The hormonal influence on the haemostatic system and the risk of thrombosis
Stuijver, D.J.F.
Screening for thyroid dysfunction in dyslipidemic patients

Published in Nederlands Tijdschrift voor de Geneeskunde 2012;156:A4301

Danka JF Stuijver, Bregje van Zaane, Victor EA Gerdes, Erik S Stroes
Abstract

Hypothyroidism constitutes a significant cause of secondary dyslipidemia that may predispose to the development of atherosclerotic disease. Thyroid function is however often not assessed in the screening of dyslipidemic patients. After an attempt to reduce cholesterol levels by encouraging lifestyle changes, cholesterol-lowering drugs are quite often immediately prescribed given a proven efficacy in reducing cardiovascular disease.

We describe two cases with hypothyroidism-induced dyslipidemia in whom the lipid abnormalities after thyroid hormone substitution therapy completely resolved. Besides the insidious clinical presentations and diagnostic challenges of hypothyroidism, these cases illustrate that screening for thyroid dysfunction is of paramount importance in all dyslipidemic patients both in primary and secondary care.
INTRODUCTION

Hypothyroidism is a well-known cause of secondary dyslipidemia and may predispose to the development of atherosclerotic disease. Measurement of thyroid hormone levels are however often not included in the screening of dyslipidemic patients. We describe two cases with hypothyroidism-induced dyslipidemia in whom the lipid abnormalities after substitution of the thyroid hormone completely resolved.

CASE DESCRIPTIONS

The first case is a 50-year old Caucasian woman referred by the general practitioner with dyslipidemia and uncontrolled hypertension despite treatment with blood pressure lowering medication. She had been treated with hydrochlorothiazide 25 mg once daily since 6 months. Her past medical history included bilateral carpal tunnel syndrome. She complained of tiredness, swollen ankles, and easy weight gain. Within the past 4 months, her weight had increased by 7 kg. She had no cardiac complaints. The family history is positive for cardiovascular disease; the patient’s father had a fatal stroke at age 60 and her brother suffered a non-fatal myocardial infarction at age 45. The patient smoked 1 pack of cigarettes daily for 20 years, but stopped smoking a year earlier. She did not drink alcohol. She did not exercise.

Physical examination showed a moderately obese woman (weight 76 kg, height 153 cm). Blood pressure was 144/74 mmHg and the pulse rate was 72 beats/min. Stigmata for primary hyperlipidemia, such as corneal arcus and xanthoma, were absent. On palpitation of the neck, the thyroid gland did not appear to be enlarged. Laboratory tests revealed (reference values between brackets): total cholesterol 8.27 mmol/l (4.24-7.31); HDL-cholesterol (High Density lipoprotein) 1.34 mmol/l (0.96-2.37); triglycerides 1.22 mmol/l (0.58-2.45); LDL-cholesterol (Low Density lipoprotein) 6.38 mmol/l (2.29-5.23); thyroid stimulating hormone (TSH) 46.7 mE/l (0.5-5.0); free thyroxine (FT4) 3.6 pmol/l (10-23); and anti-thyroid peroxidase antibodies (anti-TPO) >3000 kU/l (<60). Kidney and liver function tests were normal. The diagnosis of hypothyroidism was made with, most likely, secondary dyslipidemia. Levothyroxine 50 µg once daily for 2 weeks was prescribed, gradually increased to 100 µg.

Blood pressure lowering medication was not changed.

Two months later the patient visits the outpatient clinic. She feels a lot better. The weight has dropped from 76 kg to 70 kg. The bloodpressure is 130/75 mmHg and the pulse rate 70 beats/min. Laboratory tests reveals: FT4 19 pmol/l; TSH 0.05 mE/l; total cholesterol 6.43 mmol/l; HDL-cholesterol 1.34 mmol/l; LDL-cholesterol 4.31 mmol/l (80th percentile); triglycerides
1.74 mmol/l. Levothyroxin was reduced to 75 µg once daily. The patient was referred back to the general practitioner for further control and treatment.

The second case is a 49-year old Hindi-Surinamese male, referred to the outpatient clinic with complaints of shortness of breath and muscle aches after minimal exertion, for three months. The general practitioner diagnosed an impaired renal function. The past medical history included cholesteatoma of the left middle-ear, for which several operations had been performed. The patient is treated with betahistin 20 mg three times a day for complaints of dizziness since the operations. The patient smokes two cigarettes per day and drinks 3 units of alcohol per week. The family history is positive for diabetes mellitus, cardiovascular disease and dyslipidemia. On physical examination we saw a slightly dyspnoic man of normal posture (weight of 79 kg, height 175 cm). Blood pressure was 160/90 mmHg and the pulse rate was 78 beat/min. Both eyes had a thin arcus lipidis. His remaining physical examination revealed normal findings. Pulmonary function tests concluded: normal spirometric parameters, slightly reduced diffusion capacity for carbon monoxide at reduced alveolar volume, somewhat flattened inspiratory flow pattern. Vasculitis was considered in differential diagnosis. Immunoserology was negative and a thoracic CT scan revealed no abnormalities. Laboratory tests revealed: TSH 77 mE/L (0.5-5.0); FT4 4.6 pmol/L (10-23); anti-TPO 280 kU/l (<60); antithyreoglobulin (anti-TG) positief; total cholesterol 8.6 mmol/L (4.24-7.15); HDL-cholesterol 1.2 mmol/l (0.78-1.66); LDL-cholesterol 6.4 mmol/l (2.55-5.25); triglycerides 2.1 mmol/l (0.62-3.07); creatinin 134 umol/L (50-100); creatinekinase (CK) 6000 U/L (20-170). Hypothyroidism with secondary dyslipidemia, myopathie, and renal insufficiency was diagnosed. Levothyroxine was prescribed.

Seven months after start of levothyroxin treatment, the complaints of shortness of breath and myalgia resolved. Laboratory tests showed: TSH 1.5 mE/L; FT4 14.6 pmol/L; total cholesterol 5.2 mmol/L; HDL-cholesterol 1.0 mmol/l; LDL-cholesterol 3.5 mmol/l; triglycerides 1.6 mmol/l; creatinin 99 umol/l; CK 192 U/L.

**DISCUSSION**

We describe two cases with hypothyroidism-induced dyslipidemia in whom the lipid abnormalities after thyroid hormone substitution completely resolved. These cases also show the diversity in clinical presentations which makes that the diagnoses is often missed.
Thyroid hormone and dyslipidemia

Dyslipidemia is a general term for various disorders in the lipid metabolism. Elevated levels of total plasma cholesterol, LDL-cholesterol and triglycerides, and decreased levels of HDL-cholesterol has been associated with the development and progression of atherosclerosis. Therefore, it is an important risk factor for cardiovascular disease. Dyslipidemia is often caused by a combination of factors, such as obesity, insulin resistance, an unhealthy diet, and genetic predisposition. Also less common secondary causes can result in an imbalance in the fat metabolism. An overview of these secondary causes with the required basic laboratory tests is shown in table 1.

The link between the thyroid hormone and the lipid metabolism was noted 70 years ago. This association was first described in het Nederlands Tijdschrift voor Geneeskunde in September 1928. We now know that thyroid hormone plays a key factor in the regulation and control of the metabolism in the body, especially the lipid metabolism. In patients with hyperthyroidism, for example with Graves’ disease, lower cholesterol levels have been found. On the other hand, hypothyroidism can lead to a dyslipidemia associated with endothelial dysfunction, diastolic hypertension and an increased risk of cardiovascular disease. (Table 2)

Table 1. Overview of secondary causes of dyslipidemia and required basic laboratory tests.

<table>
<thead>
<tr>
<th>Secondary causes</th>
<th>Laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypothyroidism</td>
<td>FT4/TSH</td>
</tr>
<tr>
<td>• Kidney disease</td>
<td>Creatinine</td>
</tr>
<tr>
<td>o Glomerular nephritis</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>o Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>o Chronic kidney insufficiency</td>
<td></td>
</tr>
<tr>
<td>• Diabetes Mellitus</td>
<td>Fasting glucose</td>
</tr>
<tr>
<td>• Liver disease</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>o Alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>• Drugs</td>
<td></td>
</tr>
<tr>
<td>o Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>o thiazide diuretics</td>
<td></td>
</tr>
</tbody>
</table>

FT4 indicates free thyroxine; TSH, thyroid stimulating hormone

Epidemiology

The prevalence of elevated TSH-levels in patients with hypercholesterolemia is around 12-13% against 2.2% in the general population. In a study from the Mayo Clinic, the lipid profiles of 268 consecutive patients with overt hypothyroidism were reviewed and it was found that
91.4% of these patients had abnormal lipid values; 56% hypercholesterolemia, 34% both hypercholesterolemia and hypertriglyceridemia, and 1.5% solely hypertriglyceridemia. In subclinical hypothyroidism (elevated TSH-levels with relatively normal FT4-levels) lipid disorders have been found only when TSH-levels were greater than 10 mE/l.

Pathophysiology
In hypothyroid patients there is an increase in the serum total cholesterol concentration, mainly due to raised levels of serum LDL cholesterol. This is caused by a reduced number of LDL-receptors on the liver cell surface, which results in a decreased clearance of LDL-particles from the circulation. Decreased thyroid hormone levels also promote the oxidation of LDL-particles, thereby increasing the atherogenecity of these particles. Hypertension is common in hypothyroidism and more specifically, diastolic hypertension may be present in approximately 20% of hypothyroid patients. The coexistence of hypertension and lipid disorders may accelerate the process of atherosclerosis.

Some studies also reported an increase in triglyceride and HDL-cholesterol levels, however other studies did not support this finding. An increase in LDL-cholesterol is therefore a more specific finding in hypothyroidism.

Table 2. Plasma lipid levels in thyroid disease.

<table>
<thead>
<tr>
<th></th>
<th>Hypothyroidism</th>
<th>Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-cholesterol</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>Normal/ Increased</td>
<td>Normal/ Decreased</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Normal/ Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

HDL indicates high density lipoproteins; LDL, low density lipoproteins

Cardiovascular disease
Both overt and subclinical hypothyroidism have been found to be associated with an increased cardiovascular risk. According to observational studies, levothyroxine treatment in patients with TSH-levels ≥ 10 mE/l leads to a 8% reduction of serum cholesterol concentration. Studies have shown that particularly in the initial phase of substitution therapy, the risk of developing cardiovascular disorders is increased. The reason for this is still not entirely clear, however it is thought that approximately one fifth of these patients is given an excessive amount of medication in the initial treatment phase. Also, thyroid hormone stimulates the cardiac performance and increases the cardiac output. Finally, a rise in coagulation factors, such as factor VIII and von-Willebrand factor may induce a hypercoagulable state.
Among the widespread actions of thyroid hormones, increasing metabolic rate and lowering atherogenic serum lipoproteins are clinically interesting metabolic responses since these could hypothetically be of use to treat obesity and its related co-morbidities such as dyslipidemia. However previous attempts to mimic the effects of thyroid hormones using thyroid hormone metabolites and analogues have been complicated by the induction of thyrotoxic adverse effects in other organ systems such as the heart and skeleton. 15

Selective thyroid hormone analogs, that stimulate the LDL receptors on the liver to remove cholesterol particles from the circulation without inducing undesirable systemic effects, are nowadays tested and have shown to effectively lower multiple cardiovascular risk parameters such as obesity, insulin resistance, hepatic steatosis, and dyslipidemia.15

Symptomatology

Back to clinical practice: why are still so many patients with hypothyroidism missed when screening for dyslipidemia? An important reason might be that the phenotype of patients with hypothyroidism is very similar to an ‘average’ cardiovascular high risk patient. Both types of patients often suffer from obesity and hypertension. In addition, it has been shown that a lack of thyroid hormone can lead to a diminished sensitivity to insulin which explains an increased incidence of type 2 diabetes.8 Treatment with metformine lowers TSH levels which only restores after the metformin is stopped for at least 3 months. Metformine treatment can therefore conceal a hypothyroidism. It is therefore advisable in patients treated with metformin as well as levothyroxine to check both TSH and FT4 levels. 16

Although both cases described here presented themselves at the general practitioners with a different pattern of complaints, in both cases this resulted from thyroid deficiency. The first patient was treated for bilateral carpal tunnel syndrome approximately three months before here visit to the outpatient clinic. This condition is associated with hypothyroidism. Also, the second patient had complaints in resulting from thyroid deficiency, such as dyspneu d’effort, myalgia and, tiredness. If the thyroid function would have been assessed sooner, the CT-scan would not have been required.

Hypothyroidism is associated with reversible acute renal dysfunction as showed in the second case. Like in most cases the creatinine levels returned back to normal within a few months after start of thyroid replacement therapy. In some cases however, especially in combination with increased muscle degradation as visible in the CK-level, the damage to the kidney can be al lot greater.17
Hypothyroidism and statin therapy

In patient with hypothyroidism, there is a reduced activity of the enzyme HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-CoA reductase), the rate-limiting enzyme in cholesterol catabolism. Statins, also known as HMG-CoA-reductase inhibitors, are therefore less effective. In addition, the use of statins in patients with hypothyroidism is not without risk. Hypothyroidism is by itself a risk factor for rhabdomyolysis and kidney failure as seen in case B, but it also increases the risk of statin-induced myopathy with sometimes dramatic results.\textsuperscript{18}

In conclusion, thyroid hormone deficiency can induce a secondary dyslipidemia and must always be substituted before start of lipid lowering therapy. Clinical and biochemical screening for thyroid dysfunction is of vital importance in patients with dyslipidemia characterised by increased levels of LDL-cholesterol. In general, it takes approximately 4–6 weeks of full replacement treatment with LT\textsubscript{4} to correct the dyslipidemia in overt hypothyroidism.\textsuperscript{19}
Reference list


4. Ringer. De schildklier en stofwisseling der vetten. NVG;1928;72;II;38.

5. Duntas L. Thyroid disease and Lipids. Thyroid 2002;12,287–293.


