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REVIEW ARTICLE

# Fibromyalgia and chronic widespread pain in autoimmune thyroid disease

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**Abstract** Fibromyalgia and chronic widespread pain syndromes are among the commonest diseases seen in rheumatology practice. Despite advances in the management of these conditions, they remain significant causes of morbidity and disability. Autoimmune thyroid disease is the most prevalent autoimmune disorder, affecting about 10 % of the population, and is a recognized cause of fibromyalgia and chronic widespread pain. Recent reports are shedding light on the mechanisms of pain generation in autoimmune thyroid disease-associated pain syndromes including the role of inflammatory mediators, small-fiber polyneuropathy, and central sensitization. The gradual elucidation of these pain pathways is allowing the rational use of pharmacotherapy in the management of chronic widespread pain in autoimmune thyroid disease. This review looks at the current understanding of the prevalence of pain syndromes in autoimmune thyroid disease, their likely causes, present appreciation of the pathogenesis of chronic widespread pain, and how our knowledge can be used to find lasting and effective treatments for the pain syndromes associated with autoimmune thyroid disease.

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## Introduction

Fibromyalgia and chronic widespread pain (CWP) syndromes are among the commonest conditions seen in rheumatology practice. Fibromyalgia alone constitutes about 10 % of all outpatient visits while CWP accounts for over 30 % [1, 2]. Close study of rheumatology outpatient prevalence data shows poor patient retention for fibromyalgia patients suggesting a tendency to migrate among providers of multiple disciplines in their quest to find ideal treatments. By contrast, patients with other chronic conditions like rheumatoid arthritis are more likely to remain in the care of a rheumatologist, perhaps reflecting more satisfactory outcomes [1]. Fibromyalgia and CWP collectively carry a significant economic burden and are associated with tremendous monetary losses to society in direct healthcare costs and productivity [3, 4]. Despite major improvements in the treatment of fibromyalgia and CWP, they remain significant causes of disability and failure to reintegrate into the workforce with rehabilitation [5].

Autoimmune thyroid disease (AITD) constitutes a spectrum of autoimmune disorders with considerable overlap including Grave's disease and Hashimoto thyroiditis, also referred to as chronic lymphocytic thyroiditis (CLT) [6]. Both conditions have significant musculoskeletal manifestations. Though AITD and CLT are often used interchangeably, in this review, the focus is on the association of CLT in particular with chronic pain syndromes as seen in clinical practice. Perhaps 10 % of women and 1 % of men have CLT. These numbers double in those over 50 years [6]. Our current understanding of the biology of these conditions provides no clues for the reasons for such high prevalence rates.

Early CLT seems to involve antigen presenting cell and T cell infiltration of the thyroid gland perhaps in response to presentation of autoantigens presumed to include thyroglobulin and thyroid peroxidase. Eventual T cell help of immunoglobulin-producing B cells results in production of antibodies to thyroglobulin and thyroid peroxidase in over 90 % of CLT patients [7]. The possible disease-causing roles of other autoantibodies including thyroid-stimulating hormone (TSH) receptor autoantibodies, antibodies to pendrin, and antibodies to the thyroidal iodide $Na^+/I^-$ symporter are uncertain [8]. The immunological reaction to the gland is more proliferative in Grave's disease, causing the formation of goiter, and more destructive in CLT but does lead to goiter formation in some proportion of patients. The characteristic histological findings in CLT include lymphocytic infiltration of the thyroid parenchyma, followed by the appearance of Askanazy cells, cellular destruction, and eventual fibrosis [9].

The majority of persons with CLT remain asymptomatic throughout their lives. However, in about 20 % of patients, there is eventual failure of the thyroid gland leading to overt hypothyroidism, and there are significant numbers who develop a host of rheumatologic, nervous system, psychological, dermatologic, metabolic, endocrine, and other associations, some of which are autoimmune in nature. The plethora of associated findings seems to reflect the complex functions of the thyroid gland as well as the immunological processes accompanying thyroid autoimmunity. From the early days of such reports, chronic pain syndromes and CWP have featured prominently but not without problems related to classification and nomenclature. Thus, Carette and Lefrançois were able to detect pain syndromes in 19 % of a cohort of primary hypothyroid patients, but only 5 % met the then definition of fibrositis [10]. This review will avoid the intricacies of pain syndrome nosology and focus on the clinical syndromes of CWP in CLT as they relate to clinical practice.

## Autoimmune thyroiditis and chronic widespread pain

Chronic widespread pain is estimated to affect between 4.1 and 13.5 % of the population and has been shown to have close association with multiple musculoskeletal disorders [5, 11]. The relationship with AITD in particular has been known for decades. Becker and colleagues from the Mayo Clinic described multiple rheumatic associations of Hashimoto thyroiditis a half-century ago [12]. Secondary fibrositis was seen in 7.9 % of Hashimoto thyroiditis patients. Overall, 23.5 % of 119 Hashimoto patients had rheumatic diagnoses, 18.5 % associated with chronic pain [12]. Golding studied nine hypothyroid patients and tried to make the distinction between myositis, well recognized as a complication of hypothyroidism at the time, and fibrositis, characterized by muscle, body, and joint pain but not weakness, which he found to be present in all nine patients in his case series [13]. Wilke and others also reported their experience of fibrositis in eight patients with subclinical hypothyroidism and mild elevations in TSH. Six of the patients improved in terms of their fibrositis symptoms with thyroid hormone replacement [14]. Bland et al. described a similar experience with hypothyroid patients and supported the hypothesis that elevations in thyroid-stimulating hormone (TSH) might increase deposition of proteoglycan in musculoskeletal tissues through stimulation of adenylate cyclase causing pain and stiffness [15]. This hypothesis led to the belief in the reversibility of the musculoskeletal findings with thyroid hormone replacement providing they were not inflammatory [16]. More recent reports challenge the simplicity of that assertion because treatment of hypothyroidism does not always relieve pain [17]. Neck and upper thoracic pain has been reported by several authors including Golding in his review of AITD and associated rheumatic manifestations [18]. Aarflot and Bruusgaard noted a significant association between thyroid autoimmunity and CWP, speculating that the abnormal regulation of thyrotropin-releasing hormone (TRH) might modulate abnormal pain perception in autoimmune thyroid patients [19].

## Autoimmune thyroiditis and fibromyalgia

Following the introduction of the American College of Rheumatology (ACR) classification criteria for fibromyalgia syndrome (FMS) in 1990, a number of groups were able to describe the chronic pain manifestations of AITD and CLT in patients selected for the presence of fibromyalgia [20–23]. These authors found the prevalence of fibromyalgia in AITD to be in the range of 30 to 40 % [21–23]. Suk and colleagues presented compelling evidence of an association because they looked at the question from the point of view of endocrinology and not rheumatology, thus dispelling any referral bias peculiar to the latter discipline. They found a 19 % prevalence of thyroid autoimmunity in a cohort of fibromyalgia patients compared to 7 % of controls, a statistically significant difference [24]. Ribeiro and Fernando found an association between fibromyalgia and thyroid autoimmunity with an odds ratio (OR) of 3.87 among 147 women with fibromyalgia and 74 case-controls. Interestingly, there was also an association of fibromyalgia with depression with an OR of 3.94 in their univariate analysis, but no association between depression and AITD. In their final adjusted logistic regression model, the association between fibromyalgia and AITD strengthened to an OR of 4.52 [25]. These data compare with a background prevalence of fibromyalgia of about 2.4 % in women and 1.8 % in men in one study using the 2010 preliminary diagnostic criteria for fibromyalgia from the ACR [26]. Estimates using the 1990 criteria are twice as high [2]. Of course, the

symptom complex associated with hypothyroidism tends to overlap with that of fibromyalgia and includes complaints of insomnia, weight gain and subjective swelling, chronic fatigue, headaches, irritable bowel syndrome, mood disorders, and arthralgias. Furthermore, symptoms can wax and wane in both conditions making differentiation and diagnosis a challenge. However, as mentioned previously, treatment of the underlying endocrine disorder seldom completely relieves patients of their chronic pain suggesting that AITD itself contributes to the pathogenesis of the pain syndromes [17].

Thyroid autoimmunity can extend beyond the thyroid alone and overlap with other autoimmune conditions [6]. This autoimmune context was observed by Soy and colleagues who noted that fibromyalgia was the most common rheumatologic presentation, seen in 31 % of 65 AITD patients [27]. Another study looked at a similar population of AITD patients but excluded all those with known connective tissue disease and still found a prevalence of FMS of 59 % [28].

## Autoimmune thyroiditis and spinal pain

There is an association of widespread pain with spinal pain that makes the distinction between fibromyalgia pain and secondarily generalized spinal degenerative disc disease-associated pain difficult. Spinal pain was noted in several of the earlier reports and has been mentioned by more recent reports as well [12, 15, 28]. Indeed, the study by Tagoe et al. found spinal degenerative disc disease in 45 % of their cohort of 46 AITD patients with no well-defined connective tissue disease [28]. The etiology of spinal and paraspinal pain is likely multifactorial and might indeed include fibromyalgia pain; CWP centering around the neck, shoulders, and upper thoracic region; and secondarily generalized spinal arthritis pain.

## Autoimmune thyroiditis and chronic widespread pain associated with connective tissue diseases

Because of the complex overlap of AITD with more generalized autoimmunity, it can be difficult to separate chronic pain pertaining to AITD per se from other overlapping autoimmune phenomena [6]. The association with other connective tissue diseases was examined by one group, who showed that 51 % of Hashimoto thyroiditis patients had an association with a well-defined systemic autoimmune disease including mixed connective tissue disease (MCTD), Sjogren's syndrome (SS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), and polymyositis/dermatomyositis [29]. Other authors have reported similar findings, and it is well known that the genetics of AITD are closely interlinked with those of other autoimmune diseases [30, 31]. Lazurova et al. found a prevalence of AITD of 24 % in both SLE and RA compared to 8 % in their control population [32]. The prevalence of persistent fibromyalgia in SLE and RA has been estimated in one review article to be about 40 and 17.1 %, respectively [33]. These numbers are considerably higher in acute active disease and suggest that there are multiple causes of widespread pain and fibromyalgia in well-defined connective tissue diseases. The active inflammatory state most likely contributes significantly to widespread pain in established systemic autoimmune disease. Given the considerable overlap between these conditions and AITD, it is possible that mechanisms of chronic pain generation peculiar to AITD contribute to the generation of widespread pain in connective tissue diseases when the two coincide. The fact that patients with no established well-defined connective tissue disease experience severe fibromyalgia and CWP even in the absence of clinically demonstrable active inflammation suggests separate and perhaps non-inflammatory mechanisms for AITD-induced widespread generalized pain [28].

## Pathogenesis of pain syndromes in autoimmune thyroiditis

### Small-fiber polyneuropathy

The causes of chronic pain in hypothyroid and AITD patients are poorly understood. There are few studies exploring the etiology of pain in thyroid diseases. Small-fiber polyneuropathy, which mainly affects the small myelinated (Aδ) and unmyelinated (C) fibers, is well described as a feature of several conditions including diabetes and connective tissue diseases like SLE and SS. It has also been demonstrated in and suggested as a cause of fibromyalgia. Although this is an attractive hypothesis explaining the total body pain of fibromyalgia, some authors have observed significant differences between the chronic pain of fibromyalgia and the peripheral neuropathic pain of diabetes mediated by small-fiber neuropathy suggesting that the mechanisms of pain production are distinct [34]. However, it is quite reasonable to assume that small-fiber polyneuropathy is one of many compounding pathologies responsible for generalized pain in fibromyalgia. Oaklander and colleagues identified 27 patients with fibromyalgia and 30 matched controls using the 2010 ACR diagnostic criteria [35]. They assessed distal leg neurodiagnostic skin biopsies plus autonomic function testing (AFT) and found that 41 % of skin biopsies from subjects with fibromyalgia compared to 3 % of biopsies from normal control subjects were diagnostic for small-fiber polyneuropathy. There was some attempt at elucidating the causes of fibromyalgia in that study. The 13 subjects with fibromyalgia and positive small-fiber polyneuropathy on biopsy had normal hemoglobin $A_{1C}$ <6.0 mg/dL making diabetes an unlikely

cause. Furthermore, none of the 13 had abnormal serum chemistries, blood counts, thyroid function, folate levels, triglycerides, C-reactive protein, and serum angiotensin-converting enzyme or positive tests for Lyme disease, SLE, SS, or celiac disease. However, thyroid autoantibodies or evidence of AITD were not ascertained. Given the high prevalence of fibromyalgia in AITD, such information would be extremely useful in future studies in discerning the cause of AITD-related widespread pain. Direct evidence of small-fiber polyneuropathy in hypothyroid patients is provided by a number of publications including those by Ørstavik and colleagues [36]. They looked at 38 hypothyroid patients and 38 normal controls and found statistically significant differences for various measures of small-fiber polyneuropathy. Some serological testing was done, which showed that eight patients had positive ANAs. Twenty-one of the 38 patients had serological evidence of AITD, and all patients were adequately treated for their hypothyroidism. The authors therefore suggest a possible mechanism of pain and small-fiber injury independent of the endocrine defect and possibly involving immunological cross-reactivity with some component of nervous tissue.

## Immunological cross-reactivity

Cross-reactivity of autoantibodies in AITD with components of the nervous system has not been systematically examined as a cause of generalized pain. It is not clear whether there is an association between either the anti-thyroid peroxidase antibody or the anti-thyroglobulin antibody with CWP. Although early studies suggest a lack of correlation, more detailed work is clearly needed [28]. Certainly, thyroglobulin, which is subject to extensive post-translational modification including iodination and glycosylation, and is one of the largest autoantigens in man, is known to share sequence homology with several proteins [37]. Thyroglobulin shares close sequence homology at its C-terminal end with acetylcholinesterase [38, 39]. This similarity has generated interest in a possible association of antithyroglobulin antibodies with Grave's ophthalmopathy [40]. Much less interest has been directed towards the possibility of such cross-reactivity being involved in the generation of pain through peripheral mechanisms or perhaps through the involvement of the cholinergic interneurons that mediate central sensitization.

## Central sensitization

Central sensitization clearly has a role in fibromyalgia, and given the overlap of fibromyalgia with AITD could help to explain the generation of pain in AITD patients [41]. Glial cells are increasingly known to play a role in the generation of central sensitization through the secretion of cytokines, chemokines, nitric oxide, prostaglandins, reactive oxygen species, and excitatory amino acids [42]. Glial cells are involved in the cell surface activation of TNF-α-converting enzyme (TACE), crucial for the activation of TNF-α [43]. Together, the molecules produced by glial cells enhance and prolong spinal cord hyperexcitability [44]. This is particularly relevant since the function of glial cells is directly regulated by thyroid hormones and their metabolites [45].

Another possible mechanism of pain generation could involve immunological involvement indirectly of ion channels or more directly through cross-reactivity with such channels. To date, no such acquired "channelopathy" has been described in AITD although sodium channel mutations have been implicated in fibromyalgia. It remains to be seen if there is any more pervasive association between such inherited traits and an acquired condition like AITD [46]. The access of the central nervous system to circulating autoantibodies has always been a sticking point in such immunologically mediated theories because of the blood–brain barrier, which normally prevents such access. One would therefore have to explain how in those patients with fibromyalgia the blood–brain barrier is breeched. Obviously, not all patients with AITD experience generalized pain. Therefore, a breakdown in the blood–brain barrier would be an attractive hypothesis to explain why a subset of patients experience widespread pain. More than likely, there is interplay between a number of peripheral and central nervous system mechanisms leading to generalized pain in AITD patients.

## Spinal pain

Our own finding of the prominence of spinal degenerative disc disease in AITD suggests that secondarily generalized widespread pain could be very prominent as a cause of secondary fibromyalgia and other forms of CWP in that syndrome [28]. The involvement of the immune system and in particular leukocytes in the generation of pain following injury to the nucleus pulposus has been known for some time [47]. Whether there is an exaggerated response to the otherwise normal processes of spinal degeneration or a targeted and de novo assault on the intervertebral bodies by an activated immune system in AITD is unknown. Again, this is an area calling for more research and clearly begs the question of whether immunological cross-reactivity with matrix components of the vertebral discs is at play in AITD.

## Inflammation

The role of inflammation and inflammatory cytokines in generating chronic pain syndromes is very well established [48, 49]. Several cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α) are associated with causing hyperalgesia [49]. There are numerous other inflammatory byproducts that mediate pain and contribute to chronic pain syndromes

including bradykinin, prostaglandins, growth factors, nitric oxide, and substance P. However, these molecules can be expected to operate only in the subset of patients who are inflammatory as part of their AITD or have an overlap syndrome expressing more generalized autoimmunity [50]. The clinical implication is that maximal treatment of any underlying inflammatory condition would improve fibromyalgia and widespread pain that are caused or augmented by inflammation [51, 52]. Any residual pain could therefore be expected to be from non-inflammatory causes including the immunological cross-reactivity speculated on above.

## Implications of mechanisms of widespread AITD pain for therapy

Because of the high prevalence of CLT and its direct association with CWP, serologic testing for CLT should probably be an integral part of any rheumatologic work up for chronic generalized pain or FMS. Understanding the various causes of pain is central to defining rational therapy for the chronic debilitating widespread pain suffered by CLT patients. The role of autoantibodies and immunologically derived pain needs clarification. The use of B cell depletion with the anti-CD20 agent rituximab has not been shown to improve the thyroid function of AITD or hypothyroid patients with other autoimmune diseases like rheumatoid arthritis [53]. However, serial measurements of antithyroid antibody levels would have to be made to demonstrate consistent reduction of immunoglobulin levels with rituximab since long-lived plasma cells are not affected by that agent. Such treatments would likely not work if long-lived plasma cells contribute significantly to the pathologic antithyroid autoantibodies. Although one group has suggested improvement in thyroid autoantibodies levels and thyroid function in rheumatoid arthritis patients treated with adalimumab, an anti-TNF inhibitor, the improvements over the course of the 6-month study were modest and did not reduce the need for standard therapies

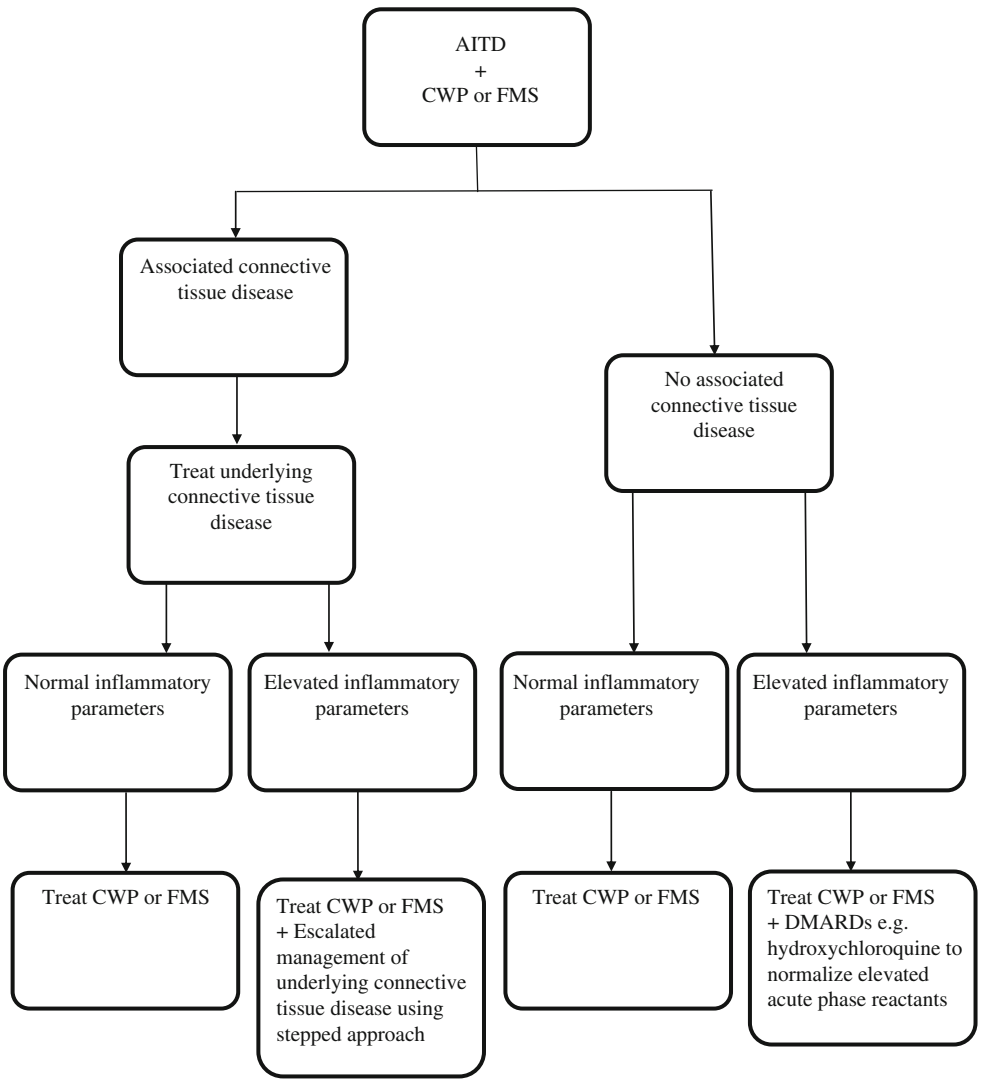


**Fig. 1** Treatment algorithm for chronic widespread pain (CWP) and fibromyalgia syndrome (FMS) in AITD

for thyroid insufficiency [54]. The majority of these patients were also on methotrexate and oral corticosteroids under supervised care, and it is not clear if improved medications adherence under those conditions could have improved the measured indices. There was no comment on the presence of chronic pain in the patients. Indeed by contrast, Atzeni and colleagues did not find any influence on thyroid autoimmunity by adalimumab in their clinical experience [55].

Current evidence suggests that it is important to separate the presence of inflammatory from non-inflammatory causes in the management of AITD patients with CWP. Purely inflammatory pain responds well to traditional anti-inflammatory and immunomodulatory treatments. Patients rapidly improve once serum acute phase reactants and other indicators of inflammation return to normal and cytokine, chemokine, and other inflammatory mediator levels decline. However, there is clearly a subset of patients in whom non-inflammatory pain-generating mechanisms are prominent [51]. Understanding the role of AITD in these pain syndromes helps to identify such patients and prevent their excessive exposure to escalating regimens of potentially toxic immunosuppressive medication. In such patients, the focus should rapidly shift to the treatment of chronic pain using traditional pain and fibromyalgia medications along with non-pharmacologic interventions. Clearly, identifying causes like severe spinal degenerative disc disease with secondarily generalized pain can allow specific targeting of interventions designed to curb spinally generated pain including spinal epidural corticosteroid injections and neurotropic medications like gabapentin and pregabalin. It is unclear at this point if thyroidectomy might alleviate some or all of the symptoms of chronic pain in AITD that are autoantibody mediated. Although thyroid autoantibody levels fall after thyroid removal in the majority of patients requiring thyroidectomy, it is unknown if clones of antibody producing cells persist in some similar to what is seen in chronic hepatitis C infection after viral eradication where persistence of B cell clones leads to continued production of autoimmune phenomena including cryoglobulin generation. This is an area which clearly requires more investigation. A rational therapeutic approach to the patient with AITD-associated CWP or fibromyalgia based on current evidence is summarized in Fig. 1.

## Conclusion

We have presented a succinct review of the CWP syndromes associated with AITD, in particular, its CLT manifestation. We have examined the possible mechanisms of pain generation and their implications for therapy. An emphasis on separating inflammatory from non-inflammatory etiologies is central to rational management of this patient population. That distinction allows a combination of pharmacologic and non-pharmacologic measures to be used as part of our armamentarium for non-inflammatory causes of pain. We acknowledge the scarcity of knowledge in this field and agree that a clearer understanding of the causes of pain in AITD would hold promise and hope for millions of women and men who at present have their misery compounded by a lack of knowledge of the mechanisms underlying their pain. Most patients with AITD-associated pain feel bewildered, lost, misunderstood, and frequently neglected because many physicians still do not make the association between AITD and chronic pain. Because the pain of CWP and fibromyalgia associated with AITD like the apparition of Banquo to Macbeth, is perceived by the sufferer alone, it exacts a heavy physical toll but perhaps just as much an enormous psychological burden. It is our fervent hope that these pain syndromes should get the full attention they deserve and that further research into AITD as the commonest autoimmune syndrome with significant morbidity and enormous economic costs would greatly improve the lives of what now constitutes a silent multitude of suffers.

**Disclosures** None.

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