

Comparison of Two Timings of Levothyroxine Intake in Hypothyroid Patients: A Cross-over Randomized Control Trial

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Study Protocol

Although optimal levothyroxine absorption occurs when taken on an empty stomach, current guidelines generally recommend treatment intake either 30 minutes before breakfast or at bedtime, at least three hours after the evening meal. Restricting intake to these two timings can be challenging for patients, resulting in a lower adherence and lack of TSH control. Offering an alternative timing of intake could provide better flexibility and improve TSH control and patients quality of life by adapting the treatment to the patient's lifestyle.

To our knowledge, the only study that compared a morning fasting intake to a three-hours-after-breakfast intake didn't find any significant difference in TSH levels. The objectives of our study are to confirm TSH stability between these two treatment schedules, and to assess treatment adherence, quality of life, and patient preference for each timing of intake.

We will perform a randomized open-label crossover trial including patients aged between 18 and 65 years, diagnosed with primary hypothyroidism for at least one year, taking a stable levothyroxine dosage for at least six months, and with TSH levels within the target.

Participants will be randomized to start with one of two sequences:

1. **Fasting state:** 30 minutes before breakfast
2. **Post-breakfast state:** 3 hours after breakfast **and at least** 30 minutes before the next meal

After a 6-week period, participants will crossover to the alternate intake timing for another 6 weeks. At the end of each 6-week sequence, TSH levels, quality of life, and treatment adherence will be evaluated.

There is no washout period, as patients must remain on continuous levothyroxine therapy

Statistical analysis plan

1)Sample size :

A pilot study including the first 24 patients was conducted to estimate the required sample size based on intra-individual TSH variability. The calculation was performed considering a two-sided significance level of 5% ($\alpha = 0.05$), a statistical power of 90% ($1 - \beta = 0.90$), and a minimum clinically relevant difference in TSH levels of 1 μ IU/mL.

The standard deviation of TSH levels in the pilot study was 2.97 μ IU/mL for fasting intake and 3.66 μ IU/mL for three-hours after breakfast intake. After accounting for an anticipated 20% patient drop-out rate, the target sample size is 113 patients.

Primary statistical analysis will be performed on an intention-to-treat basis. TSH variation between the two timings of intake will be analyzed using a linear mixed-effects model accounting for period, sequence and treatment effect. Bonferroni corrections will be applied for repeated measures.

2) Secondary outcomes

Secondary outcomes, including treatment adherence, quality of life (QoL) will be evaluated at the end of each 6-week treatment period.

- Treatment Adherence: Adherence scores will be reported as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR), depending on data distribution. Comparisons between the two intake schedules will be performed using a paired t-test or a Wilcoxon signed-rank test.
- Quality of Life: Changes in overall and dimension-specific quality of life scores between periods will be evaluated using linear mixed-effects models or paired non-parametric tests as appropriate.

3) Missing Data Handling

Every effort will be made to minimize missing data through close patient follow-up.

- Primary Analysis: The linear mixed-effects model used for the primary outcome (TSH levels) inherently handles data missing at random (MAR) under maximum likelihood estimation, allowing all randomized patients with at least one post-baseline measurement to be included in the intention-to-treat (ITT) analysis.
- Drop-out Patterns: Reasons for withdrawal or loss to follow-up will be documented and compared between treatment sequences to assess potential attrition bias.

-Participants who refuse blood sampling, withdraw consent or are lost to follow-up, due to or personal preference will be categorized as "Early Study Discontinuations / Drop-outs".

-If a participant alters their assigned intake timing or discontinues therapy during the first treatment sequence, the steady-state conditions required for biological evaluation are violated. To maintain data integrity and avoid unnecessary procedures, the investigator will formally discontinue the participant from the study prior to the crossover phase. They will be categorized as "Investigator-initiated assessment cancellation due to major schedule deviation"

4) Analysis Populations

- Modified intention-to-Treat (mITT) Population: The primary efficacy analysis will be conducted on the mITT population, defined as all randomized patients who completed baseline assessments and had at least one valid post-baseline TSH measurement, with the exceptions of exclusion criteria that may significantly change the interpretation of TSH levels (i.e treatment discontinuation, intercurrent condition)

- Per-Protocol (PP) Population: A secondary sensitivity analysis will be performed on the PP population, including all mITT patients without any protocol violations. The PP population includes patients with a perfect adherence score, with a respect for the schedule of levothyroxine intake during all days of the study.

Adverse events (AEs) and symptoms of hypo- or hyperthyroidism will be monitored and recorded at each clinical visit.

No interim analysis is planned for this study. The trial will proceed to full completion, unless major adverse events arise, requiring early termination by the principal investigator.

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. The protocol and informed consent form have been reviewed and approved by the Rabta Hospital ethics committee (CERB 23/2025). Written informed consent will be obtained from all participants prior to enrollment.

Data Management and Confidentiality

All participant data will be pseudonymized using unique identification codes to ensure confidentiality. Data will be entered into a secure, password-protected electronic database accessible only to authorized study personnel.