HHS Public Access

Author manuscript

Clin Rheumatol. Author manuscript; available in PMC 2017 August 04.

Published in final edited form as:

Clin Rheumatol. 2016 December ; 35(12): 2983–2987. doi:10.1007/s10067-016-3330-x.

Hypogonadism and the risk of rheumatic autoimmune disease

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Abstract

Testosterone deficiency has been linked with autoimmune disease and an increase in inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor, and interleukin-6 (IL-6). However, no large-scale longitudinal studies have examined this association. We examined whether untreated hypogonadism was associated with an increased risk of rheumatic autoimmune disease in a large nationally representative cohort. Using one of the nation's largest commercial insurance databases, we conducted a retrospective cohort study in which we identified 123,460 men diagnosed with hypogonadism between January 1, 2002 and December 31, 2014 and with no prior history of rheumatic autoimmune disease. We matched this cohort to 370,380 men without hypogonadism, at a 1 to 3 ratio, on age and index/diagnosis date. All patients were followed until December 31, 2014 or until they lost insurance coverage or were diagnosed with a rheumatic autoimmune disease. Cox proportional hazards regression was used to calculate adjusted hazard ratios (aHRs). Untreated hypogonadism was associated with an increased risk of developing any rheumatic autoimmune disease (HR = 1.33, 95 % CI = 1.28, 1.38), rheumatoid arthritis (HR = 1.31, 95 % CI = 1.22, 1.44), and lupus (HR = 1.58, 95 % CI = 1.28, 1.94). These findings persisted using latency periods of 1 and 2 years. Hypogonadism was not associated with the control outcome, epilepsy (HR = 1.04, 95 % CI = 0.96, 1.15). Patients diagnosed with hypogonadism who were not treated with testosterone had an increased risk of developing any rheumatic autoimmune disease, rheumatoid arthritis, and lupus. Future research should further examine this association, with particular attention to underlying mechanisms.

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Compliance with ethical standards

Disclosures None.

Keywords

Androgen; Autoimmune disease; Rheumatic disease; Testosterone replacement therapy

Background

The incidence of rheumatic autoimmune diseases—such as rheumatoid arthritis, systemic lupus erythematosus, and scleroderma—is substantially higher in women than in men [1]. The mechanisms that underlie this difference are unclear but evidence points to the modulatory roles of sex hormones in the pathogenesis of autoimmune disease. Testosterone deficiency has been linked with autoimmune disease [2–5] and an increase in inflammatory markers, such as C-reactive protein (CRP), tumor necrosis factor, and interleukin-6 (IL-6) [6–8]. Notably, testosterone is reported to have anti-inflammatory functions via suppression of both the cellular and humoral immune system [9]. Studies have reported low levels of androgens in blood and other body fluids of men and women with rheumatoid arthritis [3, 10]. Unfortunately, because much of these data were collected cross-sectionally, it is difficult to establish the temporal sequence of the observed associations—whether low testosterone affects inflammation and autoimmunity or vice versa. A small number of cohort studies and randomized control trials, each with relatively small sample sizes, have examined whether testosterone deficiency at baseline predicts the development of rheumatic autoimmune disease [11–16]. These investigations, however, have yielded conflicting results. To date, no large-scale, longitudinal, population-based studies have examined whether men with untreated hypogonadism have an increased risk for rheumatic autoimmune disease. We therefore conducted a cohort study using a one of the nation's large commercial insurance databases to examine this association.

Methods

We conducted a retrospective cohort study using administrative health data from the Clinformatics Data Mart (CDM) database, a database of one of the nation's largest commercial health insurance programs. CDM data have been used in numerous epidemiologic and health services studies [17–20]. Persons enrolled in this insurance program may be included in either a fee-for-service plan or a managed care plan, which includes health maintenance organizations, preferred provider organizations, and exclusive provider organizations. For each of these plans, providers are required to submit complete claims to receive reimbursement. During the study period (2002–2014), a total of 27,234,289 men aged ≥19 years were included in the database. We used a combination of outpatient, inpatient, and pharmacy claims data. This retrospective study was approved by the Institutional Review Board of the University of Texas Medical Branch at Galveston.

Study subjects

We identified 123,460 males aged >19 years with a diagnosis of hypogonadism (ICD-9-CM = 257.xx or 758.7x) between January 1, 2002 and December 31, 2012. We matched each male with hypogonadism to males without hypogonadism, at a 1 to 3 ratio, on index date and age. To be included in the study, all patients were required to have had a minimum of 12

months continuous enrollment prior to their hypogonadism diagnosis/index date and to have not been prescribed testosterone at any point in the study period. In addition, all cohort members were required to have met each of the following criteria during the 12-month look back period: at least one physician visit, no diagnosis of any rheumatic autoimmune disease, no appointment with a rheumatologist, no laboratory test for autoimmune factors, and no diagnosis of cancer.

Covariates

Age at diagnosis/index date was obtained from the CDM database. We examined and adjusted for all conditions included in the Elixhauser comorbidity index [21]. Each condition was examined as a separate covariate. To address the potential confounding effect of increased health care utilization, we adjusted for total number of outpatient visits in the 12-month look back period.

Outcomes

The study outcomes were diagnoses of any of the following rheumatic autoimmune diseases, using the following ICD-9-CM codes, after the hypogonadism diagnosis/index date: antiphospholipid syndrome (286.5x), ankylosing spondylitis (720.x), Bechet's disease (136.1, 711.2), CREST disease/ systemic sclerosis (710.1), dermatomyositis (710.3), giant cell arteritis (446.5), granulomatosis (446.4), systemic lupus (710.0), unspecified connective tissue disease (710.9), polyarteritis nodosa (446.0), polymyalgia rheumatic (725.x), psoriatic arthritis (696.0), polymyositis (710.4), Reiter's syndrome (099.3, 711.1), rheumatic fever (390.x, 391.x, 392.x), rheumatoid arthritis (RA) (714.x), sarcoidosis (135.x), scleroderma (710.1x), Sjogren's syndrome (710.2x), Takayasu's arteritis (446.7), temporal/giant cell arteritis (446.5), thrombocytopenic purpura (287.31), and ulcerative colitis (556.x). We also examined rheumatoid arthritis and lupus as separate outcomes. Finally, we examined, as a control outcome, epilepsy (345.x) a condition reported not to be associated with hypogonadism.

Statistical analysis

Unadjusted event-free survival was estimated using the Kaplan-Meier method [22]. Multivariable survival analyses were performed using Cox proportional hazards regression, with the dependent variable being time to first occurrence of any of the three above listed outcomes. Adjusted failure rates were estimated using the Cox model [21, 22]. We tested the assumption of proportionality in the Cox models by determining that the logarithm of the baseline cumulative hazard rates and the Schoenfield residuals were proportional with follow-up time [22, 23]. Due to the limited number of events in this study, arcsine-square root transformation of the survival function was used to construct the 95 % confidence intervals (95 % CI) of the failure rates in the survival analyses [21]. Patients were censored at date they left the commercial insurance plan, or at the end of the study (i.e., December 31, 2014). Hypogonadism and comorbid disease were independent variables. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided.

Results

The baseline characteristics of men with and without hypogonadism are presented in Table 1. Hypogonadal and non-hypogonadal men had comparable distributions of anemia, congestive heart failure, coagulopathy, hypertension without complications, lymphoma, metastatic cancer, paralysis, peripheral vascular disease, pulmonary circulation disorders, and weight loss. Hypogonadal men had a higher prevalence of COPD, deficiency anemia, depression, diabetes with complications, drug abuse, hypothryroidism, obesity, renal failure, and tumor (no metastasis). Non-hypogonadal men had a higher prevalence of alcohol abuse, arrhythmia, diabetes without complications, electrolyte disorders, HIV, hypertension without complications, liver disease, neurological disorders, peptic ulcer disease, psychosis, and valvular disease.

We evaluated event-free survival among hypogonadal and non-hypogonadal men using Kaplan-Meier curves. Table 2 presents the risk of developing any of the three outcomes across the two groups at three time points (1, 3, and 5 years). Overall, hypogonadal men had a higher risk of developing any rheumatic autoimmune disease at each of the three time points and a higher risk of developing lupus at the 5-year time point.

Table 3 presents the results of the Cox regression models. In these multivariable analyses adjusting for the number of outpatient visits in the prior year and over 30 comorbid diseases, untreated hypogonadism was associated with an increased risk of developing any rheumatic autoimmune disease (3.2 versus 2.2 %; HR = 1.33, 95 % CI = 1.41, 1.52), rheumatoid arthritis (1.0 versus 0.7 %; HR = 1.31, 95 % CI = 1.32, 1.46), and lupus (0.12 versus 0.07 %; HR = 1.58, 95 % CI = 1.28, 1.99).

We conducted several sensitivity analyses. First, we ran Cox models excluding outcomes that occurred within 1 and 2 years following the hypogonadism diagnosis/index date. The aHRs for hypogonadism yielded for each of these models were comparable to those of the original models. In addition, our analysis showed that an outcome, epilepsy, was not associated with hypogonadism [HR = 1.04, 95 % CI = 0.96, 1.15).

Discussion

In this nationally representative cohort study of almost 500, 000 commercially insured men, we found that a diagnosis of hypogonadism was associated with an increased risk of developing any rheumatic autoimmune disease, rheumatoid arthritis, and lupus. To our knowledge, this is the first large-scale, longitudinal, population-based study to examine this association.

Previous studies on hypogonadism and rheumatic autoimmune disease have produced conflicting results. A small number of longitudinal studies, each with relatively small sample sizes, have examined whether testosterone deficiency at baseline predicts the development of rheumatic autoimmune disease. In their study of 32 males in Finland, Heikkila et al. [11] reported no association between baseline serum testosterone levels and the subsequent development of rheumatoid arthritis. By contrast, in their nested case–control study of 278 patients, Pikwer et al. [12] reported that low serum testosterone was predictive of RF-

negative rheumatoid arthritis. A small number of clinical trials have also yielded conflicting results. Some have shown that testosterone replacement is associated with a lowering of inflammatory markers (CRP, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNFα) [13, 14], while others have reported no association [15, 16]. In view of these conflicting findings, it will be important for future investigations, particularly those with large study samples and prospective designs, to continue to examine this association.

The results of our study may have been influenced by the several limitations. First, information on outcomes and risk factors came from diagnosis codes included in charges for outpatient and hospitalization services. Such diagnoses are not always accurate or complete [21]. For example, we were unable to determine whether diagnoses of hypogonadism met the established serum and symptom criteria for this condition. Second, given the retrospective nature of this study, it is possible that undetected selection bias may have affected the findings. For example, men who were tested and diagnosed with hypogonadism have been more likely than their counterparts to have had subsequent diagnoses made. However, we attempted to address this potential bias by restricting both groups to patients who met the following criteria in the 12 months before hypogonadism diagnosis/index date: at least one physician visit, no diagnosis of any rheumatic autoimmune disease, no appointment with a rheumatologist, no laboratory test for autoimmune factors, and no diagnosis of cancer. In addition, we adjusted for number of outpatient visits in the prior year as well as over 30 comorbid conditions. Third, our database lacked information on several important health behaviors such as smoking status, body mass index, exercise, and diet. Fourth, prescription claims data do not capture information on pharmaceutical agents purchased outside the plan. Given the perceived social stigma associated with receiving testosterone therapy, some men may have accessed testosterone therapy outside their usual health care setting, such as specialty hormone clinics. However, such misclassification would have likely biased our findings toward the null hypothesis.

Conclusion

Despite these limitations, we believe this study has important strengths including a large sample size, a long follow-up period, representation of all US geographic regions, and inclusion of a clinically diverse cohort. In view of the large increase in the use of testosterone therapy in recent years, [24] examining the risks of untreated testosterone deficiency holds broad clinical and public health relevance. Future research should continue to examine the association of hypogonadism and rheumatic autoimmune disease, with particular attention to underlying mechanisms.

Acknowledgments

This study was supported in part from the Clinical and Translational Award (UT1TR001439) from the National Center for Advancing Translational Sciences, National Institutes of Health.

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Table 1

Baseline demographic and clinical characteristics for hypogonadal and non-hypogonadal men

Characteristic[a]	Hypogonadal *n* (%) or mean (st.dev)	Non-hypogonadal *n* (%) or mean (st.dev)	*P* value
All	123,460 (100)	370,380 (100)	
Age (years) at index date (mean)	46.5 (11.4)	46.5 (11.4)	1.00
Number of outpatient visits in prior year	5.6 (5.2)	4.6 (4.5)	<0.0001
Duration of follow-up (days) (mean)	765.7 (672.3)	779.5 (658.3)	<0.0001
Comorbdity[b]			
Alcohol abuse	1.3	1.4	0.001
Arrythmia	6.2	6.5	0.0003
Anemia	0.3	0.3	0.9
Congestive heart failure	1.9	2.0	0.4
COPD	8.4	7.5	<0.0001
Coagulopathy	0.5	0.6	0.30
Deficiency anemia	1.7	1.5	<0.0001
Depression	10.3	6.0	<0.0001
Diabetes with complications	2.9	2.5	<0.0001
Diabetes without complications	13.1	13.7	<0.0001
Drug abuse	0.7	0.5	<0.0001
Electrolyte disorders	1.5	1.6	0.0004
HIV	0.4	1.0	<0.0001
Hypertension with complications	2.0	2.0	0.27
Hypertension without complications	32.4	33.1	<0.0001
Hypothyroidism	5.3	4.9	<0.0001
Liver disease	1.2	1.7	<0.0001
Lymphoma	0.0	0.0	0.3
Metastatic cancer	0.0	0.0	0.5
Neurological disorders	0.6	0.8	<0.0001
Obesity	4.8	4.0	<0.0001
Paralysis	0.1	0.1	0.97
Peptic ulcer disease	0.1	0.2	<0.0001
Peripheral vascular disease	0.8	0.9	0.8
Psychosis	0.1	0.1	0.03
Pulmonary circulation disorders	0.2	0.2	<0.74
Renal failure	0.8	0.0	<0.0001
Tumor (no metastasis)	0.1	0.0	0.01
Valvular disease	1.2	1.5	<0.0001
Weight loss	0.6	0.6	0.98

[a] Cohorts were matched at a 1 to 3 ratio, on age, and index/diagnosis date.

[b] Comorbid conditions were measured using the factors that comprise Elixhauser comorbidity index [21]

Table 2

Risk based on Kaplan-Meier estimates of developing any rheumatic autoimmune disease, rheumatoid arthritis, and lupus

	Any rheumatic Autoimmune disease	Rheumatoid arthritis	Lupus
	Absolute risk, 95 % CI	Absolute risk, 95 % CI	Absolute risk, 95 % CI
Hypogonadal			
1 year	1.4 (1.3, 1.6)	0.4 (0.3, 0.5)	0.1 (0.1, 0.2)
3 years	4.2 (4.0, 4.4)	1.4 (1.3, 1.5)	0.2 (0.3, 0.3)
5 years	7.6 (7.3, 8.0)	2.4 (2.2, 2.5)	0.3 (0.2, 0.4)
Non-hypogonadal			
1 year	0.9 (0.8, 0.9)	0.5 (0.4, 0.6)	0.1 (0.1, 0.2)
3 years	2.9 (2.8, 3.0)	1.0 (0.9, 1.1)	0.2 (0.2, 0.3)
5 years	5.3 (5.1, 5.3)	1.6 (1.3, 1.9)	0.2 (0.2, 0.3)

Table 3

Hazard ratios for diagnosis of all rheumatic diseases, rheumatoid arthritis, and lupus, associated with hypogonadism, analyzed by various approaches

Analytic method	All rheumatic diseases HR (95 % CI)	Rheumatoid arthritis HR (95 % CI)	Lupus HR (95 % CI)
Unadjusted[a]	1.46 (1.41, 1.52)	1.41 (1.32, 1.51)	1.73 (1.42, 2.13)
Adjusted for total outpatient visits	1.35 (1.30, 1.40)	1.33 (1.28, 1.38)	1.60 (1.31, 1.97)
Adjusted for total outpatient visits and all comorbid diseases[b] using multivariable Cox proportional hazards regression	1.33 (1.28, 1.38)	1.31 (1.22, 1.41)	1.58 (1.28, 1.99)
Adjusted for total outpatient visits and all comorbid diseases[b] using multivariable Cox proportional hazards regression, with 365-day latency period	1.32 (1.26, 1.39)	1.30 (1.24, 1.35)	1.26 (1.21, 1.32)
Adjusted for total outpatient visits and all comorbid diseases[b] using multivariable Cox proportional hazards regression, with 730-day latency period	1.33 (1.25, 1.42)	1.30 (1.23, 1.35)	1.26 (1.20, 1.32)

[a] Total outpatient visits in the year before diagnosis/index date

[b] Comorbid conditions were measured using the factors that comprise Elixhauser comorbidity index [21]