A national randomized placebo-controlled double-blind multicenter trial of LT4/LT3 combination therapy in patients with autoimmune hypothyroidism: the T3-4-Hypo trial.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22866

Source
Nationaal Trial Register

Brief title
T3-4-Hypo Trial

Health condition

overt or subclinical hypothyroidism

Sponsors and support

Primary sponsor: Erasmus Medical Center Rotterdam
Source(s) of monetary or material Support: ZonMw Project number 848043003

Intervention

Outcome measures

Primary outcome

The effects of LT4/LT3 combination therapy compared to LT4 monotherapy on tiredness in those patients with autoimmune hypothyroidism and persisting tiredness on LT4 monotherapy, after 1 year of treatment.

Secondary outcome

1. other determinants of effects of LT4/LT3 combination therapy compared to LT4 therapy alone on tiredness.
2. the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on other thyroid related complaints and quality of life.
3. the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on cardiovascular, metabolic, and bone outcomes.
4. the (determinants of the) effects of LT4/LT3 combination therapy compared to LT4 therapy alone on neurocognitive function.
5. an economic evaluation including cost-effectiveness analysis comparing LT4/LT3 combination therapy and LT4 monotherapy.
6. the number of adverse events during LT4/LT3 combination therapy vs LT4 therapy alone

Study description

Background summary

Rationale: Hypothyroidism is common, affecting 5% of the general population, for which levothyroxine (LT4) monotherapy is the standard treatment. Despite normalized serum thyroid hormone levels, 10-15% of LT4 treated patients have various persistent complaints, the most important of which is tiredness. This could be explained by the fact that physiological T4/T3 ratios cannot be reached with LT4 monotherapy, as in a healthy individual T3 is not only derived from T4/T3 conversion but is also directly produced by the thyroid itself. Studies have reported contradicting results as to whether addition of liothyronine (LT4/LT3 combination therapy) in patients with persistent tiredness on LT4 monotherapy is effective or not. Studies have suggested higher effectiveness in patients carrying genetic variation in the type 2 deiodinase (DIO2-rs225014) and monocarboxylate transporter 10 (MCT10-rs17606253) genes.
Objective: To investigate whether addition of liothyronine (LT4/LT3 combination therapy) in in patients with persistent tiredness on LT4 monotherapy is effective or not in relieving tiredness.
Study design: National randomized placebo-controlled double-blind multicenter trial.
Study population: Six hundred patients ≥ 18 years with autoimmune hypothyroidism who despite biochemical euthyroidism with LT4 monotherapy have persistent tiredness with a negative impact on daily life.
Intervention (if applicable): First, all participants are switched to the same generic LT4 preparation as there are seven LT4 preparations available in the Netherlands with different pharmacokinetic properties, which would otherwise introduce bias. Next, the intervention group is treated with once daily a LT4 tablet and twice daily a LT3 tablet with a LT4:LT3 ratio

16:1. The control group is treated with once daily a LT4 tablet and twice daily a placebo tablet. Treatment duration is 52 weeks.
Main study parameters/endpoints: The ThyPRO tiredness subscale scores at 52 weeks follow-up. In case it is confirmed that LT4/LT3 combination therapy reduces tiredness compared to LT4 treatment alone, we will simultaneously investigate whether effect sizes are higher in patients with genetic variation in DIO2 (rs225014) and MCT10 (rs17606253), ensuring control of the study-wise type 1 error (of 5% two-sided) across these three main questions.

Study objective

Addition of liothyronine (LT4/LT3 combination therapy) in patients with persistent tiredness on LT4 monotherapy is effective in relieving tiredness.

Study design

Primary outcome after 52 weeks of treatment

Intervention

First, all participants are switched to the same generic LT4 preparation as there are seven LT4 preparations available in the Netherlands with different pharmacokinetic properties, which would otherwise introduce bias. Next, the intervention group is treated with once daily a LT4 tablet and twice daily a LT3 tablet with a LT4:LT3 ratio 16:1. The control group is treated with once daily a LT4 tablet and twice daily a placebo tablet. Treatment duration is 52 weeks.

Contacts

Public
Erasmus Medical Center
Marco Medici

+31 10 7040570
Scientific
Erasmus Medical Center
Marco Medici

+31 10 7040570

Eligibility criteria

Inclusion criteria

- Patients with overt or subclinical primary hypothyroidism aged 18 years or older.*
- LT4 monotherapy for at least 6 months.
- LT4 monotherapy dose of 75-225 microg, with at least a dose of 1.2 microg/kg.
- TSH levels within the assay-specific reference ranges for at least 3 months.
- Severe tiredness with a large negative impact on daily life for at least 6 months, with or without other persisting complaints. This is based on the patient's own experience, without judgment of the treating physician.
- Sufficiently fluent in Dutch and able to read Dutch.

*Thyroid peroxidase (TPO) and/or thyroglobulin (Tg) antibody positivity is not a requirement as these have frequently not been determined. Instead, we ensure that we only include patients with autoimmune hypothyroidism by excluding other causes of hypothyroidism (see exclusion criteria).

Exclusion criteria

- Congenital hypothyroidism, hypothyroidism after (sub)acute thyroiditis, secondary (central) hypothyroidism.
- Thyroid surgery, radioactive iodine treatment, or head and/or neck radiotherapy.
- Use of thyroid interfering drugs (current/past use of amiodarone, immunotherapy, tyrosin kinase inhibitors, interferon, or lithium and current use of oral or iv corticosteroids or dopamine).
- Current psychiatric disease treated at a "gespecialiseerde GGZ instelling"*
- Clinical diagnosis of dementia.
- Pregnancy, breastfeeding or wish to become pregnant within 2 years.
- Women of reproductive age not using adequate contraception, who are not sterilized and do not have a sterilized partner. Adequate contraceptives include the contraceptive pill, patch, injection, implant, intrauterine device or system, vaginal ring, diaphragm or cap, and condom.
- Functional or structural abnormal heart (e.g., cardiomyopathy or valve disease)
- Recent acute coronary syndrome or unstable angina pectoris (<4 weeks)
- Current/past atrial fibrillation
- Current conduction disorder on ECG (i.e, QRS>100 ms or prolonged QTc (women≥460 ms and men≥450 ms)).
- Frequent ventricular extrasystole (=doublet, trigeminy, bigeminy or (non-sustained) ventricular tachycardia) in the past or on current ECG.
- Other obvious medical explanation for tiredness (e.g. end-stage renal disease, anemia, COPD stage IV, cancer, etc.)
- Other obvious major life event explanation for tiredness (e.g., mourning, loss of job)

*Treatments of mild non-complex psychological/psychiatric complaints are done in the " basis GGZ", e.g. consisting of conversations with a psychologist or psychotherapist, or via internet (e-health). "Gespecialiseerde GGZ" encompasses treatments of more severe

psychological/psychiatric complaints.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-06-2022
Enrollment:	600
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	08-03-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 54941
Bron: ToetsingOnline

Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9314
CCMO	NL74281.078.21
OMON	NL-OMON54941

Study results