

# Coagulation and fibrinolysis in patients with resistance to thyroid hormone due to a thyroid hormone receptor $\beta$ -gene mutation

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To investigate the effect of resistance to thyroid hormone (RTH) due to a TR $\beta$  mutation on coagulation and fibrinolysis

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Chromosomal abnormalities, gene alterations and gene variants
<b>Study type</b>	Observational invasive

## Summary

### ID

NL-OMON38471

### Source

ToetsingOnline

### Brief title

The TR $\beta$  study

### Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Thyroid gland disorders
- Embolism and thrombosis

### Synonym

insensitivity for thyroid hormone because of a change in the DNA, thyroid hormone resistance because of a gene mutation

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum

**Source(s) of monetary or material Support:** via de SKWOSZ (stichting klinisch wetenschappelijk onderzoek slotervaartziekenhuis)

## Intervention

**Keyword:** coagulation, gene mutation, thyroid hormone receptor, thyroid hormone resistance

## Outcome measures

### Primary outcome

The following groups of lab markers will be tested: labmarkers: thyroid function and SHBG, coagulation markers and fibrinolysis markers.

### Secondary outcome

not applicable

## Study description

### Background summary

Recent interest has focused on the association between thyroid dysfunction and venous thromboembolism (VTE). Hyperthyroidism is associated with a hypercoagulable state (1-3). Several coagulation and fibrinolytic parameters appear to be affected by thyrotoxicosis; elevated plasma levels of factor VIII (FVIII), factor IX (FIX), von Willebrand factor (VWF), and fibrinogen, and a reduced fibrinolytic activity due to increased levels of plasminogen activator inhibitor-1 (PAI-1) have been reported in both hyperthyroid patients and healthy subjects after taking thyroid hormones (1, 4-10).

A retrospective cohort study was done to determine the risk of VTE in all patients with overt hyperthyroidism and to compare this to the risk of VTE in the general population (11). The incidence rate of VTE in patients with hyperthyroidism appeared to be high.

The exact mechanism of hyperthyroidism leading to affected coagulation and fibrinolytic parameters and thus the hypercoagulable state is unknown. It was shown that in cultured endothelial cells triiodothyronine (T3) induces upregulation of mRNA expression and protein synthesis of VWF, fibronectin (FN) and endothelin-1 (ET-1) (12). The effect of T3 treatment on target gene

regulation was investigated in a thyroid hormone receptor (TR)-overexpressing hepatoma cell line by performing cDNA microarrays (13). Thrombin for example, was multiplied 8-fold by T3 induction and coagulation factor X (FX) 4.9-fold. We hypothesize that the hypercoagulable state in hyperthyroidism is mediated by the thyroid hormone receptor (TR). Patients with a mutation in the thyroid hormone receptor beta (TR $\beta$ ) gene have elevated plasma T3 and T4. Therefore, patients with a TR $\beta$  mutation can serve as the optimal clinical model to investigate the role of TR $\beta$  in the hypercoagulable state seen in patients with hyperthyroidism.

### **Study objective**

To investigate the effect of resistance to thyroid hormone (RTH) due to a TR $\beta$  mutation on coagulation and fibrinolysis

### **Study design**

cross-sectional study

### **Study burden and risks**

Blood will be drawn once. Participation in the study will not influence the treatment of the patients.

## **Contacts**

### **Public**

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## **Trial sites**

## Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

- Patients with thyroid hormone resistance due to a mutation in the thyroid hormone receptor beta gene
- Elevated T3 and/or T4 according to the local reference ranges; For the control groups:
  - a) hyperthyroid patients with elevated serum T4 and/or T3 according to the local reference ranges
  - b) euthyroid controls with general good health, both matched for age ( $\pm 5$  years) and gender

### Exclusion criteria

- No informed consent
- Oral anticoagulant therapy (warfarin, vitamin K antagonists)
- Hemophilia or von Willebrand's disease
- Oral corticosteroid therapy
- Previous VTE within the last 6 months
- Previous thyroid surgery or radio-iodine treatment
- Current anti-thyroid drugs

## Study design

### Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose: Basic science

## Recruitment

NL  
Recruitment status: Recruitment stopped  
Start date (anticipated): 22-01-2014  
Enrollment: 36  
Type: Actual

## Ethics review

Approved WMO  
Date: 12-12-2013  
Application type: First submission  
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	NL46481.018.13