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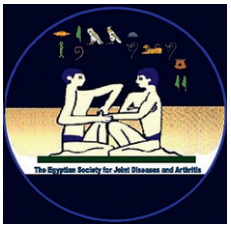

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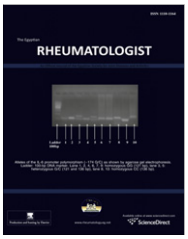

ORIGINAL ARTICLE

Sjögren syndrome and fibromyalgia after radioiodine therapy in cancer thyroid patients

Tamer A Gheita [a], Samar M Fawzy [a,*], Ahmed A Kandeel [b], Hossam M. Khalil [c]

[a] *Rheumatology Department, Faculty of Medicine, Cairo University, Egypt*
[b] *Nuclear Medicine Department, Faculty of Medicine, Cairo University, Egypt*
[c] *Ophthalmology Department, Faculty of Medicine, Cairo University, Egypt*

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KEYWORDS

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Abstract *Introduction:* Salivary and lacrimal gland dysfunction is relatively frequent after radioiodine therapy. An association of Sjögren's syndrome (SS) and other autoimmune rheumatic diseases as fibromyalgia syndrome (FMS) has been reported. Thyroid autoimmunity in FMS patients is higher than normal subjects.

Aim of the work: To detect the occurrence of Sjögren syndrome (SS) and any rheumatologic association in cancer thyroid patients after radioactive iodine therapy (I-131) and evaluate the salivary and lacrimal glands function.

Patients and Methods: Thirty-one patients with post-surgical differentiated thyroid carcinomas with a mean age 40.13 ± 9.82 years, were referred for I-131 therapy (mean dose 212.9 ± 101.63 mCi) and continued the follow-up study. All patients had no symptoms or signs of SS. Thorough rheumatological examination was performed for any musculoskeletal manifestation or associated fibromyalgia syndrome (FMS). Before and 8–12 months after I-131 therapy, salivary glands function was estimated by sequential scintigraphy, while lacrimal gland function was assessed by Schirmer's test. Antinuclear antibody (ANA), anti-Ro (SS-A), anti-La (SS-B) and rheumatoid factor (RF) were performed.

* Corresponding author. Address: 17 Sheikh Ali Youssif, Cairo, Egypt. Tel.: +2 0101805126; fax: +2 02 25085372.
E-mail address: samarfawzy1@yahoo.com (S.M Fawzy).

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Results: All patients had a normal salivary glands scintigraphy and Schirmer's test before I-131 therapy. On follow up, primary SS occurred in 8 patients (25.81%) while a significant decrease in salivary function occurred in 18 (58.1%) patients and significantly correlated with the I-131 dose. Schirmer's test was significantly abnormal in those with SS. Serum Anti Ro and Anti La levels became significantly higher in SS patients (18.25 ± 11.61 and 25 ± 13.06 U/ml) compared to the others (6.57 ± 1.8 and 7.35 ± 1.8 U/ml), respectively, (p 0.025 and 0.006). Fibromyalgia syndrome was present in 12 patients (38.71%) and 6 of them developed SS.

Conclusion: Assessment and follow up of salivary and lacrimal glands function is essential in patients receiving radioiodine therapy. Abnormal level of anti-Ro and Anti-La increase the risk for SS that should be closely monitored and fibromyalgia is a common association.

1. Introduction

Sjögren's syndrome (SS), the second most common autoimmune rheumatic disease, refers to keratoconjunctivitis sicca and xerostomia resulting from immune lymphocytes that infiltrate the lacrimal and salivary glands. However, differential diagnosis remains confusing due to the high prevalence of vague symptoms of dryness, fatigue, and myalgias in the general population. The problems of diagnosis are further compounded by the finding of "positive" antinuclear antibodies in a high percent of the general population [1]. Autoantibodies to Ro (SSA) or La (SSB) antigens are present in the serum of SS patients [2].

An association of SS and other autoimmune rheumatic diseases as fibromyalgia syndrome (FMS) has been reported [3,4]. Thyroid autoimmunity in FMS patients was similar to that in RA and higher than normal subjects [5]. Salivary and lacrimal gland dysfunction is relatively frequent after radioiodine therapy. In most cases this is a transient side effect, but in some patients it may persist for a long period or appear late [6]. The parotid glands have proven to be more susceptible to the development of radiation sialadenitis than the submandibular [7,8].

Salivary scintigraphy is a useful investigation in salivary gland diseases. In SS, pertechnetate imaging can estimate the severity of involvement, which may not be accurately reflected by xerostomia and other features of the sicca syndrome [9]. Salivary scintigraphy with semiquantitative method is useful for accurate and reproducible assessment of salivary gland function providing quantitative changes after parenchymal insult whether inflammatory or radiation induced [10–12]. Tc-99m sodium pertechnetate scintigraphy is a noninvasive technique that provides functional imaging. In addition, physiologic intervention by administration of a sialogogue such as lemon juice provides information on the patency of the salivary ducts and on the overall functional integrity [13].

Iodine-131 (I-131) is an effective treatment for differentiated thyroid carcinomas (DTC) after surgery. Salivary and lacrimal gland dysfunction has been described in patients receiving high doses of I-131 due to radiation damage. Iodine-131 secondarily targets the salivary glands where it is concentrated and secreted in the saliva 50–100 times to that found in serum [14–18]. As radioiodine is concentrated at the choroid plexus [17] and lacrimal sac [19], long-term effects on tear secretion including xerophthalmia are considered [20]. Xerostomia, salivary swelling, pain in the parotid region, altered taste, and dysphagia have been described [21,22]. The symptomatology is in direct proportion to the I-131 dosage and the passage of time. Almost two thirds of patients who receive 100–200 mCi of I-131 will develop salivary gland dysfunction within three months as evidenced by scintigraphy [7,8].

Symptomatic improvement in patients with radiation-induced xerostomia has been reported after pilocarpine treatment [23]. Moreover, significant improvement in SS symptoms was shown [24]. Usually only increased fluid intake and lemon juice consumption is recommended for prevention of salivary gland damage [6]. Early use of sialogogue may enhance the salivary gland side effects of I-131 therapy and for preventing life-long complications the timing of lemon candy sucking should be given after 24 h [25].

The aim of the present study was to identify the occurrence of Sjögren syndrome (SS) in cancer thyroid patients after radioactive iodine therapy (I-131), to assess the salivary and lacrimal glands function and anti-Ro/anti-La autoantibodies and find a possible association to any rheumatologic diseases including fibromyalgia syndrome.

2. Patients and methods

Thirty-one patients with post-surgical differentiated thyroid cancer (5 men, 26 women with a mean age of 40.13 ± 9.82 years (range, 25–60 years) continued the study and were referred 6–8 weeks after thyroidectomy for oral radioiodine-131 therapy to ablate the remnant thyroid tissue or to treat metastatic tumor. They received a mean total dose of 212.9 ± 101.63 mCi (range 110–400 mCi).

A low-iodine diet was started 10 days before ^{131}I therapy and thyroid hormone replacement was withdrawn 3–4 weeks before ^{131}I therapy. All patients were in the hypothyroid state prior to I-131 administration with their mean serum TSH level done 2–3 days before therapy was 28.08 ± 7.34 μIU/ml (reference normal range was 0.4–4.2 μIU/ml). All patients were treated with L-thyroxin after therapy and none had hypothyroidism that might influence salivary gland function. Subjective clinical evaluation was performed to check for salivary and lacrimal gland dysfunction before and after radioiodine treatment. On history taking and clinical examination, there were no symptoms or signs of sicca symptoms [26]. All the patients were rheumatologically examined and any associated fibromyalgia syndrome (FMS) was considered according to the ACR criteria [27].

Diagnosis was performed according to the revised version of classification criteria for Sjögren's syndrome [2]. Patients with a previous history of salivary gland disorders, diabetes, sarcoidosis, Hepatitis C infection, pre-existing lymphoma, Graft versus host disease, external irradiation to the head and neck, use of anticholinergic drugs or previous I-131 therapy were excluded from the study.

Salivary gland function was estimated by sequential scintigraphy. The patients fasted for 2 h before the study and placed supine on the dual-head gamma camera (Siemens e-cam). After an intravenous injection of 185 MBq (5 mCi) 99mTc-pertechnetate, dynamic anterior acquisition was acquired in a 128×128 matrix, 1 frame/30 s for 30 min set at 140 KeV and 15% window with ×1.85 zoom. At 15th min after injection, Salivary gland secretion was stimulated with a 2 ml freshly squeezed lemon juice (without dilution) administered orally using a straw without moving, while imaging was continued. Patients were also instructed to minimize swallowing during imaging. Rectangular-shaped regions of interest (ROIs) were drawn and the time–activity curves were generated for each region. Semiquantitative functional parameters were calculated to obtain time at maximum count (T_{max}) and clearance fraction (CF). The mean values of the right and left glands were used for data analysis.

Lacrimal gland function was measured by Schirmer's test performed before and after I-131 therapy during the follow-up on the same day of doing the salivary scan using standardized sterile 5×35 mm Schirmer's test strips placed, without local anesthesia, at the junction of the middle and temporal thirds of the lower lid of the right orbit. After 5 min, the strips were removed and evaluated by measuring the length of the moistened area. Wetting of the paper after 5 min was considered normal when $\geqslant 15$ mm. Dryness was considered mild, moderate and severe when the wetting of the paper was 10–14, 6–9 and $\leqslant 5$ mm, respectively [28].

Additionally, a blood sample was obtained from each patient to investigate antinuclear antibodies (ANAs) by indirect immunofluorescence, autoantibodies anti-Ro (SS-A) and anti-La (SS-B) by ELISA, and rheumatoid factor (RF) by the Latex test, before and after the I-131 therapy.

Statistical Package for Social Science (SPSS) program version 18 was used for analysis of data. Data was summarized as mean ± SD. Mann–Whittney test was used for comparing and analysis of two quantitative data. Spearman's correlation was used for detection of the relation between two variables. *p*-Value was considered significant if $< 0.05^{*}$.

3. Results

Initially, before radioiodine therapy the patients had no clinical symptoms of dry mouth or dry eye with normal Schirmer's test. Salivary scintigraphy, time activity curves pattern and semiquantitative parameters showed no abnormality. In the follow up study (8–12 months) after last I-131dose, 18/31 patients (58.1%) gave manifestations of variable severity of salivary dysfunction with xerostomia being the most common manifestation (48.39%), xerophthalmia in 25.81%, epiphora in 19.35%, dental problems in 48.39%, vaginal and nasal dryness in 12.9 and 19.35%, respectively. Eight patients (25.81%) fulfilled the criteria of classification of primary SS. These patients showed deterioration of the salivary glands function assessed by scintigraphy. Fig. 1 shows the follow up deterioration in one of the patients who developed SS.

Abnormal Schirmer's test was present in the 8 patients with SS (2 severe, 2 moderate and 4 mild) with a mean of 7.63 ± 4.24 mm which was significantly different from the

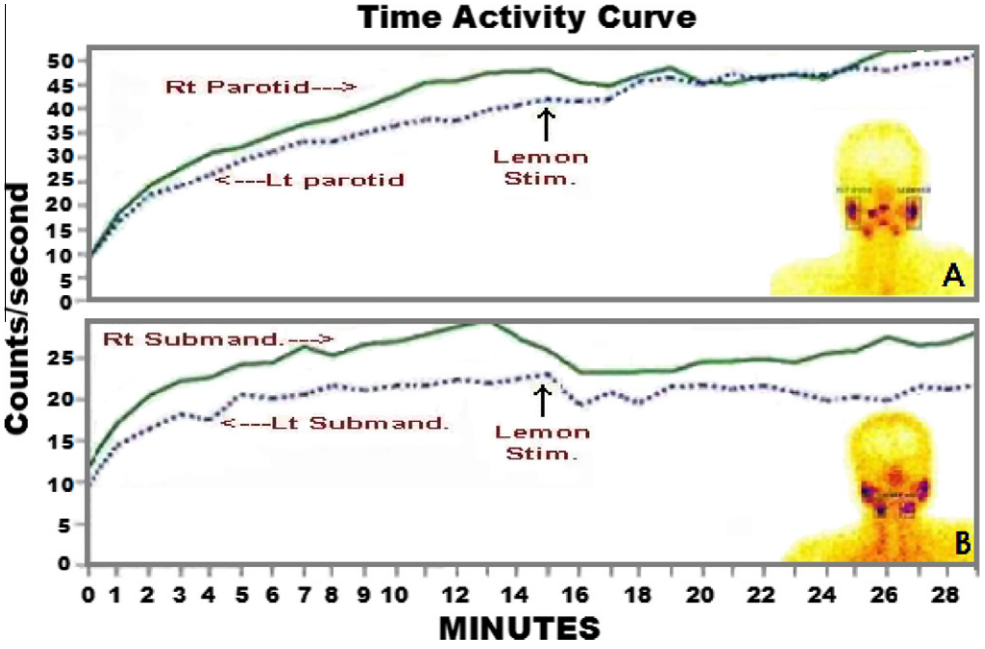

Figure 1 ROIs and actual time–activity curves of (A) parotid glands and (B) submandibular glands, of a 54-years-old woman in follow up study 10 months after total I-131 dose of 320 mCi with lemon stimulation at 15th min post-injection. Parotid gland curves show obstructive pattern. Submandibular curves show moderate and mild clearance of radioactivity in the right and left glands, respectively.

Table 1 Comparison of the salivary and lacrimal function parameters and autoantibodies in thyroid cancer patients before and after iodine therapy.

Parameter (mean ± SD) (No. = 20)	After ^{131}I	Before ^{131}I	Sig. *p*
T_{max} parotid (min)	14.32 ± 3.98	12.33 ± 0.68	**0.01**
T_{max} submandibular (min)	13.68 ± 2.45	11.82 ± 1.33	**0.001**
Parotid clearance (%)	58.65 ± 13.38	69.19 ± 2.89	**0.000**
Submandibular clearance (%)	57.19 ± 12.28	64.82 ± 4.07	**0.002**
Schirmer test (mm)	13.1 ± 3.87	14.74 ± 0.86	**0.027**
Anti/Ro (U/ml)	9.58 ± 7.8	5.55 ± 2.51	**0.01**
Anti/La (U/ml)	11.9 ± 10.19	7.58 ± 2.3	**0.03**

Bold values are significantly different at $p < 0.05$.

Table 2 Comparison of the semiquantitative salivary parameters, lacrimal function and autoantibodies in thyroid cancer patients with and without Sjögren syndrome after iodine therapy.

Parameter (mean ± SD)	SS (8)	Without SS (23)	Sig. *p*
T_{max} parotid (min)	16.65 ± 7.25	13.52 ± 1.51	0.26
T_{max} Submandibular (min)	14.93 ± 3.4	13.24 ± 1.93	0.22
Parotid clearance (%)	60.46 ± 13.2	58.03 ± 13.68	0.66
Submandibular clearance (%)	55.71 ± 14.41	57.7 ± 11.76	0.73
Schirmer test (mm)	7.63 ± 4.24	15	**0.002**
Anti/Ro (U/ml)	18.25 ± 11.61	6.57 ± 1.8	**0.025**
Anti/La (U/ml)	25 ± 13.06	7.35 ± 1.8	**0.006**

Bold values are significantly different at $p < 0.05$.

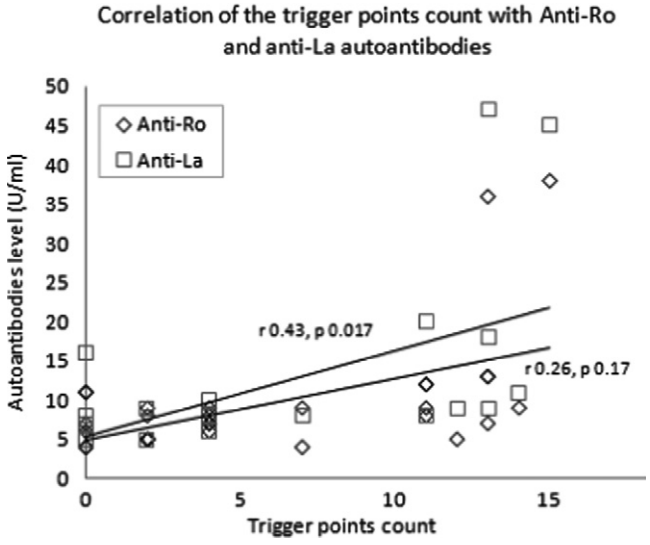

Figure 2 Correlation of the trigger points count with anti-Ro and anti-La autoantibodies.

non SS patients (p 0.002). Salivary and lacrimal function parameters and autoantibodies before and after iodine therapy and in those who developed SS compared to the others are shown in Tables 1 and 2.

Fibromyalgia syndrome (FMS) was initially present in five (16.13%) patients and after I-131 therapy became present in 12 patients (38.71%) and 6 of them developed SS. The mean count of tender trigger points was 5.97 ± 5.25 as almost all the other patients had a low incomplete count. Arthralgias were present in 12 patients and myalgias in 15 (48.39%). The ANA was initially positive in three patients (speckled pattern) and after I-131 therapy became positive in 10 (32.26%) with speckled pattern in eight and homogenous in two with titers above 1/160 in all 10 patients. The Rheumatoid factor was positive in 6 patients (19.35%) before and 32.26% after I-131 therapy.

It was observed that 14 patients had received total doses >150 mCi (mean 309.29 ± 73.11) with a significantly altered salivary function parameters when compared with the other 17 patients who received doses ⩽150 mCi (mean 133.53 ± 14.12) ($p = 0.031$ and 0.001 for T_{max}; $p = 0.009$ and 0.001 for CF in the parotid and submandibular glands, respectively). No significant sex and age differences were found in patients receiving above and below 150 mCi. The parotid gland was affected more often (38.71%) than the submandibular gland (25.81%). Six patients showed involvement of all four major glands.

The Schirmer test showed a significant negative correlation with both anti-Ro and anti-La before (r −0.52, p 0.003) and after (r −0.77, p 0.000 and r −0.78, p 0.000) I-131 therapy respectively. It significantly negatively correlated with the T_{max} of the parotid (r −0.4, p 0.027) and submandibular salivary gland (r −0.43, p 0.015) and significantly correlated with the CF% in the parotid and submandibular salivary glands (r 0.36, p 0.049 and r 0.49, p 0.006, respectively) before I-131 therapy. The anti-Ro and anti-La did not correlate with any of the studied parameters of the parotid or submandibular salivary glands. The total dose of I-131 therapy significantly negatively correlated with the Schirmer test (r −0.36, p 0.045). It significantly correlated with T_{max} parotid and submandibular (r 0.54, p 0.002 and r 0.68, p 0.000) while it was negative with the CF% of both glands (r −0.44, p 0.013 and r −0.54, p 0.002, respectively). After I-131 therapy, the count of tender

FMS trigger points significantly correlated with the anti-Ro level (r 0.43, p 0.017) but not with the anti-La (r 0.26, p 0.17) (Fig. 2). Furthermore there was a tendency to a negative relation between the trigger point count and the Schirmer test (r −0.34, p 0.07).

4. Discussion

Radioiodine (I-131) secondarily targets the salivary glands causing considerable radiation damage to these glands resulting in xerostomia, pain, swelling, altered taste and dysphagia. In addition, long-term effects on the lacrimal glands causes affection of tear secretion leading to ocular dryness and in some cases, nasolacrimal duct obstruction [16].

In the current study 8 patients (25.81%) fulfilled the criteria of classification of primary SS. Deterioration of salivary glands function assessed by scintigraphy indices was present in 58.1% of patients. This is in agreement with the study of Solans et al. who reported that abnormal objective test results were more frequent than subjective symptoms when the salivary glands were evaluated [6]. Salivary gland dysfunction occurred in patients receiving low and high-dose radioiodine therapy [14–16,21,22].

In the present study, a reliance on total dose of radioiodine was significant for dysfunction and deterioration of the salivary parameters on follow up especially in patients receiving a total dose of >150 mCi. In accordance were the results that found that the incidence of severe xerostomia was greater with increasing doses of radioiodine [6] and the significant activity-related functional impairment after I-131 [22]. Other studies found that severe salivary gland parenchymal destruction occurred among patients who received large doses of I-131 [14,16,21,22].

In the current study the parotid gland was affected more often (38.71%) than the submandibular gland (25.81%). Although all salivary glands are involved in the transport of I-131 into the saliva, the parotid glands have proven to be more susceptible to the development of radiation sialadenitis [7,8,29]. Parotid gland secretion is usually reduced by about 40% after doses of 270 mCi of I-131 [30] and by 50–60% in those who receive 500 mCi of I-131 [31,32], and approaches 100% in those who receive one curie of I-131or more [33]

The most common symptom of the studied patients was xerostomia. The obstructive hypothesis affirms that the radiation damage causes glandular inflammatory infiltration and concomitant swelling which may lead to an increased periductal pressure with subsequent ductal constriction [7,8,34].

In the current study, abnormal Schirmer's test was documented in 25.81% with variable severity depending on the dose given. There was associated xerostomia and impaired salivary function parameters which is in accordance with the finding of Solans et al. [6]. Schirmer's tear test was found to be abnormal in 40% of patients after I-131 therapy [20] as I-131 is excreted in tears and actively accumulated in the nasolacrimal duct [35]. Obstruction of the lacrimal drainage system could occur after high-dose radioiodine therapy [36].

Fibromyalgia syndrome (FMS) was associated in 38.71% and half of them developed SS. Arthralgias were present in 38.71% and myalgias in 48.39% of the patients. The ANA was initially positive in 9.68% of cases with a speckled pattern and after I-131 therapy became positive in 32.26% (speckled in eight and homogenous in two). with titers above 1/160 in all 10 patients. The Rheumatoid factor was positive in 6 patients (19.35%) before and 32.26% after I-131 therapy. In agreement with these results are the findings of Solans et. al., [6] who found that 11.4% of their patients had a positive ANA during the first year follow up after they were initially negative. On the other hand, they found that those patients with initially positive ANA, became negative during the first year followup. This might throw light on the possible role of autoimmunity on the glandular abnormalities and SS in these patients. They further found RF to be positive in about 4% of cases. While another study found that RF was positive in 25.8% of primary SS and was closely associated with ANA and anti-SSA/SSB [37]. This unchanged association during the study with FMS and the increased positivity of ANA and RF after I-131 therapy makes the responsibility of an underlying autoimmune disease for the salivary glandular abnormalities and SS questionable. This may be explained by the hypothesis that most hypothyroid fibromyalgia patients are thyroid hormone resistant [38], the often occurrence of FMS with other rheumatic disorders and almost 50% of FMS patients develop Sjögren's syndrome [3]. Unlike with other rheumatic diseases, the associated FMS may exceptionally antedate the appearance of Sjögren's syndrome [4].

It is believed that iodine therapy might exaggerate or unmask the sicca symptoms in cancer thyroid patients with associated FMS. Yet, this suggestion warrants further studies on a larger number of patients with a longer follow up. The incidence of sialadenitis after I-131 therapy is lower than before with administration of pilocarpine if given with concurrent stringent application of physiologic sialogogues (candy, gum, fluids), dexamethasone, and dolasetron mesylate, a serotonin receptor antagonist [39].

It may be concluded that objective assessment of salivary and lacrimal glands function provides a reproducible means for follow-up after radioiodine therapy especially those receiving a total dose more than 150 mCi. Those associated with abnormal levels of autoantibodies in association with FMS are more prone to develop Sjögren's syndrome and should be closely monitored after radioiodine therapy. Salivary gland biopsy is recommended to verify the underlying pathogenesis. Effective protection is required in patients undergoing this treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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