IJMA

International Journal of Medical Arts

2/2022 (volume 4, Issue 2)

http://ijma.journals.ekb.eg/

Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Ophthalmology]

Original Article

Conjunctival Impression Cytology in Patients with Thyroid Disorders

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Article information

Received: 16-11-2021

Accepted: 24-02-2022

DOI: 10.21608/ijma.2022.106467.1394

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Citation: Elwan AA, Aly MM, Hegazy HS, Abosaif AI. Conjunctival Impression Cytology in Patients with Thyroid Disorders. IJMA 2022 Feb; 4 [2]: 2188 -2194. doi: 10.21608/ijma.2022.106467.1394

ABSTRACT

Background: Impression cytology is a noninvasive technique for assessing the ocular surface cells and can be used for recognition of changes that occur in the conjunctiva especially among patients who had thyroid diseases.

Aim of the work: To assess the efficacy of impression cytology in the diagnosis of ocular surface changes in patients with thyroid diseases in relation to other noninvasive diagnostic methods.

Patients and Methods: The study included 30 patients [60 eyes] with thyroid disease [both hypo- and hyper-thyroidism] aged 20–40 years, in which an ocular tear film was evaluated. In addition, 30 subjects [60 eyes] in age from 20–40 years were also examined as control group. All patients finished the routine ophthalmological assessment, fluorescein tear breakup time [TBUT], Schirmer test and conjunctival impression cytology [CIC].

Results: The eyes in the thyroid disorder patients showed grade 1, 2 and 3 in CIC with decreasing Schirmer test and tear breakup time test values less than 10 seconds, while the control group showed grade 0 in the CIC with increasing Schirmer test and tear breakup time test values more than 10 seconds [P-value < 0.01].

Conclusion: Impression cytology is a non-invasive method for evaluating ocular surface cell morphology and can be used to recognize, and assess the severity of the changes occurring in the conjunctiva in patients with thyroid disease.

Keywords: Dry eye; SPEED questionnaire; Tear Breakup Time; Schirmer's; Conjunctival Impression Cytology.

INTRODUCTION

Dry eye is a medical disorder affecting the tears and the external surface of the eye leading to irritant sensation in the eyes, visual troubles and injury to the surface of the eye globe [1].

The syndrome of dry eye was found to be more frequent in association with thyroid disorders, as they are accompanied with many factors that contribute to the development of eye dryness [2].

Although the pathogenesis of this eye dryness is not obvious so far, many factors are suggested, including decreased production of tears, excess tear vaporization, tear disturbance, and instabilities of the lipid layer of the tear film [2]; furthermore, the corneal sensation is decreased at some stage in the early phases of thyroid disease [3]; also, microscopic confocal analysis showed lower corneal nerve fibers in people with thyroid disease compared to people with normal eyes [4].

Thyroid diseases may have direct inflammatory effects on the orbit, and many conditions are identified as thyroid-associated orbitopathy [TAO], thyroid eye disease [TED], and Graves' ophthalmopathy [GO], which are usually connected with eye dryness [2, 5].

There is no unique test to diagnose dry eye; in addition to clinical symptoms, some tests can recognize the amount of tears like the Schirmer test, while others detect the quality of tears like tear breakup time [TBUT], and combination of multiple tests must be used [6, 7].

For the clinical assessment of eye dryness, numbers of questionnaires were created to evaluate patients with dry eye symptoms to produce more objective data which can be utilized for better management and treatment of patients with dry eye disease [8].

Impression cytology denotes the testing of the superficial layers of the conjunctival epithelium for histological study [9].

Conjunctival impression cytology [CIC] is a non-invasive and simple to do test that can be applied with different tests for the diagnosis of dry eye [10, 11].

Dry eye syndrome is a frequent finding among patients who had thyroid disorders, which is usually underdiagnosed. Impression cytology used in the early detection of eye dryness in patients with thyroid disorders; however, few studies.

THE AIM OF THE WORK

Assessing the benefits of impression cytology for the detection of ocular surface changes in thyroid diseases patients and correlate its results with the obtained symptoms and clinical evaluation data.

PATIENTS AND METHODS

Prospective comparative non-randomized case-control study conducted at Ophthalmology and Histopathology Departments, AL-Zahraa University Hospital, Egypt, in the period from May 2021 until November 2021.

This study included 120 eyes of 60 subjects were classified into 2 groups; group 1: 60 eyes of 30 patients with thyroid disorders age up to 40 years, and group 2: consisting of 60 eyes of 30 healthy subjects [control group].

Recent ocular surgery, diabetic patients, smokers, pregnant and lactating women, patients with disorders involving the eyelids or eyelashes, previous history of operation in the thyroid gland or radioactive iodide, patients under treatment with steroid or immune-suppressive and patients had Lasik surgery were excluded from the study.

Ethical Considerations:

All patients included in the study have submitted a written consent after illustrating the study purpose and each subject had the right to accept or not, also, the approval of the ethics committee of Al-Azhar University has been obtained.

Methods:

All subjects completed the SPEED Questionnaire. In addition, regular examination of the eyes comprising examining the visual acuity, slit lamp testing, and eye movement, fundus examination, after that fluorescein tear breakup time [TBUT], Schirmer test was done and examination ended by impression cytology.

Thyroid gland disorder diagnosis: It was dependent on the estimation of thyroid-stimulating hormone [TSH] and free thyroxine [FT4]. Hypothyroidism was diagnosed with high TSH and low FT4, while hyperthyroidism was diagnosed as low TSH and high FT4 [12].

SPEED sheet:

It is a scoring questionnaire [0 to 28 point], which are the summation of 8 factors evaluating the severity and frequency of symptoms related to eye dryness; the symptoms include dryness, irritation, grittiness, burning, soreness, scratchiness, watering, and eye fatigue, the questionnaire also evaluates whether these symptoms weren't problematic, uncomfortable, tolerable, bother-some, or intolerable the questionnaire also monitored symptoms changes and diurnal over three months [13]. If score:

- 0-4 indicating mild dry eye symptoms.
- 5-7 indicating moderate dry eye symptoms.

- 8+ indicating severe dry eye symptoms [14].

TBUT test:

The subjects were inquired to gaze downward, and then a strip was smoothly swapped alongside the upper conjunctival surface. The patients were directed to do frequent blinks and to maintain his / her eye open while looking at a faraway focus. The time period from the final blinking and the initial development of dark stains on the pre-corneal tear film was documented in seconds; values of 10s or less were considered abnormal [15].

The Schirmer's test:

It was done by measuring the amount of tears produced by the lacrimal gland through inserting a sterilized paper stripe in the inferior eyelid for 5 min, while in contact with the eye surface to estimate the quantity of the strip wetting. The lower the moisture content on the paper, the less tears are produced, and values of 10 mm or less was considered abnormal [16].

Impression cytology:

Cellulose acetate filter paper was incised to little bands [5 mm×5mm], and topical anesthesia was applied to the conjunctival surface. The paper was then introduced with a blunted smooth-bordered forceps, with the blunt side directed inferiorly towards the bulbar conjunctiva, and soft pressure was inserted with a fine glass rod for 4–6 seconds and then taken away. Then, immediately pressing the filter paper onto a clear slide, the slides are placed in the dish for 3-4 s in an 95% alcohol-containing solution, then fixed with alcohol 100% and stained with hematoxylin and eosin, slides were then tested under a light microscope using both low and high powers.

Nelson's grading system was followed for the staging process [17]**.** We stain the impression with hematoxylin and eosin, in this stain goblet cells not appears, but the epithelial cells appear very good. Nelson graded impression cytological findings into four grades.

- Grade 0 shows small round epithelial cells with abundant goblet cells [Figure 1].
- Grade 1 shows a slightly larger epithelial cells and a decrease in the number of goblet cells [Figure 2].
- Grade 2 shows larger and polygonal epithelial cells and few goblet cells [Figure 3].
- Grade 3 shows cells with basophilic cytoplasm, small pyknotic nucleus, and complete absence of goblet cells [18] [Figure 4]

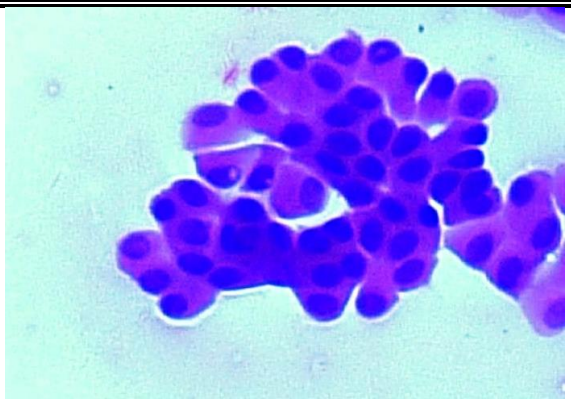

Figure [1]: G0: Small cells with large hyperchromatic nuclei and scanty cytoplasm. Magnification power x200

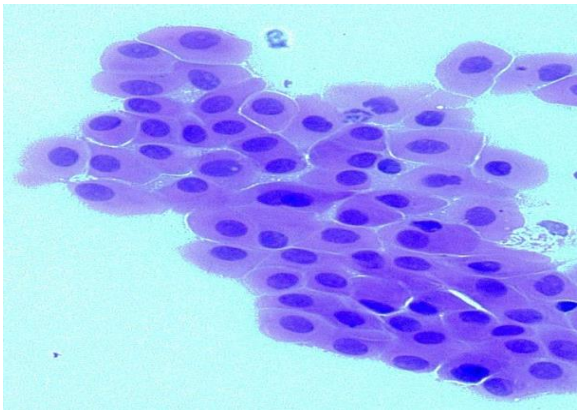

Figure [2]: G1: Slightly larger epithelial cells with increase in amount of cytoplasm. Magnification power x200

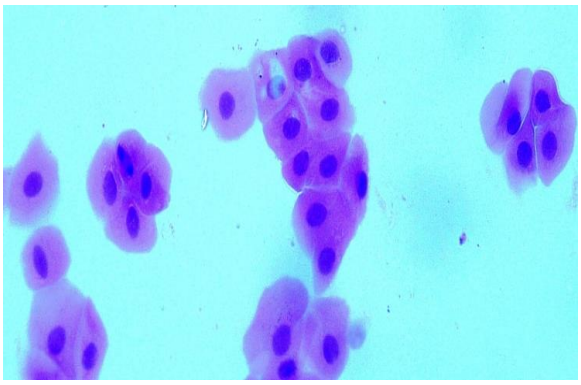

Figure [3]: G1-2: Larger and polygonal epithelial cells with increase in amount of cytoplasm. Magnification power x200

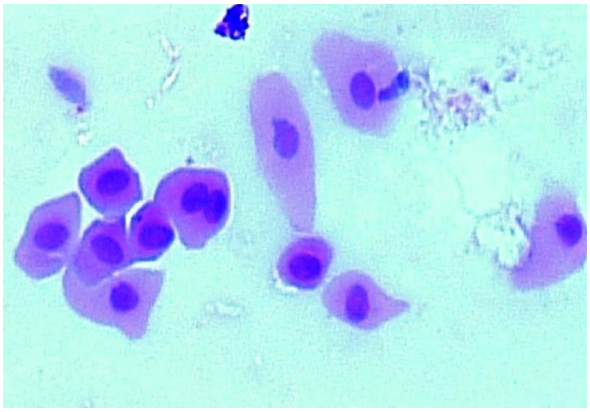

Figure [4]: G2-3: Larger epithelial cells with increase in amount of cytoplasm and pyknotic nucleus. Magnification power x200

Statistical analysis: Data were analyzed using the "Statistical Package for Social Science [IBM SPSS., Chicago, Illinois, USA]" version 24. Quantitative data were expressed as mean, standard deviations, while qualitative variables were presented as numbers and percentages. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent sample's *t*-test, while data with non-parametric distribution were done using Kruskal-Wallis test. The confidence interval was set to 95% and the margin of error accepted up to 5%. So, the P value was considered significant [P < 0.05] or non-significant [P> 0.05].

RESULTS

There was no significant difference between both groups regarding age and sex. In group 1, there were 11 males [36.7 %] and 19 females [63.3 %], the mean age was 29.37±6.77. In group 2, there were 11 males [36.7 %] and 19 females [63.3 %], and the mean age was 30.87±7.473. The mean score for the SPEED questionnaire in the thyroid disorder subjects was [8.50± 6.806], while the mean score for the control subjects was [0.00±0.00] with P < 0.05. The mean score for the TBUT and Schirmer scores for the thyroid disorder's subjects [9.00±3.037s] [9.10±3.007mm], respectively, while the mean score for the TBUT and Schirmer scores for the control group [13.00 ±1.484s] [13.70 ±1.670mm], respectively with P < 0.05 [table1].

Most of the thyroid disorder subjects showed grade 1, 2& 3 in CIC results [73.3%] of eyes, while in the control subjects, impression cytology results showed that all cases were grade 0 [100%] with P < 0.05 [Table 2]. The mean score for the SPEED questionnaire for the hypothyroid patients was [4.20 ±4.341], while the score for the hyperthyroid patients was [10.65± 6.869] with P <0.05. For the hypothyroid patients, the mean score for the TBUT and Schirmer scores [10.65± 2.796s] [10.80± 2.984mm], respectively, while in the hyperthyroid patients the mean score for the TBUT and Schirmer scores [8.18 ±2.836s] [8.25 ±2.667mm], respectively, with P < 0.05 [Table 3].

Most of the hypothyroid patients showed grade 0& grade 1 in CIC results, while most of the hyperthyroid patients showed grade 2 to 3 P < 0.05 [Table 4].

Regarding TBUT test and Schirmer test; for the hyperthyroid patients without TED, the mean score for the TBUT and Schirmer test scores were 10.81±2.455s and 10.69± 2.469 mm, respectively. The mean TBUT and Schirmer scores within the hyperthyroid patients with mild TED were 7.63 ±1.061s and 7.63 ±1.061mm, respectively. The mean TBUT and Schirmer scores within the hyperthyroid patients with moderate TED were 6.50±0.756s and 6.63 ±0.518 mm, respectively. While the mean TBUT and Schirmer scores within the hyperthyroid patients with severe TED were 5.13 ±0.354s and 5.63±0.51mm, respectively. There was a statistically significant difference with P-value < 0.05 [table5].

Regarding SPEED questionnaire; for the hyperthyroid patients without TED, the mean score for the SPEED questionnaire scores was 3.00± 3.251. The mean score for the hyperthyroid patients with mild, moderate and severe TED were 14.00 ± 1.414, 16.63 ±1.915 and 16.75 ±1.500, with P < 0.05 [Table 5].

In the CIC, most of patient with hyperthyroidism without eye changes showed grade 0 to grade 1, while most of patients with mild TED were grade 2, most of patients with moderate TED were grade 2-3. All patients with severe TED were grade 3, with P < 0.05 [Table 6].

Table [1]: Comparing between the control group and the diseased groups regarding TBUT, Schirmer test, and SPEED scores of the study subjects

	N.	Control group			Diseased group			t	P value
		N	M	SD±	N	M	SD±		
TBUT	120	60	13.00	1.484	60	9.00	3.037	-9.167-	0.0001
Schirmer test	120	60	13.70	1.670	60	9.10	3.007	-10.359-	0.0001
SPEED score	60	30	0.00	0.000	30	8.50	6.806	6.840	0.0001

SPEED [Standard Patient Evaluation of Eye Dryness Questionnaire], TBUT [Tear breakup time]; TBUT 120 eyes, Schirmer's test 120 eye, SPEED score 60 subjects.

Table [2]: Comparing between the control group and the diseased groups regarding the CIC of the subjects being studied.

Impression cytology			Control group		Diseased group			
			N.=60		N.=60			
			N.	%	N.	%	T	P value
Grade	G0	0	60	100.00	16	26.7	10.222	0.0001
	G1-G2	1	0	00.00	14	23.3		
	G2-G3	2	0	00.00	20	33.3		
	G3	3	0	00.00	10	16.7		
Total			60	100	60	100		
			M=0.00	SD=0.000	M=1.40	SD=1.061		

Note; Significant [S] with P-value< 0.05: Independent t-test, N [Number], M [Mean], SD [Standard deviation]
Nelson's grading system used for staging.

Table [3]: Comparing between the hypothyroid patients and hyperthyroid patients regarding TBUT, Schirmer test, and SPEED scores of the subjects being studied.

	N	Hypothyroid patients			Hyperthyroid patients			t	P value
		N	Mean	±SD	N	Mean	±SD		
TBUT	60	20	10.65	2.796	40	8.18	2.836	3.201	0.01
Schirmer test	60	20	10.80	2.984	40	8.25	2.667	3.355	0.001
SPEED score	30	10	4.20	4.341	20	10.65	6.869	-3.131-	0.01

TBUT [Tear breakup time], SPEED [Standard Patient Evaluation of Eye Dryness Questionnaire].

Table [4]: Comparing between the hypothyroidism patients and hyperthyroidism patients regarding the CIC of the study subjects.

Impression cytology			Hypothyroid patients N.=20		Hyperthyroid patients N.=40			
			N.	%	N.	%		P value
Grade	G0	0	8	40.00	8	20.7	-2.718-	0.01
	G1-G2	1	6	30.00	8	20.3		
	G2-G3	2	6	30.00	14	35.3		
	G3	3	0	00.00	10	25.7		
Total			20	100	40	100		
			M=0.90	SD=0.852	M=1.65	SD=1.075		

Table [5]: Comparing between the hyperthyroid patients with or without thyroid eye disease [TED] regarding TBUT, Schirmer test, and SPEED scores of the patients under study.

	Hyperthyroid patients		N.	M	SD±	Mean Rank	Kruskal-Wallis	p value
TBUT	**Hyperthyroid pt without TED**		16	10.81	2.455	31.34	31.054	0.0001
	Hyperthyroid pt with TED	Mild	8	7.63	1.061	20.81		
		moderate	8	6.50	0.756	14.13		
		Severe	8	5.13	0.354	4.88		
	Total		40	8.17	2.836			
Schirmer test	**Hyperthyroid pt without TED**		16	10.69	2.469	31.38	30.453	0.0001
	Hyperthyroid pt with TED	Mild	8	7.63	1.061	20.69		
		moderate	8	6.63	0.518	13.31		
		Severe	8	5.63	0.518	5.75		
	Total		40	8.25	2.667			
SPEED score	**Hyperthyroid pt without TED**		8	3.00	3.251	4.50	15.730	0.001
	Hyperthyroid pt with TED	Mild	4	14.00	1.414	11.38		
		moderate	4	16.50	1.915	15.75		
		Severe	4	16.75	1.500	16.38		
	Total		20	10.65	6.869			

Note; Significant [S]: Kruskal-Wallis test, SPEED [Standard Patient Evaluation of Eye Dryness Questionnaire], TBUT [Tear breakup time], pt [patients], TED [Thyroid eye disease], N [Number], M [Mean], SD [Standard deviation]

Table [6]: Comparing between the hyperthyroid patients with or without thyroid eye disease regarding the CIC of the study patients.

Impression cytology			Hyperthyroidism without TED N.=16		Hyperthyroidism with TED Mild N.=8		Moderate N.=8		Severe N.=8		Mean Rank		
			N.	%	N.	%	N.	%	N.	%		Kruskal-Wallis	p value
Grade	G0	0	8	20.00	-	0.00	-	0.00	-	0.00	4.50	39.000	0.0001
	G1-G2	1	8	20.00	-	0.00	-	0.00	-	0.00	12.50		
	G2-G3	2	-	0.00	8	20.00	-	0.00	-	0.00	20.50		
	G2-G3	3	-	0.00	-	0.00	6	15.00	-	0.00	27.50		
	G3	4	-	0.00	-	0.00	2	5.00	-	0.00	31.50		
	G3	5	-	0.00	-	0.00	-	0.00	8	20.00	36.50		
Total			16	40	8	20.00	8	20.00	8	20.00			
			M=2.25 SD=1.780±										

TED [Thyroid eye disease], N [Number], M [Mean], SD [Standard deviation], Nelson's grading system used for staging.

DISCUSSION

Conjunctival impression cytology is easy to perform, non-invasive, and provides reliable information about the sampled area with minimal patient discomfort. Therefore, it is a fundamental way to understand ocular surface disorders [9].

Our results indicated the increased frequency of eye dryness in patients with abnormal thyroid function compared to the control group.

Clinical assessment of eye dryness using SPEED questionnaire revealed that patients with thyroid diseases had moderate to severe eye dryness, which was higher among patients with hyperthyroidism [10.65± 6.869] indicating moderate to severe dry eye, while the hypothyroid subjects [4.20 ± 4.341] indicate mild dry eye condition. Furthermore, the mean score for SPEED questionnaire increased with the severity of TED.

These findings were in agreement with the study of **Turkyilmaz *et al.*** [19] that used another questionnaire "Ocular Surface Disease Index" [OSDI] and showed that the average OSDI scoring documented among the patients with thyroid disorders was elevated than the score obtained for normal eye subjects.

Also, **Alanazi *et al.*** [20] reported a higher OSDI score in hyperthyroidism compared to patients with hypothyroid subjects.

All the performed tests in this study indicated a higher frequency of dry eye in association with thyroid disorders compared to controls [TBUT test, Schirmer test and CIC].

In the same way, **Turkyilmaz *et al.*** [19] showed that the mean TBUT scores in the patients with thyroid disorders were lower [6.8±3.7 s] than for the control group subjects [12.7±1.9s], and the average amount of tears obtained by the Schirmer test was much lower among thyroid diseases group [5.1±2.3 mm] versus [11.4±3.3mm] for the control.

Also, the present work agrees with the study of **Gürdal *et al.*** [5] that revealed that the mean for the TBUT test has been lower in cases presented with thyroid disorders [5.8-7.1 s] than the score in the control group [10.0-11.4 s] and showed that the mean for the Schirmer test was [14. ±8.3 mm] among thyroid disorders patients, which is significantly lower than the mean in normal eye subjects [24.9±3.6 mm].

The obtained results revealed that the severity of dry eye in hyperthyroid patients were more than in hypo-thyroid patients. This study agrees with the study of **Alanazi *et al.*** [20] that showed that the main score for the TBUT test was higher in hypothyroid patients [5.4±1.5] than those in hyperthyroid subjects [4.3±1.4].

The current results also revealed that the stage of dryness increased by increased stage of Thyroid Eye Disease [TED]. Thus, impression cytology can be used to confirm the severity of thyroid eye diseases among thyroid diseases.

This is in agreement with the study of **Ozkan *et al.*** [21] about evaluation of conjunctival morphology in TED with use of IC, which showed that [82.26%] of the samples obtained from temporal bulbar conjunctiva of [62] patients with TED were grade 2 or 3, and this percentage near our study.

Another study by **Xu *et al.*** [22] included 56 patients with TED, IC was done for only [39] TED patients [19 active TED, 20 inactive TED] and showed that 61.5%] were grade 2 or 3 which was less than our study, the difference between the percentage of both studies may be due to in their study they include [20] inactive TED cases, which affect the percentage of the results, while at the same time the percentage of grade 2 or 3 CIC results in active TED was [94.7%].

In thyroid disorders, the soft tissues of the eyes are affected resulting in the protrusion of the eye with exophthalmos [23], which lead to inability to close the eyelids totally, with disruption of the ocular surface and enhancement of tear evaporation [24]. Therefore, dry eye syndrome is commonly noticed in patients with abnormal thyroid conditions and more in patients with TED [25].

The main limitation of the study is small number of patients and the cross-sectional design, which limit the follow up, thus we could not compare the diagnostic values of different studied tests. Finally, the correlation between various thyroid hormones levels and the obtained results were not made.

Conclusion:

Eye dryness was a common finding among patients with thyroid diseases [both hypo- and hyperthyroidism]. The severity of dryness increased in the hyperthyroid state more than in the hypothyroid one, and the severity of dryness was higher in patients with thyroid eye disease [TED] more than the hyperthyroid patients without eye symptoms; in addition, the degree of dryness increased by the advanced stage of TED. Impression cytology is a noninvasive technique for assessing the morphology of the ocular surface cells and can be used for recognition of changes that occur in the conjunctiva in patients with thyroid disorders.

Financial support and sponsorship:

Nil

Conflicts of interest:

There is no conflict of interest.

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2/2022

International Journal of Medical Arts

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Print ISSN: 2636-4174
Online ISSN: 2682-3780