

Evaluation of Tear Secretion in Thyroid Patients in Relation to the Thyroid Status and Previous I¹³¹ Treatment for Thyroid Cancer

ABSTRACT

Aims: To evaluate tear secretion of thyroid patients with no clinical evidence of thyroid ophthalmopathy in relation to thyroid status and history of I¹³¹ treatment by the use of the 2-minute Schirmer test I (test without topical anesthesia).

Study design: Prospective study.

Place and Duration of Study: 1st University Eye Clinic, AHEPA Hospital, Thessaloniki, Greece and Laboratory of Experimental Ophthalmology, Aristotle University of Thessaloniki, Greece, between June 2013 and July 2014.

Methodology: 128 consecutive thyroid patients, 111 females and 17 males, aged from 18 to 82 years 49.48±14.61 (mean±sd) were recruited for this study. None of the thyroid patients had clinical signs or symptoms of thyroid ophthalmopathy. 49 of them had history of I¹³¹ treatment for thyroid carcinoma. The 2-min Schirmer test I was performed on the same day the patients underwent the routine exams for thyroid hormones. As abnormal were considered Schirmer test I values <10 mm.

Results: Out of 49 thyroid patients with history of I¹³¹ therapeutic treatment, 35 (71.4%) had 2-minute Schirmer test I values <10 mm. However there was no statistically significant difference in relation to their thyroid status. Regarding patients, with no previous I¹³¹ treatment, 55 out of 79 patients (71.4%) had Schirmer test I values <10 mm and there was no statistically significant difference in relation to their thyroid status. There was no statistically significant difference in Schirmer test I values between patients who received I¹³¹ and those who did not.

Conclusion: Thyroid patients without clinical evidence of thyroid ophthalmopathy have impaired Schirmer test I scores irrespective of the thyroid status and previous I¹³¹ exposure and thus they more likely to develop ocular surface abnormalities. Patients with previous I¹³¹ treatment had no statistically significant differences in the tear secretion values as compared with the non-irradiated thyroid patients.

Keywords: Schirmer Test I, Thyroid Status, Tear Secretion, Dry Eye, I¹³¹ Treatment

1. INTRODUCTION

Dry eye syndrome or keratoconjunctivitis sicca is a common problem among middle-aged and older adults, and very often has a serious impact on quality of life. The treatment of the condition often causes frustration to both patients and ophthalmologists.[1-4] Sjögren syndrome, thyroid disease and other autoimmune diseases are main causes of dry eye syndrome. [5-8] Recent findings suggest that there is a direct involvement of the lacrimal gland in the pathological mechanism of the dry eye syndrome in thyroid patients[9] and lacrimal glands were found to be enlarged in patients with hyperthyroid Grave's disease.[10] Furthermore, octreotide was found in the lacrimal glands of thyroid patients.[11] Octreotide is a somatostatin analogue that exclusively binds to activated lymphocytes.

As regards the thyroid tumors, they are relatively common. Differentiated thyroid cancer (DTC) accounts for approximately 90% of all thyroid cancer.[12] Initial management is surgical. A near-total thyroidectomy is favored by many.[13- 16] Postoperative I^{131} therapy is effective for ablation and treatment of loco-regional or metastatic disease, while L-thyroxin therapy diminishes the recurrence and improves survival rates.[17, 18] In Graves' disease, I^{131} produces thyroid ablation without the complications of surgery.[19,20]

Our objective in the present study is to evaluate the tear secretion of thyroid patients with no clinical evidence of thyroid ophthalmopathy in relation to their thyroid status and previous I^{131} treatment. The 2-minute Schirmer test I (without topical anesthesia) was performed due to the advantage of shorter duration and acceptability from the patients. [21]

2. MATERIAL AND METHODS

One hundred twenty-eight thyroid patients were recruited for the study (17 males and 111 females). The age of our patients ranged from 18 to 82 years and mean age was 49.48 ± 14.61 years. Seventy-nine patient underwent thyroidectomy due to cancer or hyperthyroidism and the rest forty-nine had history of I^{131} treatment. All of the patients were under substitution or suppression treatment. The therapeutic dose of the I^{131} treatment was 100 150 mCi (3.70 to 5.55 GBq). All these patients were frequently examined (RIA methods) for their thyroid status. All patients were evaluated for possible signs and symptoms of thyroid ophthalmopathy. In order to detect and quantify the patients' symptoms of possible ocular surface complications, we administrated the Ocular Surface Disease Index (OSDI).[22] All patients had normal OSDI values (2.08 ± 4.2). The eyelids, eyelid margins, conjunctiva and puncti as well as the cornea and the whole ocular surface were carefully evaluated for possible changes. Furthermore, all patients were examined for soft tissue involvement including periorbital oedema, ptosis, chemosis and epibulbar injection. To exclude possible proptosis, the patients were tested with the Hertel exophthalmometer. Readings greater than 20mm or a difference equal or greater than 2 mm between two eyes considered as abnormal and patients were excluded from the study. As regards the control group one hundred and thirty healthy individuals free of symptoms and without any known or apparent pathology affecting tear secretion or drainage were recruited for this study. The Schirmer test was performed without topical anesthesia (Schirmer test I). Only one eye of the patients was examined, so as to eliminate the patients' discomfort and the 2-minute test was preferred for the advantage of shorter duration and better acceptability by the patients. Every subject was asked to be seated, while the 5-mm-long bend-end piece of the strip was placed on the lower lid margin in a temporal position. The subject was asked to keep both eyes open looking upwards while being observed by the examiner and instructed to avoid horizontal eye movements that might cause corneal irritation and consequent tear hypersecretion.

Two minutes later, the wetted length of the strip was measured and recorded. For the statistical analysis of the results, the Kolmogorov-Smirnov test was used. Using this test, we rejected the zero hypothesis for 0.05 significance level that variables follow normal distribution. Consequently, non parametric tests were used. Abnormal values for the 2-min Schirmer test were considered values <10 mm (based upon a previous study of our laboratory in a sample of 162 individuals without dry eye symptoms and normal tear secretion). [21]

In the day of the tear secretion testing, blood samples were obtained as part of routine clinical evaluations of the thyroid patients, for serum FT3, FT4 and TSH. Blood samples were centrifuged and the sera collected were stored at -20°C . Serum FT3, FT4 and TSH were assayed by immunoradiometric (IRMA) methods (DiaSorin, Saluggia, Italy). All assays were performed in duplicate. In our laboratory, reference values for FT3 were 2.2-5.5 pg/ml (3.4–8.5 pmol/L), for FT4 were 7.8-19.4 pg/mL (10–25 pmol/L) and for TSH were 0.30-4.0 mU/L. As concerns FT3 the detection limit of the assay and the intraassay and interassay variation expressed as coefficients of variation were 0.73pmol/L, 5.0 %, and 4.4 %, respectively, for FT4, 1.25 pmol/L, 3.4 %, and 5.1 %, respectively and for TSH 0.04 mU/L, 2.5 %, and 4.1 %, respectively.

3. RESULTS AND DISCUSSION

The distribution of normal and abnormal Schirmer test I values, in relation to the thyroid status and previous history of I¹³¹ treatment, in our material is deployed in table 1.

Table 1. Distribution of normal and abnormal Schirmer test I values in relation to the thyroid status and previous history of I¹³¹ treatment

	Number of Patients		
	Euthyroids	Hypothyroids	Hyperthyroids
Normal values (with I ¹³¹ treatment)	2	12	-
Abnormal values (with I ¹³¹ treatment)	6	29	-
Normal values (no I ¹³¹)	12	1	11
Abnormal values (not I ¹³¹)	24	6	25

3.1 Statistical analysis

In the statistical analysis the variables did not reach normality (Kolmogorov-Smirnov); we used non-parametric techniques, such as Mann-Whitney U test, Kruskal Wallis test and Spearman's Rank Correlation. Statistical significance was based on alpha level of .05.

- a) Mann-Whitney Test was conducted to compare the Schirmer test's I *median value* of normal individuals and patients who did and did not have history of I¹³¹ treatment.

Statistically significant difference was found between Schirmer test I values of normal individuals and patients with no history of I¹³¹ treatment. (p<.005). Statistically significant difference was found between Schirmer test I values of normal individuals and patients with history of I¹³¹ treatment. (p<.005). There was no statistical significance (sig= .741 >.05) between the *median values* of patients with and without I¹³¹ treatment. (Table 2)

Table 2. Schirmer test's I median value of normal individuals and patients who did and did not have history of I¹³¹ treatment

Normal	12.5
Without I ¹³¹ Treatment	7.5

With I ¹³¹ Treatment	7
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- b) Chi-square test (χ^2) was conducted to assess the relationship between patients with *pathological* Schirmer test I in relation to having received I¹³¹ treatment or not.

There was no statistically significant difference ($P = .985 > .05$) between patients with pathological Schirmer test I and who were treated with I¹³¹ and those who were not. However, though there is no statistical significance between the two groups, the thyroid patients who received I¹³¹ treatment tended to have lower Schirmer test I values. (Table 3)

Table 3. Patients with pathological Schirmer Test I in relation to having received I¹³¹ treatment or not

N	With I ¹³¹ Treatment	Without I ¹³¹ Treatment
Pathological Schirmer test	35 (out of 49)	55 (out of 79)
Chi Square test $p = .985$		

- c) Kruskal-Wallis test was conducted to assess the difference among the *mean values* of Schirmer test I of all patients who did and did not receive I¹³¹ treatment, in relation to their thyroid status (euthyroids and hypothyroids).

In patients who receive I¹³¹ treatment, there was no statistically significant difference ($P = .535 > .05$) in relation to their thyroid status (euthyroids and hypothyroids). In patients who did not receive iodine, no statistically significant difference ($p = .867 > .05$) was found in relation to their thyroid status (euthyroids, hypothyroids and hyperthyroid). (Table 4)

Table 4. Schirmer Test I values $\pm$ SD and Thyroid Status in patients with and without I¹³¹ treatment

	Euthyroid	Hypothyroid	Hyperthyroid	
Patients with I ¹³¹ treatment	8.437 $\pm$ 5.447	8.908 $\pm$ 4.848		Kruskal Wallis Test $p = .385$
Patients without I ¹³¹ treatment	8.902 $\pm$ 5.332	9.000 $\pm$ 3.719	9.097 $\pm$ 4.823	Kruskal Wallis Test $p = .867$

d) Mann-Whitney Test was conducted to compare the Schirmer test's I median value of hypothyroid and euthyroid patients who received I¹³¹ treatment and those who did not.

There was no statistical significance (sig= .645 >.05) between the median values of hypothyroid and euthyroid patients with and without I¹³¹ treatment. (Table 5)

Table 5 . Schirmer Test I median score of hypothyroids and euthyroids in relation to I¹³¹ Treatment

	With I ¹³¹ Treatment	Without I ¹³¹ Treatment	
Hypothyroids	7	8.5	Mann-Whitney Test p=.645
Euthyroids	6	8	Mann-Whitney Test p=.645

The above analysis indicates that thyroid patients, who receive I¹³¹ for thyroid cancer, have statistical significant abnormal Schirmer test I values irrespective of the thyroid status on the day of the examination and also, thyroid patients who did not receive I¹³¹ treatment have statistical significant abnormal Schirmer test I values irrespective of the thyroid status, when compared with Schirmer test values on normal individuals. Comparing the results of the two groups, there was no statistically significant difference between the Schirmer test I values of those patients.

The Schirmer test I is a simple test and one of the commonest in use in the every day practice for the evaluation of tear secretion. The 2-minute test was preferred due to the shorter duration and less discomfort for the patients. Values ≥ 10 mm in 2 minutes were considered as normal.[21] We use to perform the test with open eyes so as to observe the eye movements of the patients and also to give him/her a target to see and thus to eliminate undesirable eye movements which may cause irritation and tear hypersecretion . Others prefer to perform the test with closed eyes.[23,24,25]

Thyroid associated ophthalmopathy is related with impaired tear secretion and to the best of our knowledge there are no reports in the international literature investigating tear production in thyroid patients who have no clinical signs and symptoms of thyroid associated ophthalmopathy and in relation to their thyroid status. As regards patients with thyroid associated ophthalmopathy, researchers evaluated the relationship between ocular surface damage, elevated lid aperture/impaired Bell's phenomenon and reduced tear production. Investigating the possible role of autoantibodies specific for TSH receptor (TSHR), they also investigated TSHR expression in the healthy lacrimal gland (LG). They concluded that ocular surface damage in thyroid associated ophthalmopathy significantly correlates with reduced tear production and not significantly with mechanical alterations and that LG impairments seem to be a major cause of eye dryness. They also concluded that physiological expression of TSHR by LG suggests that, in thyroid disease, autoantibodies may bind to lacrimal TSHR and contribute to LG impairment.[9] It is interesting to see that other investigators, who tried to define the clinical, laboratory, and histological features of patients with dry eyes and mouth syndrome (DEMS) and patients with sicca asthenia polyalgia syndrome (SAPS), found out that these patients have positive titers of antibodies against thyroid peroxidase. [26] Other researchers also investigated thyroid associated eye disease. In a study with Schirmer test II (with topical anesthesia) 21 patients with orbital echographic findings consistent with thyroid eye disease were evaluated. Only 19% of patients had abnormal Schirmer test II values and the symptomatology of eye dryness appeared to be attributable to an underlying ocular surface inflammation.[27] Also, in a study that aimed to evaluate preoperative and postoperative tear function tests and conjunctival surface changes in multinodular goiter (MNG) patients, and to compare their results

with healthy control subjects, both tear function tests (including Schirmer test I values as well) and cytology findings of the MNG cases were statistically different from the results of the control group during the pre- and postoperative period. When thyroid hormone values of MNG patients were examined, it was seen that preoperative mean fT3 and mean fT4 values were lower than the mean values of the control group. After surgery and despite treatment, fT3 values were still in normal limits but were closer to the lower limit and they were significantly lower than the preoperative values, suggesting insufficient T4-T3 turnover in some of the patients. This is suggesting that there is a probable relationship between postoperative low fT3 and high TSH levels indicating subclinical hypothyroidism that developed after nearly total thyroid gland excision that affects tear function tests. [28]

The present study recruited thyroid patients without clinical evidence of thyroid ophthalmopathy. According to our results these thyroid patients tend to have impaired tear secretion. 128 patients were examined. 79 had no history of previous I^{131} treatment. 36 of them were euthyroids, 7 hypothyroids and 36 hyperthyroids. 67% of euthyroids, 86% of hypothyroids and 69% of hyperthyroids had abnormal Schirmer test I values in 2 minutes. From 49 patients, who received I^{131} treatment for thyroid cancer, 8 were euthyroids and 41 were hypothyroids on the day of tear secretion evaluation. 75% of these euthyroids and 71% of these hypothyroids had abnormal Schirmer test I values.

As regards patients who received iodine, other researchers also investigated the long term effects of high dose I^{131} therapy on tear secretion. In a study concerning 175 eyes of 88 patients with history of I^{131} treatment, all patients received at least 2.96 GBq I^{131} . Schirmer test was decreased (<10 mm in 5 minutes) in 47 out of 88 patients and it was definitely abnormal (<5 mm in 5 minutes) in 35 out of 88 patients. All participants were free of any disease and of any drug that may affect tear production.[29] In another study concerning patients who received high dose of I^{131} , the researchers studied 100 eyes of 50 patients who were treated for differentiated thyroid carcinoma and 100 eyes of 50 unexposed patients, who consisted the control group. Both groups (exposed and unexposed to I^{131} treatment) were consisted of thyroid patients of euthyroid status and they were free of any disease and of any drug that could affect tear secretion. Lower Schirmer test values were measured in the exposed group 14.5 ± 10.8 mm, as compared with the control group (18.2 ± 11.0 mm) ($p=0.016$). Relative risk of an abnormal Schirmer test in the exposed cases to control group was 1.78 ± 0.62 . Correlation coefficient analysis showed no significant relationship between Schirmer test values and cumulative doses of administered I^{131} . [30] In the present study no statistically significant difference was found between exposed and non exposed to I^{131} treatment thyroid patients of euthyroid status. Furthermore, no statistically significant difference was found between exposed and non exposed to I^{131} treatment of hypothyroid status. In our study, 35 out of 49 patients (71.4%), who had history of previous I^{131} treatment, had abnormal Schirmer test I (<10 mm in 2 minutes) but no statistically significant difference was found between them and the thyroid patients who had no previous history of I^{131} treatment. Our patients received 3.70 to 5.55 GBq I^{131} .

Considering all thyroid patients in the present study (patients with I^{131} treatment and patients without I^{131} treatment and without clinical evidence of thyroid ophthalmopathy) have statistically significant lower Schirmer test I values in 2 minutes when compared with normal individuals. [...text removed...] No statistically significant difference was found among the mean scores of Schirmer test I of euthyroids, hypothyroids and hyperthyroids. No statistically significant difference was found among the mean scores of Schirmer test I of those thyroid patients who received I^{131} treatment and those who did not and also there was no statistically significant difference of the pathological Schirmer test I values between them.

4. CONCLUSION

Conclusively, thyroid patients without clinical evidence of thyroid ophthalmopathy tend to have impaired Schirmer test scores irrespective of the thyroid status and previous I^{131} exposure and thus it is more likely to develop ocular surface abnormalities. Also, patients with history of I^{131} treatment have no statistically significant differences in the tear secretion values as compared with the non-irradiated thyroid patients.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this research. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the ethics committee of AHEPA Hospital and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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