Autoimmune thyroid disease in patients with rheumatic diseases

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ABSTRACT

Thyroid function abnormalities and thyroid autoantibodies have been frequently described in patients with rheumatologic autoimmune diseases, such as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and scleroderma. Limited data are available regarding the prevalence and clinical characteristics of autoimmune thyroiditis in other rheumatologic disorders, such as rheumatic fever and juvenile systemic lupus erythematosus. The authors review the association of endocrine autoimmune and rheumatic autoimmune diseases, assessing various age groups and clinical conditions. The bibliographic survey was conducted through the search for scientific articles indexed in the general health sciences databases, such as Latin American and Caribbean Health Sciences Literature (LILACS), Medline/PubMed, and Scientific Electronic Library Online (SciELO). The following descriptors were used: "rheumatic autoimmune diseases and autoimmune thyroid diseases"; "thyroid disorders and rheumatic diseases"; "thyroiditis and rheumatic diseases"; "autoimmune diseases and thyroid"; and "pediatric rheumatic diseases and autoimmune thyroid diseases". This study showed that, despite contradictory results in the literature, there is a greater prevalence of the association between autoimmune thyroid diseases and rheumatic diseases, highlighting the possibility of common pathogenic mechanisms among them.

Keywords: rheumatic diseases, child, adult, autoimmune thyroiditis.

INTRODUCTION

Autoimmune diseases (AID) are divided into organ-specific and non-specific diseases.[1] Autoimmune thyroid diseases (AITD) are considered organ-specific, being represented by Graves' disease and Hashimoto's thyroiditis (HT) or chronic autoimmune thyroiditis (CAT). The most common AITD is CAT, considered the prototype of organ-specific AID, characterized by diffuse lymphocytic infiltration of the thyroid gland, presence of anti-thyroglobulin antibodies (anti-Tg) and anti-thyroid peroxidase antibodies (anti-TPO), and endocrine abnormalities ranging from hypothyroidism to myxedema.[1,2]

Although specific for AITD, the anti-Tg and anti-TPO antibodies have been reported in many patients with non-thyroid diseases, and even in the healthy population.[1,2] On the other hand, a high prevalence of autoantibodies directed against specific non-thyroid antigens has been described in patients with AITD, such as antinuclear antibodies (ANA) in HEp-2 cells, whose clinical meaning is unknown[3,4] and whose positivity varies from 9%–35%,[4,5] reaching 75% and 69% in anti-TPO and anti-Tg positive patients, respectively.[5] An organ-specific and non-specific polyclonal immune response is likely to exist in patients with AITD.[3,5]

Abnormalities in thyroid function and the presence of thyroid autoantibodies have been frequently described in patients with rheumatologic diseases, with different results according to different authors (Table 1). This study aimed at reviewing the association of endocrine and rheumatic autoimmune diseases, assessing different age groups and clinical conditions.

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Table 1
Association between rheumatic and autoimmune thyroid diseases

Rheumatic disease	Pathophysiological mechanism	Association with AITD	Genetic participation	Major thyroid disease	Most frequent hormone change
Sjögren syndrome	Polyclonal autoimmune response[3,8,9]	+[3,8,9,11]	HLA-B8 and DR3[1,6-9]	HT[13]	Clinical and subclinical hypothyroidism[8,12]
SLE	Polyclonal autoimmune response, drugs, low T3 syndrome, chance[17,18,22]	+[17,19]	HLA-B8 and DR3 Susceptibility gene in 5q14.3-q15[20,21]	HT[17,22]	Clinical and subclinical hypothyroidism[18,22,23]
Rheumatoid arthritis	Polyclonal autoimmune response[5]	+[3,5,28–31]	HLA-DR3 HLA-DR4 HLA-A24[24,26]	HT[3,5,28–31]	Hypothyroidism[31]
JIA	Polyclonal autoimmune response	+[63–69]	+[68]	HT[23,63–69]	Subclinical hypothyroidism [63–69]
Scleroderma	Polyclonal autoimmune response, thyroid fibrosis[1,39]	+[39,42]	HLA-DR15[40]	HT[11,41]	Hypothyroidism[39,42–44]
RP/GCA/other vasculitides	?	?	?	HT[1,46]	Hypothyroidism[47–49]
Rheumatic fever	?	? Report of patients with CRCD[53,54,56–60]	?	HT[60]	Hyper/hypothyroidism[59]
Fibromyalgia	?	?	?	ATA +[72]	Decrease in thyroid hormones after stimulus with TRH[71]

SLE: systemic lupus erythematosus; JIA: juvenile idiopathic arthritis; RP: rheumatic polymyalgia; GCA: giant cell arteritis; AITD: autoimmune thyroid disease; HT: Hashimoto's thyroiditis; CRCD: chronic rheumatic cardiac disease; ATA: antithyroid antibodies; TRH: thyrotropin-releasing hormone; +: positive; ?: inconclusive

THYROID AND RHEUMATIC AUTOIMMUNE DISEASES

Sjögren syndrome

The most often reported association of endocrine and rheumatic autoimmune diseases is that between Sjögren Syndrome (SS) and AITD, mainly in adult women, positive for anti-thyroid (ATA) and anti-parietal cell antibodies, suggesting the presence of common environmental and genetic factors, with similar pathogenic mechanisms. The participation of the histocompatibility antigens (HLA) of the haplotypes HLA-B8 and DR3 in both AITD and primary SS (pSS) has been suggested, because of the high frequency of those haplotypes in Caucasian patients with those diseases.[1,6–9]

The lacrimal, salivary and thyroid glands are very similar from the histological and functional viewpoints, and are greatly susceptible to immune damage. The histopathological lesions of thyroid and salivary glands evidence focal or diffuse infiltration of T lymphocytes, suggesting the same autoimmune response directed to the thyroid follicular cells and the salivary gland epithelium, respectively.[8,9] Hansen et al.[10] have found five cases of focal autoimmune sialadenitis in 19 patients with AITD, similarly to that which has been shown in patients with primary biliary cirrhosis. Thus, sometimes it can be difficult to clearly establish whether the salivary and eye involvement of SS represents an extrathyroidal manifestation of AITD or, inversely, whether that is an extra-exocrine manifestation of SS.

A retrospective study involving 218 patients with AITD has reported the occurrence of AIDs in 13.7% of their cases, of which the most frequent were SS and systemic lupus erythematosus (SLE).[11]

Primary SS is ten times more frequent in patients with AITD, and HT is nine times more frequent in patients with pSS as compared with the general population. The major cause of thyroid disease in pSS is HT, and the most frequent hormonal change is hypothyroidism.[8]

Regarding pSS, hypothyroidism and thyrotoxicosis were found in 14% and 1.8% of the patients, respectively.[12] In another study with 479 patients with SS, the frequency of HT found was greater than that in the general population, 6.26% and 1%–2%, respectively, with no increase in frequency, however, for Graves' disease. In addition, symptoms of SS, such as conjunctivitis *sicca* and xerostomia, have been reported in up to 32% of the patients with HT.[13]

On the other hand, 10% of the patients with AITD and positive for ANA will be diagnosed with SS, reinforcing once more the possibility of polyclonal autoimmune response to organ-specific and non-specific autoantigens.[3]

Thus, most authors tend to screen periodically both the thyroid function in all adult women with SS, even in the absence of symptoms compatible with thyroid disease, and the possible coexistence of SS in all women with AITD, which is justified by the several references in the literature associating SS and AITD.[8]

Systemic lupus erythematosus

The association between SLE and thyroid dysfunction was first described in 1961 in reports of the association between SLE and HT.[14,15] Although the study by Scofield[16] has not evidenced greater risk of AITD in patients with SLE, several studies have shown that association.[17–19]

Although the pathogenic mechanism has remained unknown, genetic influence has been suggested in a study of 35 families with several cases of SLE concomitant with AITD, in which a gene of susceptibility was identified in 5q14.3-q15 (major *locus* of susceptibility for SLE, also found in AITD). That locus can be shared by patients with SLE and AITD, evidencing a potential genetic link between both diseases.[20] Another study has suggested that the presence of HLA-B8 and DR3 is significantly greater in patients with SLE and HT than in the general population.[21]

The most common thyroid changes in patients with SLE are clinically overt and subclinical hypothyroidism,[22,23] estimated in approximately 5.7%, five times more frequent than in the general population.[18] The association between SLE and Graves' disease has been less often described, ranging from 0%–8.9% in different studies, with no increase in prevalence when compared with that of the healthy population.[18,22–24]

Autoimmunity is one of the several pathogenic mechanisms involved in thyroid dysfunction in SLE – other pathogenic mechanisms include the effect of drugs, such as corticosteroids or immunosuppressors, the effect of the underlying systemic disease (low T3 syndrome or sick euthyroid syndrome), iodine intake, or, simply, chance.[17]

When assessing the thyroid function of patients with SLE, some interfering factors, such as patient's age, use of immunosuppressants, and disease activity, should be considered. Acute and chronic systemic diseases have been associated with a significant reduction in total and free T3, a situation known as low T3 syndrome (sick euthyroid syndrome, nonthyroidal illness syndrome), described in patients with several clinical and surgical conditions and after the use of drugs, such as amiodarone, propranolol, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.[17] Corticosteroids slightly inhibit the secretion of thyroid-stimulating hormone (TSH), while NSAIDs interfere with the binding with carrying proteins, reducing the serum concentration of the thyroid hormones.[18] The prevalence of that syndrome is controversial, ranging from 0%–47.8%, according to different authors.[22]

The studies assessing the disease activity in SLE and thyroid dysfunction are not conclusive, and have controversial results.[17] However, patients with greater clinical activity and severity of SLE have significant changes in the hypothalamus-pituitary-thyroid axis, even with no evidence of thyroid disease. Few hours after the disease beginning, T3 levels decrease and those of reverse T3 increase, being proportional to disease severity and duration.[22] In the adult population, whether the presence of SLE is an independent risk factor for thyroid abnormalities or whether it is a coincidental association is still questioned, since the group at the highest risk for the disease (young women) is also the group at the highest risk for HT.[17]

However, it is a well-known fact that many signs and symptoms can reflect manifestations of both the thyroid disease and SLE. Because of the frequent association of those diseases, the presence of unspecific symptoms in a patient with SLE should be carefully taken into account, especially when disease activity is low, considering the possibility of an underlying thyroid disease.[17]

Anti-Tg and anti-TPO antibodies have been more often found in SLE than in the general population, even in patients with no thyroid disease, ranging from 14%–68% in different studies, with increased positivity in those with thyroid dysfunction.[17–22]

Regarding juvenile SLE, hypothyroidism and ATA have been found in 9% and 20%–34% of the patients, respectively.[25] Another study has evidenced anti-Tg in seven of 12 patients with juvenile SLE (58.3%), whose serum levels of TSH, T3 and T4 were normal.[23]

Rheumatoid arthritis

The association between AIDs, with or without thyroid dysfunction, has also been reported in adults with RA, the pathogenic mechanism being still uncertain.[5] The association of the HLA-DR2 and DR4 with the seronegative and seropositive forms of RA, and the greater presence of the HLA-A24, DR3 and DR4 antigens in patients with RA and HT have been evidenced by some authors.[24–26]

Positivity for the thyroid autoantibodies has been detected in 11% of the patients with RA,[27] ranging from 2%–32% in different case series.[3,5,28–31] In a study with 58 patients with RA in United Kingdom families, 6% of the patients had thyroid

diseases and 5% of the men and 15% of the women were anti-TPO positive.[30] In another study with 101 patients with RA of Greece, 12.9% had anti-TPO *versus* 8.6% of the controls.[27] Similar results have been found in Norway and Canada.[31,32] Innocencio et al.[33] have reported positivity for anti-Tg and anti-TPO of 32% and 4%, respectively. El-Sherif et al.[34] have reported an increase in thyroid disorders in patients with RA and/or SLE. Buchanan et al.[35] have demonstrated a statistically significant increase in the association between HT and RA. In addition, Silman et al.[36] have reported high frequency of HT and ATA not only in patients with RA, but also in their families. Deighton et al.[37] have reported a higher prevalence of RA in same-sexed siblings with thyroid diseases as compared with those without thyroid disease.

Although different series have reported an increase in AITD in RA, there is still controversy between the presence of those antibodies and hormone function.[38] Atzeni et al.[5] have reported positivity of 37.1% and 22.9% for anti-TPO and anti-Tg, respectively, subclinical hypothyroidism being present in only 2.8% of the patients. That can be related to the presence of a subclinical thyroiditis or to interactions between free T4 or ATA and other serum factors, such as rheumatoid factor (RF), positive in 65% and 69% of the patients positive for anti-TPO and anti-Tg, respectively.[5]

A study has found a three-fold higher association between thyroid disease (hypothyroidism and HT) and adult women diagnosed with RA, as compared with control women of the same demographic region.[31]

Scleroderma and mixed connective tissue disease

The association between scleroderma and thyroid disease is the only leading to fibrosis of the thyroid gland in the absence of lymphocytic infiltration.[1,39]

An Italian study has assessed the frequency of ATA and the genetic association with HLA class II antigens in 85 patients with scleroderma. The proportions of patients with anti-Tg and anti-TPO were 12% and 19%, respectively. Individuals with anti-TPO had a higher frequency of the HLA-DR15 allele than patients without those antibodies, suggesting that the HLA-DR15 allele can be a marker of immunogenicity for the formation of anti-TPO.[40]

One case of scleroderma was found in a group of 506 patients with HT and in another of 218 patients with AITD.[11,41] Kahl et al.,[39] in a prospective study have shown that 18 (23%) of 77 clinically euthyroid patients with scleroderma had alterations in their thyroid function tests. In addition, eight (10%) had hypothyroidism, of whom, four had ATA.[39] Such results have confirmed those of the study by Gordon et al.,[42] in which 14% and 25% of the patients with scleroderma had severe thyroid fibrosis and hypothyroidism, respectively. In addition, six of seven patients with hypothyroidism (85.7%) had high ATA titers. In the study by De Keyser et al.,[43] of 39 patients with clinically stable scleroderma assessed for the presence of thyroid disease, two had hypothyroidism while other seven were euthyroid, but with an exaggerated TSH response to the thyrotropin-releasing hormone, compatible with subclinical hypothyroidism. ATA and thyroid ultrasound were positive in 18% of the patients. Those results indicate an increased frequency of clinically overt and subclinical hypothyroidism in patients with stable scleroderma, which seems to be of autoimmune nature,[43] and has been confirmed by another study carried out in 36 patients with scleroderma.[44]

The association of localized scleroderma or morphea with HT has also been reported, aiming at suggesting that even the localized forms might share an autoimmune pathogenesis.[1] In the mixed connective tissue disease, ATAs have been found in 25% of the patients and clinical hypothyroidism in less than 20%.[45]

Rheumatic polymyalgia and vasculitis

Although rheumatic polymyalgia (RPM) and giant cell arteritis (GCA) have been studied since 1971, there is no definite conclusion about their association with HT.[1,46] Myklebust et al.[47] and Barrier et al.,[48] in prospective studies with 287 and 39 patients, respectively, have reported no association between RPM or GCA and thyroid abnormalities. Wiseman et al.,[49] however, studying 367 patients, have reported hypothyroidism in 4.9% of them.

Of the 250 patients with HT, Dent et al.[50] have found seven (2.8%) with RPM or GCA, with a 9.3% prevalence in women over the age of 60 years. Regarding the prevalence of thyroid disease in RPM or in GCA, two prospective controlled studies have excluded any association between them,[47,48] contrary, thus, to other authors who have reported an increased risk of thyroid disease in those patients.[1,49]

The largest of those studies has been conducted with 367 patients, 4.9% of whom had hypothyroidism. It is worth noting that, despite the statistically significant results, the population controls of 84 normal participants showed an abnormally low disease rate.[49]

Regarding the association of CAT with other vasculitides, sporadic cases have been reported, and they might not be sufficient to establish a relation between them. Takayasu's arteritis[51] and IgA-associated vasculitides or Henoch-Schönlein purpura[52] are among the most interesting cases. In that context,

however, special attention should be given to the possibility of false positivity or cross-reactivity induced by the presence of ATA or ANCA in the serum. The cross-reactivity between TPO and myeloperoxidase (MPO) molecules has been studied by Haapala et al.[53] in the sera of six patients with HT and four patients with systemic vasculitis, evidencing that the TPO and MPO molecules contained cross-reaction epitopes exposed in the denaturated molecules, which could lead to false-positivity in solid-phase immunoenzyme assays.

In addition, Farsi et al.[54] have reported that some anti-TPO positive sera recognized "normal" MPO, but the sera of most patients with CAT and positive for p-ANCA in human neutrophils also recognized an "abnormal" MPO. On the other hand, a small proportion of MPO-ANCA can react with TPO and be inactivated by heat, providing false-positive results for p-ANCA in human neutrophils fixed in ethanol.[55] Anticardiolipin and antiphospholipid antibodies have also been reported in CAT, but rarely in association with a true syndrome.[56]

Rheumatic fever

In the literature, studies assessing the association between thyroid dysfunction and rheumatic fever, in which all adults have chronic rheumatic cardiac disease (CRCD), are scarce.

The first references to the association between rheumatic fever and thyroid dysfunction date back to 1961, with the study of six women with rheumatic heart valve disease, who evolved with thyroiditis, anti-Tg and hyperthyroidism.[57,58]

Since then, few studies have been published; their results are contradictory, either showing no association between rheumatic fever and AITD[57] or evidencing a greater frequency of some type of thyroid dysfunction in patients with CRCD.[53,55,59–61]

A retrospective study with 76 patients with DCRC has evidenced thyrotoxicosis, hypothyroidism and positivity for ATA in the presence of normal thyroid function in nine, three, and seven patients, respectively.[60] More recently, Ertugrul et al.[61] have evidenced a greater frequency of HT in patients with rheumatic mitral stenosis (16 of 55; 29%) as compared with their healthy controls. Both studies have suggested the possible existence of an association between CRCD and thyroid disease, which requires, however, further studies.

Juvenile idiopathic arthritis

The association between juvenile idiopathic arthritis (JIA) and HT was first described as a case report in 1968.[62] A new reference in the literature was only made in 1975, with a case report of hypothyroidism secondary to HT associated with diabetic coma in a patient with JIA.[63]

In 1980, Fisher et al.[64] reported the case of a 15-year-old adolescent who had been diagnosed with type 1 diabetes mellitus and HT at the ages of six and nine years, respectively, and who developed clinical findings compatible with polyarticular JIA with positivity for RF and ANA. On the occasion, those authors raised the possibility of some association between the diseases, ruling out the likelihood of chance.

Later, HT was diagnosed in 12 of 27 children diagnosed with JIA (44.4%), most of whom were females (91.7%) with the pauciarticular form of the disease (75%). Of those female patients, 85%, 11.1% and 3.7% had normal thyroid function, compensated hypothyroidism, and thyrotoxicosis, respectively. Anti-Tg was positive in 17 patients (63%) and anti-TPO, in seven (25.9%), with simultaneous elevation of both antibodies in 18.5% of those patients.[23]

In 2001, Koga et al.[65] reported the case of a 17-year-old female adolescent, who had been diagnosed with JIA, pauciarticular form, at the age of six years, being positive for ANA and negative for RF, and who had developed HT with hypothyroidism at the age of 7 years. At the age of 17 years, the patient was diagnosed with autoimmune cholangitis, then progressing to Graves' disease. The authors emphasized the following physiopathological similarities found in the target-organs in HT, in cases of primary biliary cirrhosis, and in the synovial fluid of pauciarticular JIA: high levels of cytokines, such as tumor necrosis factor-α, interleukin-1β, and interleukin-2 soluble receptor.

In 2002, a study with 66 patients with JIA reported the frequency of ATA in nine patients (14% – nine girls, of whom, eight had the pauciarticular form, and one had the polyarticular form) as follows: anti-Tg, in three; anti-TPO, in five; and anti-Tg and anti-TPO in one patient. Three patients showed an echotexture alteration in the thyroid gland parenchyma on ultrasound, being diagnosed with HT (4.5%), a high incidence as compared with that of the general population (1%–2%).[66]

Prahalad et al.[67] have reported that at least 12.6% of the relatives of patients with JIA had at least one AID, as compared with 4% of the relatives of controls ($P < 0.000001$). Of all AIDs, HT was significantly more prevalent in relatives of patients with JIA ($P = 0.0008$), while the prevalence of other disorders did not significantly differ.

In an Italian study with 151 patients with JIA, 14 (9.3%) had subclinical hypothyroidism (10 females and four males; mean age, 7.4 years, ranging from 2.3–14.9 years). Two patients had HT. Neither clinical nor biochemical hypothyroidism was found in the children with JIA. Seventeen patients (11.9%) were

positive for ATA (16 females; median age, 9.2 years) as follows: positive for anti-TPO, six; positive for anti-Tg, five; and positive for both ATAs, six children. Of all patients, nine (6%) showed a hypoechoic ultrasound pattern compatible with HT.[68]

A study involving four centers of pediatric rheumatology in Israel with 66 patients with JIA has revealed a higher incidence of ATA (positivity for anti-Tg and anti-TPO of 11.3% and 7.9%, respectively) and subclinical hypothyroidism (12% of the patients) as compared with the normal population. Neither clinically overt hypothyroidism nor symptoms related to the thyroid gland was observed in any patient, and all of them had the pauciarticular form of the disease. The authors have suggested that the following pathogenic mechanisms could be involved in JIA and AITD: immunomodulating effects of the ATAs; molecular mimicry between thyroidal and organ-specific epitopes; and genetic link between thyroidal autoimmunity and susceptibility to the development of JIA.[69]

On the other hand, a more recent study assessing 80 patients with JIA has evidenced HT in only four (5%), most of whom (three) were females, as follows: systemic onset in one patient; enthesitis-related arthritis in another; and the polyarticular form in the other two. The status of the thyroid function in those patients was euthyroidism, subclinical hypothyroidism, hypothyroidism and hyperthyroidism, respectively. Contrary to other findings in the literature, neither a case of HT in the pauciarticular form of JIA nor a statistically significant association between JIA and HT was observed. The authors have attributed that to the low frequency of girls (33%) and of the pauciarticular forms of JIA in their study, demographic and clinical characteristics related to HT in the other case series.[70]

Regarding Graves' disease, there is only one report of two cases associated with JIA. In the first case, the diagnosis of Graves' disease preceded the diagnosis of RF-positive polyarticular JIA by 10 years; in the other case, Graves' disease was diagnosed five years after the onset of psoriatic JIA. Graves' disease has been known to be an AID associated with the major histocompatibility complex and the T cell inhibitory receptor, CTLA-4. Despite the probable association between JIA and HT, whether a similar genetic relationship exists between Graves' disease and JIA remains unknown.[71]

Fibromyalgia

Patients with fibromyalgia (FM) have shown a decrease in the secretion of thyroid hormones two hours after stimulus with TRH, as compared with controls.[72] Another study has reported a 20%–24% prevalence of ATA in patients with FM with no evidence of clear thyroid disease, mainly in the elderly and post-menopausal ones.[73]

CONCLUSION

The development of AITD in the course of rheumatologic AIDs is frequent, although its pathogenesis and clinical significance remain unclear. Regarding pathogenesis, the following hypotheses have been raised: participation of autoantibodies; overlapping of AITD and some AIDs; and systemic inflammatory reaction associated with thyroiditis. Most findings are limited to the occurrence of ATA and subclinical alterations, requiring further studies to assess the clinical impact of thyroid changes in rheumatic patients. Larger studies approaching children are also required, because of the few case series involving that age group, assessing only JIA.

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