Thyroid disease and haemostasis: a relationship with clinical implications?
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Chapter 5

Thyroid diseases and cerebrovascular disease

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**Abstract**

**Introduction:** Acute cerebral ischemia has been described in different diseases of the thyroid gland, and not only as a result of thyrotoxic atrial fibrillation and cardioembolic stroke. The purpose of this review is to summarize the studies on the relationship between thyroid diseases and cerebrovascular diseases, discussing the main findings for overt hyperthyroidism and hypothyroidism, as well as for subclinical thyroid dysfunction.

**Summary:** In overt hyperthyroidism, cardioembolic stroke is clearly associated to thyrotoxic atrial fibrillation, and in subclinical hyperthyroidism with serum thyroid-stimulating hormone levels <0.1 mU/L, the incidence of atrial fibrillation is increased. Although in vitro and in vivo studies indicate a hypercoagulability state in hyperthyroidism, there is insufficient evidence to prove that this state leads to an increased risk of cardiac emboli. However, the hypothesis that overt hyperthyroidism may cause acute cerebral venous thrombosis is intriguing. Possible associations between hyperthyroidism and Moyamoya or Giant cell arteritis have only been described in case reports. There is enough evidence that overt hypothyroidism is associated with several traditional and newer atherosclerotic risk factors, especially hypertension, hyperlipidemia, and hyperhomocysteinemia. For subclinical hypothyroidism, these associations are less certain. Hypothyroidism has been associated with signs of aortic or coronary atherosclerosis, but no case-control or cohort studies have ever investigated hypothyroidism as a possible risk factor for atherothrombotic stroke.

**Conclusions:** Hyperthyroidism is associated with atrial fibrillation and cardioembolic stroke. Hypothyroidism is associated with a worse cardiovascular risk factor profile and leads to progression of atherosclerosis. Associations between hyperthyroidism and acute cerebral venous thrombosis, Moyamoya, and Giant cell arteritis have been suggested, but sound evidence is lacking. Additional studies are needed to clarify these issues.
**INTRODUCTION**

Acute ischemic stroke is a well-described manifestation of thyrotoxic atrial fibrillation (AF). However, AF and cardioembolic stroke are not the only underlying pathological mechanisms of acute cerebral ischemia in thyroid disease. The purpose of this review is to summarize the studies on the relationship between thyroid disease and cerebrovascular diseases. We reviewed the published literature from in vivo studies through case reports to epidemiological and prospective studies. The main findings are highlighted and discussed for overt thyrotoxicosis and hypothyroidism, as well as for subclinical thyroid dysfunction.

**HYPERTHYROIDISM**

Thyrotoxicosis was originally a clinical term that described the appearance of affected patients and is commonly used to refer to any condition in which there is an excessive amount of circulating thyroid hormone, irrespective of the origin. The term hyperthyroidism was restricted to the diseases in which the thyroid gland synthesizes and secretes excessive hormones. However, the distinction in the literature between thyrotoxicosis and hyperthyroidism is not always clear and does not necessarily clarify the pathophysiology of each condition[1]. Therefore, the terms will be used interchangeably. Subclinical hyperthyroidism is defined as a serum thyroid-stimulating hormone (TSH) concentration below the statistically defined lower limit of the reference range when serum free thyroxine (fT4) and free triiodothyronine (fT3) concentrations are within their reference ranges[2,3].

**AF and Cardioembolic Stroke**

AF occurs frequently in patients with hyperthyroidism and may be the presenting symptom[4]. Various studies suggest a prevalence of 10% to 15% in patients with hyperthyroidism, and it is more common in men than in women[5]. The prevalence increases with age (rare at < 40 years of age; > 25% of those > 60 years of age[6,7]). In comparison, in the general population, the prevalence increases from <1% in persons <60 years of age to >8% in those >80 years of age[8]. The clinical diagnosis of thyrotoxicosis is not always obvious in elderly patients, in whom AF may be the dominant feature[6,9,10]. The prevalence of thyrotoxicosis in patients with AF is 2% to 5%[11-14]. Although an abnormal TSH level is common in patients with recent-onset AF, only <1% of cases of new-onset AF are caused by overt hyperthyroidism[14]. So routine TSH screening of patients who had AF may be better applied to those patients at higher risk of having undiagnosed clinical thyroid disease. Otherwise, AF may be the initial manifestation of subclinical thyroid disease. In the Framingham Study, a low serum TSH level in subjects >60 years of age was associated with a 3.1-fold increased risk for AF after 10 years of follow-up: 21% of subjects with definitely low serum thyrotropin concentrations (<0.1 mU/L) compared with 12% of those with slightly low concentrations (0.2 to 0.4 mU/L) and 8% of those with normal concentrations[15]. Also, two other studies reported an increased risk of AF in patients with subclinical hyperthyroidism compared with euthyroid persons (5-fold and 2.8-fold increased risk, respectively)[16,17]. There is only limited evidence that the treatment of subclinical hyperthyroidism facilitates spontaneous reversion or cardioversion of AF to normal sinus rhythm[16,18]. It is still controversial
whether the frequency of stroke and systemic embolism is increased in thyrotoxic AF or not. Some studies\cite{19-21} have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, but all these studies have methodological flaws. In another study, there was no statistically significant difference between AF patients and age- and sex-matched patients with normal sinus rhythm\cite{20}. No studies demonstrated an increased incidence of arterial embolism in patients with subclinical hyperthyroidism. However, in a recent 10-year cohort study, a single measurement of low serum thyrotropin was associated with increased mortality from circulatory and cardiovascular diseases\cite{23}. In patients with hyperthyroidism, AF is frequently of acute onset and will spontaneously revert to sinus rhythm without associated side effects. Spontaneous reversion within 6 weeks after the return to the euthyroid state is the expected outcome in patients <60 years of age who do not have pre-existing heart disease and in whom thyrotoxicosis is of short duration. When AF does not resolve after >3 to 4 months after reaching a euthyroid state, spontaneous reversion to sinus rhythm is unlikely\cite{24}. Whether patients with hyperthyroidism who have AF should receive anticoagulant therapy is controversial. In each patient, the risk of bleeding must be weighed against the risk of systemic embolization. Some authors conclude that the epidemiological data suggest that the rate of thromboembolism in patients with thyrotoxic AF exceeds that for nonthyrotoxic nonvalvular AF\cite{25}, but the majority agree that that thyrotoxic AF is not a more potent risk factor for stroke than other causes of AF. Among major randomized control trials of stroke prevention with warfarin\cite{7}, only the Copenhagen AFASAK Study included patients with hyperthyroidism: 16 (5%) in the warfarin arm, 12 (4%) in the aspirin arm, and 13 (4%) in the placebo group\cite{11}. These data appear insufficient to draw a conclusion. Therefore, because the incidence of thromboembolic events in patients with thyrotoxic AF appears to be similar to other etiologies of AF\cite{7}, antithrombotic therapies should probably be chosen based on associated risk factors and the risk of bleeding, as stated by international guidelines\cite{7}. Patients with hyperthyroidism are particularly sensitive to anticoagulant effects of warfarin, and lower-than-normal warfarin doses are usually required because hyperthyroidism is associated with increased clearance of vitamin K–dependent clotting factor\cite{13,26}.

A Hypercoagulability State?

We conducted an extensive search in all-language literature up to April 2005 with the databases MEDLINE and EMBASE using the text words ‘hyperthyroidism’ or ‘thyrotoxicosis’ and ‘stroke,’ ‘cerebral vein thrombosis,’ or ‘cerebrovascular disease’ to identify all case reports of cerebral venous and arterial thromboembolism during a noncancer (benign) thyroid disease. We retrieved articles and reviewed the references cited. We identified 2 main groups of patients other than the ones reported before: patients with cerebral venous thrombosis (CVT) and patients with acute ischemic stroke without cardiac arrhythmia.

Cerebral Vein Thrombosis

CVT is a very uncommon disease with an estimated incidence of 4 per 1 000 000 per year and with mortality rates between 5% and 30%\cite{27}. CVT has been associated with several causes and risk factors, such as inherited thrombophilia, oral contraceptives, pregnancy, and puerperium. However, ~25% of cases of CVT are still considered to be idiopathic\cite{27}. A possible association between thyrotoxicosis and CVT was already described by Kaliebe in 1913 and Doyle in 1927\cite{28}. The other case reports are summarized in Table 1\cite{29-39}. As described by Verberne et al, it is
unlikely that the association between CVT and thyrotoxicosis is explained by chance, and in addition to thyrotoxicosis, additional procoagulant influences are probably required for CVT to develop\(^{36;40}\). As suggested by different authors, it is necessary to stress that hemodynamic factors, dehydration, and stasis of venous blood flow attributable to goiter may also contribute to the multifactorial pathogenesis of CVT.

**Ischemic Stroke Without Cardiac Arrhythmias**

In thyrotoxic patients without cardiac arrhythmia, only 7 cases of acute cerebrovascular ischemic disease have been identified (references available on request), and even in some of these cases, paroxysmal AF or vasculitis were not excluded entirely. Because acute cerebral ischemia is less rare than CVT, these case reports do not prove that there is an increased rate in thyrotoxic patients without cardiac arrhythmia.

**Antiphospholipid Syndrome**

The antiphospholipid syndrome (APS) is defined as a combination of clinical manifestations entailing arterial or venous thrombosis and recurrent fetal loss, accompanied by abnormal laboratory tests, namely, the lupus anticoagulant or anticardiolipin antibodies\(^{41}\). Primary or secondary APS is defined by the presence or absence of concomitant viral infections, or hematologic, malignant, or autoimmune diseases\(^{41}\). Ischemic stroke and CVT are neurological manifestations accepted as clinical diagnostic criteria for the APS. We found only 3 case reports of patients with Graves disease and APS\(^{42–44}\). Conversely, patients experiencing primary APS reveal an increased prevalence of thyroid autoantibodies\(^{45;46}\). Of course, these associations may be merely coincidental. However, there are indications that genetic predisposition can explain the presence of APS in patients with autoimmune thyroid disorders\(^{47}\), and it has been suggested that anticardiolipin antibodies may act as thyrotropin receptor–stimulating antibodies\(^{48}\). However, this latter hypothesis is only speculative.

**Cerebral Vasculitis**

Giant cell (temporal) arteritis (GCA) is a chronic vasculitis of large and medium-sized vessels, which occurs among individuals >50 years of age. Although it may be generalized, vessel inflammation most prominently involves the cranial branches of the arteries originating from the aortic arch\(^{49}\). Cranial ischemic complications are the most dreaded manifestations of GCA. The incidence of visual loss in most recent studies is \(\sim 15\%\). Stroke occurs in 3% to 4% of the patients \(^{50;51}\). Ischemic damage in GCA is usually attributed to an occlusive vasculopathy caused by intimal proliferation (and usually not by thrombosis) in carotid and vertebrobasilar arteries\(^{49}\) or as a result of aortic dissection\(^{52}\). The association between GCA and thyroid dysfunction is controversial\(^{53;54}\) but because giant cells are a possible feature of Graves’ disease, a common pathway has been suggested. In 2 series, of 101 and 98 patients, respectively, the prevalence of hyperthyroidism was reported to be 6 times higher in cases of GCA than in controls\(^{55;56}\), which was not confirmed in a multicenter case-control study\(^{57}\). An association between hyperthyroidism and Takayasu arteritis was described in 2 patients in the literature\(^{58}\).
Table 1. Case reports of acute cerebral vein thrombosis associated with hyperthyroidism reported in the literature.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age</th>
<th>Site of thrombosis</th>
<th>Thyroid disease</th>
<th>Thyroid hormone state</th>
<th>Associated risk factors for thrombosis</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>24</td>
<td>SSS</td>
<td>Graves' disease</td>
<td>fT4: 35.5 pmol/L, TSH: &lt;0.05 mU/L</td>
<td>No thrombophilia. No AF</td>
<td>[29]</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>32</td>
<td>SSS Transverse sinus sx</td>
<td>Graves' disease</td>
<td>fT4: 80 pmol/L, TSH: &lt;0.05 mU/L</td>
<td>No thrombophilia. No AF</td>
<td>[29]</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>28</td>
<td>Superior sagittal vein Transverse sinus dx</td>
<td>Graves' disease</td>
<td>fT4: 57.3 pmol/L, TSH: &lt;0.05 mU/L</td>
<td>No oral contraceptive pill. Factor V Leiden heterozygous</td>
<td>[30]</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>18</td>
<td>Deep cerebral veins Inferior sagittal sinus Straight sinus Left lateral sinus</td>
<td>Graves' disease</td>
<td>fT4: 130 pmol/L, TSH: &lt;0.05 mU/L</td>
<td>No thrombophilia. Low-dose oral contraceptive pill.</td>
<td>[31]</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>Lateral sinus sx Jugular vein sx</td>
<td>Graves' disease</td>
<td>fT4: 28.8 pmol/L, TSH: &lt;0.02 mU/L</td>
<td>Oral contraceptive. Increased FVIII</td>
<td>[32]</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>32</td>
<td>Sigmoid sinus sx</td>
<td>Not specified</td>
<td>fT4: 65 pmol/L, TSH: &lt;0.06 mU/L</td>
<td>Protein C deficiency.</td>
<td>[33]</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>32</td>
<td>SSS Lateral sinus sx</td>
<td>Not specified</td>
<td>Not reported</td>
<td>Obesity. Oral contraceptives. APC-R. No family history of VTE</td>
<td>[34]</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>34</td>
<td>Dural sinuses Internal jugular veins</td>
<td>Not specified</td>
<td>T4 uptake by radioimmunoassay 17.8</td>
<td>Plasminogen deficiency. Chronic inflammatory disease.</td>
<td>[35]</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>28</td>
<td>Transverse sinus sx Sigmoid Sinus Rectus sinus Internal jugular vein sx</td>
<td>Graves' disease</td>
<td>fT4 &gt;70 pmol/L, TSH &lt;0.01 mU/L</td>
<td>Oral contraceptives. aCL IgG FVIII 190%</td>
<td>[36]</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>60</td>
<td>SSS Transverse sinus dx</td>
<td>Graves' disease.</td>
<td>fT4: &gt;77 pmol/L, TSH: 0.002 mU/L</td>
<td>Low protein C activity 52%. Increased fibrinogen. AF.</td>
<td>[37]</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>42</td>
<td>SSS Transverse sinus dx</td>
<td>Subacute De Quervain’s thyroiditis</td>
<td>fT4: 76.2 pmol/L, TSH: &lt;0.01 mU/L</td>
<td>Prothrombin G20210A heterozygous mutation</td>
<td>[38]</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>38</td>
<td>Lateral sinus sx</td>
<td>Graves' disease</td>
<td>fT4: &gt;75 pmol/L, TSH: &lt;0.10 mU/L</td>
<td>No thrombophilia</td>
<td>[39]</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>44</td>
<td>Longitudinal superior sinus Lateral sinus dx</td>
<td>Not specified</td>
<td>fT4: &gt;49 pmol/L, TSH: &lt;0.15 mU/mL</td>
<td>No deficit protein C and S</td>
<td>[39]</td>
</tr>
</tbody>
</table>

SSS indicates superior sagittal sinus; AF, atrial fibrillation; FVIII, factor VIII; APC-R, activated protein C-resistance; VTE, venous thromboembolism; aCL, anticardiolipin; sx, left; and dx, right.
Moyamoya
Moyamoya disease is a rare cerebrovascular disorder that is characterized by bilateral stenosis or occlusion of the distal segments of the internal carotid arteries accompanied by typical collaterals vessels. The pathogenesis of Moyamoya disease is unknown, but hyperactivity of cervical sympathetic nerves may contribute to the stenosis of the cerebral arteries. In general, transient ischemic attacks and infarction are more common in the juvenile group, whereas intracranial hemorrhage is a more prevalent clinical manifestation in adult cases. A total of 10 cases of Graves’ disease associated with Moyamoya disease or Moyamoya variant have been described. In most cases, cerebral infarcts occurred when the patients were thyrotoxic. There is no clear pathogenetic relationship between Graves disease, an autoimmune disorder, and Moyamoya.

Table 2. Thyrotoxicosis and cerebrovascular disease.

<table>
<thead>
<tr>
<th>Possible pathogenesis</th>
<th>Frequency of association</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioembolic stroke</td>
<td>AF (certain)</td>
<td>25% of AF in patients &gt;60 ys.</td>
</tr>
<tr>
<td>Non cardioembolic stroke</td>
<td>Hypercoagulability state, APS</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cerebral vein thrombosis</td>
<td>Hypercoagulability state, APS, vascular compression</td>
<td>Rare</td>
</tr>
<tr>
<td>Giant Cell Arteritis</td>
<td>Autoimmunity</td>
<td>From 0 to 6-fold increase</td>
</tr>
<tr>
<td>Moyamoya</td>
<td>Unknown</td>
<td>Rare</td>
</tr>
</tbody>
</table>

APS indicates antiphospholipid syndrome
*Insufficient evidence of an increased risk compared to non-thyrotoxic AF patients

Evidence for Tables 2, 3, 4:
Grade A: well-designed controlled cohort and/or case control studies with concordant results.
Grade B: one well designed controlled cohort or case control studies.
Grade C: cohort or case control studies with one or two of the following limits: not concordant results; not well designed (not controlled study, limited number of patients, etc.); insufficient statistical power.
Grade D: only case reports or case series; or more than two limits in Grade C; or indirect evidence from studies with other primary and secondary objectives.

Vascular Compression
A goiter may lead to venous stasis or a reduction in arterial cerebral blood flow attributable to carotid compression. At least 1 patient with a large goiter that directly compressed the brachiocephalic vessels and no other risk factors have been reported in the literature. This patient had a goiter and a left hemiparesis attributable to right temporoparietal infarction. Cerebral arteriography showed a brachiocephalic and right subclavian stenosis secondary to compression by a thyroid nodule.
Hypothyroidism

Overt hypothyroidism can be classified on the basis of its time of onset, severity, and pathogenesis[89]. In patients with primary hypothyroidism, in whom serum thyrotropin is elevated, the distinction between overt and subclinical hypothyroidism can be defined biochemically by whether the serum free thyroxine concentration is below or within the reference range[2;3]. The term myxedema is now usually reserved for cases of overt hypothyroidism that are severe or complicated.

Atherosclerosis

In 1878, Greenfield found diffuse atherosclerosis in a 58-year old woman with myxedema at autopsy: ‘There was edema of the skin . . . much serous effusion in the pericardium . . . the heart was large . . . the arteries were everywhere thickened, the larger ones atheromatous[70;71]. In 1883, Kocher noted that arteriosclerosis occurred commonly after thyroid extirpation and raised the hypothesis of a causal relationship between hypothyroidism and atherosclerosis[72]. Since then, a body of clinical case reports, epidemiological studies, biochemical observations, and case-control and cohort studies have linked hypothyroidism and atherosclerosis[73]. Coronary artery atherosclerosis is twice as common in patients with hypothyroidism compared with sex and age-matched controls, and adequate thyroid hormone replacement therapy may protect against progression[73;74]. The frequency of atherosclerosis in other arteries is less studied. Early arterial structural and functional alterations involve the muscular arteries more than the elastic arteries[75]. A raised serum TSH has been proposed as one of the risk factors for the development of peripheral arterial disease in women[76]. A decrease in carotid intima-media thickness as a result of thyroid hormone replacement therapy has been described for overt hypothyroidism and for subclinical hypothyroidism[77;78]. There are no randomized studies that have assessed the impact of L-thyroxin replacement therapy on important cardiovascular outcomes[10]. Subclinical hypothyroidism certainly influences cardiovascular risk factors; however, the relationship with atherosclerosis is still a matter of debate. Some studies showed a relationship[79–82] that was not confirmed in other studies[83–85]. These inconsistent results can be explained by differences in design and the relatively small size of most studies. Also in euthyroid patients, a correlation between levels of thyroid hormones and atherosclerosis has been suggested. One study showed that low fT4 is a risk factor for atherosclerosis in male euthyroid hyperlipidemic patients measuring carotid atherosclerotic lesions[86], and an angiographic study in 100 patients suggested that a variation of thyroid function within the normal range might influence the presence and severity of coronary atherosclerosis[87]. We performed an extensive search through MEDLINE and EMBASE databases in the all-languages literature using the text words ‘hypothyroidism’ and ‘stroke’ or ‘cerebrovascular disease’. We did not identify any cohort or case-control studies that investigated hypothyroidism as a possible risk factor for atherothrombotic stroke. Nonetheless, hypothyroidism has a clear influence on atherosclerotic risk factors, and this may lead to cerebrovascular disease[88].

Cardiovascular Risk Factors

The increased cardiovascular morbidity in hypothyroid patients has been attributed to the traditional cardiovascular risk factors: elevated low-density lipoprotein (LDL) cholesterol levels...
and diastolic hypertension\cite{89}. Important associations have been identified for other risk factors for atherosclerosis (eg, hyperhomocysteinemia and endothelial dysfunction)\cite{90} in individuals with overt hypothyroidism and, in some cases, subclinical hypothyroidism.

**Lipids**
The composition and the transport of lipoproteins are disturbed in thyroid diseases. Overt hypothyroidism is characterized by hypercholesterolemia\cite{91}, and conversely, 4% to 14% of hypercholesterolemic patients have been reported to have hypothyroidism\cite{92}, a relationship that is often unsuspected. The lipid profile is presented as a marked increase in LDL and apolipoprotein B because of a decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver\cite{93}. The high-density lipoprotein (HDL) levels are normal or even elevated in severe hypothyroidism because of decreased activity of cholesteryl-ester transfer protein and hepatic lipase, which are regulated by thyroid hormones. The low activity of cholesteryl ester transfer protein, and more specifically of hepatic lipase, results in reduced transport of cholesteryl esters from HDL to very low-density lipoproteins, and intermediate LDLs and reduced transport of HDL\cite{2;93}. Moreover, hypothyroidism increases the oxidation of plasma cholesterol\cite{94}. However, thyroxine therapy, in a thyrotropin (TSH)-suppressive dose, usually leads to a considerable improvement of the lipid profile. The changes in lipoproteins are correlated with changes in free thyroxine levels. The effects of subclinical hypothyroidism on serum lipid levels remain controversial, probably because of a great individual variability. Some\cite{95}, in contrast to other\cite{96}, cross-sectional studies have demonstrated that serum levels of total cholesterol and LDL cholesterol are higher in patients with subclinical hypothyroidism than in euthyroid controls. A recent meta-analysis on the effect of therapy for subclinical hypothyroidism on serum lipid levels demonstrated a very limited mean reduction in the total cholesterol level (7.9 mg/dL [0.2 mmol/L]) and in the LDL cholesterol level (10 mg/dL [0.26 mmol/L]), and no clear effect on HDL cholesterol\cite{97}. Patients with higher cholesterol levels (>240 mg/dL [6.21 mmol/L]) and patients with subclinical hypothyroidism as a result of inadequately treated overt hypothyroidism had greater reductions in cholesterol levels. Small studies\cite{92} have suggested that patients whose serum thyrotropin level is <10 mU/L may have no reduction in cholesterol levels with thyroxine replacement, but the meta-analysis did not directly address this issue. Two population-based studies have added to the uncertainty in this area. In the first, based on a 20-year follow-up of the Whickham cohort, there was no relationship between subclinical hypothyroidism, cardiovascular outcome, and lipids after adjustment for age\cite{85}. In the second study, a cross-sectional cohort study of middle-aged Dutch women, those with subclinical hypothyroidism were approximately twice as likely as euthyroid control women to have calcification of the aorta on a chest X-ray film and a history of myocardial infarction after adjustment for known cardiovascular risk factors\cite{82}. Remarkably and unexplained, at baseline, women with subclinical hypothyroidism had age-adjusted serum cholesterol levels that were lower than those of the euthyroid control women. In conclusion, overt hypothyroidism has a clear influence on lipids, especially on LDL cholesterol, whereas mild thyroid hormone deficiency may have a limited effect.

**Hypertension**
Overt hypothyroidism may alter blood pressure, in particular diastolic values\cite{89;98}. In a study of 169 women with overt hypothyroidism, the prevalence of hypertension was nearly 3 times higher
Table 3. Influence of hypothyroidism on cardiovascular risk factors.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids Increased total and LDL cholesterol</td>
<td>A</td>
</tr>
<tr>
<td>Blood pressure Diastolic hypertension</td>
<td>A</td>
</tr>
<tr>
<td>Smoking Impaired thyroid hormone actions</td>
<td>B</td>
</tr>
<tr>
<td>Homocysteinemia Mild increase</td>
<td>A</td>
</tr>
<tr>
<td>Endothelium Endothelial dysfunction</td>
<td>C</td>
</tr>
<tr>
<td>CRP Mild increase</td>
<td>C</td>
</tr>
<tr>
<td>Coagulation abnormalities Different coagulation profile in moderate and severe hypothyroidism</td>
<td>C</td>
</tr>
</tbody>
</table>

Table 4. Subclinical diseases and risk factors.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub. hyper Increased incidence (2.8-5-fold)</td>
<td>Serum TSH &lt;0.1 mU/L: A Serum TSH 0.1-0.45 mU/L: C</td>
</tr>
<tr>
<td>AF</td>
<td>Serum TSH &gt; 10 mU/L: A Serum TSH 4.5-10 mU/L: C</td>
</tr>
<tr>
<td>Sub. hypo</td>
<td>Serum TSH &gt; 10 mU/L: A Serum TSH 4.5-10 mU/L: C</td>
</tr>
<tr>
<td>Lipids Mild increased in total and LDL cholesterol</td>
<td>C</td>
</tr>
<tr>
<td>Blood pressure Mild increase in diastolic pressure</td>
<td>C</td>
</tr>
<tr>
<td>Homocysteine None</td>
<td>B</td>
</tr>
</tbody>
</table>

than in a euthyroid control group (14.8% versus 5.5%)[89], and euthyroid normotensive patients had an increase in diastolic blood pressure after thyroidectomy-induced hypothyroidism[89]. In a survey of consecutive hypertensive outpatients, 3.6% were found to be hypothyroid, and in this subset, diastolic blood pressure fell significantly after adequate thyroid replacement therapy[100].

Regarding subclinical hypothyroidism and hypertension, there is less published evidence. Luboshitzky et al observed in 2 small case-control studies that mean diastolic blood pressure was higher in 57 and 44 women with subclinical hypothyroidism than in euthyroid controls[101,102]. Potential mechanisms for reversible diastolic and systolic hypertension in hypothyroidism include increases in peripheral vascular resistance[103] and arterial stiffness[104]. Vasoconstriction
may reflect the absence of demonstrated vasodilatory T3 effects on vascular smooth muscle\textsuperscript{[105]} or be the result of a higher circulating noradrenaline level and a decrease in the number of vascular $\beta$-adrenergic receptors\textsuperscript{[89]}. More than half of hypothyroid hypertensive patients display low plasma renin activity\textsuperscript{[106]}. Low angiotensin levels have also been reported in hypothyroidism\textsuperscript{[107]}, and prohormone natriuretic peptide and atrial natriuretic factor are decreased\textsuperscript{[106]}. Finally, vasopressin plasma levels are mildly increased and improve after replacement therapy\textsuperscript{[109]}.

**Smoking**

Synergistic effects between smoking and hypothyroidism have been reported. Smokers with overt hypothyroidism have been shown to have higher serum concentrations of total and LDL cholesterol, higher clinical symptom scores, more prolonged ankle-reflex times, and higher creatine kinase concentrations than nonsmokers with hypothyroidism. These differences were noted despite similar concentrations of TSH, fT4, and triiodothyronine, suggesting that cigarette smoking may impair thyroid hormone action in target tissue\textsuperscript{[71;110]}.

**Endothelial Dysfunction**

Endothelial dysfunction occurs early in the atherosclerotic process and may be a key initiating event\textsuperscript{[111]}. Endothelial dysfunction is present in hypothyroid patients, thereby providing an additional link between hypothyroidism and vascular disease\textsuperscript{[112]}. Nevertheless, its presence in hyperlipemic subjects makes it difficult to discern which abnormality is responsible for the endothelial dysfunction. Recently, 2 studies showed that endothelial function improved with thyroid replacement therapy, in agreement with animal studies suggesting that thyroid hormone exerts part of its vascular effect through an endothelial mediated mechanism\textsuperscript{[90;113]}. In one study, the improvement occurred without change in medications, blood pressure, serum lipids, homocysteine levels, or high-sensitive C-reactive protein (CRP) levels. In thyrotoxic patients, increased levels of soluble endothelial molecules such as thrombomodulin, endothelin, and adhesion molecules have been observed as well\textsuperscript{[114;115]}.

**Homocysteine**

Homocysteine is an independent risk factor for cardiovascular disease, premature atherosclerotic vascular disease, and venous thrombosis\textsuperscript{[116]}. It is still controversial whether mild hyperhomocysteinemia is a causal factor. Plasma homocysteine concentration is controlled by genetic (MTHFR C677T mutation), nutritional (vitamins folate, B12, or B6), and acquired factors (renal function, malignancies, inflammation, and cigarette smoking\textsuperscript{[116]}. Thyroid hormones act by modulating gene expression and by influencing a multitude of enzyme systems, including several enzymes involved in homocysteine metabolism\textsuperscript{[117]}, thereby modulating homocysteine levels\textsuperscript{[118;119]}. Other studies indicated that the increase in homocysteine concentrations during hypothyroidism might also be explained by changes in folate status\textsuperscript{[120]} or by concurrent changes in renal function\textsuperscript{[121]}. Mildly elevated total plasma homocysteine levels (mean value <20 μmol/L) have been reported in patients with overt hypothyroidism and mildly decreased levels in overt hyperthyroidism\textsuperscript{[91;120;122]}. Plasma fT4 is an independent determinant of homocysteine concentrations. In fact, lower folate levels, lower creatinine clearance in hypothyroidism, and a higher creatinine clearance in hyperthyroidism only partially explain the changes in homocysteine\textsuperscript{[122]}. A normalization
of hyperhomocysteinemia has been achieved after treatment for hyperthyroidism and for hypothyroidism\cite{120,123,124}. Clearly, clinical relevance of these alterations in homocysteine levels and the response on L-thyroxine treatment is uncertain. Different from overt hypothyroidism, subclinical hypothyroidism has not been found to be associated with hyperhomocysteinemia, and L-thyroxine supplementation has no influence on homocysteine levels\cite{101,125}.

**CRP, Insulin Resistance, and Coagulation Abnormalities**

CRP is an acute-phase protein that circulates in higher concentrations in a variety of acute and chronic diseases. Increased concentrations have been measured in overt and subclinical hypothyroid patients compared with controls\cite{125}. However, CRP levels did not decrease with T4 treatment of subclinically hypothyroid patients\cite{102}. Insulin resistance or metabolic syndrome is an independent risk factor for cardiovascular disease even in individuals without diabetes. Hypothyroidism does not seem to cause insulin resistance\cite{126}, but LDL cholesterol concentrations were higher in insulin-resistant subjects with high normal TSH levels compared with insulin-sensitive individuals\cite{127}. Hypothyroidism may have procoagulant and anticoagulant influences. It leads to lower von Willebrand factor levels, a decreased fibrinolytic activity in patients with moderate hypothyroidism, and, conversely, a tendency toward increased fibrinolytic activity in subjects with severe hypothyroidism. These results suggest possible different coagulation profiles in moderate and severe hypothyroidism\cite{48,128–130}.

**Thyroid Diseases and Other Cerebrovascular Manifestations**

We searched specifically for a possible association between thyroid diseases and other types of cerebrovascular disease. We focused especially on cerebral small vessel disease (or white matter lesions), cerebral aneurysms, and subarachnoidal bleeding, but we did not find relevant studies indicating such an association.

**Conclusion**

The main findings on the relationship between thyroid disease and cerebrovascular diseases are summarized in Tables 2, 3, and 4. In subclinical hyperthyroidism with serum TSH levels <0.1 mIU/L, the incidence of AF is increased, and in overt hyperthyroidism, cardioembolic stroke is clearly associated to thyrotoxic AF. There is insufficient evidence to support the concept of an increased cardioembolic risk attributable to a hypercoagulability state. Only in vivo and in vitro studies suggest an increased thrombotic risk in thyrotoxicosis\cite{49}. Acute CVT is a relatively rare disorder that has been observed in patients with hyperthyroidism. The high rate of case reports suggests that there may be a causal relationship\cite{36}. Hyperthyroidism has also been associated with Moyamoya and GCA in some case reports. Although these associations are not definitively proven, physicians should be aware of these rare conditions. In hypothyroidism, enough evidence supports the association of several traditional and newer atherosclerotic risk factors with overt disease, such as increased LDL and endothelial
dysfunction. Nonetheless a clear influence on atherosclerotic risk factors, which may lead to cerebrovascular disease, no case-control or cohort studies have ever investigated hypothyroidism as a possible risk factor for atherothrombotic stroke. Nowadays, the usual presentation of hypothyroidism is the subclinical form, and no good evidence exists to demonstrate its association with cardiovascular risk factors. Subclinical hypothyroidism could also be a risk factor itself, but no definite evidence confirms this. Because sound evidence is lacking, well-designed case-control or prospective studies are therefore warranted to confirm the association between atherothrombotic stroke and overt and subclinical hypothyroidism.

It is not likely that subclinical hypothyroidism has a very strong influence on stroke risk. To detect an increase of 20% in stroke risk, and accepting a type I error of 0.05 and a power of 0.80, more than 2000 stroke patients and control persons have to be included in a case-control study, given a prevalence of subclinical hypothyroidism of 15% to 20% in the elderly. Even if definitive conclusion cannot be drawn, physicians must be aware of the possible role of hypothyroidism in atherothrombotic cerebrovascular disease as well.

References


Thyroid and stroke


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