# Postponing breakfast in patients using levothyroxine: old-fashioned?

Published: 24-04-2023
Last updated: 18-07-2024

Primary Objective:To investigate whether there is a difference in the number of participants that will reach optimal LT4 supplementation (i.e. stability of TSH levels and symptoms) in the breakfast group compared to the fasting group.Secondary…

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Thyroid gland disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53296

**Source**
ToetsingOnline

**Brief title**
INFINITY

### Condition

- Thyroid gland disorders

**Synonym**
''Hypothyroidism'' or ''underactive thyroid''

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Zuyderland Medisch Centrum
**Source(s) of monetary or material Support:** Zuyderland Medisch Centrum (perifeer ziekenhuis)

## Intervention

**Keyword:** Breakfast, Fasting, Hypothyroidism, Levothyroxine (LT4)

## Outcome measures

### Primary outcome

The main study endpoint will be the percentage of participants in whom two, consecutive predefined stable TSH levels will be reached when LT4 is ingested with breakfast after LT4 dose adjustments (*the breakfast group*). This will be compared with the number of participants which reach two, consecutive stable TSH levels when LT4 is ingested at least 30 minutes before breakfast (*the fasting group*). A *stable* TSH level will be defined as a maximum deviation of plus or minus 1 mIU/L compared to the TSH level at baseline of that specific participant. Any notable differences between different levothyroxine brands will be tracked.

### Secondary outcome

Secondary study endpoints will be percentages of reported yes or no answers to the questions *Are you feeling better today compared to twelve weeks ago?* and 'Do you or would you prefer LT4 intake with breakfast?'. We would like to investigate whether a self-reported well-being is associated with participant*s TSH levels and whether it is associated with taking LT4 with or without breakfast. Besides that, another secondary study endpoint will be the number of participants of the breakfast group that were able to continue LT4 intake with breakfast after a follow-up period of six and twelve months. Furthermore, changes in body weight, glucose and lipid levels will be collected for future research purposes to investigate the effect of LT4 intake with breakfast on

metabolic factors since patients with hypothyroidism have a higher prevalence

of metabolic syndrome including dyslipidaemia, diabetes and obesity.

# Study description

### Background summary

Levothyroxine (LT4) must be taken on an empty stomach 30-60 minutes before breakfast to ensure adequate intestinal absorption. However, for many patients delaying breakfast is challenging. Taking LT4 with breakfast would be a more convenient option, but this may result in reduced LT4 absorption. This will subsequently lead to under-replacement of thyroid hormones and thus a risk of developing hypothyroidism measured as an increase in serum thyroid stimulating hormone (TSH) levels. Yet, we hypothesize that this can be avoided by increasing the LT4 dose, which could enable patients to take LT4 during breakfast.

### Study objective

Primary Objective:
To investigate whether there is a difference in the number of participants that will reach optimal LT4 supplementation (i.e. stability of TSH levels and symptoms) in the breakfast group compared to the fasting group.

Secondary Objectives:
- To investigate whether reached TSH levels and taking LT4 with or without breakfast are associated with a self-reported well-being of the participant for both the breakfast and fasting group.
- To investigate whether participants of the breakfast group have been able to continue LT4 intake with breakfast after a follow-up period of six and twelve months.
- To investigate the effect of taking LT4 with or without breakfast on metabolic factors (such as body weight, glucose tolerance and lipid levels) for future research purposes.

### Study design

An open-label, randomized controlled pilot study in which patients with hypothyroidism treated with LT4 visiting the internal medicine outpatient clinic of our hospital (Zuyderland Medical Center, the Netherlands) on a scheduled appointment because of thyroid or non-thyroid related pathology will be invited to participate in this study. Moreover, patients who gave consent to contact them for future studies during a prior questionnaire study will be

invited as well. Eligible participants who had two consecutive TSH levels (the most recent available TSH and TSH at t=0 weeks) in the reference range before study enrolment will enter the study and will be randomized either to the breakfast group or to the fasting group. Participants who had one or two TSH levels outside the reference range before study enrolment, will first enter a run-in period of maximum three months to achieve a TSH level within the normal range before entering the study. Participants who do not achieve a TSH level within the normal range during the run-in period, are not eligible for this study and will be excluded. When participants of the breakfast group reach two, consecutive stable TSH levels (defined as a maximum deviation of plus or minus 1 mIU/L compared to TSH level at baseline of that specific participant) after LT4 dose adjustments with an interval of six weeks, their study period ends and they can continue LT4 ingestion with breakfast. When participants of the fasting group reach two, consecutive stable TSH levels with an interval of six weeks, their study period also ends and they have to continue fasting ingestion of LT4. The study period will thus take at least three months (t=0, t=6 and t=12 weeks), but can be longer for participants in whom TSH levels remain outside the predefined stable range (t=18 or t=24 weeks). Participants in whom TSH levels remain outside the predefined reference range after six months of LT4 with breakfast ingestion, despite LT4 dose optimalisation (at t=6, t=12, t=18 and t=24 weeks), have to go back to the fasting regimen. Their study period will end when normal TSH levels are reached under the conventional fasting regimen. For participants of the breakfast group follow-up will take place after six and twelve months to investigate how many of them have been able to continue LT4 intake with breakfast.

### Intervention

Participants of the intervention group have to take their LT4 with breakfast after a minimum dose increase of LT4 (*the breakfast group*), while participants of the control group have to take their LT4 conventionally on an empty stomach at least 30 minutes prior to breakfast (*the fasting group*). The intervention will be an alteration of the timing of levothyroxine ingestion from fasting intake to intake with breakfast for participants of the breakfast group. It will thus be an alteration in the behavior for participants of the breakfast group. Furthermore, for participants of the breakfast group a minimal dose increase of 15% relative to their levothyroxine dose at baseline will be performed to correct for impaired levothyroxine absorption. LT4 dose adjustments will be performed if necessary based on blood results in both the breakfast and the fasting group.

### Study burden and risks

We do not expect that alterting the timing of LT4 ingestion for participants of the breakfast group will be a significant burden. A burden for participants of both groups can be that participants have to physically visit our hospital at

least three times and that blood samples will be drawn at least three times. Besides that, a smaller burden can be that during the study participants will be asked to keep a small food diary in which they have to report daily the timing of their LT4 ingestion and the timing of their breakfast and they have to report whether their breakfast consisted of certain food or beverages (dairy products with calcium, coffee, fiber or soy products) during 12 weeks.

Theoretically there can be a risk of overreplacement of LT4. Previous study results showed that LT4 ingestion with breakfast will lead to an impaired LT4 absorption measured as increased TSH values (of approximately 0.99 - 1.87 mIU/L), although mean TSH values remained within the therapeutic range. To avoid the occurrence of under-replacement and thus hypothyroidism, we will perform a minimum LT4 dose increase of 15% relative to their own dose (rounded to the nearest, available LT4 dosage) at baseline only for participants of the breakfast group. Theoretically there can be a very small risk of over-replacement of LT4 and thus developing mild hyperthyroidism for participants of the breakfast group. A possible, non-expected consequence of over-replacement is a non-well feeling of the participant due to hyperthyroid symptoms (such as: nervousness, palpitations, weight loss, increased bowel movements, diarrhea). Although when LT4 dose is not increased at baseline, participants will have a much higher risk of developing hypothyroidism by expected malabsorption of LT4. Besides that, participants will be strictly controlled within a short interval of only six weeks thus when a participant develops biochemical hyperthyroidism, a decrease in LT4 dose can be very rapidly performed. Participants will also be instructed to contact us directly when they experience signs indicating hypo- or hyperthyroidism.

## Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- age of 18 years or older.
- (subclinical) hypothyroidism of any underlying cause (except the diagnoses mentioned in exclusion criteria) including hypothyroidism after thyroid surgery because of low risk thyroid carcinoma.
- receive current treatment with levothyroxine (LT4) in a dose of at least 1.0 mcg/kg.
- use breakfast on >5 days per week.
- is able to give written informed consent.
- masters a language in which sufficient communication can take place with the members of the research team.

## Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- immune-therapy mediated hypothyroidism.
- central hypothyroidism.
- high risk thyroid carcinoma.
- being pregnant or having a wish to become pregnant during the study period.
- having serious or debilitating chronic diseases (such as serious cardiac, pulmonary, gastrointestinal and chronic renal disorders (dialysis) or malignancy) according to the investigator*s opinion.
- having active malabsorptive diseases (such as celiac disease, inflammatory bowel disease, chronic pancreatitis or intestinal bypass surgery) according to the investigator*s opinion.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Treatment

## Recruitment

NL

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| Recruitment status: | Recruiting |
| Start date (anticipated): | 17-10-2023 |
| Enrollment: | 86 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 24-04-2023 |
| Application type: | First submission |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 07-05-2024 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |
| Approved WMO Date: | 09-07-2024 |
| Application type: | Amendment |
| Review commission: | METC Z: Zuyderland-Zuyd (Heerlen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| CCMO | NL83777.096.23 |