Cycling from hypothyroidism to hyperthyroidism during early treatment of differentiated thyroid carcinoma

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Primary Objective: To compare the effects of hypothyroidism and hyperthyroidism on cardiac left ventricular function, as assessed by CMR, in subjects with differentiated thyroid cancer during their early treatment.Secondary Objective(s): To compare...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON43803

Source
ToetsingOnline

Brief title
THETA study

Condition

- Heart failures
- Thyroid gland disorders
- Endocrine neoplasms malignant and unspecified

Synonym
differentiated thyroid carcinoma - cancer of the thyroid gland

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

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

Intervention

Keyword: Cardiovascular damage, Differentiated thyroid carcinoma (DTC), Hyperthyroidism, Hypothyroidism

Outcome measures

Primary outcome

The primary endpoint is the difference in left ventricular ejection fraction,

as assessed by CMR, between week 0 and week 20. Differences will be tested with

a paired t-test or, Wilcoxon test in case of a non-normal distribution.

Secondary outcome

Vascular function

• Coagulation

o Prothrombin, fibrogen, factor VIII

o Protein C, Protein S, antithrombin III

o Plasminogen, tPA

• Cardial parameters, measured by Cardiac magnetic resonance imaging (CMR)

o Left ventricular end diastolic diameter

o Right ventricular end diastolic diameter

o End diastolic thickness

o Right atrial end diastolic diameter

o Left atrial end diastolic diameter

o End diastolic volume

o End systolic volume

• Cardiac output, systemic vascular resistance, stroke volume, measured by

pulse wave analysis of noninvasive beat-to-beat heart rate and blood pressure recordings by a Portapres ®

Cardiovascular risk profile

• Total cholesterol, HDL, LDL, triglycerides, Apo A1, Apo B100

• eGFR, morning urine sample (albumin, creatinin)

• sex, age, smoking habits

• systolic and diastolic blood pressure

• Endothelial function

o Carotid distensibility

o Carotid pulse wave velocity (PWV)

• ECG

• Cardiovascular autonomic function, derived from noninvasive beat-to-beat heart rate and blood pressure recordings by a Portapres ®

o Heart Rate Variability

o Baroreflex Sensitivity

• Cardiovascular biomarkers

o NT-proBNP

o Troponin

o Galactin-3

Cardiorespiratory fitness

• Maximal oxygen uptake (VO2max)

• Maximal respiratory exchange ratio (RERmax)

• Power (W) at RER >= 1

• Maximal power (Wmax)

• Maximal heart rate (Hfmax)

• Rate pressure product (RPP) at Wmax, by measuring blood pressure during

exercise protocol.

Thyroid markers

• TSH, Tg

Metabolic function

• Body composition

o BMI

• SHBG

• Liver function

o ASAT, ALAT, gGT

• Glucose

o Glucose, HbA1c

Mood and cognitive function

• Digit Symbol Test

• Digit Span Test

• Profile of Mood States (POMS)

• Beck Depression Inventory II (BDI-II)

Quality of Life

• RAND-36

• WHO-5

• EORTC

THETA Cholesterol function and balance

• Plasma: Absorption plasma ratios of plant sterols to cholesterol,

lathosterol/cholesterol ratio,as marker fof cholersterol synthesis, biomarker

C4, cholesterol efflux capacity, anti-oxidative capacity, anti-inflammatory

capacitcapacity as markers of HDL function;y, PLTP, LCAT, and CETP and PLTP

(activity) levels as factors that affect HDL metabolism and function.

• Feces:

o Sterols: cholesterol, coprostanol, and dihydrocholesterol

o Bile acids: deoxycholic acid, cholic acid, ursodeoxycholic acid, and

chenodeoxycholic acid.

Study description

Background summary

Differentiated thyroid cancer
Thyroid carcinoma is the most common endocrine malignancy with more than 550 new cases in the Netherlands and an estimated 37.000 new cases in the European Union each year.(1) Differentiated thyroid cancer (DTC) encompasses papillary and follicular thyroid cancer. Those are the most frequent types and have a favorable prognosis: 10-year overall survival rates of 80% to 95%.(2) Patients with DTC are treated with a total thyroidectomy, followed by iodine-131 (hereafter, radioiodine) ablation therapy to destroy residual thyroid cancer. To prevent recurrences, subsequent thyroid hormone suppression therapy (THST) is administered.(3) With THST, high doses of thyroid hormone are prescribed, with the aim to lower or suppress the thyroid stimulating hormone (TSH) level, as TSH is considered to be a growth factor for thyroid (cancer) cells.

In patients with DTC, hypothyroidism arises after total thyroidectomy. This is useful for radioiodine ablation therapy, as the thyroid cells take up the radioiodine much better in a hypothyroid state. After this therapy patients need THST, which creates subclinical hyperthyroidism. After half a year of THST, patients may need a second radioiodine therapy, preceded by thyroid hormone withdrawal. Patients can therefore cycle several times from hypo- to hyperthyroidism during the initial treatment phase.

Differentiated thyroid cancer and cardiovascular risk
Various adverse (so-called *off-target*) effects of long-term exposure to THST have been described in patients with DTC, e.g. atrial fibrillation, impaired

systolic and diastolic cardiac function, and adverse metabolic and prothrombotic effects.(4-8) Our own data showed that patients with DTC have an increased risk of cardiovascular (HR 3.35, 95% CI 1.66-6.74) and all-cause mortality (HR 4.4, 95% CI 3.15-6.14).(9)

Not only THST is associated with cardiovascular mortality; hypothyroidism and hyperthyroidism themselves are also associated with cardiac changes. Thyroid hormones affect the heart directly as well as indirectly, by mediating the autonomic nervous system, the renin-angiotensin-aldosterone system, vascular compliance, vasoreactivity, and renal function.(10,11)

Hyperthyroidism
Tachycardia is the most common finding in patients with hyperthyroidism. Atrial arrhythmias, including atrial fibrillation occur, and are most common in older patients.(12) In patients with hyperthyroidism, cardiac output may be increased by 50% to 300% over that of normal subjects due to the combined effect of increased resting heart rate, contractility, ejection fraction, and blood volume with decreased systemic vascular resistance (SVR).(13) Advanced heart failure may rarely occur in patients with hyperthyroidism, usually in the setting of prolonged and severe hyperthyroidism or after the onset of atrial fibrillation. However, high-output heart failure is more common in hyperthyroidism. Because cardiac output at rest is increased, the increased output that normally accompanies exercise is blunted.(12,14)

Hypothyroidism
The cardiovascular manifestations of hypothyroidism are more subtle. Those include bradycardia, diastolic hypertension, a narrow pulse pressure, and a relatively quiet precordium. Hemodynamic changes of hypothyroidism are diametrically opposite to those of hyperthyroidism.(10) Additionally, in hypothyroidism there is increased risk of atherosclerosis often associated with hypercholesterolemia and hypertension. (11)

In patients treated for DTC, both hypothyroidism and hyperthyroidism are inevitable during common treatment of DTC. Identification of markers of early cardiovascular and metabolic abnormalities may help to identify patients at highest risk. In a broader perspective, patients treated for DTC may be regarded as a controlled model of both hypothyroidism and hyperthyroidism. Understanding the adverse cardiovascular and metabolic effects of these conditions may help to treat patients without DTC that suffer from (subclinical) hypo- or hyperthyroidism.

MRI for cardiac imaging
Until recently, echocardiography was considered standard for the evaluation of cardiac function. Latest ESC guidelines recommend cardiac MRI (CMR) above echocardiography to measure LV and RV dysfunction. CMR is a non-invasive technique that provides most of the anatomical and functional information. CMR is considered the reference standard for measurement of ventricular volumes and

function. (15) CMR has never been used to study the effects of standard DTC therapy on cardiac function.

Differentiated thyroid cancer and cholesterol balance
In hypothyroidism there is increased risk of atherosclerotic cardiovascular disease, often associated with hypercholesterolemia and hypertension.(11,16) Using the set-up of short-term profound hypothyroidism following thyroidectomy for DTC, we previously observed profound robust increases in total cholesterol, LDL cholesterol and triglycerides, and decreases in HDL cholesterol(17) However, the pathophysiological mechanisms that cause these changes remain unknown. The THETA-study is a unique set-up to compare the effects of thyroid hormones on the cholesterol balance. Knowledge of the effects of hypothyroidism on cholesterol balance could contribute to the discussion about the use of rhTSH in the treatment of DTC, a treatment which prevents hypothyroidism.

Study objective

Primary Objective: To compare the effects of hypothyroidism and hyperthyroidism on cardiac left ventricular function, as assessed by CMR, in subjects with differentiated thyroid cancer during their early treatment.

Secondary Objective(s): To compare the effects of hypothyroidism and hyperthyroidism on:
• Cardiorespiratory fitness
• Vascular function
• Cardiovascular risk profile
• Cholesterol function and balance
• Mood and cognitive function
• Quality of Life

Study design

Design: Single center, prospective cohort study

Duration and setting:
Patients will be recruited at the University Medical Center Groningen (UMCG) between May 2016 and November 2017. The study consists of ± 20 weeks between radioiodine ablation therapy and Thyreoglobulin (Tg) testing.

Sub-study Cholesterol function and balance:
To assess cholesterol function and balance in hypothyroidism and hyperthyroidism, in patients with differentiated thyroid carcinoma during their early treatment, an expansion of the original study is created. Subjects of the THETA-study can choose to sign an additional informed consent and participate in the sub-study THETA Cholesterol. In addition, subjects that do not participate in the THETA-study can participate in the sub-study THETA

Cholesterol.

Study visits:
The study will have three main visits, the first visit will be combined with the hospitalisation for regular treatment. The second and third visit will be combined with a normal follow-up visit to the outpatient clinic if possible. The screening visit takes place before radioiodine ablation therapy. Subjects will subsequently be invited at week 0, 10, and 20. Study visits will be planned as much as possible within those weeks. However, exceptions can be made to reschedule the study visit to two weeks prior or after the preferred week.

For the subjects participating in the sub-study THETA Cholesterol, an additional visit to a dietician will be scheduled approximately one week prior to the first main study visit. Where possible, this visit to the dietician will be combined with a pre-ablation visit (regular care). During the visit to the dietician, instructions for food diaries and advises about a diet will be given. Prior to the other two study visits, a consultation with the dietician will take place by telephone.

Study burden and risks

Benefits: patients who participate in this study receive cardiovascular evaluation. This will lead to early detection of cardiovascular risk factors and detection of (pre)clinical damage. For example, the presence of atrial fibrillation or micro albuminuria. Any abnormality will reported to the general practitioner of the regarding patient. Patients with abnormalities will be treated according to national guidelines.
Risks: Patient who participate will have prolonged visits at the UMCG, as we try to combine each study visit with a visit for regular care. Participation is accompanied with only minor risks. All measurements are non-invasive, except vena puncture and gadolinium-contrast injection for the cardiac MRI.
Group relatedness: Cardiovascular and all cause mortality risks are increased in patients with DTC. Cycling from hypothyroidism to hyperthyroidism may contribute to these risks. Identification of markers of early abnormalities may help to identify patients at highest risk. Results of the present study may contribute to personalize optimal treatment for DTC patients, including early identification and treatment of off-target 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

The subject has a histologically confirmed diagnosis of DTC.
The subject is at least 18 years old.
The subject has written informed consent
The subject is mentally competent

Exclusion criteria

The subject is 75 years or older.
The subject received treatment with rhTSH after thyroidectomy.
The subject has a history of severe lung disease (COPD gold class III or worse).
The subject has a history of cerebrovascular or coronary events.
The subject is pregnant
The subject has a history of atrial fibrillation.
The subject has a history of heart failure NYHA class III or worse.
The subject has a severe limited physical strain
The subject is unable or not willing to sign informed consent.

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-10-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	30-07-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25756
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL52832.042.15
OMON	NL-OMON25756