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REVIEW ARTICLE

Rheumatic associations of autoimmune thyroid disease: a systematic review

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Abstract

To investigate specific disease patterns in the rheumatic manifestations associated with autoimmune thyroid disease (AITD) through a systematic literature review. We performed a systematic review using the Medline OVID, PubMed, EMBASE, and Web of Science databases through May 2018 for experimental and observational studies that explored the association of AITD with degenerative joint disease (DJD), osteoarthritis (OA), chronic widespread pain (CWP) and fibromyalgia syndrome (FMS), and seronegative inflammatory arthritis (IA). A total of 2132 articles were identified. After title and abstract screening and removal of duplicates, 66 articles were retrieved for full text review. Eighteen studies were deemed eligible for inclusion. Six observational studies reported up to 45% prevalence of DJD in AITD. Hand and spinal DJD were reportedly associated with higher odds of AITD. Twelve observational studies were retrieved reporting up to 62% prevalence of FMS in AITD patients. Four studies described the occurrence of seronegative IA in AITD patients. The rheumatic associations of AITD may manifest specific patterns of disease distinct from those of other well-defined autoimmune syndromes and contribute significantly to disease burden.

Keywords Autoimmune thyroid disease · Chronic widespread pain · Fibromyalgia · Hashimoto thyroiditis · Osteoarthritis · Spinal degenerative disc disease

Introduction

The autoimmune thyroid diseases (AITD) comprise a spectrum of diseases with considerable clinical overlap that are typified histologically by the invasion of the thyroid gland by lymphocytes [1]. Graves' disease is characterized by the presence of antithyrotropin (TSH) receptor antibodies, responsible for over activation of the thyroid gland. A significant proportion of patients with Graves' disease may present with clinically significant hyperthyroidism and Graves' ophthalmopathy. Chronic lymphocytic thyroiditis (CLT) and its goitrous form Hashimoto thyroiditis (HT) are characterized by circulating antithyroid peroxidase antibodies (TPOAb) and/or antithyroglobulin antibodies (TgAb). Hashimoto thyroiditis is the commonest cause of hypothyroidism, although at presentation patients can be euthyroid or even hyperthyroid [2]. Less well recognized are the rheumatic manifestations of AITD. The genetic associations of AITD overlap with those of the autoimmune connective tissue diseases (ACTD), and thus, AITD is enriched in families with ACTD [3–7]. Indeed, AITD is the most common autoimmune disease with the prevalence of CLT alone estimated conservatively to be around 10% of the population in studies using the antithyroid autoantibodies TPOAb and TgAb as markers of disease [8]. Similarly, patients with AITD have an increased incidence of ACTD, which impacts the clinical presentation of the former [9].

Thyroid autoimmunity has been described as a classic example of organ-specific autoimmunity [10]. However, a growing body of evidence suggests that thyroid autoimmunity perhaps occurs as part of a more generalized autoimmune process

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in a significant proportion of patients where an overlap with other autoimmune diseases exists [11, 12]. Furthermore, there is emerging evidence that rheumatic manifestations can occur in AITD patients in the absence of well-defined ACTD or clinically significant endocrine disease. Thus, association of AITD with chronic widespread pain (CWP) and fibromyalgia syndrome (FMS), peripheral osteoarthritis (OA), spinal osteoarthritis, and seronegative inflammatory arthritis (IA) has been described even in the absence of clinical hypothyroidism [13]. Most of the emerging literature focuses on the rheumatic associations of CLT and HT which are much more common than those of Graves' disease. Despite the increasing appreciation of the rheumatologic impact of AITD, the rheumatology community has been slow to incorporate testing for AITD into clinical practice.

General reviews have suggested patterns of musculoskeletal manifestations of AITD, including OA, FMS and CWP, and spinal osteoarthritis. The objective of this review is to provide an initial systematic review to investigate the available scientific evidence for a characteristic pattern of rheumatic manifestations of CLT and HT, outside of the musculoskeletal manifestations of overlap with connective tissue diseases or other autoimmune inflammatory syndromes.

Materials and methods

Search strategy

A comprehensive search was conducted in the MEDLINE OVID database as suggested by Haynes et al. (up until May 31, 2018) [14, 15]. A medical librarian (KS) performed searches in three additional databases: PubMed; Embase on Embase.com, which includes the years 1971–present; and Web of Science, which includes the years 1985–present. For the PubMed searches, MeSH terms including ("Fibromyalgia," "Chronic Pain," "Osteoarthritis," or "Arthritis, Rheumatoid") were combined with ("Thyroiditis, Autoimmune" OR (("Thyroid Gland," OR "Thyroid Diseases") AND ("Autoimmune Diseases" OR "Autoantibodies"[Mesh] OR "Autoimmunity"))). Title and abstract words were included in the search. For the Embase search, Emtree terms and title and abstract words were searched. A topic search was conducted in Web of Science. Supplementary Appendix A provides the complete PubMed search. The associated rheumatic diseases were grouped into three groups: Group 1—degenerative arthritis or OA (Supplementary Appendix A1); Group 2—FMS or CWP syndromes (Supplementary Appendix A2); and Group 3—seronegative IA (Supplementary Appendix A3). These searches were then complemented with a review of the reference bibliographies of the review articles identified thus far to detect any relevant studies left out by the initial search. Fibromyalgia and chronic widespread pain were defined using the American College of Rheumatology (ACR) 1990 definition and the updated criteria respectively [16, 17]. Osteoarthritis of the hip, knee, and hand were defined using the ACR criteria for each respectively [18–20]. Spinal osteoarthritis was defined by the radiographic presence of degenerative joint disease (DJD) or degenerative disc disease (DDD) respectively. Inflammatory arthritis was included if it was seronegative and not due to a well-defined ACTD, undifferentiated connective tissue disease (UCTD), or other well-defined autoimmune syndrome and could thus be attributed to the presence of AITD alone.

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (S1 Table) and statement [21]. Experimental, quasi-experimental, and observational human studies published in English which addressed the presence of the abovementioned comorbidities in patients with AITD or vice versa were included. Qualitative research designs, review articles, meeting abstracts, protocols, and case reports were excluded. If a study addressed a heterogeneous group of patients, the study was included if the results for patients meeting our inclusion criteria were reported separately.

The authors evaluated titles and abstracts of the references identified by means of the search strategy independently. The full texts of articles of interest were evaluated for inclusion. Any discrepancies between the reviewers were resolved by consensus. Data pertaining to included studies were extracted independently using a standardized format by two authors (TS and CT or EG and CT) and verified subsequently by the third author. A narrative synthesis with tabulated results was performed. Due to the high heterogeneity in design and outcome measures of the included studies, it was not feasible to combine data by means of meta-analysis. The study selection flowchart and results of the search strategy are shown in Fig. 1.

Results

Search outcome and level of evidence

A total of 2132 references were identified. After exclusion of duplicates, 1280 titles and abstracts were reviewed for relevance to the topic. Sixty-six articles were reviewed in full text version. A total of 18 studies met the inclusion criteria for review, isolating studies that analyzed the MSK findings in AITD patients, not attributable to overlapping ACTD. Of the 18, six, twelve, and four studies addressed the association of AITD with osteoarthritis or degenerative joint disease, FMS or CWP syndrome, and seronegative inflammatory arthritis, respectively. All the isolated studies were observational studies. Level of evidence was judged using the grading of

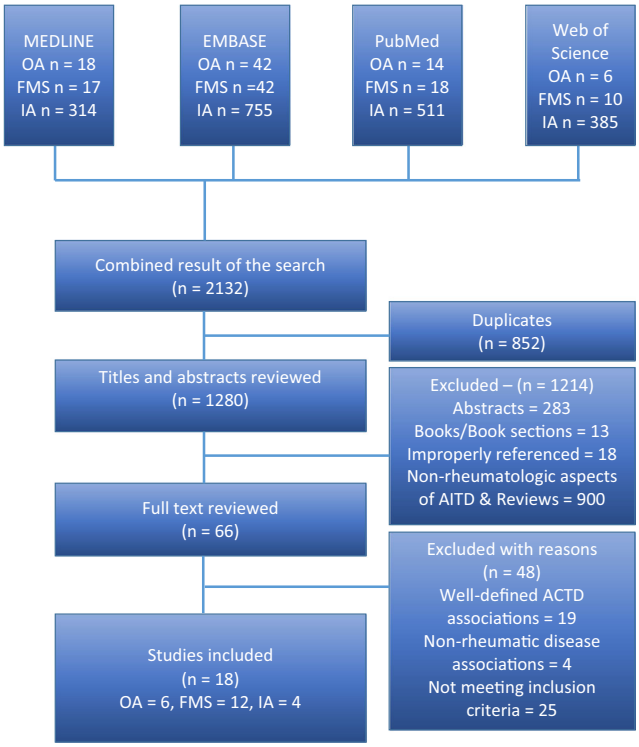

Fig. 1 Flow diagram of the search methodology

recommendation, assessment, development, and evaluation (GRADE) approach [7]. Risk of bias was assessed using the tool for nonrandomized studies by Kim et al. [22].

Osteoarthritis in autoimmune thyroid disease

Six observational studies addressing the impact of OA in patients with AITD or vice versa were identified by the search and met the inclusion criteria for review (Table 1). Most of these studies were cross-sectional; two studies explored possible association between spinal OA and hand OA, and AITD. Studies used the terms DJD and DDD interchangeably in reference to axial OA.

Soy et al. while investigating the frequency of rheumatic diseases among 65 patients with AITD found symptomatic OA as the third most common comorbid condition (15%) in this population, behind FMS and recurrent aphthous stomatitis [23]. It manifested mainly as hand OA (Heberden's nodes) and knee OA. Mobini et al. described the presence of AITD in 36.3% of 80 OA patients [24]. Addimanda and coworkers in their investigation of the clinical associations of hand OA studied 446 patients and found that they had significantly increased odds of having AITD (odd's ratio (OR) 4.85, 95% CI 1.77–13.29) compared to 307 controls [25]. Hezarkhani et al. found a prevalence rate for OA of 25% in their cohort which was 86% female with a mean age of 39 years [26]. In a recent study, Tagoe et al. reported that 88% of their cohort of 46 AITD patients had imaging evidence of OA at all sites, namely peripheral and axial, of which 45% had spinal DJD. However, the study lacked a control arm [27]. Shrestha et al. conducted a study specifically exploring the possible association between spinal DDD and AITD. The authors studied 4383 patients with radiographic evidence of spinal DDD and available data on the antithyroid autoantibodies TPOAb and TgAb, and reported a positive association between AITD and the presence of spinal DJD with an adjusted OR of 1.8 (95% CI 1.6–2.2) [28].

Fibromyalgia and chronic widespread pain in autoimmune thyroid disease

A total of 12 observational studies addressing the impact of FMS and CWP in patients with AITD or vice versa were identified by the search (Table 2).

In the study by Soy and colleagues mentioned in association with OA, the authors also examined FMS in patients with AITD [23]. They found FMS to be the most common rheumatic association in the 65 patients with AITD examined, with a prevalence rate of 31% as defined by the 1990 ACR criteria [16]. The referral base was an endocrinology clinic and only 5% of patients were euthyroid; almost half were hypothyroid. Bazzichi et al. examined 120 FMS patients and found that the prevalence of AITD was 41%. The actual prevalence in the general FMS population could be higher since the authors reported that basal thyroid hormone levels of their FMS patients were in the normal range [29]. In a follow-up study, Bazzichi and coworkers were again able to show an association of AITD with FMS of about 30%, which did not exist in patients with subclinical hypothyroidism in the absence of AITD. They concluded that the presence of AITD was likely important in the development of FMS and deserved further study [30]. Aarflot and colleagues showed a significant association between CWP and thyroid autoimmunity in a community survey of 737 men and 771 women [31]. The prevalence was significantly higher in persons with CWP than without (16.0% versus 7.39%, $p < 0.01$). Tagoe et al. specifically looked at 46 AITD patients with normal thyroid function and the absence of overlap with well-defined connective tissue disease and reported a 56% prevalence of FMS defined by 1990 ACR criteria. This prevalence was higher than in previous studies, perhaps because the study was performed at a tertiary care center with the possibility of referral bias [27].

Other studies that have examined the prevalence of AITD in the FMS population include the work of Ribeiro et al. who reported a cross-sectional study of 146 patients with FMS defined by 1990 ACR criteria. Patients were evaluated for the presence of either TPOAb and/or TgAb. The authors reported an association between AITD and FMS with an OR of 3.87 (95% CI 1.54–10.13) [32]. Pamuk et al. detected a 34.4% frequency of at least one thyroid antibody in a cohort of 128 patients with FMS [33].

Table 1 Characteristics of observational studies for OA and AITD

Study year	Study author	Country and source population	Study population	Outcome and results	Level of evidence	Risk of bias
2007	Soy et al. [23]	Cross-sectional study at an endocrinology clinic in Turkey	65 patients with AITD No control arm	15% prevalence of OA	Low	Low
2011	Mobini et al. [24]	Cross-sectional study in Pakistan	80 patients with RA compared to 80 patients with OA	36.3% prevalence of AITD as defined by presence of TPOAb	Very low	High
2012	Addimanda et al. [25]	Prospective study at 3 tertiary rheumatology clinics in Italy	446 patients with hand OA 307 control subjects	5.4% prevalence of AITD as defined by presence of TPOAb and/or TgAb	Low	High
2013	Tagoe et al. [27]	Retrospective cohort study at a tertiary rheumatology clinic in USA	65 patients with AITD No control arm	88% prevalence of any OA findings 45% prevalence of spinal DDD	Low	Low
2014	Hezarkhani et al. [26]	Cross-sectional study at a rheumatology clinic in Iran	65 patients with AITD No control arm	23% prevalence of OA	Low	Low
2016	Shrestha et al. [28]	Cross-sectional study at a tertiary rheumatology clinic in USA	1557 patients with AITD No control arm	AITD is associated with higher frequency of spinal DDD with an adjusted OR of 1.8	Low	Low

In a recent study, Suk et al. reported similar results to the other studies and showed that among patients with normal thyroid-stimulating hormone (TSH) levels (mean TSH 1.58 mIU/L), specifically in a cohort of 149 FMS patients and 68 healthy controls, there was a 19% prevalence of anti-TPO antibodies in the FMS patients compared to 7% in the controls, which was statistically significant [34].

Two studies have attempted to evaluate the presence of thyroid autoimmunity and/or FMS in the specific context of rheumatoid arthritis (RA). Pamuk et al. examined thyroid autoimmunity in 128 euthyroid FMS patients, 64 RA patients, and 64 healthy control subjects [33]. Thyroid autoimmunity was found in 34.4% of FMS patients and 29.7% of RA patients, significantly higher than in controls (18.8%) ($p < 0.05$). Furthermore, 20.3% of FMS patients had positive TgAb and 24.2% had positive TPOAb. The differences were significant for TPOAb between FMS and RA as compared to controls. Ahmad et al. reported a similar frequency of TPOAb positivity (29%) in a cohort of 203 RA patients [35]. The authors reported a 40% prevalence of FMS or CWP in TPOAb and/or TgAb-positive patients versus 17% for thyroid antibody-negative RA patients. Logistic regression analyses adjusted by age, sex, diabetes, and BMI indicated significantly higher odds (OR = 4.64, 95% CI = 2.11–10.20) of development of FMS in RA patients with TPOAb-positive thyroid autoimmunity.

In the same brief report mentioned above in reference to OA, Hezarkhani and coworkers described the rheumatic manifestations of a cohort of 65 AITD patients; 56 of whom were women. They found that 39.3% of them had carpal tunnel syndrome, the commonest rheumatic presentation in their cohort, 10.7% had Raynaud's phenomenon, and 5.3% had fibromyalgia compared to the Turkish female population FMS prevalence rate of 3.6%. The sample size was small and lacked a control arm making generalization of findings difficult [26]. Baskan et al. studied the relationship between FMS, AITD, and RA by examining the prevalence of TPOAb and TgAb in 65 FMS, 39 RA, and 40 control patients respectively. Although a trend towards high TPOAb and TgAb was seen in FMS, the sample size was small and did not reach statistical significance [36].

Using a population of FMS patients in whom the updated ACR classification criteria were used, Haliloglu and colleagues found a prevalence rate of 62% for fibromyalgia pain in 79 consecutive patients with HT, and they noted the higher prevalence compared to the rate of 30 to 40% using the older classification criteria. There was also a strong positive correlation between the presence of FMS and being positive for TPOAb [37, 38].

Inflammatory arthritis in autoimmune thyroid disease

In a survey-based study, Mosca et al. found a 34% prevalence of AITD among the first and second-degree relatives of 626 patients with inflammatory arthritis [39]. In another study, Soy et al. reported a 6% prevalence of inflammatory arthritis among the 65 patients with documented AITD mentioned earlier. However, according to the authors, the patients had arthritis patterns consistent with RA, psoriatic arthritis (PsA), and arthritis associated with mixed connective tissue disease (MCTD) [23]. The search identified four studies that

Table 2 Characteristics of observational studies for FMS and AITD

Study year	Study author	Country and source population	Study population	Outcome and results	Level of evidence	Risk of bias
1996	Aarflot et al. [31]	Cross-sectional study in Norway	1508 volunteers attending National Health Screening Service's mobile unit	Higher prevalence of thyroid autoimmunity in persons with than without CWP (16.0% vs 7.3%, $p < 0.01$)	Low	Low
2004	Riberio el al. [32]	Cross-sectional study at a rheumatology clinic in Brazil	146 women with FMS 76 control patients	Association between FMS and AITD after adjustment for depression and age, OR = 4.52	Low	High
2007	Pamuk et al. [33]	Prospective study at a rheumatology clinic in Turkey	128 euthyroid FMS patients 64 RA patients 64 healthy controls	34.4% prevalence of AITD in FMS population, significantly higher than controls (18.8%, $p < 0.05$)	Low	Low
2007	Soy et al. [23]	Cross-sectional study at an endocrinology clinic in Turkey	65 patients with AITD No control arm	FMS most frequent rheumatic disease in AITD patients, 31% prevalence	Low	Low
2007	Bazzichi et al. [29]	Prospective study at a rheumatology clinic in Italy	120 FMS patients No control arm	Higher frequency of AITD in post-menopausal patients as compared to pre-menopausal patients	Low	High
2010	Baskan et al. [36]	Cross-sectional study in Turkey	65 FMS patients 39 RA patients 40 healthy controls	15.4% prevalence of AITD in FMS patients, no statistical significant differences in rates of TPOAb and TgAb positivity among the groups	Low	High
2011	Erkoc et al. [64]	Prospective study	30 patients with AITD and thyroid dysfunction	50% prevalence of FMS	Low	High
2012	Bazzichi et al. [30]	Prospective study at a rheumatology clinic in Italy	52 patients with AITD 25 healthy subjects	31% prevalence of FMS	Low	Low
2012	Suk et al. [34]	Prospective study at a rheumatology clinic in the Republic of Korea	149 euthyroid FMS patients 68 healthy controls	Euthyroid FMS patients with significantly higher prevalence of AITD as compared to age and sex-matched control (19% vs 7%, p 0.04)	Low	Low
2013	Tagoe et al. [27]	Retrospective cohort study at a tertiary rheumatology clinic in the USA	65 patients with AITD No control arm	59% prevalence of FMS	Low	Low
2014	Hezarkhani et al. [26]	Cross-sectional study at a rheumatology clinic in Iran	65 patients with AITD No control arm	5.3% prevalence of FMS	Low	Low
2017	Haliloglu et al. [37]	Cross-sectional study in Turkey	79 consecutive patients with HT using updated classification criteria for FMS	Higher prevalence of FMS than using old classification criteria (62%)	Low	Low

Table 3 Characteristics of observational studies for IA and AITD

Study year	Study author	Country and source population	Study population	Outcome and results	Level of evidence	Risk of bias
1984	LeRiche et al. [40]	Prospective study at a rheumatology clinic in Canada	15 patients with AITD No control arm	60% prevalence of seronegative IA	Low	Low
2013	Tagoe et al. [27]	Retrospective cohort study at a tertiary rheumatology clinic in the USA	65 patients with AITD No control arm	26% prevalence of seronegative IA	Low	Low
1997	Punzi et al. [42]	Prospective study with mean follow-up of 6.4 years in Italy	33 patients with CLT and arthritis	25% prevalence of seronegative IA	High	Low
1993	Golding [41]	Observational study	11 patients with AITD and arthritis	No prevalence data	Very low	High

described seronegative IA solely attributable to AITD in various cohorts (Table 3).

Lerich and Bell described in 1984 a group of 15 patients with HT who presented with inflammatory polyarthritis. Two were hypothyroid, five were euthyroid, and eight had incipient hypothyroidism, defined by elevated TSH or mild symptoms. Nine patients had non-erosive seronegative polyarthritis which the authors felt was a unique presentation of HT while the rest had rheumatoid factor positive erosive arthritis indistinguishable from seropositive rheumatoid arthritis [40]. Similarly, Golding described 11 patients with AITD who had high levels of antithyroid antibodies and were euthyroid or marginally hypothyroid. These patients had clinical features of a seronegative inflammatory polyarthritis resembling early, mild rheumatoid disease. In these patients, the joint changes markedly improved with thyroid therapy, whereas in the patients with more definite rheumatoid-like features and positive RF, the joint symptoms were unaffected by thyroid therapy. Thus, it was believed that this was a group of patients with a distinctive non-rheumatoid syndrome of seronegative polyarthritis associated with AITD. This study lacked a control arm [41].

In a more recent report, Tagoe et al. found that 26% of a cohort of 46 euthyroid patients with no known well-defined connective tissue disease or spondyloarthropathy (SpA) had evidence of synovitis in the wrists and hands. Two patients (4%) had seronegative arthritis resembling RA with evidence of spinal arthritis and FMS. The authors suggested a separate etiology for the inflammatory arthritis, perhaps related to AITD [27].

Punzi et al. conducted a prospective study to explore the natural history of arthritis in patients with AITD [42]. During a mean follow-up of 6.4 years of 33 patients with CLT and arthritis, almost half of the patients with polyarthritis developed severe RA characterized by bony erosions, high levels of IL-1, and increased frequency of HLA DR4. The other half had seronegative, non-erosive arthritis with a milder clinical course, low levels of IL-1, and increased frequency of HLA DR3. The arthritis was independent of the degree of thyroid dysfunction and had a clinical pattern similar to the arthritis found in the context of connective tissue diseases [42]. The small number of study subjects did not allow for generalization.

Discussion

We have performed a systematic review of the rheumatic manifestations of AITD with specific reference to CWP and FMS, peripheral osteoarthritis, axial OA, and IA. The quality of evidence was deemed to be low for most of the studies. However, using the GRADE protocol, several of the studies could be upgraded to a level of moderate based on the odds ratios of association exceeding two [43]. These findings suggest that AITD may be a risk factor for CWP and FMS, peripheral osteoarthritis, and axial OA. The association with IA was less definite based on the available data. Elatter et al. studied 150 RA patients and found a 24% prevalence of hypothyroidism [44]. High rates of association between RA and AITD are reported in other studies, some of which report an influence on disease prognosis [45–47]. However, these reports did not suggest AITD as a cause of inflammatory arthritis and the possible influence of AITD on RA disease severity was not a focus of this review. Insufficient data were available for other reported rheumatic disease associations like adhesive capsulitis, carpal tunnel syndrome, Dupuytren's contracture, and trigger finger, to be included in this review [48].

The association between AITD and osteoarthritis has been known for at least a century [49]. Early reports focused specifically on the association with hypothyroidism. Subsequent publications including one by Gillan and colleagues describing knee OA were able to clearly identify the association with AITD [50]. Further studies have extended findings of association to include spinal degeneration and axial OA [28].

Fibromyalgia and CWP account for an estimated 10% and 30% respectively of outpatient rheumatology visits [51, 52]. Thus, a significant association between AITD and FMS/CWP would suggest a significant burden of disease attributable to

the former. Like the connection between AITD and OA, a possible link with generalized pain is not a new finding. Becker et al. described in 1963 a significant association between HT and fibrositis, a term now supplanted by FMS, in 40 (7.9%) of 506 patients [53]. Our current understanding of the association of AITD with FMS is now well documented and has been reviewed elsewhere [54].

Although the literature supports the association between AITD and rheumatic manifestations, the precise role of AITD in terms of direct causation versus modulation of the rheumatic presentation of co-existing autoimmune disease cannot be determined. Some evidence for AITD influencing the disease severity of some ACTD exists, and as noted before, thyroid autoimmunity occurs with enhanced frequency in patients with ACTD [55–57].

Franco et al. looked at AITD in Colombian patients with SLE and concluded that the former is more frequent in lupus but does not influence disease severity [58]. Appenzeller et al. examined the presence of AITD in 524 SLE patients and found thyroid autoantibodies in 17% who were euthyroid. About 6% of the cohort had hypothyroidism and 11.5% had subclinical hypothyroidism. Overall, about 70% of those with thyroid function abnormalities had antithyroid autoantibodies. In this study, SLE disease activity was positively correlated with occurrence of symptoms of hyperthyroidism [59]. These studies suggest that AITD may influence the severity of other autoimmune syndromes that it overlaps with although the direction of that influence is yet to be defined. The current study was not designed to address the non-rheumatologic impact of AITD on disease burden for example through effects on insulin resistance, metabolic syndrome, and cardiovascular risk which have been reported in the literature [60–62].

Conclusion

The presence of AITD not only increases the risk of clinically significant thyroid disease such as hypothyroidism in the particular case of CLT and HT, but possibly increases the frequency of axial OA, and probably increases the presence of peripheral OA characterized by Heberden's and Bouchard's nodes, knee, and hip OA. It probably increases the prevalence of FMS in some populations, including AITD with no ACTD overlap and in RA patients [35]. The quality of the evidence is low to moderate at best. However, the high strength of the associations described particularly for peripheral OA and CWP/FMS call for further studies particularly given the very high prevalence of AITD in the general population and its enrichment in ACTD. Furthermore, the data suggest a specific pattern of association involving peripheral arthritis including Heberden's and Bouchard's nodes, spinal involvement of the cervical and lumbar discs, and chronic widespread pain or fibromyalgia. A limitation of the study was its dependence on observational reports and the possibility that some patients had unrecognized well-differentiated connective tissue or autoimmune disease. Secondly, given the extended study period and the lack of uniformity between studies, there is likely to have been a lack of uniformity of diagnostic procedures between studies. This heterogeneity precluded the performance of a meta-analysis of the data. Large epidemiologic studies of high quality are required to confirm the specificity of these patterns of musculoskeletal associations with AITD. Recognizing the association is crucial to understanding any impact AITD may have on disease burden alone or in combination with well-defined ACTD.

We believe the preponderance of the evidence available now justifies the assessment of thyroid autoantibodies as part of routine rheumatology practice to better assess the disease burden of AITD in rheumatic diseases, not only generally through its endocrine and cardiovascular effects, but specifically due to its rheumatic manifestations. The association of endocrine diseases like diabetes with musculoskeletal disease is well recognized [63]. The association of AITD with rheumatic syndromes may involve metabolic processes as well as immunologic and inflammatory pathways. This review suggests that AITD, which has a population prevalence of about 10 to 20%, may indeed have an association with osteoarthritis and chronic widespread pain, implicating it as an important risk factor for these conditions. A detailed study of this association might help to provide a better understanding of these syndromes which could facilitate a more descriptive overview and allow a departure from our normative classifications of OA and chronic widespread pain.

Compliance with ethical standards

Disclosures None.

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