rhTSH and T3 stimulation tests in offspring of long-lived siblings and their partners

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Objectives: To test the hypothesis that the thyroid gland of offspring of long-lived siblings is more resistant to stimulation with TSH compared to the thyroid gland of their partners, offspring and partners will receive a low dose of recombinant...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45854

Source
ToetsingOnline

Brief title
THYRAGE

Condition

- Other condition

Synonym
healthy ageing, thyroid metabolism

Health condition

schildkliermetabolisme en weefselregeneratie in groepen die verschillen in familiaire langlevendheid

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Horizon 2020 project gefinancieerd door de Europese Unie.

Intervention

Keyword: Ageing, Longevity, Thyroid, Tissue regeneration

Outcome measures

Primary outcome

Primary outcome parameters of the study are the (precursor) hormones reflecting the physiological response of the thyroid gland after TSH or T3 stimulation, namely T3, T4, fT3, fT4, Tg and TSH. The levels of these hormones will be compared between offspring of long-lived families and their partners.

Secondary outcome

Secondary outcome parameters of the study are processes potentially influenced by thyroid metabolism, namely tissue regeneration, body temperature regulation, heart rate and metabolomics.

Study description

Background summary

The Switchbox consortium demonstrated that offspring of long-lived families display increased levels of TSH but similar levels of thyroid hormones (TH) compared to their partners. Based on these findings, two hypotheses can be formulated that will be tested in the THYRAGE (Resetting the THYRoid axis for prevention of AGE-related diseases and co-morbidities) consortium. One possibility is that the thyroid gland of offspring of long-lived siblings is more resistant to stimulation with TSH compared to the thyroid gland of their partners. An alternative explanation could be that the offspring show an increased rate of TH clearance compared to their partners. As a result higher TSH levels are required to increase the production of TH to ensure appropriate

circulating TH concentrations. The two hypotheses will be tested by performing two challenge studies, one with recombinant human TSH (Thyrogen) and one with synthetic T3 (Cytomel). In addition, offspring also displayed lower levels of circulatory markers of bone turnover compared to their partners. Decreased bone turnover could be reflective of a slower depletion of regenerative capacity, a candidate mechanism contributing to longevity. It is unknown whether lower levels of tissue regeneration are causally linked to enhanced TSH production and/or increased TH clearance.

Study objective

Objectives: To test the hypothesis that the thyroid gland of offspring of long-lived siblings is more resistant to stimulation with TSH compared to the thyroid gland of their partners, offspring and partners will receive a low dose of recombinant TSH.
To test the hypothesis that the offspring of long-lived siblings display an increased rate of TH clearance from the circulation a T3 challenge will be performed.

Secondary objectives: To determine whether there is a causative relationship between changes of TH/TSH over time and changes in markers of tissue regeneration and physiological parameters, markers of bone turnover will be measured in blood and urine, immune signatures will be determined of circulating peripheral mononuclear blood cells (PBMCs), and electrocardiography (ECG), accelerometry and skin/core body temperature measurements will be performed. In addition, biomaterial will be stored for additional future measurements of biomarkers of thyroid hormone metabolism and/or tissue regeneration.

Study design

Case-control intervention study.

Intervention

For the rhTSH challenge each participant will receive one intra-muscular (musculus gluteus maximus) injection with a low dose of 0.1 mg (in 1 ml solution) Thyrogen.
For the T3 challenge each participant will receive one oral dose of 100 µg liothyronine (Cytomel).

Study burden and risks

During the rhTSH challenge we will administer a low dose of Thyrogen to healthy subjects. In previous studies using the same Thyrogen dose only very minor adverse events such as headache and nausea were observed. To assess the outcome

of this challenge, 14 blood samples will be collected during the first study day. During the next three days one blood sample will be collected each day. In addition to blood sampling, morning urine will be collected on each study day. From study 1 onward, participants will wear an Equivital monitor to assess physiological parameters for the duration of the study (4 days). Blood drawing, collection of morning urine and wearing a physiological monitor are minimally invasive procedures, consequently no direct benefits or risk associated with study participation are expected.

During the T3 challenge we will administer one oral dose of Cytomel to healthy subjects. Previous studies using the same dose of T3 showed no adverse effects such as influences on general state of well-being or body weight. To assess the outcome of this challenge, 25 blood samples will be collected during the first study day. During the next four days one blood sample will be collected each day. In addition to blood sampling, morning will be collected on each study day. From study day 1 onward, participants will wear an Equivital monitor to assess physiological parameters for the duration of the study (5 days). Blood drawing, collection of morning urine and wearing a physiological monitor are minimally invasive procedures, consequently no direct benefits or risk associated with study participation are expected.

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

Couples will be recruited from the Leiden Longevity Study (LLS), preferably from the 135 subjects that previously participated in the Switchbox phase 1 study, and preferably from the subgroup of 20 couples that were recruited for Group A (P11.116 * Switchbox). All subjects participating in Switchbox phase 1 were healthy, middle-aged (55-77 years) males or females with a BMI in the range of 22.5 kg/m2 to 33 kg/m2. Each couple participating in LLS consists of a child from a family enriched for longevity (case, offspring of long-lived sibling) and his/her current partner (control).

Exclusion criteria

* Cardiac arrhythmias
* (History of) thyroid diseases
* TSH hoger dan 4.0 mU/l
* fT4 level outside the normal range (9-24 pmol/l)
* Any significant chronic disease
* Renal, hepatic or endocrine disease
* Hormone therapy
* Difficulties to insert an intravenous cannula
* Recent participation in other research projects (within the last 3 months), participation in 2 or more projects in one year
* (History of) alcohol abuse (meer dan 28 units per week)
* Nicotine abuse

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2016
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Liothyronine
Generic name:	Cytomel®
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Thyrotropin alfa
Generic name:	Thyrogen®
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-05-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-07-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-12-2017
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
EudraCT	EUCTR2016-001497-15-NL
CCMO	NL57406.058.16