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Gender Related Difference in Tear Quality (A Prospective Study on Indian Population)

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Abstract:- Good tear quality is fundamental for the health of the ocular structures that are exposed to the outer world such as the cornea and the conjunctiva. Deficiency of tear quantity and quality would lead to increased infections, decreased transparency of cornea, irritation, and in severe cases dry eye disease (DED). Naturally a number of factors affect the production and chemical constitution of the tear film, and gender seems to be one such factor that might affect the tear quality, especially in the tear fern patterns. As the ferning patters are very much dependent of the chemical constitution of the tear film and are susceptible to hormonal changes in humans. Although previous studies have shown no difference on tern fern patters between genders, but these studies had very small sample size. So, in our study we measured the tear break up time [TBUT], Schirmer's, and grades of stimulated and unstimulated tear ferning patters for 120 participants (60 Males, 60 Females), to see if there are quantitative difference between genders. We found that tear film stability as measured by TBUT may be influenced by age, but not gender. TBUT increased significantly from young to middle-aged individuals, but then remains stable between middle-aged and old individuals. Similarly, the Schirmer's test results showed a significant difference in tear production between young and middle-aged groups and young and older age groups, but no significant difference between middle-aged and older age groups. And, the tear-ferning test showed that gender had a significant effect on tear ferning grades, with a larger proportion of males having poorer tear film quality compared to females. This study provides valuable insight into the effect of gender and age on tear film stability and production in Indian subjects.

Keywords:- *Tear Breakup Time [TBUT], Schirmer's Test, Tear Ferning Pattern, Stimulated Tears, Unstimulated Tears.*

I. INTRODUCTION

The pre-ocular tear film is a thin, complex and moist layer, which covers the cornea, bulbar and palpebral conjunctiva [1]. Tear film constitutes of three layers: outer lipid layer produced by meibomian gland of eye lid margins, middle aqueous layer produced by accessory and lacrimal gland, inner mucous layer produced by conjunctiva goblet cells [2], [3]. Tear film plays role in protecting and providing oxygen to cornea, lubricate and moist the ocular surface, washes the debris and foreign bodies from eye [3]. The lipid layer influences tear film stability, dysfunction of meibomian gland secretions leads to changes in both the quality and quantity of tears [4]. Instability and evaporation of tear film manifest to dry eye symptoms and reduced the quality of vision. The quality and quantity of the tears are measured using several tests like non-invasive and invasive tear break up time, phenol red thread, tear meniscus height, Schirmer's and tear evaporation test [5]. Tear ferns test is a simple test that provides insight into the quality of the tears, fern patterns reflects the chemical composition of the tears when dried. Depending on the tear film composition, a variety of tear ferning patterns (TFP) can be observed; healthy tear samples produce full dense ferning patterns, while the ferning pattern is fragmented or absent in a dry eye sample [6]. The tear ferning test has been applied in different studies of both aqueous deficient and evaporative dry eye [6]. In studies involving aqueous-deficient dry eye, it was used alongside the Rolando grading system in the diagnosis of keratoconjunctivitis sicca and was found to have high sensitivity (94 per cent) and specificity (75 per cent), which are comparable with other tests commonly used to test Sjogren's syndrome [7]. With regard to evaporative dry eye, the tear ferning test has been recommended for all prospective contact lens wearers because it is very easy to perform and will help exclude patients with poor tear quality [8]. There are three different types of tears, each with unique biochemistries [5]. Basal tears are typically present on the ocular surface, providing nutrients to the ocular surface, maintaining ocular comfort, and ridding the surface of debris [5]. Reflex tears are those released in response to irritants, including chemicals and foreign bodies [5]. Reflex tears are produced in higher quantities than basal tears and are involved in flushing the ocular surface of irritants [9]. Closed eye tears are those lubricating the eyes during sleep. Some components of the tear film, such as lactoferrin, lipocalin-1, and lysozyme, remain relatively constant between different types of tears [10]. However, the total amount of protein, lipid, and secretory IgA varies between types; protein and lipid content is highest in basal tears, despite differences in composition, the osmolarities in tear types remain relatively constant [11]. A study on effect of age and gender on tear film break up time results showed that there was high statistically significance difference ($p<0.001$) between male and female as regard TBUT, and that the values of TBUT were higher in males than in females [12]. The study on Age- and gender related tear function changes in normal population showed

Schirmer's test values were similar in all groups when a comparison was carried out according to sex, But significant differences between male and female subjects were detected in decades 2 (P = 0.012) and 4 (P = 0.040) in respect to the TBUT test values, but there was no significant difference between the sex groups in the other decades [13]. A pilot study assessing the structure of tear ferning in a group of healthy young subjects, showed that irrespective of gender, ferning patterning and grading degenerated and increased, respectively, as the age of the participants increased. Furthermore, the grading of ferning was better in male participants compared to female participants [14]. The study on relationship between tear fern and non-invasive tear break time in Asian population showed TFP and NIBUT was age dependent not gender and race dependent [15]. The aim of our study is to provide the effect of age and gender on tear ferns patterns of stimulated and unstimulated tears with larges simple size and wide range of ages.

II. MATERIALS AND METHODS:

The subjects were mostly from working population and student from A.J Medical College in Mangalore, India. Subjects with previous history of dry eye, binocular pathologies, recent ocular surgery, known cases of lacrimal grand related pathologies, and other subjects with systemic diseases were excluded from our study. Ethical approval was obtained from the ethical committee of A.J Medical Collage, Mangalore, India. Informed consent was obtained from all our participants. The study adhered to the tenants of the Declaration of Helsinki. All the measurements were taken by a single examiner. We conducted experiment in the following manner tear break-up test (TBUT), Schirmer's test, collected tear for grading tear ferning (first unstimulated tears were collected followed by stimulated tears). Apart from these measures we recorded some demographic data of our participants which included age, occupation, gender, and a compressive ocular workup was done.

A. Invasive tear film breakup time (TBUT)

The time between a full blink and the appearance of the first irregularly dispersed dry area on the cornea is known as TBUT. It is determined by applying a drop of fluorescein and analyzing the cornea under a cobalt-blue filter of a slit lamp. The adequacy of the mucin component of tears can be determined by TBUT. A typical range for TBUT is 15 to 35 seconds. If the value is less than 8 seconds, it indicates an unsteady tear film.

B. Schirmer's I

The Schirmer's test is a way to quantitatively assess tear production by the lacrimal gland. Schirmer's I is conducted without anesthesia and measures the total secretion of tears, including basal and reflex tears. During the test, a Whatman 41 filter paper strip (5 mm by 30 mm) is placed over the outer third of the lower eyelid, and the patient may either blink naturally or keep their eyes closed. After 5 minutes, the strip is removed, and the length of the strip moistened by tears is measured. If less than 15 mm of the Schirmer's strip is moistened without anesthesia, it indicates the presence of dry eyes.

C. Tear Fern Test

A glass capillary tube (10 µL) was used to collect a tear sample (1 µL) from the lower meniscus of both eyes in each subject. First unstimulated tears collected after 1mintue of installation proparacaine from lower tear meniscus and after 10 minutes stimulated tears were collected by irritating the temporal conjunctiva with a cotton bud. The tear samples were dried for 10-15 minutes. The Lawerence & Mayo N-400M, digital microscope with a magnification power of 16x was used to observe the tear ferning patterns. The obtained TF patterns were graded using Ronaldo tear ferning grading scale. The tears were collected and was graded by the same investigator.

There are four grades of ferning patterns: Type I (Grade 1) features closely packed ferns with no gaps between the branches. Type II (Grade 2) has smaller ferns with gaps between the branches. Type III (Grade 3) features small, incomplete ferns with minimal branching, leading to wider gaps. Type IV (Grade 4) does not display any ferning phenomenon.

III. RESULTS

One hundred and twenty subjects (60 males (34.92 ± 12.67), 60 females (34.40 ± 11.87)) with normal/ corrected to normal eyes were enrolled in the study.

A. Tear break-up time and Schirmer's test

We collected tear break-up time (TBUT) measurements for all 120 participants in both eyes, resulting in a total observation of 240 eyes. This was done as unilateral cases of dry eye syndrome are highly unlikely in subjects. Our analysis revealed no significant differences in TBUT values between males and females (Figure 1A). Furthermore, we found no effect of gender on the Schirmer's test (Figure 1B). Descriptive statistics and t-test results for TBUT and Schirmer's test by gender and age are presented in Table 1.

TABLE 1. Descriptive Statistics and t-Test Results for Tear Break-Up Time (TBUT) and Schirmer's Test by Gender and Age (*p < 0.05).

		Age	TBUT	Schirmer's
Young	Male	22.55(±2.32)	14.95	22.00
	Female	22.55(±2.32)	15.98	23.28
	p-value		0.09	0.28
Middle	Male	32.45(±3.80)	16.78	23.48
	Female	32.15(±4.88)	16.8	23.70
	p-value		0.94	0.86
Old	Male	49.75(±9.03)	17.08	27.75
	Female	48.95(±4.94)	16.85	28.08
	p-value		0.47	0.70
Overall age (Sig)			0.31	0.39

To check the effect of age on TBUT we divided the data into three age groups by simply rank ordering the data by their age and dividing into three equal parts forming groups young (18-26 years), middle age (26-40 years), and old (40-67 years). A two-sample t-test assuming equal variances was performed for each comparison. The mean TBUT was 15.4625 seconds for young individuals, 16.7875 seconds for middle-aged individuals, and 16.9625 seconds for old

individuals. The t-test results indicated a significant difference between young and middle-aged individuals and between young and old individuals, but no significant difference between middle-aged and old individuals (see table 2).

TABLE 2. Means and t-Test results for Tear Break-Up Time (TBUT) between Age Group (*p < 0.05).

	Young	Middle	Middle	Old	Young	Old
Mean	15.46	16.79	16.79	16.96	15.46	16.96
t-Stats	-3.74		-0.74		-4.36	
p-value	0.00*		0.46		0.00*	

The results suggest that TBUT increases significantly from young to middle-aged individuals, but then remains stable between middle-aged and old individuals (see Table 2). There was no effect of gender observed within the three age groups (see Table 1). Same patten of effects of age and gender was seen in Schirmer's test as well (see Table 3).

TABLE 3. Means and t-Test results for Schirmer's test between Age Groups (*p < 0.05).

	Young	Middle	Middle	Old	Young	Old
Mean	22.43	25.75	25.75	25.96	22.43	25.96
t-Stats	-3.72		-0.32		-3.98	
p-value	0.00*		0.75		0.00*	

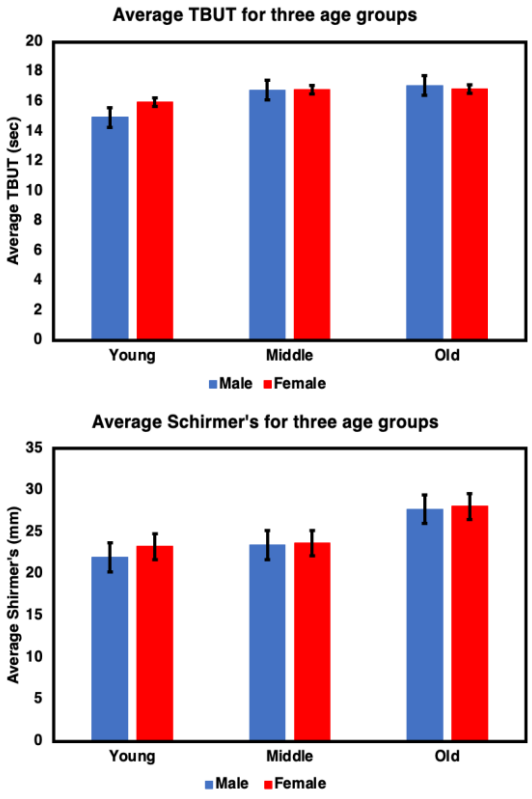

Fig 1. Results for TBUT and Schirmer's test by gender and age groups. The plot shows, A. average TBUT and B. Schirmer's values for both Males (blue) and Females (red) grouped into three groups young, middle, and old. Error bars represent the standard error of the mean.

B. Ustimulated and Stimulated Tear ferning test

TABLE 4. Unstimulated tear ferning grades by gender. The table shows the number of participants in each unstimulated tear ferning grade (G1-G4) separated by gender. Chi-Square, degrees of freedom (df), and p-value are reported for the analysis of gender differences in tear ferning grades (*p<0.05).

Unstimulated tear ferning by gender								
Gender	G1	G2	G3	G4	Total	Chi-Square	df	p- value
Male	41	52	22	5	120	8.078144	3	0.049994*
Female	55	49	16	0	120			
Total	96	101	38	5	240			

The results indicate that there were significant gender differences in the unstimulated tear-ferning grades ($\chi 2$ = 8.078, df = 3, $p < 0.05$). Specifically, a larger proportion of males (52.5%) were in G2 and G3 combined, while a larger proportion of females (45.8%) were in G1, indicating better tear quality (see Table 4). Furthermore, no females were observed in the worst category (G4), whereas 5 males were classified as G4 (Figure 2A).

We investigated gender differences in stimulated tear ferning grades. Our findings indicate significant differences between males and females ($\chi 2$ = 8.319, df = 3, $p < 0.05$). Specifically, a greater proportion of males (44.16%) were classified in G2 and G3, while a greater proportion of females (43.33%) were in G1, indicating superior tear quality (see Table 5). Additionally, no females were classified in G4, the worst category, while 5 males were identified as G4 (Figure 2B).

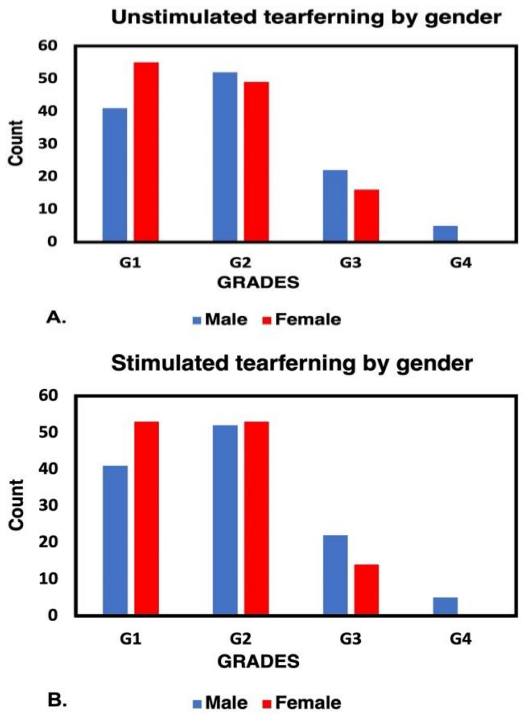

Fig 2. Effect of gender on tear film quality measures. The figure shows the average values of unstimulated tear ferning (A) and stimulated tear ferning (B) for males (blue) and females (red) grouped by gender. The data are further

stratified by age groups: young, middle, and old.

TABLE 5. Stimulated tear ferning grades by gender. The table displays the distribution of participants in each stimulated tear ferning grade (G1-G4) stratified by gender. Chi-Square, degrees of freedom (df), and p-value are reported to examine gender differences in tear ferning grades (*p<0.05).

Stimulated tear ferning by gender								
Gender	G1	G2	G3	G4	Total	Chi-Square	df	p- value
Male	41	52	22	5	120	8.31922	3	0.03986*
Female	55	53	14	0	120			
Total	94	105	36	5	240			

We investigated unstimulated tear ferning test results in different age groups. In the young population, no significant differences were found between males and females ($\chi2$ = 3.128, df = 3, p = 0.367). Similarly, no significant differences were observed in the middle-aged population ($\chi2$ = 6.231, df = 3, p = 0.101). However, in the older population, significant gender differences were observed ($\chi2$ = 6.888, df = 2, p = 0.032), with a larger proportion of females exhibiting better tear quality.

Similarly, we also investigated further to determine whether there were any gender differences in stimulated tear ferning grades across different age groups. The results revealed that there were significant gender differences in the stimulated tear ferning grades among the older group ($\chi2$ = 6.888, df = 2, p < 0.05), with a larger proportion of females exhibiting better tear quality. However, no significant gender differences were observed among the young and middle-aged groups. These findings suggest that the effect of gender on tear quality may vary across different age groups.

IV. DISCUSSION

The study aimed to investigate the effect of gender and age on tear film quality measures in normal/corrected to normal eyes in Indian subjects. Tear break-up time (TBUT), Schirmer's test, and tear-ferning test were conducted to measure the tear film quality of the subjects. We merged the measurement values for each eye (OD & OS) such that we obtained a total number of 240 individual eye to compare.

The study found that gender differences had a significant effect on the both stimulated and unstimulated tear-ferning grades, with a larger proportion of males having poorer tear film quality compared to females.

A. Effect of gender and age on Tear-Break-Up time and Schirmer's test

The findings of our study suggest that tear film stability, as measured by tear breakup time (TBUT), may be influenced by age but not gender. Our results are consistent with previous studies that have reported an influence of age on tear film stability, but instead of decreasing tear film stability with age, regardless of gender [16]-[18]. We observed a significant increase in TBUT values between young and middle-aged individuals and between young and old individuals, but no significant difference between middle-aged and old individuals. This suggests that TBUT increases significantly from young to middle-aged individuals but then remains stable between middle-aged and old individuals. However, no effect of gender was observed within the three age groups, which is in contrast to some previous studies that have reported gender differences in tear film stability [19]. Our findings also highlight the potential influence of other factors, such as meibum composition and efficacy of eyelid function, on tear film stability with age [20], [16] - [21].

The Schirmer's test is an important tool for evaluating tear production, and we tried to investigate age-related changes in tear production in a sample of 240 individuals of varying ages. Our results showed that there is a significant difference in Schirmer's test results between the young and middle-aged groups (t=-3.723, p=0.0003) and between the young and older age groups (t=-3.984, p=0.0001), but there is no significant difference between the middle-aged and older age groups (t=-0.320, p=0.749).

These findings suggest that tear production increases significantly from young to middle age but remains relatively stable in later life. However, it is important to note that our results contrast with some previous research on age-related changes in tear production, which has shown a gradual decrease in Schirmer's test results with advancing age in both sexes [13]. Further research is needed to better understand the mechanisms and patterns of age-related changes in tear production.

Our study also found no significant difference in Schirmer's test results between males and females in any of the three age groups (young: t=-1.091, p=0.279; middle: t=-0.178, p=0.859; old: t=-0.387, p=0.700). These findings suggest that there is no sex-specific effect on age-related changes in tear production. This finding is consistent with previous research, however [13].

B. Effect of gender and age on tear ferning pattern

The present study examined whether gender was a significant predictor of different grades of tear ferning in both stimulated and unstimulated conditions. The results of the chi-square tests showed that there was a significant relationship between gender and tear ferning grades for both stimulated and unstimulated tear ferning.

For stimulated tear ferning, the chi-square test revealed a significant relationship between gender and tear ferning grades, with a small to medium effect size ($\chi2(3, N = 240)$ = 8.319, p = 0.0040, V = 0.178). Specifically, male participants had worse tear ferning patterns compared to female participants, with a higher proportion of males in the G3 and G4 categories.

For unstimulated tear ferning, the chi-square test also revealed a significant relationship between gender and tear ferning grades, with a small effect size ($\chi2(3, N = 240)$ = 8.078, p = 0.050, V = 0.174). Similar to the stimulated tear ferning results, male participants had worse tear ferning patterns compared to female participants, with a higher proportion of males in the G3 and G4 categories. These results suggest that gender may be an important predictor of

tear ferning grades regardless of whether the tear film was stimulated or not.

It is important to note that while the statistical analyses revealed significant relationships between gender and tear ferning grades, further research may be needed to determine the clinical or practical significance of these findings. Additionally, there may be other factors that could impact tear ferning patterns, such as age, ocular surface disease, or medications.

The results were further analysed by dividing participants into three age groups, i.e., young, middle, and old. The effect of gender was not seen in younger age group and middle age groups. However, we found females to have better tear ferning patters in older age group. These findings suggest that age may play a role in tear quality.

In a study done by [15], where the study aimed to investigate the relationship between tear ferning patterns (TFP) and non-invasive tear break-up time (NIBUT) in normal Asian subjects [15]. The sample population consisted of 145 adults, no significant difference was found between gender in tear ferning patters (TFP) and NIBUT [15]. Which is in contrast with what we found, and this could be due to environmental factors, and other uncontrollable factors.

In summary, the study found that gender is a significant predictor of tear ferning grades in both stimulated and unstimulated conditions, with male participants having worse tear ferning patterns than females. However differences between two studies seems to suggest that we need measurements from a much bigger population to conclude the effects of gender on tear ferning patterns.

C. Occupational Implications of tear quality difference between males and females.

A review in 2021 studied the association between dry eye disease (DED) and prolonged use of visual display terminals (VDTs) [22]. DED is a multifactorial disease that causes ocular symptoms, reduced quality of life, and a considerable economic burden on society. Prolonged use of VDTs has been suggested as an important risk factor for DED [22]. The review aimed to examine the prevalence of DED among VDT users and the harmful daily duration of VDT use [22]. The far majority of the studies review in this review showed an association between VDT use and DED or DED-related signs and symptoms [22]. The prevalence of definite or probable DED in VDT and office workers ranged from 26% to 70%, with as few as 1-2 hr of VDT exposure per day being associated with DED [22].

Connected to this in our study a majority of female participants (47.6% of females in data) were non-office workers and were not subjected to equal amount of VDT use. We speculate this might have an effect on our data, which is why we see females having better objective tear quality than males. And because of that the overall tear chemist might be differed in between VDT user's and non-VDT users, however this is a speculation and needs proper research to be carried out in the future.

Anyway, VDT use is strongly associated with DED, and more research is needed on the effect of digitalization and digital transformation, which were particularly high during the time of the COVID-19 pandemic [22].

V. CONCLUSION

In conclusion, the study investigated the effect of age and gender on tear film quality measures in Indian subjects using three different methods, tear break-up time (TBUT), Schirmer's test, and tear-ferning test. The results showed that tear film stability as measured by TBUT may be influenced by age, but not gender. Furthermore, the Schirmer's test results showed a significant difference in tear production between young and middle-aged groups and young and older age groups, but no significant difference between middle-aged and older age groups. Interestingly, there was no sex-specific effect on age-related changes in tear production. The tear-ferning test showed that gender had a significant effect on tear ferning grades, with a larger proportion of males having poorer tear film quality compared to females.

It is crucial to understand the factors influencing tear film quality measures, as it is an essential part of diagnosing and managing ocular surface diseases and dry eye syndrome. This study provides valuable insight into the effect of gender and age on tear film stability and production in Indian subjects. The findings indicate the need for further investigation into the underlying mechanisms that contribute to changes in tear film quality over the lifespan. Identifying the factors that affect tear film quality can lead to better management and treatment of ocular surface diseases, as well as the development of personalized treatment strategies based on patient demographics.

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