Aberrant receptor expression in thyroid tissue: A role in the pathogenesis of multinodular goiter?
A pilot study

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ObjectiveThe main goal of this investigation is to evaluate the thyroid hormone response in patients with TMNG and control subjects in response to various pharmacological and physiological stimuli, administered according to the dynamic exposure test...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON40001

Source
ToetsingOnline

Brief title
Aberrant receptor expression in thyroid tissue

Condition

- Thyroid gland disorders

Synonym
(Toxic) Multinodular Goiter

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 1. (Toxic) Multinodular Goiter, 2. ACTH independent macronodular adrenal hyperplasia, 3. Aberrant receptor expression, 4. Lacroix protocol

Outcome measures

Primary outcome

Endpoint

The % increase in total T4, T3 and Free T4, defined as: ([T4/T3/FT4 max *

T4/T3/FT4 at baseline]/ T4/T3/FT4 at baseline) x 100%

Secondary outcome

none reported

Study description

Background summary

Aberrant receptor expression in thyroid tissue: A role in the pathogenesis of multinodular goiter? A pilot study

Background
Toxic Multinodular Goiter (TMNG): Two key factors in the development of TMNG are hyperplasia * i.e. nodule and goiter - and hyperfunction * i.e. thyroid autonomy. Although TMNG is associated with iodine deficiency, this factor alone can not explain sufficiently the pathogenesis of TMNG, since TMNG also occurs in individuals from iodine sufficient areas. So the underlying mechanism of both hyperplasia and hyperfunction is not yet completely understood.
ACTH-independent macronodular adrenal hyperplasia (AIMAH): Recent research has shown that the enhanced cortisol production in patients with AIMAH, despite a suppressed ACTH, is regulated by hormones other than ACTH, via the aberrant expression of several G-protein coupled hormone receptors mimicking the cellular events that in normal circumstances are triggered by ACTH receptors.
AIMAH and TMNG: similarities: Two important similarities can be noted in the abovementioned diseases: 1) Hyperfunction: overproduction of cortisol and thyroid hormone, respectively and 2) Hyperplasia: gradual development of macronodular hyperplasia, overpassing the midline * i.e. bilateral hyperplasia

in the adrenal glands and multinodular goiter in the whole thyroid gland.

Study objective

Objective
The main goal of this investigation is to evaluate the thyroid hormone response in patients with TMNG and control subjects in response to various pharmacological and physiological stimuli, administered according to the dynamic exposure test as described by Lacroix.

Study design

Design
After an overnight fast, patients will visit the research unit on three separate days, between each day a one-week interval, in order to prevent uncertainty about the agent causing the peak in FT4 and T3. We will evaluate the thyroid response to three different stimuli that we think are most likely involved in the pathogenesis of TMNG. Starting 30 minutes after administration of each stimulatory agent * GnRH, metoclopramide and a mixed meal - blood will be drawn every 30 minutes for determination of the thyroid hormone response * i.e. T4, T3, TSH and FT4 * in 10 drug naive patients with toxic multinodular goiter en in 5 age and sex matched healthy controls.
On each testing day, blood is sampled at baseline and once every 30 minutes, starting 30 minutes after administration of the stimulatory agent/ mixed meal until 5 hours thereafter. The following thyroid hormones will be measured: FT4, T3, total T4 and TSH, using routine immunoassay: T4 and T3 with in-house RIA, FT4 and TSH by a commercial (Delfia, PerkinElmer) method.

Intervention

no intervention

Study burden and risks

Burden for the participants
The risk for participants is judged to be minor. Participation mainly requires an investment of time, undergoing insertion of an intravenous catheter for blood sampling and administration of a single dose of 10 mg metoclopramide and a single dose of 100 mcg gonadorelin. We do not expect any side effects from a single gift of these agents. Side effects of metoclopramide are dose-related and include drowsiness, diarrhea and extrapiramidal symptoms, like rigidity of the muscles and tremor. These extrapiramidal symptoms dissappear spontaneously after discontinuing the metoclopramide. For gonadorelin, short-term nausea, headache and abdominal pain have been described as side effects.

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

* Informed consent form signed
* Age 18 years and over
* Multinodular goiter, confirmed with thyroid ultrasound
* Subclinical hyperthyroidism, defined as TSH < 0.10 mE/l and free T4 within reference range [10.0 * 23.0 pmol/l]
* T3 level within reference range, i.e. between 1.30 and 2.70 nmol/l

Exclusion criteria

* Current use of antithyroid drugs
* Treatment with radioactive iodine in history

* Pregnancy. This condition may lead to subtle enlargement of the thyroid gland, secondary to iodine deficiency. All premenopausal female participants will undergo a *-hCG-urine test before inclusion.
* Born and raised in iodine deficient areas, defined as the green and dark green fields in Figure 3 (protocol, p 13) .
* Any medication known to interfere with thyroid hormone metabolism or with the study medication, like amiodarone, beta blockers, neuroleptics, corticosteroids including inhalation steroids, antihistaminics
* Any condition that the investigator feels would interfere with trial participation or evaluation of results

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-12-2012
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO

Date:	09-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL40154.018.12