Chapter 1.1
Hypothyroidism and cardiovascular diseases in rheumatoid arthritis

1.1A Rheumatoid arthritis is associated with a high prevalence of hypothyroidism that amplifies its cardiovascular risk

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ABSTRACT

Objective. Rheumatoid arthritis (RA) patients have an increased risk of developing cardiovascular diseases (CVD). Other autoimmune diseases such as hypothyroidism are also associated with an enhanced risk for CVD. Our objective was to determine first, the prevalence of hypothyroid disorders in RA patients, and second, the risk of CVD in RA patients with hypothyroid abnormalities.

Methods. Subjects were RA patients who participated in an ongoing prospective cohort study of cardiovascular mortality and morbidity (n=358) in which hypothyroid abnormalities were assessed. CVD was defined as a verified medical history of coronary, cerebral or peripheral arterial disease.

Results. Clinical hypothyroidism was observed in 16 of 236 female RA patients (6.8%), which is significantly higher than in the general population of The Netherlands.

Subclinical hypothyroidism was detected in 6 out of 236 RA women (2.5%). In female RA patients, CVD was present in 6 out of 16 (37.5%) of all hypothyroid women. The odds ratio for CVD comparing female hypothyroid RA patients with female euthyroid RA patients was 4.1 (95% CI 1.2–14.3) after adjustment for sex, age, diabetes, smoking (ever), hypertension and statin use.

Conclusions. Clinical hypothyroidism was observed three times more often in female RA patients than females in the general population. In female RA patients, clinical hypothyroidism was associated with a fourfold higher risk of CVD in comparison with euthyroid female RA patients independently of the traditional risk factors.
INTRODUCTION

Several investigators have reported similarities between atherosclerosis and inflammatory autoimmune diseases such as rheumatoid arthritis (RA).(1-3) There is increasing evidence for the important role of inflammation in the development and progression of atherosclerosis. Inflammation may change a stable plaque into an unstable plaque and can cause thrombosis, which will frequently precipitate acute vascular events. Furthermore, it has been demonstrated that RA is associated with an excess of cardiovascular mortality.(4) Moreover there is a high prevalence of preclinical carotid atherosclerosis in patients with rheumatoid arthritis.(5) Hence, generalised autoimmune diseases can be an additional risk factor for the development of CVD.(4)

Hypothyroidism can cause dyslipidemia characterized by an elevated LDL cholesterol (LDLc) and a total cholesterol (TC) by the induction of a decreased uptake of LDLc by liver cells.(6) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women and it is associated with an insulin resistance related dyslipidemia in RA patients.(7-8) Therefore, clinical and subclinical hypothyroidism are generally considered to be risk factors for CVD. However, in a very recent, population-based investigation, subclinical hypothyroidism was found not to be associated with incident cardiovascular diseases.(9)

There are scarce data available about the prevalence of CVD in patients with thyroid disorders. In the first systematic controlled autopsy study a higher prevalence of myocardial infarction in myxedema patients was found in comparison with euthyroid controls.(10) Another autopsy study demonstrated a higher incidence of severe coronary artery diseases in hypothyroid patients independent of hypertension, diabetes mellitus, or obesity.(11) Both autopsy studies have methodological limitations and conclusions of these autopsy studies are therefore difficult to interpret.(12)

The present study was undertaken to investigate the question whether hypothyroidism occurs more frequently in RA patients and to investigate the association of hypothyroidism with prevalent CVD in RA.

PATIENTS AND METHODS

Study population

For this study three hundred fifty eight RA patients, participating in an ongoing prospective cohort study of cardiovascular mortality and morbidity in RA patients performed in the Jan van Breemen Institute (JBI), Amsterdam, were included. All RA patients registered at the JBI were eligible for participation; the study-population was randomly selected and subsequently recruited during regular
outpatient visits. The participants were enrolled between January 2001 and January 2002. The patients’ ages ranged from 50 to 75 and RA was diagnosed according to the 1987 ACR criteria. At the inclusion visit patients’ demographic, clinical and laboratory data (including the assessment of thyroid function) were collected. The data and blood sera were obtained by systematic chart reviews of the medical notes.

**Thyroid abnormalities**

This study focused on hypothyroidism, hence we excluded hyperthyroid patients, resulting in three subgroups: i.e. subclinical hypothyroidism, clinical hypothyroidism and euthyroidism. Clinical hypothyroidism was defined by a documented medical history of hypothyroidism or by the criteria for thyroid abnormalities as defined by the Dutch national healthcare consensus committee. Subclinical hypothyroidism was defined by an increased (> 4.0 mU/l) serum thyroid stimulating hormone (TSH) in the presence of a normal (11-25 pmol/l) serum free thyroxine (fT4) assessed from blood samples.

As reference for thyroid abnormalities the age adjusted prevalence in the general population data of the Dutch national healthcare consensus committee was used.

**RA related data**

The 28 joints’ disease activity score (DAS 28) was assessed to measure the disease activity.

**CVD related data**

CVD was defined as verified history of coronary, cerebral or peripheral arterial diseases. coronary artery disease included a myocardial infarction, a coronary artery bypass graft procedure, percutaneous transluminal coronary angioplasty or Minnesota codes 1-1 or 1-2 on the ECG. Cerebral arterial disease was defined as a cerebral vascular accident, a transient ischaemic attack or carotid endarterectomy. Peripheral arterial disease included an aneurysm of the abdominal aorta, a peripheral arterial bypass, an ankle/brachial blood pressure index (ABPI) of less than 90% (independent of symptoms) and an amputation of the leg. The (traditional) risk factors for CVD were assessed: male gender, age, smoking, body mass index (BMI), waist circumference, the presence of hypertension (defined as a blood pressure > 140 mm Hg systolic, > 90 mm Hg diastolic or the use of antihypertensive medication), diabetes mellitus (defined as fasting glucose > 7.0 mmol/L, or the use of antidiabetics), hypercholesterolemia (defined as a total cholesterol of more than 6.5 mmol/L or
statin use) and the presence of renal insufficiency (defined as an increased serum creatinine level (for men > 114 μmol/l and for women > 88 μmol/l)). Body mass index (BMI) was defined as weight (in kilograms) divided by length in square meters and a BMI ≥ 25 was defined abnormal. An abnormal waist circumference was defined according to the International Diabetes Foundation (IDF), for men a circumference ≥ 94 cm and for women a circumference ≥ 80 cm. During the visit to the research physician the ABPI was measured and an ECG was made and assessed using Minnesota codes for myocardial infarction.

**Laboratory tests**

TSH and fT4 were assessed in all patients by the Elecsys test. IgM rheumatoid factor (IgM-RF) and anti cyclic citrullinated peptides (anti-CCP) antibodies were measured using in-house enzyme linked immunosorbent assays on an ES 300 analyser (Roche Diagnostics).

**Statistical analyses**

The prevalence of the hypothyroid subgroups was compared with the general population by means of a binomial test. The population-based prevalence was adjusted for age and gender. All patients suffering from (sub)clinical hypothyroidism were compared with the euthyroid patients for RA and CVD related parameters. The RA and CVD related data of the subgroups of thyroid dysfunction were compared, using Pearson’s Chi square test for dichotomous variables and using Mann-Whitney test for continuous variables. Logistic regression analysis was used to calculate the odds ratio (OR) with 95% confidence interval (CI) for thyroid disorders as risk factors for CVD. This OR was adjusted for possible confounders: i.e. age, gender, diabetes, smoking, hypertension, statin use, renal insufficiency, rheumatoid factor and disease duration. A P-value below 0.05 was considered to be statistically significant. For all analyses SPSS 13.0 for Windows (SPSS, Inc., Chicago, Illinois) was used.

**RESULTS**

**Patients**

The main characteristics of our population are shown in table 1. In this study 358 patients with RA were evaluated, 236 of which were women (66%). All patients with clinical hypothyroidism (n=16) were women, which is significantly higher than in the other subgroups (subclinical hypothyroidism and euthyroidism), of which respectively 6/10 and 194/308 (approximately 60% in all the other subgroups) were women (p=0.001). The median age in euthyroid women (62) was significantly lower
Cardiovascular risk factors did not differ (significantly) between (sub)clinical hypothyroid and euthyroid RA patients.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Subclinical Hypothyroidism (n = 10)</th>
<th>Clinical Hypothyroidism (n = 16)</th>
<th>Euthyroidism N = 308</th>
<th>p value *</th>
<th>p value #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, %</td>
<td>60</td>
<td>100</td>
<td>63</td>
<td>1.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td>61 (57 – 65)</td>
<td>68 (63 – 74)</td>
<td>62 (56 – 68)</td>
<td>0.43</td>
<td>0.02</td>
</tr>
<tr>
<td>RA duration, years</td>
<td>5.9 (3.2 – 7.0)</td>
<td>6.2 (3.9 – 10.5)</td>
<td>7.1 (4.2 – 10.5)</td>
<td>0.12</td>
<td>0.60</td>
</tr>
<tr>
<td>IgM-RF positive, %</td>
<td>70</td>
<td>81</td>
<td>71</td>
<td>1.00</td>
<td>0.57</td>
</tr>
<tr>
<td>Anti-CCP, AU/ml</td>
<td>20 (6 – 2088)</td>
<td>40 (9 – 2120)</td>
<td>62 (10 – 450)</td>
<td>0.64</td>
<td>0.67</td>
</tr>
<tr>
<td>DAS-28</td>
<td>4.4 (3.2 – 5.6)</td>
<td>4.2 (3.0 – 4.8)</td>
<td>3.9 (2.9 – 4.9)</td>
<td>0.30</td>
<td>0.57</td>
</tr>
<tr>
<td>Prednison use, %</td>
<td>30</td>
<td>13</td>
<td>16</td>
<td>0.38</td>
<td>1.00</td>
</tr>
<tr>
<td>CVD related variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD history, %</td>
<td>10</td>
<td>38</td>
<td>17</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking ever, %</td>
<td>60</td>
<td>63</td>
<td>79</td>
<td>0.23</td>
<td>0.13</td>
</tr>
<tr>
<td>DM, %</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>1.00</td>
<td>0.61</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
<td>90 (88 – 99)</td>
<td>94 (83 – 106)</td>
<td>92 (82 – 101)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>25 (24 – 30)</td>
<td>28 (25 – 30)</td>
<td>26 (23 – 29)</td>
<td>0.80</td>
<td>0.11</td>
</tr>
<tr>
<td>Statin use, %</td>
<td>0</td>
<td>13</td>
<td>11</td>
<td>0.39</td>
<td>1.00</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>5.4 (4.5 – 7.4)</td>
<td>5.5 (4.9 – 6.3)</td>
<td>5.7 (5.0 – 6.5)</td>
<td>0.72</td>
<td>0.48</td>
</tr>
<tr>
<td>HDLc, mmol/l</td>
<td>1.4 (1.2 – 1.6)</td>
<td>1.2 (1.1 – 1.7)</td>
<td>1.4 (1.1 – 1.7)</td>
<td>0.81</td>
<td>0.49</td>
</tr>
<tr>
<td>LDLc, mmol/l</td>
<td>3.5 (3.3 – 5.3)</td>
<td>3.6 (2.5 – 4.4)</td>
<td>3.6 (3.0 – 4.4)</td>
<td>0.53</td>
<td>0.47</td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>94 (85 – 103)</td>
<td>86 (71 – 93)</td>
<td>86 (78 – 97)</td>
<td>0.15</td>
<td>0.27</td>
</tr>
<tr>
<td>Thyroid related variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH, μU/l</td>
<td>4.9 (4.3 – 9.0)</td>
<td>1.1 (0.3 – 3.8)</td>
<td>1.3 (0.9 – 1.8)</td>
<td>&lt;0.001</td>
<td>0.44</td>
</tr>
</tbody>
</table>

N = number; % = percentage; RF = rheumatoid factor; CCP = cyclic citrullinated peptide; DAS-28 = 28 joint disease activity score; CVD = cardiovascular disease; DM = diabetes mellitus; TC = total cholesterol; HDLc = high density lipoprotein cholesterol; LDLc = low density lipoprotein cholesterol; TSH = thyroid stimulating hormone. * Subclinical hypo- vs. euthyroidism, # Clinical hypo- vs. euthyroidism.

Thyroid abnormalities

In the RA population under study clinical hypothyroidism was more frequently present in women than in men; 6.8% (95%-CI: 5.1-8.4) of the women had clinically manifest hypothyroidism in comparison with the 2.7% observed in the Dutch population (P < 0.001) (table 2). In female RA patients subclinical hypothyroidism was less prevalent than in the general female population, 2.5% (95%-CI: 1.5-3.6) versus 18%, respectively (P < 0.001).
Table 2. Prevalence of hypothyroidism

<table>
<thead>
<tr>
<th>Thyroid function</th>
<th>Sex</th>
<th>N</th>
<th>%</th>
<th>Population-based prevalence</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>114</td>
<td>93.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>194</td>
<td>82.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euthyroidism *</td>
<td>Men</td>
<td>0</td>
<td>0</td>
<td>0.3 **</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16</td>
<td>6.8</td>
<td>2.7**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypothyroidism †</td>
<td>Men</td>
<td>4</td>
<td>3.3</td>
<td>3.0**</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>6</td>
<td>2.5</td>
<td>18**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subclinical hypothyroidism ‡</td>
<td>Men</td>
<td>4</td>
<td>3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>20</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other thyroid status</td>
<td>Men</td>
<td>122</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>236</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* TSH = 0.40 – 4.0 mU/l, † TSH > 4.0 mU/l, fT4 < 11 pmol/l, ** age adjusted prevalence, ‡ TSH > 4.0 mU/l, fT4 = 11 – 25 pmol/l, N = number; % = percentage

Risk of CVD

Table 3 shows that RA patients with clinically manifest hypothyroidism had significantly more CVD in comparison with euthyroid RA patients, 37.5% and 13.0% (p = 0.05), respectively (OR 3.1 95%-CI: 1.1-8.9). After adjustments for the possible confounders age and gender the OR for CVD in hypothyroid RA patients was 3.2 (95%-CI: 1.0-10.1). After adjustments for the possible confounders age, gender, diabetes, smoking, hypertension, statin use and renal insufficiency, the OR was 4.6 (95%-CI: 1.3-16.7).

The possible confounders rheumatoid factor and disease duration had no influence on any of the models.

Table 3. Cardiovascular disease risk in thyroid subgroups

<table>
<thead>
<tr>
<th>Model</th>
<th>Subclinical hypothyroidism</th>
<th>Clinical hypothyroidism</th>
<th>(sub)clinical hypothyroidism</th>
<th>euthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 †</td>
<td>0.65 (0.08 – 5.3)</td>
<td>3.1 (1.1 - 8.9)</td>
<td>2.0 (0.80 – 5.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Model 2 †</td>
<td>0.87 (0.10 – 7.4)</td>
<td>3.2 (1.0 – 10.1)</td>
<td>2.2 (0.82 – 5.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Model 3 ‡</td>
<td>1.9 (0.21 – 17.0)</td>
<td>4.1 (1.2 – 14.3)</td>
<td>3.2 (1.1 – 9.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Model 4 ‡</td>
<td>1.9 (0.22 – 17.5)</td>
<td>4.6 (1.3 – 16.7)</td>
<td>3.4 (1.2 – 10.2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Numbers represent prevalence odds ratios (ORs) for cardiovascular disease with 95% confidence interval between brackets. * crude associations, † adjusted for age and gender, # like model 2 plus adjusted for diabetes, smoking ever, hypertension and statin use, ‡ like model 3 plus adjustment for renal insufficiency.
DISCUSSION

The main conclusion of the present study is an almost threefold enhanced prevalence of clinical hypothyroidism in secondary care female RA patients in comparison with the general population. In female RA patients, clinical hypothyroidism was associated with a fourfold higher risk of CVD in comparison with euthyroid female RA patients independently of the traditional risk factors. No clinically manifest hypothyroidism was found in men, which is in accordance with previous observations which proved that thyroid abnormalities are sex related, albeit that the number of studied males was relatively small in our investigation.(18)

The present study shows a prevalence of subclinical hypothyroidism in female RA patients which is lower than in a sex and age matched general population. This finding might be explained by the pyramid hypothesis. This hypothesis is based on the observation that subclinical hypothyroidism will develop into clinically manifest hypothyroidism in approximately one quarter of the cases. Facilitating factors for this development are old age, female gender and higher titers of antibodies for thyroid peroxidase (TPOab).(19-23) This progression into a clinical hypothyroidism is also called the “disease pyramid” theory. Autoimmune diseases such as RA may accelerate this progression of subclinical disease into a clinical disease, which might explain the lower prevalence of subclinical hypothyroidism in RA and the higher prevalence of hypothyroidism in female RA patients in comparison with women of the general population.(23)

It is known that (clinical) hypothyroidism is associated with an increased rate of CVD and an epidemiological study in patients with hypothyroidism showed an OR of 2.8 for early atherosclerosis.(24) The present study yielded an OR of 4.6 for the presence of CVD in hypothyroid female RA patients when comparing them to euthyroid female RA patients. This might indicate a synergistic detrimental effect of RA as well as hypothyroidism for the development of CVD.

In a recent study the relative risk of CVD in Hashimoto’s thyroiditis was 1.8 in comparison with healthy controls.(25) This recent investigation also showed that restoration of thyroid status does not influence the occurrence of CVD. Hence, the excess of CVD in thyroid disorders is not necessarily due to thyroid hormone abnormalities and the accompanying dyslipidaemia, but may be mediated by chronic inflammation, i.e. autoimmunity which might amplify the cardiovascular risk in RA. Literature on inflammation and hypothyroidism is scarce. Some investigations found higher inflammation markers (ESR, CRP or hsCRP) in (sub)clinical hypothyroid patients, (26-27) other studies showed no difference in inflammation markers between (sub)clinical hypothyroid and euthyroid patients.(28-29) Another study revealed that hypothyroidism was associated with endothelium dysfunction, which
was only partially dependent on the altered lipid profile. (30) Recently, these investigators found that low grade systemic inflammation causes endothelial dysfunction in Hashimoto thyroiditis patients. (31)

Hence, our finding of the threefold enhanced prevalence of hypothyroidism in female RA patients, who are at increased risk of CVD (particularly, ischemic heart disease and congestive heart failure which both are not fully explained by traditional Framingham risk factors), (32) is important, as in hypothyroid patients endothelium dysfunction is found which is related to dyslipidaemia as well as systemic inflammation, which might accelerate the development of CVD in the already high risk RA patients.

The cross sectional design of this study can be perceived as a limitation because it is difficult to establish the direction of the observed association. However, as most patients first developed hypothyroidism before clinically apparent cardiovascular disease, it appears that hypothyroidism contributes to the amplification of the cardiovascular risk in RA.

To summarize, this is the first study demonstrating that hypothyroidism in female RA patients is associated with a higher risk of CVD in comparison with euthyroid female RA patients who have an already established increased cardiovascular risk. (33-34) Hence, we should be aware of this amplified cardiovascular risk in hypothyroid female RA patients and consider screening for hypothyroidism in female RA patients.
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