



**The Relationship Between Meibomian Gland Morphology, Dry Eye Disease,  
and Electronic Device Use in Pediatric Patients**

**By**

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## **Abstract:**

**Purpose:** The purpose of this systematic study was to establish preliminary comparisons of various morphological and clinical parameters between dry eye and normal subjects in a pediatric cohort.

**Methods:** Children aged 5-17 were recruited for the study with no previous clinical diagnosis of dry eye disease (DED) or meibomian gland dysfunction (MGD). Diagnostic criteria for DED consisted of positive scoring on at least two of three components: subjective symptoms, abnormal tear function, and vital staining. All subjects completed SPEED (Standard Patient Evaluation of Eye Dryness) questionnaires to assess dry eye symptoms; scores above 5 indicated positive symptomology. Tear film and ocular surface integrity were inspected using fluorescein and lissamine green dye with slit lamp biomicroscopy. Corneal fluorescein staining, as well as temporal and nasal conjunctival lissamine green staining were graded from 1-4 (0=no staining; 4=coalesced). A staining score of more than 4 points across all 3 sections indicated positive vital staining. Abnormal tear function was defined by a tear break-up time (TBUT)  $\leq 5$ s. Meibomian gland morphology, lipid layer thickness, and blink patterns were evaluated with the use of a Lipiview Interferometer. The 5-point meiboscale for gland atrophy was used for dropout grading, while tortuosity was defined by the number of glands with  $\geq 45^\circ$  angles. Tear volume assessment was completed with the phenol red test. Questionnaires administered to both the child and family members were used to assess electronic device usage in order to screen for possible associations with average daily screen time and aforementioned parameters.

**Results:** A total of 24 subjects participated in the study. Dry eye was found in 41.7% of the subjects. The presence of meibomian gland dropout and tortuosity were 70.8% and 87.5% respectively. Dropout was significantly higher in the dry eye group ( $p=0.016$ ), although tortuosity was similar between both groups ( $p=0.93$ ). Tear breakup times were significantly lower in the dry eye group (5.30s vs 9.66s;  $p<0.001$ ) along with total staining scores (8.00 vs. 3.21;  $p=0.043$ ). Blink behavior and measurements of lipid layer thickness (LLT) did not vary between the two groups; partial blink ratios were 0.62 and 0.67 for DED and normal groups respectively ( $p=0.76$ ), and lipid layer thicknesses were 55.9nm and 57.43nm ( $p=0.84$ ). Electronic device use did not vary significantly between the two groups ( $p=0.99$ ).

**Conclusion:** The present study provides current baseline data on ocular surface characteristics and meibomian gland anatomy in healthy children with clinically dry eye vs. those without dry eye. Our results indicate that MGD and DED are highly inter-related at a much earlier age than previously acknowledged, and that the significant rise in pediatric DED represent a worthwhile cause for investigation into long-term risk factors for disease progression. Better understanding of baseline ocular surface and tear film characteristics will be crucial to identify the impact increasingly prevalent risk factors, such as visual device use, myopia interventions, and other changing environmental factors might have on the pediatric population.

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## ***Introduction:***

A multifactorial disease, such as dry eye disease (DED) is, by definition, a condition caused by many contributing factors, with no one single cause or sign/symptom. First formally defined in 1995, the research into DED has seen a surge in publications since its characterization. In 2017, the Tear Film and Ocular Surface society arrived at what they deemed an updated and all-encompassing definition, as follows:

“Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neuro-sensory abnormalities play etiological roles.”(Craig et al., 2017)

It is clear, even from this definition, that tear film instability is a hallmark of dry eye disease. An unstable tear film is one that exhibits higher rates of evaporation, which can be from decreased tear secretion, delayed clearance, or altered tear composition (“Introduction to the Report of the International Dry Eye WorkShop (2007),” 2007). These events lead to hyperosmolarity, which contributes to ocular surface damage through what has come to be known as a “cascade of inflammatory events” (Bron et al., 2017). A hyperosmolar inflammatory environment favors corneal and conjunctival epithelial and goblet cell apoptosis in a dry eye subject, which further contributes to tear film instability, and perpetuates more evaporation (Markoulli & Hui, 2019; Willcox et al., 2017). Thus, DED has been regarded as a vicious and chronic cycle of inflammation sustained by dysregulation of the immune response (Wei & Asbell, 2014).

There are two dominant categories of dry eye, including aqueous/tear deficient (ADDE), and evaporative dry eye (EDE) (“Introduction to the Report of the International Dry Eye WorkShop (2007),” 2007). The two categories, once considered exclusive from one another, are today, much more intertwined, especially as DED

progresses, and signs of both etiologies become clinically apparent (Bron et al., 2017). It has been well documented in the adult dry eye patient population, that there are significantly more individuals suffering from evaporative dry eye, versus those with aqueous deficiency (Lemp et al., 2012). ADDE describes conditions affecting lacrimal gland function. EDE includes both lid-related (e.g. MGD and blink-related) and ocular surface-related (e.g. mucin and contact lens-related) causes.

Of all the causes of EDE, meibomian gland dysfunction is regarded as the leading cause of dry eye *overall*, in both clinical and population-based studies. The meibomian glands secrete lipids, which comprise 90% of the tear film lipid layer, and prevents the evaporation of the underlying muco-aqueous layer (Foulks, 2007; Georgiev et al., 2017). In MGD, an abnormality of the glands leads to either terminal duct obstruction and/or changes in the glandular secretions (Chhadva et al., 2017). These changes to the quality and quantity of meibum can result in increased evaporation, hyperosmolarity, ocular surface changes, inflammation, and a largely unstable tear film (McCulley & Shine, 2003).

Taken alone, the diagnosis of MGD in the clinical setting is often overlooked due to its symptomatic and etiological overlap with dry eye; however, a new study in Japan suggests that even despite the overlap in ocular symptoms, MGD and DE are discrete conditions in terms of their etiology and pathogenesis (Arita et al., 2019). The world-wide report of the Workshop on MGD reported a much higher prevalence than DED in Asian populations, as high as 60%, with much lower prevalence in Caucasian populations varying anywhere from 3.5-20% (Nichols et al., 2011).

Within the last five years, the same research has begun on MGD in a pediatric population, whose physiological makeup can vary greatly from that of an adult. In a study of 3 to 18-year-old cohorts in China, Wu et al reported that 28% of participants had some form of meibomian gland atrophy (Wu et al., 2017). A similar study at Duke University revealed that among a pool of asymptomatic subjects under 18 years of age, a startling 42% had some evidence of meibomian gland atrophy (Gupta et al., 2018). Most recently in 2021, in another sample of a pediatric patients with no previous history of dry eye, 41% of cases had severe meibomian gland atrophy (Cremers et al., 2021). Each case demonstrating severe atrophy also exhibited

signs/symptoms of dry eye disease, including corneal neovascularization in 29% of individuals, which is typically regarded as an outcome of later-stage and more progressive disease. Taken together, these findings represent a troubling landscape for future pediatric ocular health concerns, as well as a potentially poorly understood pediatric equivalent of what has been considered as a disease of aging.

#### *Comparisons of Meibomian Gland Morphology in Pediatric vs Adult Populations*

Compared with adults, infants have less meibum on the lid reservoir (Borchman et al., 2010), meibum that is more saturated (Borchman et al., 2011), more ordered, and contains more proteins (Borchman, et al., 2010). Interestingly, individuals with the most ordered lipids are from subjects with dry eye as well as those with meibomian gland dysfunction (Mudgil et al., 2018). Meibum also increases in volume with age, which should provide an ample supply to cover the tear film yet tear film stability opposes this trend and actually decreases with age (Patel et al., 2000). Infants, in particular, have an unusually stable tear film (Mudgil et al., 2018). Thus, there is evidence to suggest that in a pediatric patient who does develop DED, there are other mechanisms contributing to the disease other than the characteristics that are traditionally thought of as contributing to adult dry eye, such as a deficient tear lipid layer. Major changes in tear film stability occur from birth to 25 years of age, with the largest change occurring below 20 years of age (Mudgil et al., 2018). These years evidently bear significance in the development of a healthy ocular surface, yet their impact on dry eye is not well understood.

#### *Epidemiology of Pediatric Dry Eye*

Researchers and clinicians alike have discounted dry eye disease in the pediatric population, with little interest in investigation and diagnosis, presumably due to an assumed low prevalence (Shimazaki, 2018). Doughty et al. reported that 18.7% of subjects younger than 20 years old experience dry eye symptoms as compared to 30.1% of adults (Doughty MJ, Fonn D, Richter D, Simpson T, Caffery B, 1997). A more recent study in 2008 suggested the prevalence was much higher, at 31% in those under 18 years old (Yu et al., 2008). While the prevalence of pediatric

dry eye has varied greatly in the literature, the DEWS II confirmed that after the fourth decade of life, the prevalence of dry eye increases linearly (Craig et al., 2017; Craig & Tomlinson, 1997). Diagnosis of dry eye currently relies heavily on the use of symptomatic reporting. Because of this, the prevalence of dry eye disease in children may be underestimated due in part to fewer symptoms reported, but also because the condition is often overlooked or attributed to other causes of ocular irritation, including allergies. Recently, in a study in Southwest China, 97.5% of children with allergic conjunctivitis (AC) also had DED, compared to 27.5% of control eyes (Chen et al., 2016). This may suggest that a clinician might overlook a DED diagnosis in favor of AC. Pediatric dry eye also has associations with various inflammatory, autoimmune disorders, and even eyelid abnormalities (Monica Alves, MD, PHD; Ana Carolina Dias, MSC; Eduardo Melani Rocha, MD, 2018). Nonetheless, the pathological and etiological mechanisms that play a role in pediatric dry eye from non-systemic influences remain to be assessed.

### *The Role of Electronic Devices*

One current hypothesis behind an increasingly frequent cause of dry eye in adults is an insufficient tear lipid layer and the subsequent correlation of lipid layer thickness (LLT) with rates of incomplete blinking. During a blink, the meibum reservoir that rests at the lid margin is spread over the entire ocular surface (Bron et al., 2017). This stabilizes the tear film and lipid layer, and provides a barrier towards evaporation. Without completion of the blink, there is inadequate mechanics to spread the lipid layer (Kawashima & Tsubota, 2013). Korb et al. even showed that forceful blinking significantly increased the lipid layer thickness by stimulating meibomian glands to secrete meibum. Thus, a blink that is incomplete might result in decreased meibum secretion as well as spread, and chronic incomplete blinking has been linked to damage of the inferior corneal epithelium (Collins et al., 2006).

Interestingly, many studies have linked the use of visual display terminals, VDT, to incomplete blinking. While looking at an electronic screen, lipid spread is affected two-fold, firstly by a decreased blink rate and secondly by an increased number of incomplete blinks (Tsubota & Nakamori, 1995). VDT use has been investigated

in numerous adult populations, often demonstrating that increased usage of electronic devices is associated with higher prevalence of severe DED symptoms (Uchino et al., 2008). The earliest and most influential examination of the same parameters in a pediatric sample population came from Korea in 2016. This study showed that smartphone use was more common in the individuals who met criteria for dry eye disease, and thus should be considered an important risk factor in kids as well as adults (Moon et al., 2016). These results have not been well replicated, nor has strong focus been given to the degree of gland dropout as it relates to electronic device use in children.

Today, exposure to known risk factors for ocular surface diseases in adults such as digital device use, myopia interventions (atropine/CL's), and other environmental factors are rapidly increasing among children. Prolonged use of electronic screens and devices has seen increases beyond the predicted trend due to the recent advent of the COVID-19 pandemic. School age children and working professionals alike found themselves under stay-at-home orders, with even social activities bound to electronic platforms. In a survey of 4- to 17-year-old children in Germany (N=1717), total recreational screen time (TV watching, Internet usage, and gaming) was reported to increase by 61.2 minutes per day after initial lockdown guidelines (Schmidt et al., 2020). Analogously, a cross-sectional study in Egypt examined dry eye symptoms before and after the onset of COVID-19 lockdowns and found a significantly increase in symptomology among those living in both urban areas and rural areas (Elhusseiny et al., 2021). Better understanding of baseline ocular surface and tear film characteristics is crucial to identifying the impact these factors might have; yet, clinical and epidemiological factors of pediatric ocular surface disease have been less investigated compared to the adult population.

The aim of this study was to establish preliminary comparisons of various parameters between dry eye and normal subjects in a pediatric population. These parameters included variables related to tear film quality, ocular surface integrity, blink behavior, meibomian gland anatomy, and subjective symptoms. Additionally, we explored possible associations between dry eye and meibomian gland dysfunction with electronic device usage.

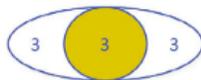
**Methods:**

*Subjects and Diagnostic Criteria:*

School aged, visually normal subjects between the ages of 5-17 were recruited for this study who were either symptomatic or asymptomatic for dry eye. Patients were not recruited based on dry eye diagnosis. Exclusion criteria included a previous diagnosis of DED, history of any ocular surgery or inflammatory disease, acne rosacea, or any systemic or ocular immune diseases known to cause dry eye. Those with any active ocular surface disease such as conjunctivitis or active contact lens use were also excluded. Dry eye diagnosis was made based on the 2006 Japanese Diagnostic Criteria for Dry Eye (Figure 1) (Shimazaki, 2007). Due to the proven decrease in reported symptoms among children, criteria consisted of positively scoring on at least two of the three components: subjective symptoms, abnormal tear function, and vital staining. Informed consent was obtained from all legal guardians, and assent was subsequently obtained from all minor participants. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board at the State University of New York College of Optometry.

**2006 Japanese Diagnostic Criteria for Dry Eye**

- 1. Subjective Symptoms**
- 2. Tear Functions**
  - 1) Schirmer test I  
≤ 5 mm (5 minutes)
  - 2) Tear film break up time (BUT)  
≤ 5 seconds
- \* Subject who meets either criteria 1 or 2 is considered to fulfill that criteria.
- 3. Vital Staining**  
Lissamine green, Rose Bengal, fluorescein staining \*
- \* A staining score of more than 3 points out of 9 is considered to be positive.



1. Subjective Symptoms	○	×	○	○
2. Tear Function Abnormalities	○	○	×	○
3. Vital Staining	○	○	○	×
Diagnosis of Dry Eye	Definite dry eye		Probable dry eye	

**Figure 1.** Diagnostic criteria of DED proposed by the JDES (2006 version). The criteria consist of three components: subjective symptoms, tear function, and vital staining test. Patients positive for all three components are regarded as “definite dry eye,” whereas those positive for any two of three components are regarded as “probable dry eye.”

### *Testing Procedure:*

All subjects completed a Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire to screen for dry eye symptoms, and to determine their frequency and severity. Subjects, and their parents on their behalf, were asked to complete identical estimates of daily visual display use; this included use of various devices such as television, tablets, laptop/desktops, as well as smartphones.

A single examiner performed all ocular assessments and procedures. For each participant, a meibomian gland image of the lower eyelid was obtained using the LipiView Interferometer (Tear Science Inc. Morrisville, NC). The lower eyelid was everted using the attached device, and the upper eyelid was everted manually. The LipiView was also used to analyze the lipid layer of the tear film. The interferometer measures the lipid layer thickness of a defined area of tear film and captures the blink profile, including partial blinks, during a specified time interval. The validated 5-point meiboscale for gland atrophy was used for grading. Meibomian gland dropout is as follows: grade 0: normal meibomian glands, grade 1:  $\leq 25\%$  gland atrophy, grade 2: 26% to 50% gland atrophy, grade 3: 51% to 75% gland atrophy, and grade 4: 75% gland atrophy (Pult & Riede-Pult, 2013). Meibomian gland tortuosity was defined as a 45-degree angle distortion of the gland. The following grading scale was used to grade tortuosity: Grade 0: no gland distortion, Grade 1: 1 to 4 glands, and Grade 2: 5 or more glands.

Slit-lamp examination included evaluation of the cornea, iris, anterior chamber, lens, and conjunctiva. Eyelids and palpebral conjunctiva were inspected for any signs of allergic conjunctivitis, as well as for expressibility and health of gland orifices. Tear break-up time (TBUT) was measured following instillation of fluorescein on a strip in the inferior conjunctival fornix. Patients were instructed to blink several times and keep their eyes open after the last blink. Tear film was evaluated for length of time until the first sign of a dry spot on the corneal surface. Fluorescein corneal staining was graded based on the Efron scale; whereas lissamine conjunctival staining was graded based on the Oxford grading scheme. Following thorough irrigation of the eyes with saline solution, tear volume assessment and tear film collection were performed with phenol red threads (Zone-Quick, Showa Yakuhin

Kako Co., Ltd, Tokyo, Japan and Menicon, Spain). The folded 3mm portion of the thread was placed against the inferior palpebral conjunctiva about 1/3 of the distance from the lateral canthus and patients were instructed to close their eyes for 15 seconds. After the fixed time period, threads were removed, and the red portion of the thread was measured. This was done in each eye. Afterwards, two threads at a time were placed in the same position until threads were saturated and then collected. All tear samples were immediately transferred to a freezer to be stored at 0°C.

#### *Statistical Analyses:*

Characteristics of subjects including demographics and clinical characteristics were first summarized using descriptive statistics in median (IQR range) for continuous variables or percentages (counts) for categorical variables. T-tests (ANOVA) and  $\chi^2$  tests were used to compare continuous and categorical patient characteristics between two (or three) groups, respectively. The correlation between dropout, tortuosity and screen time were evaluated using Pearson Correlation or Spearman Rank Correlation for non-normal data. All the continuous outcome variables were checked for normality prior to the statistical analyses. Univariate and multi-variate linear regressions were further used to test for correlations to the primary outcome: partial blinks and lipid layer thickness. All statistical analysis was conducted in R-statistical package ([www.r-project.org](http://www.r-project.org)). Statistical significance of p-value <0.05 was considered to be relevant.

#### ***Results:***

##### *Demographic Information*

A total of 24 subjects participated in the study. Ages ranged from 6-17 ( $\bar{X} = 12.92 \pm 3.29$ ) with 13 females and 11 males. None had a previous clinical diagnosis of dry eye or MGD. 41.6% of subjects self-identified as White, 25% Black, 12.5% Asian, and 12.5% Other.

*Dry Eye Symptomology and Diagnosis*

Average SPEED score among the subjects was  $5.5 \pm 3.36$ , ranging from 0-12. These SPEED scores reveal that 42% of children were either asymptomatic or exhibit mild symptoms, whereas 33% and 25% of the children experienced moderate and severe symptoms, respectively. Based on our diagnostic criteria, 10 subjects with dry eye were detected. Prevalence of dry eye was thus 41.7%. Prevalence of “definite dry eye” was 20.8% based on the Japanese criteria.

*Meibomian Gland Anatomy*

In this pediatric subject group, the mean meiboscore was  $1.13 \pm 0.64$  and the mean tortuosity score was  $1.29 \pm 0.41$ . There were 70.8% (n=17/24) of subjects who had evidence of any degree of meibomian gland atrophy (meiboscale grade  $\geq 1$ ). 90.1% (n=21/24) of subjects showed any evidence of tortuosity (tortuosity grade  $\geq 1$ ). The distribution of meiboscores ranged from 0 (no evidence of atrophy) to 3, with no subject having a score of 4 on any eyelid. Tortuosity ratings ranged from 0 (no evidence of tortuosity) to 2 (the most severe).

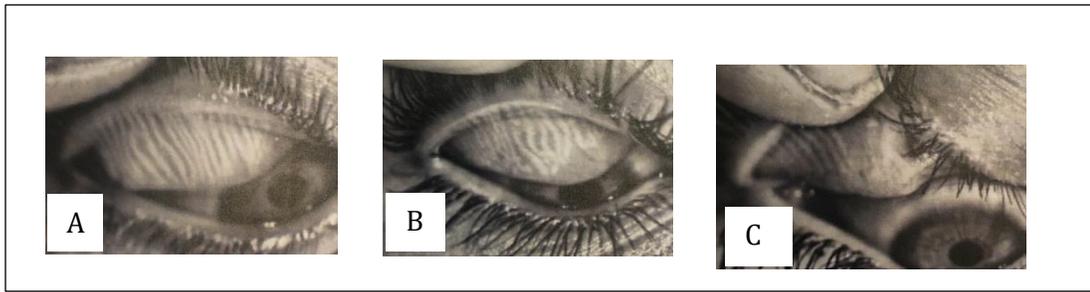
Average meiboscore among the dry eye group was significantly greater with a value of  $1.23 \pm 0.41$  compared with  $0.81 \pm 0.72$  among normal ( $p < 0.05$ ). Tortuosity did not vary between groups, with averages of  $1.25 \pm 0.38$  and  $1.2 \pm 0.426$  for DED and normal groups respectively ( $p = 0.47$ ).

<b>OD Meiboscore</b>	<b>Subjects</b>
0-<1	7
1-<2	12
2-3	5
<b>OS Meiboscore</b>	<b>Subjects</b>
0-<1	7
1-<2	16
2-3	1
<b>Any Dropout (Grade <math>\geq 1</math>)</b>	<b>Value</b>
OD	70.8%
OS	70.8%

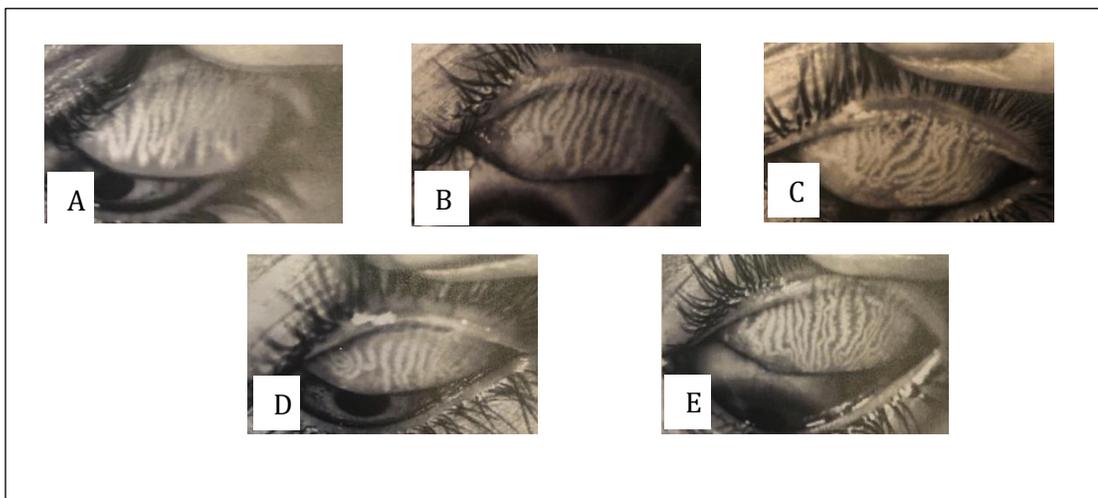
**Table 1:** Meibomian gland dropout grade distribution

<b>OD Tortuosity</b>	<b>Subjects</b>
0-<1	2
1-<2	22
2	0
<b>OS Tortuosity</b>	<b>Subjects</b>
0-<1	3
1-<2	21
2	0
<b>Any Tortuosity (Grade <math>\geq 1</math>)</b>	<b>Value</b>
OD	87.5%
OS	87.5%

**Table 2:** Meibomian gland tortuosity grade distribution



**Figure 2:** Representative images of upper eyelids in subjects with meibomian gland dropout. *A: Grade 1, 17 yr. old female B: Grade 2, 15 yr. old female C: Grade 3, 16 yr. old female*



**Figure 3:** Representative images of upper eyelids in subjects with meibomian gland tortuosity. *A: Grade 0, 16 yr. old male. B: Grade 1, 17 yr. old female. C: Grade 1, 9 yr. old male D: Grade 2, 14 yr. old male. E: Grade 2, 12 yr. old male.*

### *Dry Eye vs. Normal*

TBUT for each eye was significantly reduced in the dry eye group versus normals, with an average of  $5.20s \pm 2.86$  and  $5.40s \pm 2.17$  for the right and left eyes, respectively ( $p < 0.001$ ). Mean TBUT in normal group was over  $10.36s \pm 2.84$  in the right eye and at least  $8.96s \pm 2.28$  in the left eye (Table 3). Many subjects were unable to keep their eyes open longer than 10 seconds, so many readings were recorded as 10+ as long as no dry spots had appeared before 10s. Both fluorescein and lissamine green staining scores were significantly higher in the dry eye group than normal at

1.35±1.37 and 0.39± 1.54 for corneal staining ( $p<0.05$ ) and 2.25± 2.28 and 1.17±1.60 for lissamine staining ( $p<0.05$ ).

Partial blinks were measured as a decimal from 0-1 (0= no partial blinks, 1= 100% partial blinks). No significant difference was noted between the groups in either right or left eyes, with an average between eyes of 0.62±0.34 and 0.67±0.28 in dry eye and normal respectively ( $p=0.76$ ). Multivariate linear regression to test for partial blink fraction as the outcome variable revealed that LLT had a significantly positive predictive value in the left eyes ( $p=0.04$ ) and approached significance in the right eyes ( $p=0.08$ ).

In general, LLT is within 15 to 157nm, with a mean of 42nm (King-Smith et al., 2010). The mean LLT in the present study was 56.82nm ±18.46 with a minimum of 30nm, and a maximum of over 100nm (limited to 100+ measurement using the Lipiview Interferometer). No significant difference was found between the DED and the normal groups for either the right (56.50± 19.42 vs 59.10± 22.59) or left eyes (55.90±19.48 vs 55.89±14.23) ( $p=0.78$  and  $p=0.99$ ). Importantly, age, SPEED score, screen time, and phenol red thread testing were not statistically different between dry eye vs. normal subjects (Table 3).

#### *Dropout vs. No Dropout*

The presence of meibomian gland dropout was compared to a few selected variables. Subjects who showed any degree of dropout (meiboscore grade≥1) had a significantly lower average ( $p<0.01$ ) TBUT of 6.7±3.06s while those with less than grade 1 of dropout had a higher mean TBUT of 9.17±3.52s. The degree of fluorescein staining also varied as a function of meibomian gland anatomy ( $p\leq 0.05$ ); those with dropout (grade≥1) had a mean staining score of 1.65, while those without dropout had a mean score of 0.44 (Table 4). In contrast, lissamine green staining did not differ significantly between the two groups ( $p=0.66$ ) (Table 4). The presence of tortuosity significantly predicted lissamine green staining ( $p<0.01$ ) but not fluorescein staining ( $p=0.11$ ). There was no relationship between TBUT and the presence of tortuosity ( $p=0.34$ ).

**Table 3:** Comparison of age, symptoms, screen time, meibomian gland dropout and tortuosity and ocular surface parameters in dry eye vs. normal subjects

*\*Highlighted values represent statistically significant differences*

	Dry Eyes	Normal	p-Value
Age	13.40(2.72)	12.57(3.16)	0.59
SPEED Score	6.60(2.99)	4.71(3.50)	0.18
Average Screen Time	10.43(3.61)	10.41(3.01)	0.99
<b>OD + OS Dropout</b>	<b>1.23(0.41)</b>	<b>0.81(0.72)</b>	<b>0.02</b>
OD + OS Tortuosity	1.25(0.38)	1.26(0.42)	0.93
<b>TBUT OD</b>	<b>5.20(2.86)</b>	<b>10.36(2.84)</b>	<b>&lt;0.001</b>
<b>TBUT OS</b>	<b>5.40(2.17)</b>	<b>8.96(2.28)</b>	<b>0.001</b>
<b>Total Staining</b>	<b>8.00(6.32)</b>	<b>3.21(4.64)</b>	<b>0.04</b>
Phenol Red OD	22.70(5.58)	23.00(6.34)	0.91
Phenol Red OS	24.20(4.73)	25.50(4.09)	0.48
LLT OD	56.50(19.42)	59.10(22.59)	0.78
LLT OS	55.90(19.48)	55.80(14.23)	0.99
Partial Blinks	0.62(0.34)	0.67(0.28)	0.76

**Table 4:** Comparisons of screen time, partial blinks, LLT, and ocular surface staining in subjects with (meiboscore  $\geq 1$ ) and without (meiboscore  $< 1$ ) any degree of dropout

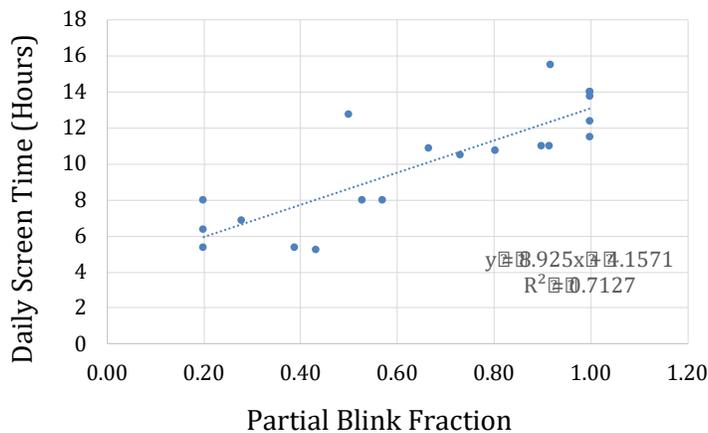
*\*Highlighted values represent statistically significant differences*

	Any Dropout (Grade $\geq 1$ )	No Dropout (Grade $< 1$ )	p-Value
Lissamine Staining	1.34	2.00	0.66
<b>Fluorescein Staining</b>	<b>1.65</b>	<b>0.44</b>	<b>0.03</b>
<b>TBUT</b>	<b>6.7</b>	<b>9.17</b>	<b>0.02</b>
Average Screen Time	10.03	10.05	0.99
Partial Blinks	0.59	0.74	0.14
<b>LLT</b>	<b>51.45</b>	<b>64.88</b>	<b>0.04</b>

### Electronic Device Use

There were three measurements of electronic device use including: self-reported usage, legal guardian/parent reported usage, and usage based on the average of the two aforementioned questionnaires. Screen time was summed across all modalities (except video games) listed in the questionnaire to obtain a single value of approximate daily screen time. The mean screen time of the dry eye group was  $10.43 \pm 3.61$ h, which was not statistically different from the normal group  $10.41 \pm 3.01$ h, ( $p=0.99$ ).

No significant correlations existed between the amount of dropout or tortuosity with screen time ( $r=0.35$  and  $0.05$  respectively). A strong positive correlation was found between partial blink fraction and average screen time ( $r=0.84$ ) (Figure 4).



**Figure 4:** Correlation between screen time and partial blink rate.

**Discussion:**

In general, DED is a disease process that is thought to increase with age (Lemp et al., 2012). In children, the prevalence of dry eye has varied anywhere from 6.6-21%, with very little data on classification as to how the disease process differs in a younger population from adults, if at all. This study was undertaken to reveal principal findings about pediatric dry eye, and also to establish any association between DED and MGD in children and electronic device use.

The present study revealed the highest prevalence of pediatric dry eye to date. This is probably compounded twofold, firstly by the diagnostic criteria used by many of the other studies in children. In most cases, positive symptomology from a dry eye questionnaire was required for the diagnosis. In one case, in an investigation of teenagers, the dry eye diagnosis was based entirely from OSDI scores (Wang et al., 2016). Secondly, while individuals included in our sample were not recruited based on the presence of the disease, it is possible that the high prevalence was influenced by subjects who volunteered based on their knowledge that this was a dry eye study, including both normal and dry eye individuals.

Regardless, the high number of subjects that were classified as dry eye is an indicator to a lack of diagnosis amongst pediatric patients. None of the subjects included had ever received a previous diagnosis of dry eye or meibomian gland dysfunction, yet 41% of the patients examined had DED, and 70.8% of the patients had meibomian gland atrophy. This begs the question of how many patients examined in optometric settings are misdiagnosed, potentially as having allergic conjunctivitis, or other anterior surface disease in favor of dry eye disease. While increasing age was significantly predictive of increasing symptomology, severity of symptoms still did not differ between the dry eye and normal groups. This points to the lack of reliability with which children can be expected to express symptoms, and that clinicians cannot rely on symptomology to arrive at a diagnosis.

As mentioned, the presence of meibomian gland atrophy was particularly high in this sample with 72% of patients showing some degree of atrophy. This is higher than some previous studies from 2017, where 28% and 42% of pediatric subjects showed some form of gland atrophy (Gupta et al., 2018; Wu et al., 2017). In the highest recorded numbers, Zhao et al (2018) showed that among 266 subjects ages 7-14, only 16 had no evidence of MG atrophy (94%). Click or tap here to enter text. Among those with dry eye in our sample, 88.8% of subjects showed atrophy, compared to 42.9% of the normal group. Of those with no dropout (grade <1) only 2 subjects fell into the DED category (22%). Of those with any degree of dropout (grade  $\geq 1$ ) 13 subjects fell into the DED category (61.5%). Meibomian gland dropout differed significantly in dry eye vs. normal subjects, implicating EDDE as having a major etiological role into

pediatric disease in an otherwise healthy population. This is further supported by the lack of differences measured in the aqueous marker of dry eye- phenol red thread. Similar to our findings, Wang et. al examined features of MGD in a population of teenagers and found scores related to gland orifices, section quality, and dropout were significantly poorer in the dry eye group vs. normals (Wang et al., 2016).

Signs of MGD often do not correlate with symptoms of discomfort and in fact, asymptomatic MGD is twice as common as symptomatic MGD (Viso et al., 2012). Symptomology of MGD also does not correlate well with signs of ocular surface damage, and both symptomatic and asymptomatic disease have been found to increase with age (Viso et al., 2012). Blackie and Korb termed this asymptomatic condition that is accompanied by a normal lid margin appearance “non-obvious MGD, or NOMGD” (Blackie et al., 2010). In NOMGD, diagnosis must be based on a change in the quality of expressed secretion. The authors regarded this form of MGD as an important risk factor for progressive symptomatic disease in adults. It remains to be seen whether this applies to a pediatric population as well, and represents an important need for future longitudinal studies in pediatric patients that exhibit significant meibomian gland dropout.

If, in fact, meibomian gland atrophy is widespread among the pediatric population, then it will be especially important to unearth the causes behind the morphology. In a study in Japan in 2013, the meibomian glands of subjects under three years of age were assessed, and were found to have no evidence of atrophy (Shirakawa et al., 2013). The authors of the study reported that in 1-month-old infants, morphologically complete meibomian glands are distributed across the whole tarsal plates in both the upper and lower eyelids. This is evidence that the atrophy found in our sample, as well as the aforementioned studies, is most likely not congenital, and possibly from other factors we are exposed to in life.

Meibomian gland function is strongly influenced by sex hormones, particularly androgens, which stimulate the synthesis and secretion of lipids by the meibomian gland and suppress the expression of genes related to keratinization (Nichols et al., 2011). Traditionally, these influences are regarded as important to the development of dry eye as it relates to menopause (Willcox et al., 2017). The same thought process

has not been assigned to research on effects of puberty on DED. It would be interesting to see if there are any changes in pre and post-pubescent individuals in particular.

An emerging risk factor for meibomian gland dropout is incomplete, or partial blinking. In various studies performed in adult populations, partial blink rate had strong correlations with MG dropout rates (Jeon et al., 2021; Jie et al., 2019; Wang et al., 2016). Adult subjects with incomplete blinks also have poorer lipid layer thickness, expressed meibum quality, and even eyelid notching, which is considered a late-stage consequence of meibomian gland disease (Wang et al., 2018). These results have also been replicated as a result of incomplete eyelid closure due to Cranial Nerve VII palsies. In a prospective study of new-onset CNVII palsies over the period of just a week and a half, those with incomplete blinks in the affected eye showed significant decreases in quality and expressibility of meibum (Wan et al., 2016). In these patients, without a complete blink, the muscles of the eyelid including the orbicularis and the Riolan muscle apply less squeezing force on the meibomian gland to secrete meibum (Knop et al., 2011). As a result, the meibum within the gland stagnates and solidifies, leading to chronic disuse, atrophy, and consequent dropout (Geerling et al., 2011).

Research has shown that partial blinking also creates a tear film that is more prone to ruptures with less effective redistribution of the tear film and poor maintenance of lipid layer integrity (Wolkoff et al., 2005). Individuals with greater amounts of partial blinking experience more frequent and wider ruptures particularly over inferior cornea (Wolkoff et al., 2005). In adults, partial blink rate is correlated with OSDI and SPEED scores, increased tear evaporation, and dryness area measured on the corneal surface (Cardona et al., 2011; Jeon et al., 2021; Jie et al., 2019). These results were not replicated in our pediatric population, with partial blinking not being predictive of any of the studies markers of dry eye or ocular surface damage. Blink patterns also did not vary between the dry eye and normal groups. Jansen et al. noted that in subjects engaged in tasks requiring a high degree of visual concentration, both the number of incomplete blinks and the interblink interval increased (Jansen et al., 2010). While studies in adults show that inter-blink

evaporation is a contributor of dry eye and suggest that assessing blink completeness may be a useful indicator, the same is not true for pediatric patients. Our results imply that the pediatric patient is not affected by desiccating stress to the same extent as an adult patient might be, and that the same blink patterns that can cause dry eye in adults are not causative in younger populations, which indicates a potentially different pathogenesis and entry point into the disease.

Partial blinking is thought to cause increased tear evaporation due to its effect on the lipid layer, with incomplete blinking being associated with a decrease in lipid layer quality and quantity (Wang et al., 2018). Studies have shown that incomplete blinking is associated with a two-fold increased risk of dry eye disease in patients with poor LLT (Wu et al., 2017). In the present study, the LLT of those with dropout was significantly lower than in those without dropout, but importantly did not differ between subjects with dry eye vs. normals. Studies of blinking in infants reveal a very low blink rate (<4/min vs. 15–30/min in adults) that has been associated with a lipid layer that has a greater ability to withstand repeated compression and expansion (Bacher & Smotherman, 2004; Isenberg et al., 2003; Mantelli et al., 2007). Our results provide evidence that while LLT may not be predictive of dry eye outcomes in pediatric subjects, there may be other qualitative factors related to the lipid layer that differ in children, such as viscosity, and factors related to compression modulus and spread that play a role in poorer ocular surface parameters that lead to dry eye.

In the present study, lipid layer thickness was significantly predictive of blink patterns, with a thicker lipid layer being associated with a higher partial blink rate. This implies that there may be a protective effect of a thicker lipid layer to the deformation of tears during the inter-blink interval in children. In a case-controlled study of children under 15 years old, a value of an LLT >57.5nm was found to be an important protective factor in tear film stability for children using a VDT for long periods (Zhao et al., 2018). Our data showed individuals with an LLT ≤57.5nm in either eye made up 58.3% of the meibomian gland dropout group vs only 25% of those with no dropout. Additionally, these individuals represented 60% of the dry eye group vs 40% of normal. While this did not translate to significant differences of LLT

between subjects with dry eye vs. normals, it represents a possible early marker of later disease.

With regards to electronic device use in our sample, screen time was not predictive of dry eye, meibomian gland dropout nor tortuosity. We were unable to replicate the results from Korea in 2016(Moon et al., 2016). One potential reason for this difference is possibly linked to the very high recorded use of electronic devices, averaging 10.43 and 10.41 hours per day in the dry eye and normal groups, respectively. In contrast, the average screen time in the same groups in the study by Moon et. al was 0.62h and 3.18h. It is likely that the excessive screen use in our population makes it difficult to obtain enough variability in the sample to elucidate possible differences with dry eye and meibomian gland dropout. Our results are similar to those obtained by other research groups (Gupta et al., 2018; Rojas-Carabali et al., 2020).

Some limitations of this study include the reliance on subjective measurements of staining, as well as on grading of meibomian gland dropout and tortuosity. There was also poor interferometry image quality obtained among a few participants, particularly of the lower lids of the youngest participants. Screen time also varied to a high degree between subjects and between different devices based on when the examination was performed; with those studied during the summer spending very different amounts of time on smartphones vs. computers from those participating during the school year. Lastly, there was a relatively low number of participants included in the study, which represents opportunities for higher-powered studies including more subjects in the future.

Other future directions include inflammatory analysis of the collected tear samples, as well as possible follow-up with patients to determine if presence of dropout in early life in fact predicts future symptomatic disease. Larger studies may also have the statistical power to determine if placing specific time-limits on pediatric electronic device use will show significant improvements in measurements of ocular health. Additional research should focus on investigating the efficacy of MGD treatments such as LipiFlow and Intense Pulsed Light (IPL) therapies that have not been studied in child populations. Current approved treatments for children include

warm compresses, lid hygiene, artificial tears, eyelid massage, and punctal plugs. The results of our study also point to the need for clinicians to consider DED in their differential diagnosis of ocular irritation in their pediatric patients.

Taken together, the high degree of atrophy found in our sample suggests that atrophy is a common morphological feature of the pediatric population occurring at much earlier ages than previously accepted and may be a feature of normal anatomy in some patients. This information calls our current understanding of morphology into question, as clearly not all patients with atrophy go on to develop either dry eye or meibomian gland dysfunction. In normal physiological responses to desiccation, compensatory responses driven by the lacrimal functional unit (LFU) can sustain an adequate tear volume (Willcox et al., 2017). These responses include compensatory increases in lacrimal secretion, increased blink rate, and general sensation of awareness of the eyes (Bron et al., 2017). Thus, if these compensatory responses are being suppressed more regularly from a younger age, such as with the excessive use of electronic devices, this may represent earlier precipitation of future disease. It is possible that the degree of device use among children in recent years exacerbates tear-film instability beyond both the resilience conferred in early life, as well as what the LFU responses can compensate for. This may be an explanation for the high degree of dropout in our study, and points to probable precipitation of non-obvious MGD, which is a known risk-factor of future symptomatic disease.

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## Screen Time Questionnaire Parent's Responses

Subject #: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_ Sex: M F (Circle) DOB:  
\_\_\_/\_\_\_/\_\_\_

1. On an average day, how much time does your child spend playing video games?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

2. On an average day, how much time does your child spend watching TV?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

3. On an average day, how much time does your child spend on a computer (laptop/desktop)?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

4. On an average day, how much time does your child spend on a smartphone?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours

- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

5. On an average day, how much time does your child spend on a tablet?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

## Screen Time Questionnaire Subject's Responses

Subject #: \_\_\_\_\_ Date: \_\_\_/\_\_\_/\_\_\_ Sex: M F (Circle) DOB:  
\_\_\_/\_\_\_/\_\_\_

1. On an average day, how much time do you spend playing video games?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

2. On an average day, how much time do you spend watching TV?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

3. On an average day, how much time do you spend on a computer (laptop/desktop)?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours
- [6] 3 hours or more

4. On an average day, how much time do you spend on a smartphone?

- [1] 0 min
- [2] 1-29 min
- [3] 30-59 min
- [4] 1 hour/less than 2 hours
- [5] 2 hours/less than 3 hours

[6] 3 hours or more

5. On an average day, how much time do you spend on a tablet?

[1] 0 min

[2] 1-29 min

[3] 30-59 min

[4] 1 hour/less than 2 hours

[5] 2 hours/less than 3 hours

[6] 3 hours or more