Salivary and Lacrimal Gland Dysfunction (Sicca Syndrome) After Radioiodine Therapy

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Salivary gland dysfunction has been described in patients undergoing radioiodine therapy but associated lacrimal gland dysfunction (sicca syndrome) has never been reported. We conducted a prospective cohort study with follow-up for up to 3 y in a tertiary care university center to determine the prevalence of sicca syndrome in patients after high-dose radioiodine treatment. **Methods:** From January 1990 to December 1995, all patients undergoing radioiodine therapy (n = 79) with a standard dose of 925 MBq to 18.5 GBq (25–500 mCi) were interviewed using a standardized questionnaire to determine subjective ocular and oral dryness and were examined for objective lacrimal and salivary gland dysfunction. **Results:** After radioiodine treatment, 32.9% of the patients reported subjective xerostomia and 25.3% reported subjective xerophthalmia in the first year of follow-up. Xerostomia persisted to the second year of follow-up in 20.3% of cases and was still present >3 y after the last dose of radioiodine in 15.2% of cases. Xerophthalmia persisted to the second year of follow-up in 17.7% of cases and was still present in the third year of follow-up in 13.9% of cases. Severe xerostomia occurred in 4 patients. Reduced salivary and lacrimal gland function was documented in 40 (50.6%) and 14 (17.7%) of the 79 cases, respectively, in the first year of follow-up. Objective xerostomia persisted in 13.9% of cases to the second year of follow-up and was still present in all patients >3 y after the last radioiodine application. Keratoconjunctivitis sicca persisted in 11 patients (13.9%) to the second year of follow-up but was only present in 6 patients (7.6%) >3 y after the last radioiodine application. Additionally, 28/79 patients (35.4%) who had a normal salivary gland scintigraphy previously showed reduced salivary gland function in the third year of follow-up. No significant dependence on cumulative treatment was found for objective xerostomia or xerophthalmia, but doses >11.1 GBq (300 mCi) were related to stage 3 dysfunction on salivary gland scintigraphy. **Conclusion:** Salivary and lacrimal gland dysfunction (sicca syndrome) 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.

Key Words: salivary glands; lacrimal glands; xerophthalmia; xerostomia; radioiodine therapy; thyroid cancer

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The use of radioiodine therapy ($Na^{131}I$) for the ablation of residual thyroid after surgery has become established in the management of differentiated thyroid cancer (*1*). Serious acute complications are extremely rare during treatment but adverse reactions after treatment have been reported (*2–4*). Thus, a significant number of patients complaining of symptoms such as dryness of mouth, pain in the parotid region, altered taste, and difficulty in swallowing have been described (*2–6*). These side effects have been related to radiation damage to the salivary glands; iodine is greatly concentrated in the thyroid gland by a carrier-mediated mechanism, but similar $Na^{131}I$ uptake is found in other organs, including the salivary glands (*7*). As a consequence and despite the standard protection regimen using ascorbic acid as a sialagogue, a loss of salivary gland parenchymal function has been documented in several studies, even with low doses of radioiodine (*3–6*). In contrast, although iodine is also concentrated at the choroid plexus (*7*), reduced lacrimal gland function (one of the diagnostic criteria in autoimmune exocrinopathy or Sjögren's syndrome) has never been mentioned as a side effect after treatment. Only one case of salivary and lacrimal gland involvement after radioiodine therapy has been described (*2*), and concurrent reduced lacrimal and salivary gland function (sicca syndrome) has not been investigated in these patients.

This study was undertaken to investigate the prevalence of subjective and objective salivary and lacrimal gland dysfunction in patients treated with therapeutic doses of radioiodine.

MATERIALS AND METHODS

Seventy-nine patients (11 men, 68 women; mean age, 46.4 y; age range, 22–80 y) who had received various cumulative activities of radioiodine for different thyroid neoplasms or hyperthyroidism, from January 1990 to December 1995, were evaluated prospectively. Sixty-five patients had papillary carcinoma, 11 had follicular carcinoma, and 2 had Basedow's disease. All subjects underwent objective clinical testing to check for gland dysfunction before radioiodine treatment was started. Self-reported symptoms were recorded by means of a detailed questionnaire covering the

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symptoms of dry mouth (dryness, dental deterioration, gingivitis, infections, parotitis, lack of taste, and difficulty in swallowing dry foods) and dry eyes (dryness, photosensivity, sticking, burning, heaviness, redness, and infection of the eyes). A detailed drug history was also obtained to assess for drugs that can cause sicca symptoms (*8*). No patient with sicca syndrome was detected before the radioiodine therapy. A follow-up of 3 y with yearly controls was conducted to study the intermediate and long-term effects of radioiodine therapy on the salivary and lacrimal glands. The study was approved by the research and ethics committee of our hospital. A written informed consent was obtained from all subjects before study startment.

Lacrimal gland function was measured by Schirmer's test, rose Bengal dye and tear break-up time, performed yearly during the follow-up. For Schirmer's test, wetting of 5 mm or less, measured over 5 min under basal conditions with the eyes lightly closed, was considered abnormal (*9,10*). Rose bengal dye (1%) was instilled into the conjunctival sac to find evidence of punctate or filamentary keratitis (*9–11*). Tear break-up time using a slit lamp was performed to measure the stability of the tear film (*9–11*). Objective lacrimal gland dysfunction was diagnosed when two of the three tests were abnormal (*9–11*).

Salivary gland function was estimated by sequential salivary gland scintigraphy using 370 MBq (10 mCi) ^{99m}Tc-pertechnetate. Fasting patients were studied in the supine position, using a single-head gamma camera (SP4P; Elscint, Haifa, Israel). The field of view included the head and the cervical area. Acquisition was dynamic (word, 128 × 128, 1 frame per minute for 60 min). Depending on the salivary gland uptake and excretion, patients were classified into one of four different patterns (Fig. 1): stage 1, normal uptake and excretion; stage 2, mild to moderate dysfunction, decreased salivary uptake and delayed excretion, oral activity equal to salivary uptake at 60 min; stage 3, moderate to severe dysfunction with markedly decreased salivary gland uptake and delayed excretion, higher salivary gland activity than oral activity at 60 min; stage 4, severe dysfunction with severely decreased salivary uptake and higher background than salivary activity during the entire study (*12,13*). Additionally, a blood sample was obtained from each patient to investigate antinuclear antibodies (ANAs) by indirect immunofluorescence, anti-Ro (SS-A) and anti-La (SS-B) antibodies by ELISA, and rheumatoid factor by the Latex test, before radioiodine treatment was started and yearly during the follow-up (*14*).

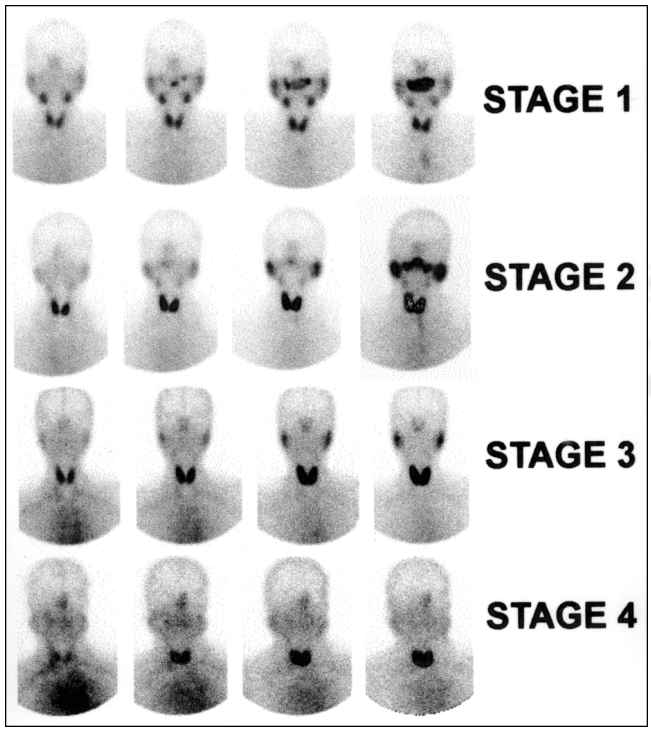

FIGURE 1. Salivary gland scintigraphy stages depend on salivary gland uptake and excretion: stage 1, normal uptake and excretion; stage 2, mild to moderate dysfunction; stage 3, moderate to severe dysfunction; and stage 4, severe dysfunction.

Radioiodine was orally administered in a single dose according to the DeGroot stages and residual thyroid remnants after surgery. The total doses of $Na^{131}I$ administered ranged from 925 MBq to 18.5 GBq (25–500 mCi). Treatment was repeated with single doses of 2.96–5.55 GBq (80–150 mCi) in cases of persisting thyroid remnants or functioning metastases. Patients were advised to increase their fluid intake and chew gum to promote radioiodine discharge from the glands. Lemon juice was administered as a sialagogue (8–10 mL with 50 mL water) 50 min after radioiodine application.

For statistical analysis, the McNemar test for paired data was used to assess changes between basal condition and the observed results at the end of each year of follow-up. When the number of discordant pairs was fewer than 10, a test based on the binomial distribution was performed. The Pearson chi-squared test was used to compare percentages of objective involvement of salivary and lacrimal glands between symptomatic and asymptomatic patients. Additionally, the Mantel-Haenszel test for linear trend was used to study the relationship between cumulative dose of radioiodine and both the subjective complaints of dry eyes and dry mouth and the objective involvement of salivary and lacrimal glands. Statistical significance was set at $P < 0.05$.

RESULTS

Subjective symptoms of dry mouth and dry eyes and objective salivary and lacrimal gland dysfunction were common in our series (Table 1). Xerostomia was recorded in 32.9% of patients during the first year of follow-up and xerophthalmia in 25.3%; both percentages were statistically significant as compared to basal conditions ($P < 0.001$). In the second year of follow-up, xerostomia persisted in 20.3% of patients and xerophthalmia in 17.7% ($P = 0.002$ and $P = 0.03$, respectively, as related to the first year of follow-up). In the third year of follow-up, xerostomia persisted in 15.2% of patients and xerophthalmia in 13.9%. In addition, 2 patients reported de novo xerostomia and 1 patient reported de novo xerophthalmia. All patients who reported xerophthalmia also reported xerostomia.

Objective xerostomia (abnormal salivary gland scintigraphy) was documented in 50.6% of patients in the first year of follow-up ($P < 0.001$ vs. basal), and was moderate to severe in 16 patients.

Objective xerophthalmia (abnormal Schirmer's test plus abnormal rose Bengal dye, abnormal tear break-up time, or both) was documented in 17.7% of patients in the first year

TABLE 1
Incidence of Lacrimal and Salivary Gland Dysfunction in 79 Patients After Radioiodine Therapy

	First year *n* (%)	Second year *n* (%)	Third year *n* (%)
Subjective xerostomia	26 (32.9%)	16 (20.3%)	12 (15.2%)
New cases*			2
Objective xerostomia	40 (50.6%)	11 (13.9%)	11 (13.9%)
Stage 2	24	6	6
Stage 3	16	5	5
Stage 4	—	—	—
New cases*		3 (3.8%)	28 (35.4%)
Stage 2		3	23
Stage 3		—	5
Stage 4		—	—
Subjective xerophthalmia	20 (25.3%)	14 (17.7%)	11 (13.9%)
New cases*			1
Objective xerophthalmia	14 (17.7%)	11 (13.9%)	6 (7.6%)
Schirmer test	14	11	6
Rose Bengal dye	8	3	3
Tear break-up time	10	8	4
New cases*		2 (2.5%)	2 (2.5%)
Shirmer test		2	2
Rose Bengal dye		1	2
Tear break-up time		1	1

*New cases: cases detected during the second or third year of follow-up.

Salivary gland scintigraphy dysfunction stages: 1, normal uptake and excretion; 2, mild dysfunction; 3, moderate dysfunction; and 4, severe dysfunction.

of follow-up ($P < 0.001$ vs. basal). All patients with objective xerophthalmia also had objective xerostomia.

In the second year of follow-up, 11 of the 40 patients with objective xerostomia persisted with abnormal salivary gland scintigraphy results and 11 of the 14 patients with objective xerophthalmia persisted with abnormal ocular test results. In addition, 3 patients with unaltered salivary gland scintigraphy in the first year showed abnormal uptake and secretion of isotope in the second year.

In the third year of follow-up, all patients with objective xerostomia and 6 of the 11 patients with objective xerophthalmia persisted with abnormal oral or ocular test results, respectively. Additionally, 28 patients with normal salivary gland scintigraphy and 2 patients with normal ocular tests showed abnormal results (Table 1). All patients with objective xerophthalmia in the third year of follow-up also had objective xerostomia.

A comparison between the percentage of objective ocular gland involvement in patients with subjective complaints of dry eyes (6/20, 30%) and those without (8/59, 13.56%) showed no statistical differences ($\chi^2 = 2.77$, $P = 0.096$). In contrast, a statistically significant difference in the percentage of objective salivary gland involvement was found between patients with subjective complaints of dry mouth (22/26, 84.62%) and those without (19/53, 35.85%) ($\chi^2 = 16.62$, $P < 0.0001$). The association between oral symptoms and abnormal salivary gland scintigraphy results was stronger (84.62%) than between ocular symptoms and abnormal Schirmer's test results (30%) ($\chi^2 = 14.16$, $P < 0.0001$).

The most commonly reported oral complaint was "dry mouth every day" and the most common ocular symptom was "burning heaviness." Dysgeusia was reported by 26 patients and in most cases appeared initially and disappeared in 2–4 wk. However, in 6 patients dysgeusia persisted for several months. In addition, 4 patients developed tender oral aphthae. Odynophagia occurred in 5 patients after the first dose of $Na^{131}I$ and lasted for 3–5 d before normalization. Sialoadenitis, which resolved with NSAIDs, was observed in 16 patients. The parotid gland was affected more often (10 patients) than the submandibular gland (6 patients). Bilateral parotitis was more frequent (8/10) than was unilateral parotitis (2/10). Relapsing parotitis was observed in only 2 cases. We found a coincidence of dry mouth and sialoadenitis after treatment in only 6 cases.

There was a positive correlation between cumulative activity and degree of salivary gland dysfunction ($\chi^2 = 3.84$, $P < 0.049$), although no linear trend was found. Thus, 12 of the 31 (38.7%) patients who had received 7.4–18.5 GBq (200–500 mCi) $Na^{131}I$ developed stage 3 salivary gland dysfunction during the follow-up (Table 2). In contrast, only 9 of the 48 patients (18.7%) who had received 925 MBq to 3.7 GBq (25–100 mCi) $Na^{131}I$ developed stage 3 salivary gland dysfunction during the follow-up. Moreover, 9 of 10 patients who showed stage 3 salivary gland dysfunction on scintigraphy in the third year of follow-up had received 11.1–18.5 GBq (300–500 mCi) of radioiodine, and the last one had received 7.4 GBq (200 mCi). Similarly, a dependence on cumulative dose of radioiodine was significant for subjective xerophthalmia with a linear trend to cumulative activity ($P = 0.002$). In contrast, we found no association between objective xerophthalmia and cumulative activity ($P = 0.29$).

Antinuclear antibodies were detected in 6 patients before radioiodine therapy. ANA titers ranged from 1/80 to 1/320 in a speckled pattern in 4 patients and a homogeneous pattern in the last 2. In all cases, ANA became negative during the follow-up. ANA were also detected in the first year of follow-up in 9 patients with initial negative test, titers ranging between 1/80 (4 patients) and 1/320 (2 patients), in a speckled pattern in 5 cases and in a homogeneous pattern in the remaining 4. In 4 cases ANA became negative during the second year of follow-up and in 3 cases during the third year. Thus, only 2 patients with thyroid neoplasms showed positive ANA (with titers above 1/160 in a speckled pattern) in the third year of follow-up. Antibodies to Ro or La, commonly associated with Sjögren's syndrome, were not detected in any patient. Rheumatoid factor was detected in 3 patients in the first year of follow-up (titers above 1/256) and remained positive at the same titers to the third year of follow-up in all cases.

TABLE 2
Lacrimal and Salivary Gland Dysfunction After Radioiodine Therapy for Groups of Increasing Cumulative Activities

	$Na^{131}I$ total dose				
	14.8–18.5 GBq (300–500 mCi)	11.1 GBq (300 mCi)	7.4 GBq (200 mCi)	3.7 GBq (100 mCi)	925 MBq–1.85 GBq (25–50 mCi)
Patients (*n* [%])	5 (6.3%)	20 (25.3%)	6 (7.6%)	46 (58.2%)	2 (2.5%)
XS subjective	3	6	2	17	—
XS objective	5	19	6	38	—
Stage 2	2	13	3	29	—
Stage 3	3	6	3	9	—
Stage 4	—	—	—	—	—
XF subjective	4	7	3	7	—
XF objective	3	4	2	9	—
Schirmer	3	4	2	9	—
Rose Bengal dye	1	3	1	3	—
Break-up time	2	2	2	7	—

XS = xerostomia; XF = xerophthalmia.
Salivary gland scintigraphy dysfunction stages: 1, normal uptake and excretion; 2, mild dysfunction; 3, moderate dysfunction; 4, severe dysfunction.

DISCUSSION

In our series, subjective symptoms consistent with ocular and oral dryness and objective lacrimal and salivary gland dysfunction were both relatively common. A high percentage of patients reported sicca symptoms in the first year of follow-up that disappeared in the course of the second or third year of follow-up in most cases. Nevertheless, a small percentage of patients remained symptomatic for >3 y after the last dose of radioiodine. Furthermore, many patients showed objective salivary and lacrimal gland dysfunction in the first year of follow-up that persisted in some cases to the end of follow-up, and many patients developed objective lacrimal or salivary gland dysfunction during the second or third year of follow-up.

Sialoadenitis was documented in 22.8% of patients, a percentage similar to that reported in the literature (*15–17*). The parotid gland was affected more often than the submandibular gland, and bilateral parotitis was more frequent than unilateral, as shown by other authors (*5,15*). Relapsing parotitis was observed in only two cases. A coincidence of dry mouth and post-therapeutic sialoadenitis was observed in only six cases. Thus, the majority of cases of reduced salivary gland function did not arise from clinically evident sialoadenitis, as reported by Alexander et al. (*3*).

Sialoadenitis and salivary gland dysfunction have been reported in patients undergoing low and high-dose radioiodine therapy (*2–6*) and related to the ability of major and minor salivary glands to concentrate iodine at a 50:1 ratio (*7*). Radioiodine has been shown to concentrate in the ductal cells of the salivary glands (*7*), which can receive 7–15 Gy. Moreover, radiation is thought to induce changes in saliva composition (increased amylase and activated kallikrein) and an obstructive process leading to reduced salivary flow (*15–17*). It seems that individual variations in salivary gland uptake of iodine, noted on $Na^{131}I$ uptake scans (*6,13,17,18*) may influence the rate of parotid gland complications. As a consequence and despite salivary gland stimulation during radioiodine treatment, a significant activity-related functional impairment of 10%–90% after application of 0.4–24 GBq of $Na^{131}I$ has been reported (*18*), and severe salivary gland parenchymal destruction has been documented among patients who received large doses of $Na^{131}I$ (*2,3,5,6*). A dependence of xerostomia on cumulative activity has been suggested (*2,3,5,6*). The present results confirm this trend. Thus, in our series, the incidence of severe xerostomia was greater with increasing doses of radioiodine whether administered as a single high dose or as multiple doses. Salivary gland damage was pronounced in patients receiving $Na^{131}I$ doses >11.1 GBq (300 mCi).

Sialoadenitis and xerostomia have been considered as transient side effects of radioiodine therapy, but long-term xerostomia has recently been described (*3,19*). Alexander et al. (*3*) reported that 42.9% of patients undergoing radioiodine therapy suffered from reduced salivary gland function >1 y after the last radioiodine application and, in some cases (4.4%), these complaints persisted up to 5 y. Our results also suggest that radiation of salivary glands may reduce salivary gland function for a lengthy time or indefinitely. In addition, these results confirm that salivary gland dysfunction does not necessarily follow immediately after application of $Na^{131}I$ but can be delayed.

In contrast to well-documented salivary gland dysfunction, the finding of ocular dryness after radioiodine treatment is novel. To our knowledge, reduced lacrimation has never been mentioned in iodine-induced salivary disorders. In addition, there are no studies on the prevalence of xerostomia and xerophthalmia (sicca syndrome) in patients treated with radioactive iodine, although iodine uptake also

occurs in the choroid plexus (*7*). There is only one record of a patient developing lacrimal and salivary gland dysfunction after radiation (*2*), and non–dose dependent chronic and recurrent conjunctivitis in 46 of 203 patients receiving radioiodine therapy has been recently reported by Alexander et al. (*3*). Although less frequent than oral dryness in our series, ocular dryness was relatively prevalent and in some cases persisted up to 3 y. All patients with reduced lacrimal gland function also showed reduced salivary gland function, fulfilling the criteria for sicca syndrome. We believe that the decrease in lacrimal gland secretion can be ascribed to a direct effect of the radioiodine concentrated at the choroid plexus (*7*,*20*).

There was a weak association between the presence of oral or ocular symptoms and their respective objective test results. Thus, abnormal objective test results were more frequent than subjective symptoms when the salivary glands were evaluated, and the reverse was true when the lacrimal glands were evaluated. Our findings are in keeping with the data of Malpani et al. (*5*), who reported that nearly 70% of their asymptomatic patients had demonstrable salivary dysfunction. Similarly, Alexander et al. (*3*) showed that only 45% of patients with dry mouth reported complaints of sialoadenitis after treatment. The association between oral symptoms and salivary gland scintigraphy changes was stronger that between ocular symptoms and abnormal Schirmer test. Subjects with oral symptoms showed the strongest association with the objective testing results, as has been described (*21*).

With regard to assessment of dry mouth or dry eyes, although no single test for ocular or salivary gland function is sufficiently precise to diagnose sicca syndrome, Schirmer's test and salivary gland scintigraphy seems to perform well (21). Schirmer's test, which measures the volume of tears produced in 5 min under basal conditions, has been shown to have high sensivity and specificity in the hospital environment (*21*). Similarly, radioisotope scintigraphy is a simple, noninvasive method for evaluating salivary gland function that correlates well with sialographyc stages (*22*), considered the gold standard in the diagnosis of Sjögren's syndrome. In addition, a good correlation has been found between ^{99m}Tc-pertechnatate scintigraphic findings and volume of saliva measured after Wharton's catheterization (*23*,*24*) and between scintigraphic findings and the histopathologic grade in patients with Sjögren's syndrome (*25*).

Although ANAs were detected in some patients their positivity was probably caused by the underlying neoplasm (*26*). Thus, autoantibodies to Ro or La, commonly associated with Sjögren's syndrome (*10*,*27*), were not detected in our patients, suggesting that autoimmune disease was not responsible for the glandular abnormalities. Finally, all patients were treated with L-thyroxine and none had hypothyroidism that might influence salivary gland function.

In our opinion, the incidence of sicca syndrome after radioiodine therapy advises regular prevention of salivary and lacrimal gland damage and the development of effective protection. Usually only increased fluid intake and lemon juice consumption is recommended for prevention of salivary gland damage. However, symptomatic improvement in patients with radiation-induced xerostomia has been reported after pilocarpine treatment (5–10 mg orally three times a day) (*28*). Moreover, significant improvement in symptoms of dry mouth and dry eyes after pilocarpine treatment has been reported in patients with Sjögren's syndrome (*29*). On this basis, clinical trials using pilocarpine could be warranted in patients who undergo radioiodine therapy to investigate the potential benefits of this drug in preventing or reducing the adverse effects of radioiodine therapy on salivary and lacrimal glands.

CONCLUSION

These results suggest that a significant percentage of patients treated with radioactive iodine may develop concurrent lacrimal and salivary gland dysfunction (sicca syndrome) in the following years. Although in the majority of cases these side effects develop early and are transient, they can persist up to three years or appear late. Furthermore, glandular function may not return to normal.

In our opinion, the incidence of sicca syndrome after radioiodine therapy advises regular prevention of salivary and lacrimal gland damage and the development of effective protection. Because the patients' complaints do not necessarily reflect the severity of their salivary and lacrimal gland disease, prolonged follow-up with performance of objective tests should be indicated in patients undergoing this treatment.

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