Hypothyroidism as a Risk Factor for Development of Cardiovascular Disease in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the frequency of hypothyroidism in patients with rheumatoid arthritis (RA), and to elucidate the association of hypothyroidism and development of cardiovascular disease (CVD) in these patients.

Methods. A retrospective medical record review was performed using all incident cases of adult-onset RA from Olmsted County, MN, USA, that fulfilled criteria for RA in the years 1988-2007. Patients with and without thyroid disease were followed longitudinally for the development of CVD.

Results. A cohort of 650 patients with RA and an age and sex-matched comparison cohort of 650 patients without RA was assembled (both cohorts mean age 55.8 yrs; 69% were women). There was no significant difference between cohorts in the presence of hypothyroid disease or subclinical hypothyroidism at time of RA diagnosis. No significant difference was found in the cumulative incidence of hypothyroid disease between the 2 cohorts. Hypothyroid disease was found to be significantly associated with CVD in patients with RA (hazard ratio 2.0; 95% CI 1.1, 3.6). This difference remained significant and unchanged after adjustment for traditional CV risk factors (HR 2.0; 95% CI 1.1, 3.6).

Conclusion. No significant difference was found in either incidence or prevalence of hypothyroidism between patients with and those without RA. Hypothyroid disease was significantly associated with CVD in patients with RA, even after adjustment for other traditional CV risk factors. (J Rheumatol First Release Feb 15 2012; doi:10.3899/jrheum.111076)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HYPOTHYROIDISM CARDIOVASCULAR DISEASE

Rheumatoid arthritis (RA) is implicated as a risk factor for cardiovascular disease (CVD), and CVD is a major contributing factor to morbidity and mortality in patients with RA[1,2,3,4,5]. It is unclear whether the prevalence of thyroid disease differs in patients with RA compared to the general population[6,7,8,9,10].

Similarly to RA, thyroid disease is linked to CVD, but the influence of thyroid disease on development of CVD in patients with RA has not been well studied. A notable increase of CVD in patients with RA who had hypothyroidism compared to euthyroid patients has been reported[7]. However, most studies are cross-sectional and include patients selectively recruited to study CVD risks. We performed a population-based cohort study to examine the relationship between hypothyroidism and development of CVD in patients with RA.

MATERIALS AND METHODS

Our study used the resources of the Rochester Epidemiology Project, a diagnostic indexing linkage system that allows access to the medical records of all healthcare providers for the population of Olmsted County, Minnesota, USA. Within this system, investigators are able to access clinical and vital status information of all clinically recognized cases of RA in this geographically defined population[11].

The study population consisted of 650 subjects from a previously assembled inception cohort of all Olmsted County residents aged ≥ 18 years who fulfilled the 1987 American College of Rheumatology classification criteria for RA between January 1, 1988, and December 31, 2007[12,13]. For each patient with RA a corresponding comparator subject without RA (referred to as non-RA) of similar age, sex, and calendar year was selected. Patients in both cohorts were followed longitudinally through their medical records until death, migration from Olmsted County, or December 31, 2008. The study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center.

Data collection. Patients in both cohorts were classified according to their thyroid status. Subclinical hypothyroidism was defined as a measured thyroid stimulating hormone (TSH) level > 5.0 mIU/l with a normal free thy-

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roxine (T_4) in the range of 0.8–1.8 ng/dl (reference range of TSH 0.3–5 mIU/l). A T_4 < 1.8 ng/dl with elevated TSH was considered consistent with overt hypothyroidism. Date of detection of abnormal TSH or T_4 was recorded along with the use of thyroid-replacement medication. Clinical diagnosis of Hashimoto's or Graves' disease was recorded. Patients with and without thyroid disease were followed longitudinally for the development of CVD. CVD was defined as myocardial infarction (MI; hospitalized or silent), CV revascularization procedures, angina, and/or physician diagnosis of coronary artery disease (CAD). Silent infarcts were defined as a recorded physician diagnosis of characteristic echocardiogram (ECG) findings in a patient with no previously documented history of MI, or the presence of characteristic ECG findings in a nonacute setting. Heart failure was defined based on the Framingham criteria[14,15]. Information on RA disease and comorbidities was collected, including erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antinuclear antibody (ANA), erosive changes, large joint swelling, severe extraarticular manifestations, joint surgery, nodules, and medication use [methotrexate, hydroxychloroquine, disease-modifying antirheumatic drugs (DMARD), biologic agents, corticosteroids, COX-2 inhibitors, aspirin]. Information on CV risk factors was collected for all cases and comparator subjects, including body mass index (BMI), preexisting CVD, alcoholism, hypertension, diabetes mellitus, dyslipidemia, smoking status, and family history of CAD.

Statistical analysis. Descriptive statistics were used to summarize the data. The cumulative incidence of hypothyroid disease adjusted for the competing risk of death was estimated[16]. These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last followup. However, patients who die before experiencing hypothyroid disease are appropriately accounted for to avoid the overestimation of the rate of occurrence of hypothyroid disease, which can occur if such subjects are simply censored. Patients who were diagnosed with hypothyroid disease prior to the diagnosis of RA, or prior to the index date for subjects in the non-RA comparison cohort, were excluded from the analysis of cumulative incidence. Cumulative incidence comparisons between the cohorts were performed using methods by Gray[17].

Cox proportional hazards models were used to compare the rate of development of hypothyroid disease between patients with RA and the non-RA comparison cohort. In addition, Cox proportional hazards models were used to assess the association of risk factors with the development of hypothyroid disease among patients with RA.

Cox models were also used to assess the influence of hypothyroid disease on the development of CVD or mortality among patients with RA and non-RA subjects. Age was used as the timescale for these models to provide optimal adjustment for age under the assumption that age is likely the most important time determinate of CVD. Subjects entered the model at the age they met criteria for RA and remained in the model until the age of each CVD event. Subjects without events were censored at the age of death or last followup. The models were stratified by sex. Traditional CV risk factors were included in these models as adjustors. Time-dependent covariates were used to model risk factors that developed over time. These time-dependent covariates allowed patients to be modeled as unexposed to the risk factor during the followup time prior to development of the risk factor, then change to exposed following development of the risk factor. Interactions between cohort and hypothyroid disease were examined.

RESULTS

A total of 650 patients with RA and 650 subjects without RA were included in the study. The 2 cohorts had similar characteristics including age at incidence (mean 55.8 yrs) and sex (69% were women). There was a statistically significant difference between rate of testing in RA (50 TSH tests per 100 person-yrs) and non-RA patients (44 tests per 100 person-yrs; p < 0.001). The remainder of characteristics of the cohorts at index is illustrated in Table 1.

Table 1. Characteristics of 650 patients with rheumatoid arthritis (RA) and 650 subjects without RA.

Characteristic	RA	Non-RA	p
Age at incidence, yrs, mean ± SD	55.8 ± 15.7	55.8 ± 15.7	1.0
Sex, female, n (%)	448 (69)	448 (69)	1.0
Length of followup, yrs	7.9 ± 5.2	9.0 ± 5.4	—
Hypothyroid disease at incidence/index, n (%)	107 (16)	88 (14)	0.14
Subclinical hypothyroidism prior to incidence/index, n (%)	20 (3)	27 (4)	0.30
Hashimoto's disease at incidence/index, n (%)	36 (6)	35 (5)	0.90
Graves' disease at incidence/index, n (%)	4 (0.6)	4 (0.6)	1.0
Use of levothyroxine at incidence/index, n (%)	97 (15)	75 (12)	0.07
Rate of TSH testing	50 tests per 100 person-yrs (95% CI 48, 52)	44 tests per 100 person-yrs (95% CI 43, 46)	< 0.001

TSH: thyroid-stimulating hormone.

There was no significant difference between presence of hypothyroid disease at index among patients with and those without RA. Additionally, the cumulative incidence of hypothyroid disease did not vary significantly among patients with and without RA (Table 2). When further subcategorized to autoimmune thyroid disease (Graves' and Hashimoto's), the difference remained nonsignificant. Subclinical hypothyroidism did not vary significantly between patients with and without RA. Use of levothyroxine did not vary between RA and non-RA subjects at the RA incidence date or with cumulative incidence.

A total of 69 patients with RA and 77 non-RA subjects had CVD prior to RA incidence/index date and were excluded from the analysis of CVD, as they were not at risk of developing CVD. During followup, 65 patients with RA and 58 non-RA subjects developed CVD. The cumulative inci-

Table 2. Cumulative incidence of hypothyroid disease in 650 patients with rheumatoid arthritis (RA) and 650 subjects without RA.

Condition	No. Events After Incidence/Index in RA/non-RA	Cumulative Incidence (%) at 10 Years for RA Patients (± SE)	Cumulative Incidence (%) at 10 Years for non-RA (± SE)	p
Hypothyroid disease	39/33	7.7 ± 1.4	6.7 ± 1.3	0.25
Subclinical hypothyroidism	35/24	4.9 ± 1.0	4.0 ± 0.9	0.063
Hashimoto's disease	7/10	1.4 ± 0.6	1.8 ± 0.6	0.56
Graves' disease	2/2	0.2 ± 0.2	0.4 ± 0.3	0.92
Use of levothyroxine	31/29	6.1 ± 1.2	5.5 ± 1.1	0.51

dence of CVD 10 years after RA incidence/index date was 6.1% ± 1.2% in RA and 5.5% ± 1.1% in non-RA subjects. In patients with RA there was a significant association between hypothyroidism and CVD [hazard ratio (HR) 2.0; 95% CI 1.1, 3.6]. This association persisted after adjustment for traditional CV risk factors, including smoking, hypertension, dyslipidemia, diabetes mellitus, and obesity (HR 2.0; 95% CI 1.1, 3.6). When analyzed independently, Hashimoto's disease was found to be significantly associated with CVD in patients with RA (HR 2.7; 95% CI 1.1, 6.3). Patients with Graves' disease could not be analyzed separately due to inadequate sample size. Subclinical hypothyroidism in patients with RA was not significantly associated with CVD or mortality. Use of levothyroxine was significantly associated with CVD in patients with RA (HR 2.1; 95% CI 1.2, 3.8).

In contrast, among the non-RA comparator subjects, there was no association between hypothyroidism and CVD (HR 0.7; 95% CI 0.4, 1.5). Additionally, no association with CVD was found in patients with Hashimoto's disease or with subclinical hypothyroidism (HR 0.2; 95% CI 0.03, 1.5; and HR 1.3; 95% CI 0.5, 3.2, respectively).

Examination of the association of RA disease characteristics failed to reveal an association between RA characteristics and CV risk factors and the development of hypothyroid disease. The disease characteristics included ESR, RF, ANA, erosive changes, large joint swelling, severe extraarticular manifestations, joint surgery, nodules, medication use (methotrexate, hydroxychloroquine, DMARD, biologic agents, corticosteroids, cyclooxygenase-2 inhibitors, aspirin); other CV risk factors were high BMI, preexisting CVD, alcoholism, hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of CAD. However, patients with RA who had atrial fibrillation were more likely to develop hypothyroid disease (HR 3.1; 95% CI 1.3, 7.7).

DISCUSSION

Our study did not demonstrate a significant difference in the presence or development of hypothyroid disease in patients with RA compared to non-RA patients. Further, there was no difference in the presence or development of subclinical hypothyroidism in patients with and those without RA, despite increased rates of testing among patients with RA.

Information in the literature regarding hypothyroidism in patients with RA is conflicting. Studies have demonstrated an increased rate of hypothyroidism in patients with RA[7,8,18,19]. In 3 cross-sectional studies, the rate of hypothyroidism ranged from 3% to 11%[7,8,18]. Results from a prospective case-control study revealed that 20% of women with RA had evidence of hypothyroidism compared to 6% in the control population[19]. Other studies, however, reported no significant difference in rates of thyroid dysfunction[9,10,20].

Among the studies that did not show statistical significance, rates of hypothyroidism in patients with RA ranged from 0% to 3%, and the rates of subclinical hypothyroidism ranged from 4% to 7%[9,10,20]. Most studies of thyroid disease in RA are cross-sectional, with limited followup, with a range of reported prevalence of thyroid disease, including hypothyroidism. Despite increased TSH testing rates in patients with RA compared to non-RA patients, we did not detect a statistically significant difference of thyroid disease. Our findings suggest that there is no difference in the prevalence of thyroid disease (subclinical and clinical) in patients with RA.

In contrast to subjects who do not have RA, we found a significant association between hypothyroid disease and CVD. This is in agreement with another study, in which patients with RA who had clinical hypothyroidism had a 4-fold higher risk of CVD than patients with RA who were euthyroid[7]. An interesting related finding of our study was that there was no apparent change in CVD risk in patients with RA despite treatment with levothyroxine at any point during the followup period. This observation suggests that treatment of thyroid disease may not affect development of CVD, and is a subject for further investigation. Another interesting finding was that RA patients with atrial fibrillation were more likely to develop hypothyroid disease. This may be explained by the presence of hyperthyroidism with subsequent treatment-induced hypothyroidism.

Patients with RA have higher rates of a number of risk factors for CVD than persons without RA, including metabolic syndrome as well as components of metabolic syndrome (hypertension, insulin resistance, and central obesity) and dyslipidemia[18,21,22]. In addition to these classical risk factors for CVD, RA is associated with a chronic inflammatory state that further contributes to development of CVD and heart failure[3,23,24,25,26,27,28].

The pathogenesis of CVD in patients with clinical and subclinical hypothyroidism may relate to inflammatory-based endothelial dysfunction secondary to reduced nitric oxide levels[29,30]. Lipid abnormalities, as observed in hypothyroidism, may also play a role in atherosclerosis[31,32,33,34,35,36]. Increased atheroma formation has been found in patients with RA and hypothyroidism compared to those with RA alone[37]. Inflammation is an important contributor to atherogenesis, a relationship reflected in the correlation between elevated C-reactive protein (CRP) and CVD[35,38,39,40]. Indeed, reductions of serum cholesterol and CRP levels with statin therapy have been shown to significantly reduce CVD[28,41,42]. Although some reports describe increased ESR or CRP in hypothyroid patients, others have failed to confirm these findings[43,44].

There is no consensus on whether thyroid replacement alters the risk for CVD, although some studies indicate that thyroid hormone replacement may improve cardiac function; others deny any effect on CVD risk factors[45,46,47]. One possible explanation for the influence of hypothyroidism on CVD in patients with RA relates to the amplification of the

effects of inflammation and endothelial damage from hypothyroidism in the context of the systemic inflammation of RA[29].

Our study has several potential limitations. From this observational study, we cannot draw any causal relationship between hypothyroid disease and CVD. Additionally, only thyroid tests available from medical records were used to define hypothyroid disease. Over time the thyroid assays have changed, but the reference range has remained the same. It was not possible to adequately determine the reasons for ordering thyroid testing in these patients. However, since the rates of hypothyroid disease were not increased in patients with RA compared to non-RA subjects, despite the higher testing rates among patients with RA, it is likely that the issues of clinical indications for testing affected the results of our study only minimally. Finally, the population of Olmsted County, Minnesota, is predominately white and therefore may not be generalizable to other more diverse populations.

Strengths of the study include the population-based longitudinal design, with a large RA cohort and comparison cohort. A comprehensive medical records linkage system with complete medical information for each patient adds strength to our study. The review process of medical records ensures an accurate assessment of thyroid disease without recall bias.

Our results have implications on monitoring RA patients with hypothyroidism as they may have increased risk of CVD. Since no difference was found in the prevalence of hypothyroidism among RA and non-RA patients, the need to screen patients with RA for hypothyroidism more frequently than patients without RA may be called into question. Additionally, clinicians should be aware of the heightened risk for CVD in those patients in whom a hypothyroid state occurs.

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