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Thyroid Autoimmunity In Patients With Recurrent Aphthous Stomatitis

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is an inflammatory disease which is characterized with the appearance of self healing and recurrent aphtous ulcerations in the oral mucosa. Though the etiopathogenesis of RAS is not clear many factors including autoimmunity have been implicated in the pathogenesis. We aimed to investigate if thyroid autoimmunity is increased in RAS patients as autoimmune thyroid diseases are frequently accompanied by various other autoimmune diseases.

Material and Methods: Forty patients with RAS and 20 sex and age matched healthy volunteers were included in the study. Thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroglobuline, anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobuline antibody (anti-TG) levels were measured and thyroid ultrasonography was performed in the patient and control groups.

Results: In the patient group the mean fT3 levels were 3,26±0,41 pg/mL, fT4: 1,03±0,23 ng/d, TSH: 2,08±2,09 mIU/mL, thyroglobuline: 22,71±78,23 ng/ml, anti-TG: 122,41±631,49 mIU/mL, anti-TPO: 38,50±130,79 mIU/mL. In the control group the mean fT3 levels were 3,53±0,60 pg/mL, fT4: 0,83±0,191 ng/d, TSH: 1,56±1,14 mIU/mL, thyroglobuline:11,79±11,04 ng/ml, anti-TG: 2,82±4,55 mIU/mL, anti-TPO: 1,39±2,11 mIU/mL. In RAS patients, the fT4, anti-TPO and anti-TG levels were significantly higher than the control group ($p < 0.05$). Thyroid ultrasonography revealed nodules in 67.5% patients and 70% controls and heterogenity in 17.5% patients and 15% controls. No significant difference was found in ultasonography findings between the patient and the control groups ($p>0,05$).

Conclusion: As the frequency of thyroid autoimmunity was higher in the patient group we advise to investigate associated autoimmune thyroid disorders in patients with RAS.

Introduction

Recurrent aphthous stomatitis (RAS) is a common clinical condition characterized with recurrent painful ulcers in the oral cavity [1]. RAS lesions present as multiple, small, round or ovoid ulcers with circumscribed margins, erythematous haloes and yellow or grey floors [1]. Three different forms of presentation of ulcers in RAS have been described including, minor, major and herpetiform aphthosis. The lesions are often painful and interfere with mastication and speech with a negative effect on the life quality of the patients [2, 3].

The etiology of RAS is not known, but several factors including genetic factors, immune imbalance, infections, mechanical trauma, smo-

king cessation, deficiency of vitamins and minerals, hypersensitivity to foods, hormonal changes and stress have been proposed as etiolologic factors. It has been thought that immune dysfunction linked to various trigger factors facilietes the development of RAS and autoimmunity is thought to play a role in the pathogenesis [**2, 4, 5**].

Autoimmune thyroid diseases comprimise the most common autoimmune diseases in humans and thyroid is one of the most sensitive sites for autoimmunity [**6**]. Autoimmune disorders may accompany each other and coexistence of thyroid function disorders and autoimmune thyroid diseases have been reported in various rheumatologic and dermatologic diseases [**7, 8, 9**]. Thyroid autoimmunity and thyroid function disorders have been rarely studied in RAS patients in the literature [**10**]. The aim of this study was to determine whether RAS is significantly associated with thyroid autoimmunity and thyroid function disorders.

Materials and Methods

Forty patients with RAS were included in the study group. Patients with minor, major and herpetiform aphthous ulcerations occuring more than three times a year were included in the RAS group. Patients' medical history regarding thyroid diseases was taken before the initiation of the study and all of the subjects that were under treatment for known thyroid disease were excluded. A detailed history was taken from the patients including the age of onset, duration, family history of RAS and thyroid diseases, associated diseases and drug use. Dermatological and physical examinations of the patients were made.

Twenty age and sex matched volunteers were included in the control group. The control group consisted of individuals with no RAS lesions and who were not taking any treatment for known thyroid disease. Serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), thyroxine, anti-thyroglobulin (Anti-TPO) and anti-thyroid peroxidase (Anti-TG) were measured for each subject. Thyroid ultrasonography was performed and the presence of nodules and/or inhomogeneous parenchyma of the thyroid gland were recorded.

Mann-Whitney, chi-square, Spearman's rho correlation tests were used for statistical analysis and a p value ≤ 0.05 was considered statistically significant.

Results

The mean ages of the patient and control groups were 38.82 ± 13,14 and 36.45 ± 12.68 years respectively and there was no significant difference between the ages of the patient and control groups (p>0,05, chi-square test). 23 (57.5%) of the patients were women and 17 (42.5%) were men in the patient group and 11 (55.0%) individuals were women and 9 (45.0%) were men in the control group. No significant difference was found between the genders of the patient and control groups (p>0,05, chi-square test). The mean of the duration of the disease was 7,50 ± 7.43 months in RAS patients.

Ten (25%) of the RAS patients had associated diseases; 1 patient had epilepsy and hypertention, 2 had hypertention and diabetes mellitus, 1 had fibromyalgia, 1 had hyperlipidemia and migraine, 1 had hyperlipidemia and depression, 1 had vertigo, 1 had hypertention and 1 had mitral insufficiency.

Four (20%) of the control group had associated diseases. 1 individual in the control group had hypertention, 1 had diabetes mellitus and hypertention and 2 had iron deficiency anemia.

Twenty-seven (67.5%) of the patients and 12 (60%) of the controls had family history of thyroid disease. There was no statistically significant difference in the number of patients of controls who had family history of thyroid disease (p>0,05, Mann-Whitney test).

The thyroid hormone and autoantibody levels of the patient and control groups are displayed in **table 1**. In RAS patients, the fT4, anti-TPO and anti-TG levels were significantly higher than the control group (p≤0.05). No significant difference was found in ultasonography findings between the patient and the control groups (p>0,05).

No significant relation was found between the duration of RAS and thyroid parameters including serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), thyroxine, anti-thyroglobulin (Anti-TG) and anti-thyroid peroxidase (Anti-TPO) (Spearman's rho correlation test, p>0,05).

Discussion

RAS is a common oral mucosal disorder which affects 5-20% of the general population with a female predominance [**11**]. Although the pathogenesis of RAS is not fully understood it has been thought that autoimmunity may play a role in the pathogenesis [**5**]. RAS occurs as a result of enhanced immunological response and the activation of proinflamma-

Table 1. Thyroid Hormone and Autoantibody Levels and Thyroid Ultrasonography Findings in Patient and Control Groups Patient Group

	Patient Group (median±SD)	Control Group (median±SD)	P-value	Test
sT3 pg/mL	3.26±0.41	3.53 ±0.60	0.095	Chi-square test
sT4 ng/d	1.03±0.23	0.83±0.19	**0.001**	Chi-square test
TSH mlU/mL	2.08±2.09	1.56 ±1.14	0.069	Chi-square test
Thyroglobulin ng/ml	2.08±78.23	11.79±11.04	0.832	Chi-square test
Anti-TPO IU/mL	38.50±130.79	1.39±2.11	**0.001**	Chi-square test
Anti-TG IU/mL	122.41 ±631.49	2.82±4.55	**0.005**	Chi-square test
Presence of thyroid nodules, % (n)	67.5% (27)	70.0% (14)	0.846	Mann-Whitney Test
Inhomogenous thyroid parenchyma, % (n)	17.5% (7)	15.0% (3)	0.808	Mann-Whitney Test

tory cytokines' cascade directed against the selected regions of oral mucosa [**4**]. Increased expression of Th1 gene cluster in comparison to Th2 cluster was found indicating increased activity of Th-1 type immune response which was also described in other autoimmune-mediated diseases [**4**]. The immune response in RAS lesions and the nature of cytokine profile indicates a T-helper type 1 immune response [**11**].

Autoimmune thyroid diseases are autoimmune disorders characterized by the presence of antibodies against the thyroglobulin, thyroid peroxidase or thyrotropin receptor antigens [**7**]. The etiology of autoimmune thyroid diseases is multifactorial which involves genetic and enviromental factors. Linkage and association studies identified several major genes relevant for the onset of autoimmune thyroid diseases including thyroid-specific genes and also many immune-regulatory genes [**12**]. As increased amounts of IL-2, TNF-alpha and IFN-gamma are found in the serum of patients with autoimmune thyroiditis and it is thought that Th1-secreted inflammatory cytokines may contribute to the pathogenesis. Th1 cytokines may be the common immunological factor causing autoimmune thyroid disease and RAS [**13**]. Also thyroid hormones have been suggested to enhance production of inflammatory cytokines and higher circulating levels of proinflammatory cytokines including have been demonstrated in patients with hypertiroidism [**14**]. Thus the higher levels of inflammatory cytokines may also contribute to the proinflammatory cytokines' cascade directed against the selected regions of oral mucosa in RAS patients.

An association between thyroid autoimmunity and other autoimmune disorders has been reported, including rheumatoid arthritis, Sjogren's syndrome and autoimmune hepatitis [**7**]. Also some dermatological diseases including chronic urticaria, vitiligo, pemphigus vulgaris, which might have autoimmune pathogenesis have been found to be associated with thyroid autoimmunity [**8, 9, 15, 16**]. It is thought that overlapping autoimmune diseases may have common physiopathological mechanisms and genetic origins [**17**].

The relation between autoimmune thyroid diseases and RAS has been studied rarely. Soy et al investigated the frequency of rheumatic diseases in patients suffering from autoimmune thyroid diseases and reported that RAS was detected in 20% of the patients and they advised regular checking for rheumatic diseases in patients with autoimmune thyroid diseases [**7**]. Özdemir et al studied thyroid autoantibodies, thyroid functions and thyroid ultrasonography in RAS patients and they found significantly higher levels of fT3, tT3 anti-TG and lower levels of fT4 and thyroglobulin levels in RAS patients. Also thyroid ultrasonography revealed nodules more frequently in the patient group. They concluded that follow-up of thyroid autoantibody levels in RAS patients can expose the sub-clinical disease that lies under [**10**].

In our study fT4, anti-TPO and anti-TG levels were significantly higher than the control group which supports a significant association between RAS and thyroid autoimmunity. In patients with autoimmune diseases the appearance of autoantibodies may preceede the clinical manifestations by many years. We suggest screening for thyroid au-

toantibodies and thyroid function tests in patients with RAS even if they do not have a clinical indication for thyroid disease.

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