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Hypothyroidism as a risk factor for development of cardiovascular disease in patients with rheumatoid arthritis

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Abstract

Background/Purpose—To determine the frequency of hypothyroidism in patients with rheumatoid arthritis (RA), and to elucidate the association of hypothyroidism and development of cardiovascular disease in these patients.

Method—A retrospective medical record review was performed using all incident cases of adult onset RA from a defined geographic population base that fulfilled criteria for RA in the years 1988–2007. Patients with and without thyroid disease were followed longitudinally for the development of cardiovascular disease (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; 69% female). 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 two cohorts. Hypothyroid disease was found to be significantly associated with CVD in patients with RA (hazard ratio 2; 95% confidence interval 1.1,3.6). This difference remained significant and unchanged after adjustment for traditional cardiovascular 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 or without RA. Hypothyroid disease was significantly associated with CVD in patients with RA, even after adjustment for other traditional cardiovascular risk factors.

Key Indexing Terms

Rheumatoid arthritis; Hypothyroidism; Cardiovascular Disease

Introduction

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 [1–5]. It is unclear whether the prevalence of thyroid disease differs in patients with RA compared to the general population. [6–10]

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Similar 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 when 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 better examine the relationship between hypothyroidism and development of CVD in patients with RA.

Patients and Methods

Study Population

This study utilized the resources of the Rochester Epidemiology Project (REP), a diagnostic indexing linkage system that allows access to the medical records of all health care 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 a 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 Board of the Mayo Clinic.

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 of greater than 5.0 mU/L with a normal free thyroxine (T_4) in the range of 0.8–1.8 ng/dL (reference range of TSH: 0.3–5 mIU/L). A T_4 of less than 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. The 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), cardiovascular revascularization procedures, angina and/or physician diagnosis of coronary artery disease. Silent infarcts were defined as a recorded physician diagnosis of characteristic ECG findings in a patient with no previously documented history of MI, or the presence of characteristic ECG findings in a non-acute 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), anti-nuclear antibody (ANA), erosive changes, large joint swelling, severe extra-articular 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, preexistent CVD, alcoholism, hypertension, diabetes mellitus, dyslipidemia, smoking status and family history of coronary artery disease (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 Kaplan-Meier method with censoring of patients who are still alive at last follow-up. 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 on the development of hypothyroid disease among patients with RA.

Cox models were also used to assess the impact of hypothyroid disease on the development of CVD or mortality among patients with RA and non-RA subjects. Age was used as the time scale 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 follow-up. The models were stratified by sex. Traditional cardiovascular 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 follow-up 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 two cohorts had similar characteristics including age at incidence (55.8) and sex (69% female). There was a statistically significant difference between rate of testing in RA (50 TSH tests per 100 person-years) and non-RA patients (44 tests per 100 person-years; $p<0.001$). The remainder of characteristics at index between cohorts is illustrated in Table 1.

There was no significant difference between presence of hypothyroid disease at index among patients with or without RA. Additionally, the cumulative incidence of hypothyroid disease did not significantly vary among patients with or without RA (Table 2). When further sub-categorized to autoimmune thyroid disease (Graves' and Hashimoto's), the difference remained non-significant. Subclinical hypothyroidism did not significantly vary between patients with or without RA. Use of levothyroxine did not vary between RA and non-RA subjects at the incidence RA date nor 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 follow-up, 65 patients with RA and 58 non-RA subjects developed CVD. The cumulative incidence of CVD at 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% confidence interval [CI] 1.1, 3.6). This association persisted after adjustment for traditional cardiovascular 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 RA patients (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 RA patients was not significantly associated with CVD or mortality. Use of levothyroxine was significantly associated with CVD in RA patients (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; HR 1.3; 95% CI 0.5, 3.2).

Examination of the association of RA disease characteristics including ESR, RF, ANA, erosive changes, large joint swelling, severe extra-articular manifestations, joint surgery, nodules, medication use (methotrexate, hydroxychloroquine, DMARDs, biologic agents, corticosteroids, COX-2 inhibitors, aspirin use) and other CV risk factors (BMI, CVD, alcoholism, hypertension, diabetes mellitus, dyslipidemia, smoking status, family history of CAD) failed to reveal an association between RA characteristics and cardiovascular risk factors with the development of hypothyroid disease. 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

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

Information in the medical literature regarding hypothyroidism in RA patients is conflicting. Several studies have demonstrated an increased rate of hypothyroidism in RA patients.[7, 8, 18, 19]. In three 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 demonstrate 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 follow-up, with a range of reported prevalence of thyroid disease, including hypothyroidism. Despite increased TSH testing rates in RA patients compared to non-RA patients, our study did not detect a statistical 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 finding is in concert with another study in which patients with RA who have clinical hypothyroidism have a fourfold higher risk of CVD than patients with RA who are euthyroid [7]. An interesting related finding of our study is that there was no apparent change in CVD risk in RA patients despite treatment with levothyroxine at any point during the follow up period. This observation suggests that treatment of thyroid disease may not have an impact on development of CVD, and is a subject for further investigation. Another interesting finding of this study was that RA patients with atrial fibrillation were more likely to develop hypothyroid disease. This finding

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, 23–28].

The pathogenesis of CVD in patients with clinical and subclinical hypothyroidism may relate to inflammatory-based endothelial dysfunction secondary to reduced nitric oxide levels [29–31]. Lipid abnormalities, as observed in hypothyroidism, may also play a role in atherosclerosis [32–37]. Increased atheroma formation has been found in patients with RA and hypothyroidism compared to those with RA alone [38]. Inflammation is an important contributor to atherogenesis, a relationship reflected in the correlation between elevated C-rp and CVD [36, 39–41]. Indeed, reductions of serum cholesterol and C-rp levels with statin therapy have been shown to significantly reduce CVD [28, 42, 43]. Although some reports demonstrate increased ESR or C-rp in hypothyroid patients, others have failed to confirm these findings [44, 45].

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 [46–48]. 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, 31].

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 explore 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 only minimally affected the results of our study. Finally, the population of Olmsted County, Minnesota is predominately white and therefore may not be generalizable to other more diverse populations.

Strengths of this 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.

The results of this study 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 more frequently for hypothyroidism 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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Table 1

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

	RA	Non-RA	p-value
Age at incidence, years, mean ± SD	55.8 ± 15.7	55.8 ± 15.7	1.0
Sex, female, n (%)	448 (69%)	448 (69%)	1.0
Length of follow-up, years	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	97 (15%)	75 (12%)	0.07
Rate of TSH testing*	50 tests per 100 person-years (95% CI: 48, 52)	44 tests per 100 person-years (95% CI: 43, 46)	P<0.001

TSH = Thyroid stimulating hormone

Table 2

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

	Number of 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 subjects (±SE)	p-value
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

TSH =Thyroid stimulating hormone