

Original Article

Association between Fibromyalgia and Autoimmune Thyroid Disease

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ABSTRACT

Objective: To investigate the prevalence of fibromyalgia (FM) among patients with Hashimoto's thyroiditis (HT) and association of thyroid antibodies with FM severity among affected individuals.

Design: Cross-sectional

Setting: Two endocrinology outpatient clinics

Subjects: Euthyroid patients with HT were recruited

Intervention: Assessment for detection of fibromyalgia

Main outcome measure(s): Prevalence of fibromyalgia and association with Hashimoto's thyroiditis. Diagnosis of FM was made using the 2010 American College of Rheumatology criteria. Serum concentrations of thyroid stimulating hormone (TSH) and anti-thyroid peroxidase (anti-TPO) antibodies were determined.

Results: Average age of the patients was 38.5 years and

93.1% were female. Among the 102 patients, diagnosis of FM was made in five patients (prevalence rate, 95% CI: 4.9%, 0.7 - 9.1). Age, sex, level of education, marital status, menopause status, duration of thyroid disease, TSH, and anti-TPO concentrations were comparable between patients with and without FM ($p > 0.05$ in all tests). Among patients with FM, the indices of FM severity (widespread pain index, and symptom severity) were not significantly correlated with TSH or anti-TPO concentrations.

Conclusion: Despite previous reports suggesting an increased risk of FM in HT, among Iranian patients with HT, the prevalence of FM seems to be comparable with the prevalence reported in the female general population. A possible link between HT and FM needs further investigation in large population-based studies.

KEYWORDS: hashimoto disease/diagnosis, rheumatic diseases/diagnosis, thyroid disorders

INTRODUCTION

Hashimoto's thyroiditis (HT), the most common cause of hypothyroidism, is a disorder of autoimmune origin characterized by the activation of auto-reactive, thyroid-specific antigen T cells and subsequent aberrant production of anti-thyroid antibodies by B cells^[1]. While elevated concentrations of thyroid antibodies might be present in as many as 10% of the general population^[2], the evident dysfunction of the thyroid gland – often manifesting as hypothyroidism – is found in around 0.1 - 2% of adults^[3]. A female preponderance, similar to several other autoimmune

disorders, is noted^[3]. The prevalence of HT increases with age, peaking between 45 - 65 years^[3].

Rheumatologic manifestations of HT have long been recognized^[4]. Musculoskeletal complaints seem to be present even in the absence of frank thyroid hormone abnormalities^[5]. In the past few years, a number of clinical studies have suggested that the prevalence of fibromyalgia (FM) – a common diagnosis in rheumatology practice – is increased among patients with HT and the two disease entities might somehow be interrelated. Initial reports have suggested FM comorbidity among patients with HT is

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a common occurrence and can be identified in 31 - 59% of the subjects^[4,6]. Additionally, a high prevalence of thyroid autoimmunity among FM patients have also been documented^[7]. No study to date has investigated the possible association among Iranian patients. In the present study, we aimed to determine the prevalence of FM in a sample of Iranian euthyroid patients with HT. From an epidemiological perspective, we hypothesized that if there is a link between FM and HT, the prevalence of FM is expected to be greater than the general population. Further, assuming such an association, we postulated that serum concentrations of thyroid antibodies among patients with comorbid HT and FM would positively correlate with FM disease severity.

SUBJECTS AND METHODS

Patients

In this cross-sectional study, between March 2009 and July 2013, consecutive patients with a confirmed diagnosis of HT who visited the endocrinology and metabolism clinics of two teaching hospitals (Arash and Vali-Asr), affiliated with Tehran University of Medical Sciences (Tehran, Iran), were assessed for eligibility. Inclusion criteria were as follows: 1) confirmed diagnosis of HT; 2) age equal or greater than 18 years; 3) being euthyroid for at least the past three months; and 4) having complaints of non-specific musculoskeletal and/or somatic symptoms. Patients were not included if they had previous diagnoses of comorbid autoimmune or connective tissue diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis, spondyloarthropathy, polymyalgia rheumatica, and Sjögren's syndrome), degenerative joint diseases, bursitis, tendinitis, myofascial pain syndrome, comorbid infections with hepatitis C or human immunodeficiency virus or malignancy. Patients with a previous diagnosis of neuropsychiatric disorders including multiple sclerosis, schizophrenia, bipolar mood disorder, and major depression were also excluded. Patients with peripheral neuropathies were excluded as well.

Diagnosis of HT was made on the basis of clinical history, physical examination, ultrasonography assessment, measurement of serum concentrations of anti-thyroid peroxidase antibodies (anti-TPO). Serum concentrations of thyroid stimulating hormone (TSH) were measured using the chemiluminescence immunoassay method and the range 0.5 - 4.3 mIU/L was deemed normal according to the manufacturer's instructions. Serum concentrations of anti-TPO were measured using the enzyme-linked immunosorbent assay method and values > 35 IU/ml were considered higher than normal. All procedures dealing with human subjects in the present study were conducted

in accordance with the ethical guidelines laid down in the latest revision of Helsinki declaration. Ethics committee of the Tehran University of Medical Sciences also approved the study protocol. Written informed consent was obtained from all participants prior to enrollment.

Assessment and diagnosis of fibromyalgia

Eligible patients were referred to the Rheumatology clinic of the hospital and underwent assessment for diagnosis of FM using history and physical examination. A thorough medical history along with the information obtained from patient's file was recorded in pre-designed standard questionnaires. In physical examination, patients complaining of bodily pains were carefully examined and if a competing diagnosis that could explain the symptom pattern was suspected (e.g. osteoarthritis, inflammatory arthritis, discopathies), the patient was excluded. Additionally, in more ambiguous cases, serum concentrations of rheumatoid factor, and anti-nuclear antibodies were ordered, and patients with positive results on either of the tests were excluded as well.

The 2010 American College of Rheumatology (ACR) criteria was used to diagnose FM^[8]. Using the 2010 updated criteria, an FM diagnosis can be made if the following three conditions are satisfied: 1) presence of symptoms for at least three months; 2) absence of disorders that could otherwise explain the pain; and 3) a widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 . If WPI < 7, then a diagnosis can be made only if WPI is between 3 - 6 and SS ≥ 9 . The evaluation for FM diagnosis was done by two independent assessors (S. M.) and (H. K.). The independent assessors then compared their evaluations and disagreements were resolved by consensus. The kappa measure of inter-rater agreement was 0.884, indicating an excellent level of agreement.

Statistical Analysis

Statistical analyses were conducted using the Software Package for Social Sciences (SPSS) version 17 for Windows (SPSS Inc., Chicago, IL). Continuous variables with normal distributions are presented as mean \pm standard deviation and categorical variables as proportions. Given the non-normal distribution of thyroid disease duration, it is presented as median (interquartile range). Independent t-test (or Mann-Whitney U test where appropriate) was used to compare continuous variables between patients with and without FM. To compare the distribution of proportions between the two groups, Chi square test (or Fisher's exact test where appropriate) was used. In the subset of patients with FM, the correlations between continuous variables and WPI/SS were assessed using

Table 1: Baseline characteristics of euthyroid Hashimoto thyroiditis patients

Variable	Value
Age, years (mean± SD)	38.5 ± 11.9
Sex (female) n (%)	95 (93.1)
Education (years) (mean± SD)	11.5 ± 4.2
Marital status (married, n) (%)	90, (88.2)
Menopause status ^b (menopause, n) (%)	18, (18.9)
Duration of thyroid disease ^a (months)	36 (14-99)
Anti-TPO (IU/ml) (mean± SD)	364.1 ± 37.7
TSH (mIU/l) (mean± SD)	2.53 ± 1.37

TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone

^a presented as median (interquartile range)

^b the denominator is the total number of females (n=95)

Pearson's product moment correlation coefficient. In all tests, a two-sided p-value <0.05 was considered necessary to reject the null hypothesis.

RESULTS

Initially, 131 patients met the inclusion criteria and underwent detailed assessment for diagnosis of FM. However, among these, 29 patients did not agree to participate, had an exclusion criteria unraveled only after the second assessment, or the diagnosis of HT could not be confirmed. Therefore, the final statistical analyses were conducted on the remaining 102 patients. Baseline characteristics of the patients with HT are summarized in Table 1. Females comprised the majority of the sample (93.1%). The average age of the patients was 38.5 years and ranged from 20 to 65 years. The median duration of thyroid disease was 36 months and ranged from 1 to 444 months. Among the 102 patients, five fulfilled the ACR criteria set for FM, giving rise to a prevalence rate of 4.9% (95% CI: 0.7 - 9.1). A case-by-case description of HT patients with FM is presented in Table 2. All diagnosed cases

were female and the sex distribution between FM positive and negative groups was not significantly different ($p = 1.000$). The average age of cases was 46.8 ± 9.3 years. Compared with patients without FM, cases were on average 8.7 years older, yet the inter group difference did not reach statistical significance (46.8 vs. 38.1 , $p = 0.111$). Level of education, marital status, and menopause status were also comparable between FM positive and negative patients ($p = 0.961$, 1.000 , and 0.371 , respectively). The median duration of thyroid disease in FM patients was 143 months and was higher than the rest of the sample (median: 36 months), yet the difference did not reach statistical significance ($p = 0.413$). The mean serum concentrations of anti-TPO and TSH among FM patients were 270 ± 51 IU/ml and 2.53 ± 0.37 mIU/L, respectively and were similar to the rest of the sample ($p = 0.554$ and 1.000 , respectively). The association between FM severity (WPI and SS) and serum concentrations of anti-TPO and TSH was evaluated in the subgroup of FM patients using correlation analysis. Neither WPI nor SS were significantly correlated with anti-TPO or TSH ($p > 0.05$ for all tests).

Among the 97 patients without FM, complaints of fatigue, waking unrefreshed, and cognitive symptoms were frequent and were collectively seen in 69 patients (71.1%). However, in all cases, the somatic symptoms were not accompanied by the wide-spread pain syndrome characteristic of FM or the severity of symptoms were not high enough to warrant the diagnosis of FM.

DISCUSSION

In the present cross-sectional study, we aimed to elucidate the frequency of FM among patients with HT and to also investigate whether thyroid antibody concentrations correlate with FM severity among

Table 2: Case by case description of patients with fibromyalgia

Age (years)	Sex	Duration of thyroid disease (months)	Anti-TPO (IU/ml)	TSH (mIU/l)	WPI ^a	Somatic symptoms ^b		Cognitive symptoms	Somatic symptoms	SS score
						Fatigue	Waking unrefreshed			
1	36	F	5	169	2.23	8	2	1	1	5
2	38	F	120	297	2.84	6	3	2	2	9
3	51	F	12	148	2.20	13	3	2	1	7
4	52	F	120	310	1.60	7	1	2	1	5
5	57	F	444	425	3.80	7	1	1	2	6

TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone; WPI: wide-spread pain index; SS: symptoms severity

^a describes the number of painful areas in the past week. Nineteen areas (from jaw to lower leg) are reviewed and hence WPI can range between 0 and 19.

^b each of the three somatic symptoms is scored from 0 (no problem) to 3 (severe, life-disturbing problems) which describes the severity of each complaint over the past week. A fourth indicator (somatic symptoms) is then scored from 0 (no symptoms) to 3 (a great deal of symptoms) to present a semi-quantitative index of the number of somatic symptoms. The four indicators are then summed to calculate a single score (SS) which is indicative of the extent of the somatic symptoms a patient is having and can range between 0 and 12. A diagnosis of fibromyalgia can be made if $WPI \geq 7$ and $SS \geq 5$ or $WPI = 3-6$ and $SS \geq 9$

these patients. Based on our findings, among 102 patients with HT, a concomitant diagnosis of FM was warranted in only five, giving rise to a prevalence rate of 4.9% (95% CI: 0.7 - 9.1). This rate is comparable to the prevalence rate of the disease among a nationally-representative community-based sample of urban females in Iran. Recently, Sandoughi *et al* using the Community Oriented Program for the Control of Rheumatic Disease survey method investigated the prevalence of musculoskeletal disorders in a large sample of urban residents comprising of 1179 females aged 15 and above^[9]. Based on this report, the prevalence of FM among the general population is believed to be around 3.66 (2.59 - 4.73)^[9]. Therefore, given the level of confidence limits, the rate observed among HT patients herein falls in the same range as to that of the general population. In concert with our findings, Hezarkhani *et al* also demonstrated that the prevalence of FM among patients with thyroid autoimmunity is relatively low^[10]. In their assessment of 65 Iranian patients with either HT or Graves' disease, while 86.2% of the patients had musculoskeletal symptoms, clinical diagnosis of FM was made in only three patients (5.3%), which is again comparable to 4.9% prevalence rate observed herein^[10]. Similar observations have also been made in Turkey. In a 2003 study of patients with a range of thyroid diseases (euthyroid, toxic, or partially thyroidectomy goiter, HT, and Graves' disease), Cakir *et al* reported prevalence rates ranging from 4.3% in patients with subclinical thyrotoxicosis to 8.7% in hypothyroid patients^[11].

Our findings are in stark contrast to a number of previous studies that have reported FM to be highly prevalent among HT patients. In a sample of 46 patients with HT from a referral rheumatology practice in New York by Tagoe *et al*, a diagnosis of FM was made in 27 (59%) of the cases^[5]. The prevalence of FM in the general female population of the United States appears to be significantly lower and around 3.4%^[12]. In another study of Italian HT patients, with or without subclinical hypothyroidism, FM comorbidity was found in 31% of the subjects^[6]. Further, they observed that duration of thyroid disease was higher among patients with comorbid FM^[6]. Similar finding was replicated here, yet the inter group difference failed to reach statistical significance. Among FM patients identified within our sample, the serum concentrations of thyroid antibodies did not correlate with FM disease severity, further questioning a possible association between the two entities, albeit indirectly. In a case-control study of FM versus healthy subjects, Suk *et al* demonstrated that FM patients are significantly more likely to have positive anti-TPO antibodies (19% versus 7%). However, as shown here, anti-TPO concentrations were not associated with the severity of

FM defined using a pain visual analogue scale and also a continuous scale for degree of disability caused by the musculoskeletal disease^[13].

The precise reasons for significant discrepancies between the aforementioned studies remain to be determined. However, two points in this regard should be borne in mind. First, the criteria used for the diagnosis of FM among different studies differ; whereas previous studies have based their assessment on the original ACR criteria or clinical judgement, in the present study, the modified ACR criteria published in 2010 was employed. This is particularly relevant since previous research has suggested that the prevalence of FM varies according to the classification scheme used^[14], and a moderate discordance between different criteria sets is ineluctable^[15]. Therefore, a direct comparison between rates reported by different research groups may not be feasible. Second, an important caveat inherent to all studies investigating the prevalence of FM in patients with thyroid autoimmunity, the present study included, is that a relatively small number of patients have been recruited from outpatient clinics often limited to a single or few clinical centers. We believe that this introduces an important source of selection bias and might result in notable overestimation, or less likely underestimation of the FM prevalence among the recruited sample. Consequently, the conduct of large and multi-center studies involving HT patients are clearly needed to determine the prevalence of FM devoid of selection bias. Such a study should preferably include a sample of age- and sex- matched control subjects to provide a comparative perspective.

Two plausible scenarios can explicate the link between thyroid autoimmunity and FM. First, patients with autoimmune thyroid disease are at an increased risk for other diseases of autoimmune aberration. A large population-based study of Caucasian subjects with autoimmune thyroid disease indicated that another autoimmune disease can be detected in 14.3% of the patients diagnosed with HT^[16]. HT significantly increased the risk of celiac disease, pernicious anemia, vitiligo, Addison's disease and systemic lupus erythematosus by more than tenfold^[16]. Indeed, if FM is considered an autoimmune entity, a genetic predisposition toward FM could be expected in patients with HT. Fragmentary evidence suggest a role for autoimmunity in the pathogenesis of FM^[17]. For instance, elevated levels of an anti-nuclear antibody to a 68/48 KDa protein have been reported in patients with primary FM but not in healthy individuals or patients with other connective tissue diseases^[18]. Further, increased concentrations of several inflammatory cytokines such as interleukins 8 and 10, and tumor necrosis factor alpha have been found in

plasma of patients with FM and correlated with clinical manifestations of the disease^[19]. These findings suggest that a heightened immune-inflammatory response might be involved in the hyperalgesia phenomenon observed in FM. In an alternative scenario however, the widespread pain syndrome observed in the context of FM could be viewed as a systemic manifestation of thyroid disease, and not a separate but overlapping entity. Once considered an organ-specific condition confined to the thyroid gland, autoimmune thyroid disease is now being widely described as a systemic disease with its ramifications extending well beyond merely endocrine dysfunction.

CONCLUSION

Implications of the hypothetical association between thyroid autoimmunity and FM for patient management are far-reaching. Yet, we could not establish a firm relationship between HT and FM in our study as suggested by other research groups. In our study, the frequency of FM among HT patients was comparable to the prevalence reported in the female general population. Further, among HT patients, levels of thyroid antibodies did not correlate with indices of FM severity. From an epidemiological stand point, further case-control studies which recruit large numbers of patients from several clinical settings are paramount to establish or refute a possible link between the two disease entities.

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REFERENCES

1. Cogni G, Chiovato L. An overview of the pathogenesis of thyroid autoimmunity. *Hormones (Athens)* 2013; 12(1):19-29.
2. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med* 2003; 348(26):2646-2655.
3. Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Roliński J. Immune disorders in Hashimoto's thyroiditis: what do we know so far? *J Immunol Res* 2015; 2015:979167.
4. Tagoe CE, Zeron A, Khattri S. Rheumatic manifestations of autoimmune thyroid disease: the other autoimmune disease. *J Rheumatol* 2012; 39(6):1125-1129.
5. Tagoe CE, Zeron A, Khattri S, Castellanos P. Rheumatic manifestations of euthyroid, anti-thyroid antibody-positive patients. *Rheumatol Int* 2013; 33(7):1745-1752.
6. Bazzichi L, Rossi A, Zirafa C, Monzani F, Tognini S, Dardano A, *et al.* Thyroid autoimmunity may represent

a predisposition for the development of fibromyalgia? *Rheumatol Int* 2012; 32(2): 335-341.

7. Pamuk ON, Çakir N. The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms. *Clin Rheumatol* 2007; 26(1):55-59.
8. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, *et al.* The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)* 2010; 62(5):600-610.
9. Sandoughi M, Zakeri Z, Tehrani Banihashemi A, Davatchi F, Narouie B, Shikhzadeh A, *et al.* Prevalence of musculoskeletal disorders in southeastern Iran: a WHO-ILAR COPCORD study (stage 1, urban study). *Int J Rheum Dis* 2013; 16 (5):509-517.
10. Hezarkhani S, Sedighi S, Aghaei M, Shamekhi M, Nomali M. Rheumatologic manifestations in Iranian patients with autoimmune thyroid diseases. *J Clin Diag Res* 2014; 8(10):MC06-MC08.
11. Cakir M, Samanci N, Balci N, Balci MK. Musculoskeletal manifestations in patients with thyroid disease. *Clin Endocrinol (Oxf)* 2003; 59(2):162-167.
12. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38(1):19-28.
13. Suk JH, Lee JH, Kim JM. Association between thyroid autoimmunity and fibromyalgia. *Exp Clin Endocrinol Diabetes* 2012; 120(7):401-404.
14. Jones GT, Atzeni F, Beasley M, Fließ E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol* 2015; 67(2):568-575.
15. Katz RS, Wolfe F, Michaud K. Fibromyalgia diagnosis: A comparison of clinical, survey, and American College of Rheumatology criteria. *Arthritis Rheum* 2006; 54(1):169-176.
16. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, *et al.* Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med* 2010; 123(2): 83.e1-9.
17. Buskila D, Sarzi-Puttini P. Fibromyalgia and autoimmune diseases: the pain behind autoimmunity. *Israel Med Assoc J* 2008; 10(1):77-78.
18. Nishikai M, Tomomatsu S, Hankins RW, Takagi S, Miyachi K, Kosaka S, *et al.* Autoantibodies to a 68/48 kDa protein in chronic fatigue syndrome and primary fibromyalgia: a possible marker for hypersomnia and cognitive disorders. *Rheumatology (Oxford)* 2001; 40(7):806-810.
19. Bazzichi L, Rossi A, Massimetti G, Giannaccini G, Giuliano T, De Feo F, *et al.* Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. *Clin Exp Rheumatol* 2007; 25(2):225-230.