Increased risk of levothyroxine-treated hypothyroidism preceding the diagnosis of rheumatoid arthritis: a nationwide registry study

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Abstract

Objective

To evaluate the prevalence of levothyroxine-treated hypothyroidism in rheumatoid arthritis (RA) patients at the time of RA diagnosis in comparison to age- and sex-specific general population. Other objectives were to determine whether the risk of hypothyroidism varies by age at the onset of RA, or by sex or rheumatoid factor (RF) status.

Methods

We identified 7,209 incident RA patients diagnosed between January 2004 and December 2007 from a Finnish nationwide register of special reimbursements for medication costs. The presence of hypothyroidism at RA diagnosis was identified from the same register based on special reimbursement decisions for levothyroxine substitution. The prevalence of levothyroxine-treated hypothyroidism was compared to that of an age- and sex-specific Finnish population, and a standardised rate ratio (SRR) for hypothyroidism was calculated.

Results

The SRR for levothyroxine-treated hypothyroidism preceding RA was 1.51 (95% CI 1.35 to 1.67). Neither RF status nor sex modified the risk, although the results did not reach statistical significance among men. The SRR was highest, almost 2.5 among younger female RA patients (20-49 years of age), the excess prevalence of hypothyroidism decreasing steadily and wearing off among patients who were older at the time of diagnosis. The absolute prevalence of hypothyroidism, however, increased with age as it does in the general population.

Conclusion

The risk of hypothyroidism is increased among RA patients already at the disease onset, especially among the young women, regardless of RF status. This calls for attention to screening for hypothyroidism in RA patients, preferably when RA has already been diagnosed.

Key words

rheumatoid arthritis, hypothyroidism, comorbidityepidemiology

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Introduction

Rheumatoid arthritis (RA) is associated with a wide set of comorbidities, which together with RA itself worsen the patient's functional status and quality of life (1). One of the comorbidities is hypothyroidism, as described in various research settings (2-4)

Autoimmune diathesis, a paradigm according to which there is a tendency for autoimmune diseases to co-exist within individuals in excess to that expected by chance, is a generally accepted concept (5). There are studies which have indicated that RA and chronic autoimmune thyroiditis, a common cause of hypothyroidism, co-occur to a large extent (6-8). Implications of this association have been published since several decades ago (6, 9) and the underlying etiology has been investigated, for example, with respect to interrelating genes (8, 10) and autoantibodies (11). In addition, thyroid deficiency has been linked to the development of cardiovascular disease in RA (3, 4, 12).

Studies examining autoimmune diathesis typically assess the co-occurrence of an index disease with another autoimmune disorder during a period when the index disease is already fully established (7). However, certain autoimmune processes activate several years before the development of RA symptoms (13), bringing out the question whether they affect the presence of autoimmune thyroiditis and its clinical manifestation, hypothyroidism, already before the full clinical eruption and diagnosis of RA. The dependency of thyroid function on age at the onset of RA is another interesting aspect, especially because the outcome of many autoimmune diseases is dependent on the age of onset and because early- and late-onset RA are known to have clinical differences (14). Absence of studies addressing these aspects is a remarkable gap in the current knowledge.

The major aim of the present nationwide registry study was to evaluate the prevalence of hypothyroidism in RA patients at the time of RA diagnosis compared with age- and sex-specific Finnish population. Other objectives were to determine whether the age at the onset of RA, sex or positive rheumatoid factor (RF) has an impact on the risk of hypothyroidism.

Methods

All Finnish residents are covered under the National Health Insurance, which grants special reimbursement of medications for certain chronic and severe diseases. To be entitled to special reimbursement for RA medications, a patient must file a medical certificate based on examination performed by a rheumatologist or carried out in a clinic of rheumatology. The certificate must describe the proper diagnostic procedures combined with the diagnostic ICD-10 code M05 or M06 for RF-positive or RF-negative RA, respectively, and include a treatment plan. The certificates are checked by a medical examiner physician in the Social Insurance Institution before the reimbursement is granted. All reimbursement decisions made by the Social Insurance Institution are gathered in a nationwide register. We used this register to identify all the patients over 20 years of age under ICD-10 codes M05 and M06 who were granted the special reimbursement of medications for RA between 1st January 2004 and 31st December 2007, using the date of the reimbursement decision as the RA index date.

The case identification method offers a great coverage of RA patients, as indicated by the relatively high annual incidence of RA of 44.5 per 100,000 patients during the years 2000–2007 (15), which is similar or slightly higher in comparison with incidence rates reported recently in north European or North American countries (16-18).

Patients with hypothyroidism are entitled to special reimbursement for levothyroxine substitution. The possible co-existence of RA and hypothyroidism at the RA index date was identified based on the reimbursement decision for levothyroxine substitution, requiring that it had to antedate the reimbursement decision for RA. The medical certificate, on which the reimbursement decision for levothyroxine is based, must describe the etiology, the clinical picture of hypothyroidism and the levels of thyroid stimulating hormone and thyroid hor-

mone T4. The certificate itself was not available to us when conducting this study; hence, we do not know the exact causes of hypothyroidism. The special reimbursement is not granted for subclinical hypothyroidism. The certificate can be issued not only by an endocrinologist but also by a general practitioner.

The special reimbursement for levothyroxine is granted for patients under ICD-10 codes C73, E03 and E89.0. Therefore, our data encompasses patients with chronic autoimmune thyroiditis, but also other, rarer forms of primary hypothyroidism (dysfunction in the level of thyroid gland) such as postprocedural hypothyroidism, hypothyroidism after radioiodine therapy and hypothyroidism caused by medications or malignant neoplasms of thyroid gland. However, thyroid cancer is quite rare in Finland, as indicated by its mean annual incidence of 84 in males and 266 in females in 2002-2006 (19). Furthermore, iodine-deficiency-related hypothyroidism has also been very rare in Finland for decades, since the iodine prophylaxis with iodised salt was activated already in the 1950s, and it does not qualify for reimbursement for levothyroxine substitution (20, 21).

In addition, we evaluated the prevalence of drug-treated coronary heart disease among levothyroxine users and non-levothyroxine users of the incident RA cohort. The presence of coronary heart disease was identified from the same register on special reimbursements for medication costs. To establish entitlement, the medical certificate made by the patient's physician must show that the objective criteria of CHD are fulfilled, including one of the ICD-10 codes: I20-I22, I24.0 or I25.

The register data we used is officially archived and available without any patient-specific consents. Consents for the usage of the data were obtained from the Social Insurance Institution and Statistics Finland, which are the administrators of the registers used. All patients were given an identification number according to which the data was analysed anonymously; no personal information was released from authorities.

Table I. The distribution of sex, age and levothyroxine-treated hypothyroidism among 7,209 incident RA patients.

	Women		Men	
	n	n (%) with hypothyroidism	n	n (%) with hypothyroidism
20-49 years	1,445	62 (4.3)	571	4 (0.7)
50-59 years	1,374	85 (6.2)	685	7 (1.0)
60-69 years	978	81 (8.3)	554	8 (1.4)
70-79 years	833	76 (9.1)	414	9 (2.2)
≥80 years	257	17 (6.6)	98	1 (1.0)

Statistical analysis

The patients with RA and the general population (4.0/4.1 million people over 20 years of age in 2004/2007) were stratified by gender and age in 5-year categories. Prevalence rate for levothyroxine-treated hypothyroidism per 100 persons was calculated for each group both in the RA cohort and in the general population. To calculate the standardised rate ratio (SRR), the observed prevalence of hypothyroidism among incident RA cases was divided by the expected prevalence (that is, the prevalence in the general population). The statistical significance of this relationship was qualified by using a Poisson regression model and 95% CIs were calculated.

Results

The RA cohort consisted of 7,209 RA patients over 20 years of age who were granted the special reimbursement of medications for RA. There were 4,887 (68%) women with a mean age of 56.6 (SD 15.0) year and 2,322 (32%) men whose mean age was 58.2 (SD 13.5) years. For further information about the age distribution in the cohort, see Table. RF-positivity was a dominant feature: 4,650 (65%) of all the patients, 64% of females and 66% of males, were seropositive.

A total of 350 or 4.9% of RA patients had levothyroxine-treated hypothyroidism at the time of RA diagnosis, corresponding to a SRR of 1.51 (95% CI: 1.35–1.67). Among the women with RA, 321 (6.6%) of them had also hypothyroidism, the SRR being 1.52 (95% CI: 1.36–1.69). Levothyroxine substitution was far less common among men than among women: there were 29 men with both RA and hypothyroidism, which equals 1.2% of all the men with RA. The excess risk of hypothyroidism did not reach statistical significance among men. There were 220 RF-positive and 130 RF-negative cases with levothyroxine substitution, the SRR remaining similar in both groups, 1.46 (95% CI: 1.27–1.66) and 1.61 (95% CI: 1.34–1.91), respectively.

Figure 1 shows the pattern of the SRR for levothyroxine-treated hypothyroidism in both sexes divided into five different groups according to the age at the onset of RA. Among women, especially, higher rate ratios of hypothyroidism were linked to patients with earlier RA onset, the excess prevalence decreasing steadily and wearing off in patients who were older at the time of diagnosis. The highest absolute prevalence of hypothyroidism was detected in both sexes among patients who were 70-79 years at the onset of RA (Fig. 2).

The co-existence of coronary heart disease and hypothyroidism was not increased from that expected by chance; 30 patients had a validated diagnosis of both of these diseases at the RA index date, corresponding to 8.6% of all the levothyroxine-treated RA patients. Among RA patients without levothyroxine substitution, the prevalence of coronary heart disease was essentially similar, 7.6%.

Discussion

In the present Finnish nationwide population-based registry study involving 7,209 newly diagnosed RA patients, we observed that an increased rate ratio for hypothyroidism was apparent already at the diagnosis of RA. This has not been looked at before from this specific point of view, even though studies pertaining to the prevalence of chronic autoimmune thyroiditis among RA patients have a long history that goes back to

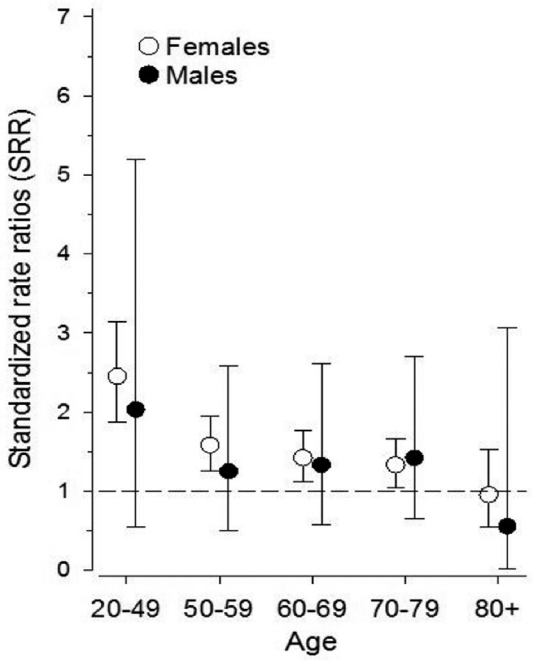

Fig. 1. Standardised rate ratios (SRRs) for levothyroxine-treated hypothyroidism according to sex and age.
The SRRs with 95% confidence intervals are shown at the diagnosis of RA among 7,209 RA patients in comparison to the age- and sex-specific general population.

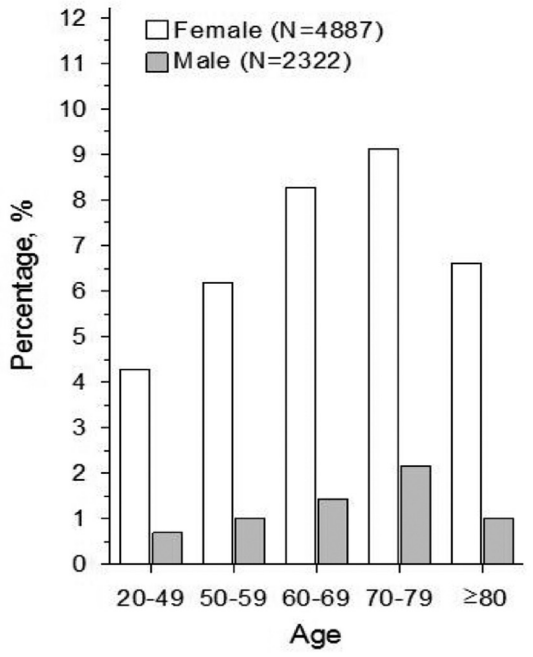

Fig. 2. Percentages of RA patients with levothyroxine-treated hypothyroidism according to sex and age at the onset of RA.

the 1960s (22). Since then, a myriad of observations from tertiary care settings have implied that these diseases tend to co-exist at a higher than expected rate, although there has been considerable heterogeneity among studies (5).

Parallel results to ours have been published in previous studies: for example, Somers and coworkers performed a series of population-based cohort studies to elucidate the co-existence of four different autoimmune diseases in a population including 22,888 patients with RA and 26,198 with autoimmune thyroiditis and found a bidirectional association between the two, the standardised incidence ratio of thyroiditis among RA patients being 61.5% above the population level and 31.8% when considering the reverse disease sequence (6). Moreover, a Swedish case-control study among 1,998 incident RA patients indicated that levothyroxine users (6%) may have a twofold risk of RA independently of the presence of anticitrullinated peptide antibodies (ACPA) (8).

Assuming that our cases of hypothyroidism equal autoimmune thyroiditis for the major part (23), our finding together with previous literature supports the hypothesis that either common susceptibility or partly shared pathogenesis exists for RA and autoimmune thyroiditis. Tyrosine phosphatase 22 risk allele may be a common susceptibility allele to these diseases (7, 24). In general, a higher vulnerability for rheumatic diseases in hypothyroid patients has been implied by an elevated prevalence of ANA autoantibodies in autoimmune thyroid disease (11). Furthermore, patients with systemic lupus erythematosus and systemic sclerosis are also shown to carry an increased risk for hypothyroidism (25, 26).

The influence of RF status on the risk of hypothyroidism has been touched in the literature, and in these relatively small study populations, thyroid dysfunction has been either inversely associated with RF positivity or independent of RF status (2, 27). We did not find a difference in RF+ and RF- subsets, which implies a shared pathogenetic mechanism independent of RF status.

To the best of our knowledge, we are the first to report a trend of an increasing excess risk of hypothyroidism among younger *vs*. older patients at the time of RA diagnosis (Fig. 1). This observation supports the statement that young patients with an autoimmune disease are at an increased risk of having comorbid autoimmune thyroiditis (14). The SRR for hypothyroidism reached almost 2.5 among women who were between 20 and 49 years at the commencement of RA therapy. This clearly advocates paying particular attention to screening for hypothyroidism in young RA patients. Furthermore, the clinician should be mindful of the possibility of RA as the underlying cause of joint symptoms in young female patients with hypothyroidism.

Prevalence of hypothyroidism is well known to increase along aging, which is also apparent in our RA cohort (Fig. 2). It is likely to explain at least a part of the age trend found: with increasing age, the overall risk of hypothyroidism increases and the influence of the risk attributable to RA loses its weight. The

point estimates were remarkably similar for men and women, but, evidently, smaller samples sizes and consequent lack of power hindered men reaching statistical significance. Therefore, our preliminary finding regarding men needs to be confirmed in even larger study populations.

Previously, we reported that the concerned register-based RA cohort of 7,209 patients carried an increased risk of coronary heart disease already at RA diagnosis (28). Thyroid deficiency has been found to be a risk factor for cardiovascular disease both in the general population (29) and among RA patients (3, 4, 12), and we wanted to explore if there was clustering of coronary heart disease and hypothyroidism in individuals with awaiting RA. However, in our RA cohort, coronary heart disease and hypothyroidism did not overlap more frequently than expected at the time of RA diagnosis. As an amplified cardiovascular risk has been observed in previous studies on hypothyroidism and longer-standing RA, it can be hypothesised that the onset of RA might just be the final hit to induce accelerated atherosclerosis and development of cardiovascular disease.

One of the study limitations is that the diagnosis of hypothyroidism encompasses not only cases of autoimmune thyroiditis but also hypothyroidism arising from other etiologies. However, chronic autoimmune thyroiditis is the most common reason of acquired hypothyroidism (23), and therefore, most of the detected hypothyroid patients are likely to represent an autoimmune etiology behind the condition. In addition, the coverage of clinical hypothyroidism may be less comprehensive than that of RA because levothyroxine is so inexpensive that in some cases, the patients may choose not to pay for the doctor's certificate needed to apply for the special reimbursement. Obviously, this is equally true both of the general population and of those who will later develop RA; hence, it will not cause bias in assessment of the relative risk of hypothyroidism. We cannot rule out the possibility that the symptoms of insidious-onset RA, such as fatigue and arthralgia, could mimic those of hypothyroidism and lead to more frequent testing for thyroid disorders in some patients diagnosed with RA a few months later.

As an aggregate, we observed an increased prevalence of levothyroxine-treated hypothyroidism among patients with newly diagnosed RA, particularly the younger women, regardless of the RF status. This calls for attention to screening for hypothyroidism in RA patients, preferably already at the first admission to a rheumatology clinic.

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