previously.^[12] In short, regimen 1: to take L-T4 60 min before Iftar and beverages, regimen 2: to take L-T4 3–4 h after Iftar, 60 min before Suhor meal, regimen 3: to take L-T4 before the start of next fast 3–4 h after an early Suhor at midnight. If patients mixed between regimens 1 and 2, this was labeled regimen 4.

Adherence was assessed by interviewing participants during post-Ramadan visit. Nonadherence was defined as stopping food and beverages for less than 3 h before L-T4 tablet(s) or stopping food and beverages for less than 45 min after L-T4 tablet(s). Patients who skipped L-T4 treatment for 2 or more days without making up for their missed doses were excluded from the study.

Thyroid status was assessed for recruited patients in pre-Ramadan visit using Thyroid Stimulating Hormone (TSH). The institution uses electrochemiluminescence immunoassay [ECLIA] on Cobas e 411 (Roche Diagnostics

GmbH, Mannheim, Germany). Patients were considered euthyroid when TSH was 0.3–4 mIU/L for patients less than 70 years of age, and 1–5 mIU/L for patients more than 70 years of age according to ETA recommendations.^[13]

Thyroid status was reassessed in post-Ramadan visit using TSH, provided that this visit comes within 6 weeks from the end of Ramadan. Patients were excluded from the study if post-Ramadan visit was delayed beyond 6 weeks after Ramadan or if they did not report TSH during post-Ramadan visit.

STATISTICAL METHODS

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov was used to verify the normality of distribution of variables, Comparisons between groups for categorical variables were assessed using Chi-square test (Fisher or Monte Carlo). Mann–Whitney test was used to compare between two groups for not normally distributed quantitative variables. Kruskal–Wallis test was used to compare different groups for abnormally distributed quantitative variables and followed by Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. Spearman coefficient was used to correlate between quantitative variables. Significance of the obtained results was judged at the 5% level.

RESULTS

Baseline characteristics

There were no significant differences regarding demographic and pre-Ramadan biochemical data in both studied groups. Most patients in both groups were females, 90.9% of group 1 and 94.7% of group 2 [$P = 0.487$]. Mean age in group 1 was 33.5 ± 12.7 years and in group 2 was 42.2 ± 14.3 years [$p = 0.094$]. All included patients in both groups were euthyroid pre-Ramadan, mean TSH in group 1 was 1.7 ± 0.74 mIU/L and in group 2 was 1.7 ± 1.01 mIU/L [$P = 0.775$] [Table 1].

Main outcomes: Preference, adherence, and thyroid status

L-T4 regimen preferences in group 1 were 72.7%, 9.1%, 9.1%, and 9.1% for regimens 1, 2, 3, and 4, respectively. L-T4 regimen preferences in group 2 were 37.2%, 46.9%, 3.5%, and 12.4% for regimens 1, 2, 3, and 4, respectively. Group 1 preferred regimen 1 significantly more than group 2 [$P = 0.03$] [Table 2].

No significant difference was observed between the two studied groups regarding adherence to L-T4 regimens, 90.9% of group 1 patients were adherent versus 88.5% in group 2 [$P = 1$] [Table 2].

Most patients in both groups were still euthyroid post-Ramadan, 81.8% of group 1 versus 82.3% of group 2, without significant difference in between groups [$P = 0.209$]. Post-Ramadan

Table 1: Baseline characteristics of the two studied groups

	Group I (n=11)	Group II (n=113)	Test of Sig.	P
Sex				
Male	10 (90.9%)	107 (94.7%)	$\chi^2=0.269$	^{FE} $P=0.487$
Female	1 (9.1%)	6 (5.3%)		
Age				
Mean±SD.	33.5±12.7	42.2±14.3	U=431.0	0.094
Median (Min. – Max.)	38 (12-52)	40 (9-71)		
Pre-Ramadan TSH			U=589.0	0.775
Mean±SD.	1.7±0.74	1.7±1.01		
Median (Min. – Max.)	1.9 (0.39-2.7)	1.5 (0.31-4)		

SD: Standard deviation U: Mann–Whitney test. χ^2 : Chi square test. P : P value for comparing between the studied groups. Group I: Twice Thrice Weekly L-T4 regimen. Group II: Standard daily L-T4 dosing

Table 2: Adherence, preference, post-Ramadan TSH, and thyroid status in both studied groups

	Group I (n=11)	Group II (n=113)	Test of Sig.	P
Adherence				
Non-adherent	1 (9.1%)	13 (11.5%)	$\chi^2=0.058$	^{FE} $P=1.000$
Adherent	10 (90.9%)	100 (88.5%)		
L-T4 Regimen preference				
1	8 (72.7%)	42 (37.2%)	$\chi^2=7.947^*$	0.030*
2	1 (9.1%)	53 (46.9%)		
3	1 (9.1%)	4 (3.5%)		
4	1 (9.1%)	14 (12.4%)		
Post-Ramadan TSH				
Mean±SD.	1.9±1.5	2±1.6	U=594.0	0.809
Median (Min. – Max.)	1.6 (0.17-4.5)	1.6 (0.01-8.8)		
Post-Ramadan Thyroid status				
Under-treated	0 (0%)	12 (10.6%)	$\chi^2=2.358$	0.209
Euthyroid	9 (81.8%)	93 (82.3%)		
Over-treated	2 (18.2%)	8 (7.1%)		

* Statistically significant at P value < 0.05. SD: Standard deviation U: Mann–Whitney test. χ^2 : Chi square test. FE: Fisher Exact. P : P value for comparing between the studied groups. Group I: Twice Thrice Weekly L-T4 regimen. Group II: Standard Daily L-T4 dosing

TSH was 1.9 ± 1.5 mIU/L for group 1 versus 2 ± 1.6 mIU/L for group 2, without significant difference in between groups [$P = 0.809$] [Table 2].

Fasting Ramadan in both groups did not significantly increase post-Ramadan TSH relative to pre-Ramadan TSH. In group 1, post-Ramadan TSH was 1.9 ± 1.5 mIU/L versus 1.7 ± 0.74 mIU/L pre-Ramadan [$P = 0.722$], while in group 2, post-Ramadan TSH was 2 ± 1.6 mIU/L versus 1.7 ± 1.01 mIU/L pre-Ramadan [$P = 0.352$]. There was

no relation between adherence to, nor preference of L-T4 regimens and post-Ramadan TSH in both groups.

DISCUSSION

The present study shows that taking L-T4 twice or thrice weekly during Ramadan resulted in similar rates of adherence and post-Ramadan euthyroidism compared to standard daily L-T4 dosing.

High rates of adherence to L-T4 regimens were observed in both groups, 90.9% in group 1 and 88.5% in group 2 without significant difference, which are higher than reported rates of adherence in Ramadan in literature. An adherence rate of 82% was previously reported by our institution in Ramadan 2018 and 2019 using the same L-T4 regimens used in the present study.^[12] Karoli *et al.*^[5] reported that only 25% of their patients adhered to stopping food 2 h before bedtime L-T4 dosing, while Sheikh *et al.*^[14] and Dabboos *et al.*^[15] reported rates of adherence between 65% and 75%.

Also, high rates of post-Ramadan euthyroidism were maintained in both groups, 81.8% in group 1 and 82.3% in group 2 without significant difference, which is also higher than reported rates of post-Ramadan euthyroidism in literature. Post-Ramadan euthyroidism rate of 74% was previously reported by our institution in Ramadan 2018 and 2019 using the same L-T4 regimens used in the present study.^[12] Sheikh *et al.*^[14] and El-Kaissi *et al.*^[16] reported post-Ramadan dysthyroidism in 44% and 32%, respectively.

Once weekly L-T4 was shown to improve thyroid function tests in treatment resistant hypothyroid patients both in short and long term whether supervised or unsupervised.^[8] Alternate day L-T4 dosing was also shown to be effective and safe in maintaining euthyroidism.^[11] Twice weekly L-T4 taken at weekend and mid-week raised concerns of increased markers of bone turn over, that is why in the present study, those assigned to twice weekly L-T4 were dosed on two consecutive days “Saturdays and Sundays” which is much similar to once weekly dosing which was proven safe regarding bone parameters.^[7,8,10]

Limitations of the present study include the small number of recruited patients in the twice/thrice weekly L-T4 arm, and lack of thyroid testing during Ramadan especially at the start and end of dosing intervals.

In conclusion, the present study shows that twice or thrice weekly L-T4 dosing during Ramadan achieves similarly high rates of adherence and post-Ramadan euthyroidism to standard daily L-T4 dosing, but with more convenience and less dosing frequency. A larger study is planned to confirm presented results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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