Chapter 1.1
Hypothyroidism and cardiovascular diseases in rheumatoid arthritis

1.1B Coexistence of hypothyroidism with inflammatory arthritis is associated with cardiovascular disease in women

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ABSTRACT

Objective. Hypothyroidism and inflammatory arthritis tend to coexist, but data on this association are sparse. In terms of cardiovascular risk this association may have clinical relevance as this coexistence may carry an additional cardiovascular risk. Therefore, this study calculates, firstly, the prevalence of hypothyroidism in inflammatory arthritis patients, and, secondly, the cardiovascular disease (CVD) prevalence rate in patients with either hypothyroidism, inflammatory arthritis, or both.

Methods. Data was used from the Netherlands Information Network of General Practice (LINH), a representative Dutch sample of 360,000 registered patients. Prevalences of hypothyroidism were calculated and multilevel logistic regression analyses were used to calculate CVD prevalence rates.

Results. Hypothyroidism prevalence was 6.5% in female arthritis patients compared to 3.9% in controls (p<0.001). The CVD prevalence was 4.3% in hypothyroidism, 5.9% in inflammatory arthritis, and 14.3% in hypothyroid inflammatory arthritis and 2.1% in controls. Adjusted CVD prevalence rates were 1.2 (95%-CI:0.99–1.4) for hypothyroidism, 1.5 (95%-CI:1.1–2.0) for inflammatory arthritis, and 3.7 (95%-CI:1.7–8.0) for hypothyroid inflammatory arthritis as compared with controls.

Conclusions. These data raise awareness for coexistence of hypothyroidism and inflammatory arthritis, but also emphasize the importance of cardiovascular risk management in these patients, particularly when hypothyroidism and inflammatory arthritis coexist.
INTRODUCTION

Autoimmune disorders are disease entities with a broad spectrum of manifestations as on one hand the manifestations are more organ specific like autoimmune thyroiditis and on the other hand more systemical like several rheumatic disorders. Traditionally, autoimmune diseases were considered separate disorders, but recently it has become clear that autoimmune diseases share similarities in genetic, immunological origin, and environmental risk factors suggesting that autoimmune disease cluster(1;2). Autoimmune thyroiditis-the most prevalent autoimmune disorder- and inflammatory arthritis appear to be associated, but data on this relationship are sparse.(3;4)

In addition to its coexistence, both hypothyroidism and inflammatory arthritis are associated with a higher cardiovascular disease (CVD) burden.(5-7) Consequently, the question arises whether clustering of hypothyroidism and inflammatory arthritis is associated with an amplified CVD prevalence. As most of the studies on CVD risk and autoimmune conditions were performed in arthritis patients from referral centers and as the CVD risk of these patients may not reflect or overestimate the actual cardiovascular risk of patients in the general population, it is important to assess cardiovascular risk in primary care patients as a more representative sample from the general population.

The aims of the present study were to ascertain the prevalence of hypothyroidism in inflammatory arthritis patients compared to noninflammatory arthritis patients and to determine CVD prevalences in patients with either hypothyroidism or inflammatory arthritis or both as compared with control subjects.

PATIENTS AND METHODS

Study population

Data was used from the Netherlands Information Network of General Practice (LINH). These data were retrieved from electronically medical records kept by a representative sample of 69 general practices with 360,000 registered patients in 2006. Data included information on consultations, morbidity, prescriptions and referrals to other health care professionals. The patients as well as general practices are representative for the Dutch population.(8) Patients under 30 years old were excluded because of their lower probability of inflammatory arthritis, hypothyroidism and/or CVD. Practices that recorded less than six months were excluded from further analysis. The study was carried out according to Dutch legislation on privacy. The privacy regulation of the study was approved by the Dutch Data Protection Authority. According to Dutch legislation, nor obtaining
informed consent nor approval by a medical ethics committee was obligatory for observational studies.

**Classification of diagnoses**

Morbidity data were derived from consultation diagnoses and furthermore from all prescriptions issued by the participating practices. Diagnoses were recorded using the International Classification of Primary Care (ICPC)-1 coding system. When issuing a prescription, a diagnostic code was recorded, and the selected drug was automatically linked to the Anatomical Therapeutic Chemical (ATC) Classification System. This study used the combination of ATC and ICPC-1 code to determine per patient, whether they were diagnosed in 2006 or in the years before with inflammatory arthritis (ICPC code L88; rheumatoid arthritis or ankylosing spondylitis), hypothyroidism (ICPC code T86 and/or ATC code H03AA01 (levothyroxine)), CVD (ICPC code K75 (myocardial infarction), K89 (transient ischemic attack), and/or K90 (stroke/cerebrovascular accident)).

**Statistical analyses**

In a first analysis, the prevalence rate of hypothyroidism was calculated in persons with and without inflammatory arthritis (reference group) for men and women separately in several age groups. Differences in prevalence rates of hypothyroidism between inflammatory arthritis patients and the reference group were tested with chi-square tests.

The prevalence rates of CVD in either inflammatory arthritis or hypothyroidism were compared with multilevel logistic regression analyses with a random intercept using the second order PQL method.

All patients were categorized as inflammatory arthritis without hypothyroidism, hypothyroidism without inflammatory arthritis, inflammatory arthritis and hypothyroidism or controls (reference group). This categorical variable was added to the model with the control-category as reference. The association of inflammatory arthritis and/or hypothyroidism with CVD was adjusted for risk factors: age, hypertension (ICPC code K86 and/or K87), hypercholesterolemia (ICPC code T93) and diabetes (ICPC code T90 and/or the ATC code A10).

We restricted the analyses to female subjects, as there were too few men with both hypothyroidism and inflammatory arthritis to yield meaningful estimates. Chi-square tests were performed with Stata10. Multilevel analyses were performed with MLwiN, a statistical program for multilevel analyses.
RESULTS

Hypothyroidism prevalence

In total 175,061 subjects were studied: 1,518 (0.9%) of these subjects were inflammatory arthritis patients. In both male and female inflammatory arthritis patients hypothyroidism prevalence rates were significantly higher than in controls, 2.4% versus 0.8% in males and 6.5% versus 3.9% in females respectively (Table 1).

CVD prevalence rates

Crude CVD prevalence rates were 4.4% in hypothyroid patients, 5.9% in inflammatory arthritis and 14.3% in hypothyroid inflammatory arthritis, as compared with 2.2% in control subjects. Multilevel analyses revealed significantly higher ORs for all groups as compared with control subjects (Table 2). Adjustment for age, hypertension, DM and hypercholesterolemia moderately attenuated these ORs, but inflammatory arthritis and hypothyroid inflammatory arthritis remained significantly associated with CVD (model II, table 2) Testing for effect modification showed no differences between those above and below 50 years of age.

Table 1 prevalence of hypothyroidism in inflammatory patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Inflammatory arthritis</th>
<th>Controls</th>
<th></th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Total</td>
<td>Prevalence rates (%)</td>
<td>Number</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>76</td>
<td>1,518</td>
<td>5.01</td>
<td>4.153</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>13</td>
<td>545</td>
<td>2.39</td>
<td>681</td>
</tr>
<tr>
<td>Female</td>
<td>63</td>
<td>973</td>
<td>6.47</td>
<td>3.471</td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>128</td>
<td>3.13</td>
<td>422</td>
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<tr>
<td>40-49</td>
<td>2</td>
<td>253</td>
<td>0.79</td>
<td>714</td>
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<tr>
<td>50-59</td>
<td>16</td>
<td>369</td>
<td>4.34</td>
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<td>60-69</td>
<td>21</td>
<td>318</td>
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<td>854</td>
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<td>70-79</td>
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<td>274</td>
<td>7.30</td>
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<tr>
<td>80+</td>
<td>13</td>
<td>176</td>
<td>7.39</td>
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Table 2. Prevalence odds ratios in hypothyroid and inflammatory arthritis patients for cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>Model 1*</th>
<th>Model 2†</th>
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<tbody>
<tr>
<td>Controls (n = 84655)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Hypothyroidism (n = 3471)</td>
<td>1.94 (1.63 – 2.31)</td>
<td>1.19 (0.99 – 1.43)</td>
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<tr>
<td>Inflammatory arthritis (n = 910)</td>
<td>2.44 (1.83 – 3.24)</td>
<td>1.48 (1.10 – 2.00)</td>
</tr>
<tr>
<td>Hypothyroidism &amp; inflammatory arthritis (n = 63)</td>
<td>6.38 (3.10 – 13.12)</td>
<td>3.72 (1.74 – 7.95)</td>
</tr>
</tbody>
</table>

* Logistic multilevel multivariate regression analyses with cardiovascular disease as outcome variable: crude analysis. † Adjustment for age, hypertension, hypercholesterolemia and diabetes. # p < 0.05. OR: odds ratio, C.I.: confidence interval.

DISCUSSION

This study demonstrated a doubled prevalence of hypothyroidism in inflammatory arthritis patients from the general population as compared to controls. This is an important observation given the association of both hypothyroidism and inflammatory arthritis with CVD, that amplifies when hypothyroidism and inflammatory arthritis coexist.

Decades ago signs of hypothyroidism have been reported in 12-30% of arthritis patients and therefore, it seems likely that prevalences of hypothyroidism are increased in patients with inflammatory arthritis.(11;12) Indeed, we observed an increased prevalence of hypothyroidism in inflammatory arthritis when compared to controls. These results emphasize the tendency of autoimmune disorders to cluster.(13) Explanations for the coexistence of autoimmune disorders involve immunological disturbances (in B and T lymphocytes), a tendency to react abnormally in the presence of an antigen or a genetic susceptibility.(13;14)

Inflammatory arthritis as well as hypothyroidism are independently associated with a higher CVD risk. Thyroid hormone deficiency is known to deteriorate endothelial dysfunction directly by increasing oxidative stress, decreasing nitric oxide production and increasing platelet activation, thereby stimulating atherogenesis.(15) Furthermore, hypothyroidism is associated with (subclinical) atherosclerosis in cardiovascular event naive female RA patients.(16;17) Moreover, we previously described an increased cardiovascular risk in CVD event naïve female hypothyroid RA patients reflected by a higher Framingham score and higher prevalence of metabolic syndrome compared to euthyroid female RA patients.(18). In the present study, CVD prevalence rates were significantly higher in female hypothyroid inflammatory arthritis patients as compared to either inflammatory arthritis or hypothyroidism patients alone. This observation in primary care (as a more representative sample of the general population) confirms previous results in secondary care female RA patients indicating a clear association between hypothyroidism and CVD.(19) In this respect, it is noteworthy that functional polymorphisms of protein tyrosine phosphatise (PTP) N22, a susceptibility factor for
several autoimmune diseases like hypothyroidism, inflammatory arthritis and diabetes, accelerate atherosclerosis. (20)

Limitations of this study merit careful consideration. Firstly, causality cannot be shown in this cross-sectional case-control study. Secondly, several CVD risk factors, like lifestyle factors, family history of CVD, socioeconomic status and ethnic background were unavailable, and could not be adjusted for in this study. Thirdly, we cannot exclude that part of our observed findings may be explained by an increased frequency of testing for thyroid disorders as we and others previously described an increased prevalence of hypothyroidism in secondary care RA patients. On the other hand, this study describes for the first time the association between hypothyroidism and arthritis in the general population and therefore, in clinical practice testing more frequent for thyroid disorders is not widely adopted. Fourthly, the ICPC-coding system has not been developed for research aims and does not differentiate between different inflammatory arthritis types, i.e. rheumatoid and psoriatic arthritis or ankylosing spondylitis. Moreover, we cannot exclude that certain patients in the reference group included patients with arthritis. However, in this case misclassification would more likely increase the strength of our findings than the opposite. Nevertheless, the results of this study concern a large representative sample of the Dutch general population and may be the best source for a more precise estimate of the cardiovascular burden, as the general practitioner acts as gatekeeper for referral to specialized care in the general population. (8) Previous studies comprised mostly secondary care arthritis patients with a possibly more severe disease, and therefore, the CVD risk of these patients may not reflect or overestimate the actual cardiovascular risk in the general population. As our study observes a clear association between hypothyroidism, inflammatory arthritis and CVD in primary care patients, this association needs further elaboration in prospective studies.

In conclusion, our observations raise awareness of the coexistence of autoimmune disorders (“polyautoimmune disorder syndromes”) as the hypothyroidism prevalence is twofold elevated compared to control subjects. This is a clinically important observation, given the substantially elevated CVD prevalence rates when hypothyroidism and inflammatory arthritis coexist and emphasizes the need for cardiovascular risk management in this case.
REFERENCES


