Association of spinal degenerative disc disease with thyroid autoimmunity

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Abstract

Objective

Autoimmune thyroiditis (ATD) has been linked to various forms of arthritis. The relationship with spinal degenerative disc disease (DDD) is not known. We studied the association between ATD and spinal DDD.

Methods

We performed a cross-sectional analysis of patients who had data on both anti-thyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb) from January 1997 to January 2014 in Clinical Looking Glass (CLG), a data analysis software platform. Spinal DDD was confirmed by radiological diagnosis.

Results

Of the 7698 patients for whom the TPOAb and TgAb values were available, 4383 patients with complete data for the following covariates; age, gender, race, ethnicity, smoking, diabetes, body mass index and thyroid stimulating hormone (TSH) levels, were included. Thirty-three percent had ATD, while 67% did not. The unadjusted odds ratio (OR) of having spinal DDD with ATD was 1.5 (95% confidence interval (CI)1.3, 1.7), p<0.001. After adjustment for covariates, ATD remained associated with a higher frequency of spinal DDD, OR 1.8 (95% CI 1.6, 2.2), p<0.001. Stratifying by BMI and TSH levels showed similar results. Additional analyses excluding patients with known connective tissue diseases and spondyloarthritis (SpA) also showed consistent results.

Conclusion

ATD is associated with increased frequency of spinal DDD independent of BMI and TSH levels, and among those without connective tissue diseases or SpA. This finding suggests that there may be an important link between thyroid autoimmunity and spinal DDD.

Key words

autoimmune thyroid disease, chronic lymphocytic thyroiditis, Hashimoto thyroiditis, spinal degenerative disc disease, spinal osteoarthritis

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Introduction

Autoimmune thyroid disease (ATD) is the commonest autoimmune disease and refers to the autoimmune infiltration of the thyroid gland by inflammatory cells, chiefly lymphocytes, leading in some patients to distinct clinical phenotypes although considerable overlap can occur (1, 2). Graves disease is characterised by production of autoantibodies to the thyrotropin (thyroid-stimulating hormone (TSH)) receptor and hyperthyroidism while chronic lymphocytic thyroiditis (CLT) or Hashimoto thyroiditis (HT) is typified by the production of anti-thyroid peroxidase antibodies (TPOAb) and/or anti-thyroglobulin antibodies (TgAb) respectively, with eventual glandular failure manifested as hypothyroidism in a proportion of patients (3, 4). Although viewed as a classic single-organ autoimmune phenomenon ATD has been linked to a number of rheumatic syndromes including arthritis and generalised pain (5, 6). Rheumatic syndromes have been more closely linked in terms of sheer predominance with CLT and hypothyroidism than to Graves disease which has well documented relationships to myopathy, periarthritis, thyroid acropachy and osteoporosis (7). An early report from the Mayo Clinic suggested an association between HT and several systemic autoimmune diseases including rheumatoid arthritis (RA) and fibrositis, an earlier term largely supplanted by our current definitions of fibromyalgia and chronic widespread pain (8). Subsequent studies have corroborated those findings and shown a significant relationship between CLT/HT and several connective tissue diseases (9, 10). Indeed, 51% of HT patients have been found in one study to have associated well-defined systemic autoimmune diseases including mixed connective tissue disease (MCTD), Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), RA, systemic sclerosis (SSc) and polymyositis/dermatomyositis (9). Furthermore Addimanda and colleagues have demonstrated a clear association between autoimmune thyroiditis and erosive or non-erosive hand osteoarthritis, knee and to a lesser extent hip osteoarthritis (11). The relationship to non-erosive osteoarthritis suggests that the association is not limited to inflammatory arthritis and is independent of the generalised inflammatory autoimmune process.

Spinal degenerative disc disease (DDD) is a common condition that increases in prevalence with age and has been linked to several factors including elevated body mass index (BMI), viral infections, genetic causes and mechanical loading (12, 13). Other hypothesised causes of spinal disc degeneration include atherosclerosis of arteries supplying the spine and vertebral discs, cigarette smoking and nutrition (14, 15). The condition is causally relevant in the pathogenesis of many clinical phenomena, including low back pain with or without radiculopathy, spinal stenosis, and disc herniation with secondarily generalised back pain. Although ATD has been associated with back pain, the relationship with spinal DDD in particular is unknown. Early reports on back pain in ATD did not look at radiographic data and did not distinguish between pain of muscular origin and pain of spinal vertebral origin (8, 16). One recent observational study suggested a significant association between ATD and spinal DDD but was limited by the small number of study patients and by a lack of a control population (6). The dearth of data in distinguishing the sources and causes of back pain is particularly relevant in attempting to tease out the etiology of pain syndromes including fibromyalgia and chronic widespread pain associated with ATD, reviewed in depth elsewhere (17).

We hypothesised that similar to previously observed associations with hand and knee osteoarthritis ATD might be associated with spinal DDD. A lack of association between ATD and spinal DDD would make any further association with ensuing degenerative changes and subsequent structural pain generators including spinal radiculopathy, spondylolesthesis and spinal stenosis unlikely. We investigated the possible association between CLT, as indicated by the presence of TPOAb or TgAb, and radiographically confirmed spinal DDD using a large data set-analysis platform.

Methods

Patients

We performed a cross-sectional analysis of patients with and without ATD and studied the association of spinal DDD with ATD. All patients with age greater than or equal to 18 years who had data on both TPOAb and TgAb from January 1997 through January 2014 were identified in the Montefiore Medical Center of the Albert Einstein College of Medicine and Affiliate Institutions' electronic health record (EHR) computer system using Clinical Looking Glass (CLG), (Version 4.2, Montefiore Medical Centre, Bronx, NY), which is a patented software tool designed to efficiently and reproducibly retrieve massive amounts of data for analysis (18). The data were de-identified prior to analysis to protect patient confidentiality. Patient consent was therefore not required for the study. The ethical requirements of the institutional review board of the Albert Einstein College of Medicine were met by the study protocol.

Patient race and ethnicity were defined by self-identified patient EHR data. Spinal DDD was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes, 721.90,721.91, 722.4, 722.5, 722.6 and 722.7. Diabetes mellitus was identified by the codes 250.XX. Serum thyroid-stimulating hormone (TSH) was measured on a Roche Cobas Modular Analyser (Roche Diagnostics, Indianapolis, IN, USA) by electro-chemiluminescence immunoassay. The normal reference range of TSH levels was (0.4–4.6 μIU/mL). The TPOAb was assayed using the Abbott Laboratories' ARCHITECT system, a chemiluminescent microparticle immunoassay (Abbott, IL, USA). The Access Thyroglobulin Antibody II assay (Beckman Coulter, Inc., Brea, CA, USA), a two-step immunoenzymatic assay was used for TgAb determination. The presence of abnormal values of TPOAb and/or TgAb, >5 IU/mL and >10 IU/mL respectively indicated the presence of ATD (19). Our main outcome measure was the presence of spinal DDD as confirmed by spinal röntgenograms of the cervical, thoracic or lumbar spinal regions.

Covariates

We established our covariates as age, gender, race, ethnicity, smoking, body mass index (BMI), TSH levels, use of thyroid medication including levothyroxine and liothyronine, and other medical conditions including diabetes mellitus (DM), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) (ICD-9-CM codes 714.0, 710.0, 710.2 respectively), and seronegative spondyloarthropathy (SpA) (ICD-9-CM codes 696.0, 720.XX and 713.1). We further classified BMI into normal weight (BMI 18.5 - <25 kg/m^2), overweight (BMI 25 - <30 kg/m^2), and obese (BMI >=30kg/m^2). Euthyroidism, hyperthyroidism and hypothyroidism were defined serologically as corresponding to TSH levels of 0.4–4.6 μIU/mL, <0.4 μIU/mL and > 4.6 μIU/mL, respectively.

Statistics

Student's *t*-test was used to assess bivariate associations of patient characteristic continuous variables with ATD and spinal DDD status. The chi-square test was used for bivariate associations with categorical variables. Adjusted odds ratios (OR) were estimated with multivariable binary logistic regression models. The models were adjusted for the determined covariates screened as significant in our bivariate analyses or considered potentially important confounders. Model fit was assessed with Hosmer-Lemeshow tests. We assessed potential interaction of ATD with BMI and thyroid function by constructing models within strata of these variables using three groups for each as previously described respectively. We did an additional sub-set analysis of ATD and spinal DDD by excluding patients with the well-defined connective tissue diseases, RA, SLE, SS, as well as SpA. A two sided *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics v. 20.0 (IBM, Armonk, New York, USA).

Results

Baseline patient characteristics

Of 7698 patients on whom the TPOAb and TgAb values were available 4383 patients also with complete data on the covariates were included. Of those 4383 patients, 1557 (35.5%) subjects had antibodies for ATD with 1110 positive for TPOAb and 988 positive for TgAb. As shown in Table I, patients with ATD were more likely to be women (86% *vs*. 82%, $p<0.001$), more likely to be hypothyroid (24% *vs*. 8%, $p<0.001$), less likely to be euthyroid (50% *vs*. 74%, $p<0.001$), less likely to be diabetic (21% *vs*. 27%, $p=0.02$) and less likely to be Black (25% *vs*. 37%, $p<0.001$). Patients with ATD were significantly more likely to be prescribed levothyroxine (31% *vs*. 9%, $p<0.001$). The BMI was significantly higher in the group without ATD than in the ATD group (29.9 kg/m^2 *vs*. 29.4 kg/m^2, $p=0.03$). There were no significant differences for age, smoking, RA, SLE, Sjögren's syndrome, and seronegative SpA between the patients with and without ATD. The unadjusted odds ratio (OR) of having spinal DDD in ATD was 1.5 (95% confidence interval (CI)1.3, 1.7), $p<0.001$.

ATD is associated with spinal DDD after adjustment for covariates

The results of the multivariable binary logistic regression analysis are summarised in Table II. Age-squared was added to the model to improve model fit. After adjustment for covariates including age, gender, race, ethnicity, smoking status, DM, BMI, and TSH levels, ATD remained significantly associated with a higher frequency with spinal DDD with an OR of 1.75 (95% CI 1.6, 2.2), $p<0.001$. Other positive associations with spinal DDD were found with age, White, Hispanic or other race, BMI and the presence of DM. Black race was found to be not significantly associated with spinal DDD in the adjusted analysis. Smoking was also determined not to be significantly associated with spinal DDD ($p=0.06$). Importantly, although 90% of those with ATD were female, gender was not significantly associated with a higher proportion having spinal DDD and was therefore not seen as a likely confounding variable (20).

The association of ATD and spinal DDD remains after stratification by BMI and TSH levels

The multivariable adjusted associa-

Table I. Baseline Characteristics of patients with and without ATD, n=4383.

	ATD (n=1557)	No ATD (n=2826)	*p*-value
Age, mean ± SD years	48.86 ± 17.17	49.41 ± 17.42	0.31
Female gender, % (n)	**86.1 (1251)**	**81.8 (2414)**	**<0.001**
Race			
White, % (n)	**20.4 (317)**	**16.4 (464)**	**<0.001**
Black, % (n)	**24.8 (386)**	**36.9 (1043)**	
Hispanic, % (n)	**40.4 (629)**	**33.4 (944)**	
Other, % (n)	**14.5 (225)**	**13.3 (375)**	
BMI, mean ± SD kg/m^2	**29.37 ± 6.98**	**29.87 ± 7.28**	**0.03**
Diabetes, % (n)	**20.8 (325)**	**26.9 (760)**	**0.02**
Current Smoker, % (n)	28.9 (450)	28.9 (816)	0.98
TSH status			
Hyperthyroid, % (n)	**25.6 (395)**	**18.5 (522)**	**<0.001**
Euthyroid, % (n)	**50.1 (773)**	**73.9 (2082)**	
Hypothyroid, % (n)	**24.4 (376)**	**7.6 (214)**	
Levothyroxine, % (n)	**31.4 (489)**	**8.6 (243)**	**<0.001**
RA, % (n)	8.1 (126)	7.3 (207)	0.35
SLE, % (n)	4.7 (73)	5.8 (165)	0.10
Sjögren's syndrome, % (n)	3.3 (51)	3.4 (96)	0.83
Seronegative spondyloarthropathy, % (n)	0.8 (13)	1.0 (29)	0.53

Table II. Adjusted odds ratios for spinal DDD and ATD.

	Outcome: Spinal degenerative disc disease	
Covariates	Adjusted OR (95% CI)	*p*-value
ATD	1.75 (1.49, 2.05)	<0.001
Age	1.11 (1.12, 1.19)	<0.001
Age squared*	0.99 (0.99, 1.00)	<0.001
Black	0.93 (0.75, 1.15)	0.51
Hispanic	1.32 (1.07, 1.63)	0.01
Other race	0.73 (0.55, 0.97)	0.03
BMI	1.02 (1.00, 1.03)	0.01
Female	1.13 (0.93, 1.38)	0.19
Smoker	1.16 (0.99, 1.35)	0.06
Diabetes	1.71 (1.45, 2.01)	<0.001
Hyperthyroidism	0.63 (0.49, 0.82)	0.001
Hypothyroidism	0.81 (0.68, 0.97)	0.02

*Age-squared was added to the model to improve model fit.

Table III. Sub-analysis by stratifying according to BMI*.

		Spinal degenerative joint disease	
Outcome	BMI	Adjusted OR* (95% CI)	*p*-value
ATD	Normal	**1.46 (1.03, 2.05)**	**0.03**
	Overweight	**1.82 (1.37, 2.41)**	**<0.001**
	Obese	**1.85 (1.45, 2.35)**	**<0.001**

*Adjusted for age, race, BMI, gender, smoking, diabetes, and thyroid status.

tions of ATD with spinal DDD stratified by BMI levels are shown in Table III. Obese patients with ATD had a significantly higher risk of having spinal DDD with an OR of 1.85 (95% CI 1.45, 2.35), $p<0.001$. Patients who were overweight also had a significantly higher frequency of spinal DDD with an OR of 1.82 (95% CI 1.37, 2.41), $p<0.001$. The significant association of spinal DDD remained, albeit modestly smaller, in patients with normal BMI with an OR of 1.46(95% CI 1.03, 2.05), $p=0.03$.

When the model was stratified by thyroid status, those who were hyperthyroid were at increased risk of spinal DDD with an OR of 1.79 (95% CI 1.05, 3.06), $p=0.03$ (Table IV). Significance remained in hypothyroid patients ($p<0.001$) and importantly being euthyroid was also significantly associated with spinal DDD in patients who were positive for anti-thyroid autoantibodies (OR 1.66 (95% CI 1.34, 2.04), $p<0.001$ (Table IV).

Spinal DDD is associated with ATD in the absence of well-defined connective tissue disease and spondyloarthritis

Because of the possibility of confounding of our results by patients known to have established systemic autoimmune diseases and hence at greater risk of generalised arthritis including spinal DDD, we repeated the analysis of our cohort excluding all patients with known RA, SLE, SS or SpA. This analysis revealed a similarly high OR for spinal DDD of 1.61 (95% CI 1.35, 1.92), $p<0.001$ (Table V).

Bivariate analysis shows association of spinal DDD with TPOAb

To determine whether one or both anti-thyroid autoantibodies were associated with the higher frequency of spinal DDD, we performed bivariate analyses of spinal DDD, with positivity for TPOAb and positivity for TgAb respectively, the results of which are summarised in Table 6. The OR for abnormal TPOAb of having spinal DDD was 1.34 (1.14, 1.57), $p<0.001$. There was a modest, non-significant trend towards an association between abnormal TgAb and having spinal DDD ($p=0.08$).

Discussion

This study shows that ATD, a common autoimmune syndrome that affects 10 to 20% of the population and is reported to be associated with non-axial osteoarthritis, may also be associated with an increased frequency of spinal DDD (11, 21, 22). Our adjusted analysis showed that ATD is significantly associated with a higher frequency of spinal DDD, even when excluding those with known connective tissue diseases, independent of BMI and TSH levels. Our study had a number of limitations including its retrospective design and the possibility of selection bias relating to testing for the anti-thyroid autoantibodies. The proper resolution of such bias would require large population based studies in which

Table IV. Sub-analysis by stratifying according to thyroid status*.

Outcome	TSH status	Spinal degenerative joint disease	
		Adjusted OR* (95% CI)	*p*-value
ATD	Hyperthyroid	**1.79 (1.05, 3.06)**	**0.03**
	Euthyroid	**1.66 (1.34, 2.04)**	**<0.001**
	Hypothyroid	**1.98 (1.48, 2.65)**	**<0.001**

*Adjusted for age, race, BMI, gender, smoking, diabetes, and thyroid status.

Table V. Sub-analysis by excluding patients with known connective tissue diseases**. n=3743 (4383-640).

Outcome	Spinal degenerative joint disease	
	Adjusted OR** (95% CI)	*p*-value
ATD	**1.61 (1.35, 1.92)**	**<0.001**

Adjusted for age, race, BMI, gender, smoking, diabetes, and thyroid status, **RA, SLE, Sjögren's syndrome, seronegative spondyloarthritis.

Table VI. Bivariate analysis of spinal DDD, and TPOAb and TgAb.

Outcome	Spinal degenerative disc disease	
	OR* (95% CI)	*p*-value
TPOAb	**1.34 (1.14, 1.57)**	**<0.001**
TgAb	1.15 (0.98, 1.36)	0.08

data including anti-thyroid autoantibodies and spinal radiographs are collected prospectively, an unlikely prospect given the enormous costs and time requirements. However the main strength of the study is the large sample size and inclusion of patients from primary care providers as well as specialty clinics. Furthermore covariates with known associations with spinal DDD, including BMI, diabetes and cigarette smoking were examined in our study group and included in multivariable models (12, 13). The internal validity of the data is supported by the frequency of diabetes and other co-morbidities in the cohort (23). The findings that patients with ATD were more likely to be women and hypothyroid in our bivariate analyses were consistent with previous studies (21). However, the overall increased number of females in our patient population could be a limitation despite the female predominance of ATD. Again, similar to what has been described in larger population studies, the prevalence of ATD was lower among Blacks than among Whites, Hispanics or other races (21). Other variables positively-associated with ATD included BMI, use of levothyroxine and abnormal thyroid status. This can likely be explained by the association of ATD with hypothyroidism. We observed 7.6% hypothyroidism in the seronegative group which may be due to either an atrophic thyroid gland or perhaps that some of these represent the minority of patients with autoimmune thyroiditis who do not express autoantibodies. In contrast to previous studies that have shown a positive association between type I DM and ATD, we found DM to be less frequent in our ATD group, likely because of our inclusion of both type I and type II DM (24). We did not find a significant difference in age between patients with ATD and those without. There is a reported increase in ATD with age and we suspect that the overall mean age of our cohort determined by age-dependent patterns of health care utilisation in our population obscured this difference, which might have been more apparent in an epidemiological study (21). The association of smoking with a lower frequency of ATD was not noted in our population (25). This may reflect population differences. However, the association between smoking and spinal DDD was suggested by our data although it did not reach statistical significance. Causes like viral infections, genetic causes, artherosclerosis, nutrition and mechanical loading could not be analysed by a study of this design (26, 27). The associations of ATD with well-defined connective tissue diseases and SpA were not statistically significant in our study population, likely due to the relatively small number of patients classified with such diseases and the high frequency of ATD in the study population. This high background of thyroid antibody seropositivity may reflect the age distribution of the cohort as well as biases and suspicions leading to the ordering of thyroid status tests in the first place. Although the scope of the study did not allow individual chart review for the indications for the ordering of thyroid autoantibody tests a limited random sampling of the cohort using available data suggested that indications included presence of goiter, abnormal thyroid function tests, palpitations, fatigue, fluctuations in weight and previously abnormal thyroid antibody testing.

The weaker, non-significant association of spinal DDD with TgAb may reflect a lower sensitivity of that autoantibody for pathology since although it signifies the presence of ATD it correlates poorly with the presence of hypo or hyperthyroidism (21, 28). The clear association of TPOAb with spinal DDD in our analyses raises questions of possible causation. Since this was an observational study and since we could not find any other studies noting this association, the question whether ATD is in a causal pathway of spinal DDD remains to be determined. The pathophysiology of spinal degeneration is temporally, biologically and mechanistically extremely complex (29). Likely players include genetics, mechanical stress, nutrient supply, hormones, cytokines, growth factors, aging, the ionic environment and matrix components (13). Since ATD has been associated with a higher prevalence of hand osteoarthritis it is possible that there are shared etiological mechanisms with hand osteoarthritis involved (11). There have also been associations with

more generalised osteoarthritis and calcium pyrophosphate dihydrate (CPPD) crystal deposition disease described in the literature (8, 30). However our study did not uncover any evidence of CPPD disease in our radiographic data making it a less likely etiological agent at least in the spine. We did not collect data on serum acute phase reactants and did not study a possible relationship between generalised inflammation and an increased frequency of spinal DDD. However the overall lack of association in patients with systemic inflammatory autoimmune disease suggests that inflammation per se is unlikely to be the cause. Furthermore the presence of the thyroid autoantibodies has not been linked to an increased likelihood of generalised inflammation (6). The possibility of causation may be strengthened by the correlation of TPOAb titers with the presence of spinal DDD. However since we did not quantify the extent of spinal DDD involvement we avoided that analysis. We also omitted that comparison because over time the upper detection limits of our anti-thyroid autoantibody assays have varied and would have made finding such a correlation problematic.

In etiopathogenic terms the association between TPOAb and spinal DDD, and the much less strong association of TgAb with spinal DDD observed in this study raises similar considerations regarding the relationship between TPOAb and TgAb, with respect to the development of hypothyroidism (31). Despite the stronger association of TPOAb with hypothyroidism, there has been considerable speculation about the possible role of thyroglobulin (Tg) antigen and perhaps TgAb earlier on in the evolution of thyroid autoimmunity. There may be a shift in reactivity from TgAb to TPOAb, a process described by some authors as constituting an escalation of the autoimmune process, leading to thyroid destruction and hypothyroidism (32). Therefore there might still be a prominent role for Tg perhaps in the initiation of the disease as has been suggested in some animal models (33). If pathophysiologic mechanisms are shared between the various manifestations of ATD then the monitoring of all thyroid-related autoantibodies may be relevant to our understanding of those mechanisms whether they relate directly to the thyroid or to extra-thyroidal manifestations (34).

Conclusions

We have presented evidence using a large data source that ATD is significantly associated with a higher frequency of spinal DDD, even when excluding those with known connective tissue diseases and SpA, and independent of BMI and TSH levels. We believe this finding is novel and suggests that there may be an important link between thyroid autoimmunity and spinal DDD. Further studies are needed to corroborate the finding, which could explain the known association of ATD with back pain and to determine if the link is causal. We suggest based on these findings that the assessment of anti-thyroid autoantibodies might be useful in rheumatology practice given the already known associations with other rheumatic conditions including, well-defined systemic autoimmune diseases, non-axial osteoarthritis and chronic widespread pain (5).

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