Effects of thyroid hormone treatment on mitochondrial function, ectopic fat accumulation, insulin sensitivity and brown adipose tissue in type 2 diabetes mellitus

Published: 31-03-2011
Last updated: 27-04-2024

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

Summary

ID

NL-OMON39459

Source
ToetsingOnline

Brief title
Thyroid function and insulin sensitivity

Condition

- Thyroid gland disorders
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
diabetes, hypothyroidism

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: ZonMW-VICI grant P. Schrauwen

Intervention

Keyword: brown adipose tissue, insulin resistance, mitochondrial function, Thyroid hormone

Outcome measures

Primary outcome

For the diabetes-group: Thyroidhormone induced changes in insulin sensitivity

and mitochondrial function of skeletal muscle.

For the non-diabetic group: Thyroidhormone induced changes is brown adipose

tissue activity.

Secondary outcome

Diabetics: Thyroid hormone-induced change of lipid content in skeletal muscle

and liver and brown adipose tissue activity.

Non-diabetics: thyroid hormone induced changes in energy expenditure.

Study description

Background summary

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are known to promote weight loss, which could be beneficial for treating obesity, and type 2 diabetes. Thyroid hormone treatment stimulates energy expenditure resulting in increased body heat production, in which brown adipose tissue play an important role. It is hypothesized that thyroid hormones would induce increased energy expenditure via a process called mitochondrial uncoupling, thereby creating an inefficient energy status. Indeed, an in vivo study showed a 70% increased flux through the tricarboxylic acid cycle (TCA) and an unchanged ATP synthesis rate upon T3 treatment in lean, healthy young men. The disproportionate increase in TCA flux compared with ATP synthesis suggests increased mitochondrial uncoupling. It is however unknown whether increased mitochondrial uncoupling

would increase fat oxidation and exerts favorable effects on insulin sensitivity. There is compelling evidence that type 2 diabetic patients have high levels of fat accumulation in non-adipose tissues, such as skeletal muscle, heart and liver. Ectopic fat accumulation is related to insulin resistance, however, why this fat accumulates in peripheral organs is not known. Recently, studies reported compromised mitochondrial oxidative capacity in type 2 diabetic patients and first-degree relatives of diabetic patients, suggested to play an important role. Therefore, subjects suffering from overweight and/or type 2 diabetes with overt hypothyroidism form an interesting group for examining the metabolic effects of thyroid hormone treatment, as less is known about the effects of thyroid hormone treatment in these groups.

Study objective

The purpose of this study is to evaluate whether thyroid hormone replacement therapy in type 2 diabetic patients suffering from overt hypothyroidism will improve muscular mitochondrial function, lower ectopic fat accumulation in muscle and liver, increase brown adipose tissue activity and enhance insulin sensitivity.
furthermore, a group of patients with hypothyroidism, but without type 2 diabetes will be included to evaluate the effects of thyroid hormone on brown adipose tissue activity.

Study design

Prospective intervention study in hypothyroidism patients (en type 2 diabetes), who undergo hormone suppletion therapy.

Intervention

Type 2 diabetic patients diagnosed with hypothyroidism will undergo 3 months of thyroid hormone replacement therapy (THRT) (Euthyrox®, Merck, Germany). Patients will be metabolically characterized (such as insulin sensitivity and fat accumulation in peripheral tissues) before and after this thyroid hormone replacement therapy. A dose of 25 µg per day of Euthyrox® will be administered orally during the first week and will be increased to 50 µg per day during the second week and to 75-100 µg per day in the third week depending on TSH, free T4 and T3 concentrations monitored throughout the treatment period.

Study burden and risks

Risks of measurements
The placement of Teflon cannula*s, blood drawing and the muscle and fat biopsies can cause bruises and hematomas. Anti-coagulants are excluded from the study for this reason. Infections or continued bleeding are very rare. The subjects will be instructed to refrain from heavy physical labour and not to

remove the pressure bandage for the biopsy at least 24 hours after the biopsy. We take 1 biopsy every clamp. The incision length (0.5cm) and depth (viscera of vastus lateralis muscle) of the biopsy are minimal, also to reduce risks. A skilled medical doctor will take the biopsies. Furthermore, MRS is a safe procedure, with no known health risk as long as no of the exclusion criteria are met. Hyperinsulinemic-euglycemic clamping is a procedure routinely performed in our laboratory without notable complications. In rare occasions subjects exhibit symptoms of hypoglycaemia (even if their blood glucose levels are still above 3 mmol). After successfully performing the clamp, blood glucose values will be monitored for an additional 60 minutes with glucose infusion stand-by if glucose levels happen to drop. Solid food and sugar-drinks will be provided directly after finalising the clamp to avoid the experience of hypoglycaemia. One week prior to the clamp, type 2 diabetic patients will be withdrawn from their diabetic medication use. The withdrawal of diabetic oral medication can lead to an increase in blood glucose levels in the type 2 diabetic patients. To minimize these effects we only include stable, well-regulated diabetic patients who are on sulfonylurea (SU)-derivates or metformin treatment. During this withdrawal period, subjects will be asked to check and report their fasting glucose to monitor changes in plasma glucose. In case they measure fasting glucoses > 13 mmol/L the study will be ended due to medical reasons and in consultation with a medical doctor, the usual oral anti-diabetic drugs are restarted again.
The advanced TF Gemini PET-CT scanner is equipped with time of flight electronics, which allows the use of a relatively low amount of radioactivity (2 mCi). The resulting total radiation dose from the low-dose CT scan and the injected radioactive tracer is 2.8 mSv is considered as a low risk (47), comparable with 2 times the yearly cosmic dose. The level of societal benefit is considered to be substantial.

Risks of Treatment
In this study, no experimental products will be used. Euthyrox® is a registered drug and prescription-based available. High dosage of Euthyrox® treatment could cause tachycardia, arrhythmia, angina pectoris, headache and muscle cramp, however, throughout the study these side-effects will be routinely checked by a medical doctor.
Also, the withdrawal of diabetic oral medication can lead to an increase in blood glucose levels in the type 2 diabetic patients. To minimize these effects we only include stable, well-regulated diabetic patients who are on sulfonylurea (SU)-derivates or metformin treatment. Their treating physician will be informed about the subject*s participation in the study. During the study the subjects will have to check their fasting glucose every morning to monitor changes in plasma glucose. In case they measure fasting glucoses > 13 mmol/L the study will be ended due to medical reasons and in consultation with a medical doctor, the usual oral anti-diabetic drugs are restarted again.

Benefits

Results of this study would be of great importance in evaluating thyroid hormone treatment as strategy for treatment of type 2 diabetes. Some weight loss could be a direct health benefit for the obese type 2 diabetic patients.

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

- Male or postmenopausal females
- Age 40-65 years
- Body mass index (BMI) < 40 and > 27 kg/m2
- Stable dietary habits (no weight loss/gain >3 kg in the last 6 months)
- Stable physical activity levels for at least six months ;- Newly diagnosed hypothyroid, non-insulin dependent type 2 diabetic patients having TSH values higher then > 4.0 mU/l and lowered concentrations of free T4 < 8.0 pmol/l

- Inclusion of patients who developed overt hypothyroidism due to subtotal thyroidectomy (strumectomy), except for those who underwent thyroidectomy because of thyroid carcinoma,
- Type 2 diabetic patients using sulphonylurea and or metformin therapy for at least six months with a constant dose for at least two months
- Hypothyroid diabetic patients due to Hashimoto disease (TPO > 100 IE/ml; Tg > 344 IE/ml), should have no auto-antibodies against glutamic acid decarboxylase (GAD), IA-2 and insulin to exclude type 2 polyglandular autoimmune syndrome (PGAII) (to exclude type 1 diabetes).
- Type 2 diabetic patients should have a HbA1c level < 8.0%
- Type 2 diabetic patients will be included when having no diabetes-related co-morbidities like cardiovascular diseases, diabetic foot, polyneuropathy, retinopathy. ;Inclusion criteria for non-diabetic de novo hypothyroid patientsMale or postmenopausal females
- Age 18-65 years
- Body mass index (BMI) < 40 and > 27 kg/m2
- Stable dietary habits (no weight loss/gain >3 kg in the last 6 months)
- Stable physical activity levels for at least six months ;- Newly diagnosed hypothyroid, patients having TSH values higher then > 4.0 mU/l (and lowered concentrations of free T4 < 8.0 pmol/l)

Exclusion criteria

- Unstable body weight
- Participation in an intensive weight-loss program or vigorous exercise program during the last year before the start of the study
- Medical history including active cardiovascular disease, i.e. history of coronary artery disease (i.e. history of angina pectoris, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting) or cardiac arrhythmias.
- Liver disease of liver dysfunction (ALT>2.5 x increased)
- Impaired renalfunction (Kreat >100 umol/L)
- Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg
- Hb <7.4 mmol/l (12 g/dl) in women, and <8.1 mmol/l (13 g/dl) in men
- Abuse of drugs and/or alcohol
- Contraindications for MRI scanning (please see appendix III: MRI contraindication questionnaire);- Patients with history of thyroid cancer
- patients using α and/or β blockers
- Severe diabetes which requires application of insulin or patients with diabetes-related complications
- History of psychiatric disease
- Diabetes related co-morbidities like cardiovascular diseases, diabetic foot, polyneuropathy, retinopathy.
- Use of medications known to interfere with glucose homeostasis (i.e. corticosteroids, thiazolidendiones)
- Hypothyroid diabetic patients due to Hashimoto disease with positive test values for auto-antibodies against GAD, IA-2 and insulin to exclude type 1 diabetes

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-07-2011
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Euthyrox
Generic name:	Levothyroxin Sodium
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-03-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-06-2011
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-09-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-09-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2011-000942-39-NL
CCMO	NL34476.068.11