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Research Article

Tear Lipid Layer Thickness in Children after Short-Term Overnight Orthokeratology Contact Lens Wear

Li Zeng,[1,2,3] **Zhi Chen**,[1,2,3] **Dan Fu**,[1,2,3] **Jiaqi Zhou**,[1,2,3] **and Xingtao Zhou**[1,2,3]

[1]*Department of Ophthalmology and Optometry, Eye and ENT Hospital, Fudan University, Shanghai, China*
[2]*NHC Key Laboratory of Myopia, Fudan University, Shanghai, China*
[3]*Shanghai Research Center of Ophthalmology and Optometry, Shanghai, China*

Correspondence should be addressed to Xingtao Zhou; doctzhouxingtao@163.com

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Meibomian gland lipid secretion is important to the stability of the tear film and ocular surface comfort. Changes in the tear film's lipid layer thickness (LLT) after orthokeratology treatment may reflect underlying changes to the meibomian gland function. The purpose of this study was to investigate the features of the tear lipid layer in normal children and the effects of short-term orthokeratology treatment. Altogether, 163 myopic children (age: 10.7 ± 1.9 years, 8–15 years; 71 males) with no contact lens use history were enrolled in this study, of whom 56 were successfully fitted with orthokeratology lenses and completed the 1-month study. The tear film's LLT (average, maximum, and minimum) and blinking pattern were measured by a LipiView® interferometer in 163 participants at baseline and in 56 orthokeratology participants at 1 week and 1 month after overnight lens wear. Results show that LLT (average) was 58.09 ± 21.66 nm in Chinese normal children. LLT was significantly correlated with rate of partial blinks at every follow-up (all $p < 0.05$). Compared to baseline, the LLT (average and minimum) and partial blinks (number and rate) at 1 week and 1 month after orthokeratology treatment both significantly increased, and the increase of LLT was correlated with elevation of rate of partial blinks. In conclusion, LLT was shown to be elevated after short-term overnight orthokeratology treatment and was related to change in rate of partial blinks. Further studies are needed to clarify the long-term effect and the underlying mechanism.

1. Introduction

Orthokeratology has been used worldwide since the advent of rigid, gas permeable lens material in the 1990s [1]. The high-Dk lens material combined with a paracentral reverse geometry design has made overnight wear possible and provides wearers with good visual acuity in the daytime [2, 3]. A previous study of over 29,500 contact lens fittings revealed that orthokeratology was gaining popularity over the past decade [4], and another study showed that over 25% of prescribed rigid contact lenses were orthokeratology lenses for children and adolescents, and 47% were for younger children (6–12 years old) [5].

The *Implementation Plan for the Comprehensive Prevention and Control of Childhood and Adolescent Myopia*, issued by the Chinese government in 2018, has made orthokeratology, amongst other myopia control modalities, even more well-established in China [6]. Therefore, the safety issues associated with the popularity of orthokeratology lens fitting have recently received unprecedented attention.

As the first and foremost protection measure for the cornea, the tear film plays an important role in maintaining safety in contact lens wear by nourishing the cornea with oxygen, clearing the debris accumulated behind the lens, rewetting the ocular surface, and decreasing friction during blinking, etc. Compared with daily wear contact lenses, overnight orthokeratology has an advantage of inducing less disturbance to tear volume during a closed-eye condition by reducing evaporation [7]. Additionally, orthokeratology has been reported to increase daily eye comfort, especially in late afternoon, as compared to soft contact lenses [8]. The impact of orthokeratology on the tear breakup time, tear volume, and meibomian gland morphology in children after long-term orthokeratology treatment suggested the common safety of orthokeratology for ocular surface health [7, 9]. However, the change in corneal shape following orthokeratology lens wear and its closed-eye wearing modality may impact the tear dynamics and biochemistry accordingly. For example, changes in tear osmolarity, composition, inflammatory mediators, and corneal nerve density after orthokeratology have been reported [10–13]. Considering these mechanical, chemical, or biological impacts, potential change in meibomian gland function in lipid secretion could occur.

Recent development of LipiView® interferometer has enabled us to directly measure lipid layer thickness (LLT) with reasonable accuracy and repeatability, both in normal and dry eye patients [14, 15]. To our knowledge, few studies have investigated the influence of orthokeratology lenses on tear LLT; however, it appears that the average level of LLT in children needs to be considered independently from adults [16, 17]. The current study aimed at evaluating the LLT in a group of normal Chinese children, and the changes in LLT after short-term orthokeratology treatment.

2. Methods

This study was performed with approval from the hospital's institutional review board (trial number: 2015013–3). Informed consent was obtained from all subjects. The whole study was performed in accordance with the Declaration of Helsinki.

This study included two parts. In the first stage, we measured LLT (average, minimum, and maximum) and blinking pattern in 163 asymptomatic participants. In the second stage, 56 of 163 participants accepted orthokeratology treatment, and LLT and blinking pattern in 56 participants were followed up to 1 week and 1 month.

2.1. Participants. Between October 1, 2017, and September 30, 2019, 163 children (71 males, 92 females; age range: 8–15 years; mean age: 10.7 ± 1.9 years) consulting the myopia control clinic of the Fudan University Eye and ENT Hospital, Shanghai, China, were enrolled in this study. No participant had previous contact lens history, dry eye symptoms, or significant meibomian gland dysfunction. They had no systemic diseases or other eye diseases affecting ocular surface health.

2.2. Collection of Ocular Biometrics of 163 Participants at Baseline. Demographic and ocular biometrics data of participants at baseline were collected. It was obtained by reviewing records of participants at regular clinic within 1 month before baseline, including slit lamp examination, spherical and cylindrical refractive error, best corrected distance visual acuity, axial length (IOLmaster 500, Carl Zeiss, Germany), thinnest corneal thickness (Pentacam, Oculus Optikgerate, Wetzlar, Germany), corneal curvature along the flat meridian (K1), and the steep meridian (K2) (NIDEK RT-5100, Japan).

2.3. Orthokeratology Lens Fitting and Wearing of 56 Participants. Among the 163 participants in the clinic, 56 accepted orthokeratology treatment. All orthokeratology lenses were fitted in accordance with the manufacturer's recommendation, demonstrated adequate movement on blink and showed good centration under slit lamp microscope and corneal topography during the trial lens fitting period. Over refraction was then performed with a refractive target being plano. Participants were requested to insert orthokeratology lenses before going to sleep, with a minimum of 8 hours of lens wear each night. Children and their guardians received instructions on how to safely insert and remove the lenses, along with the lens care regimen. Participants in this study did not use additional artificial tears other than routine drops for lens wearing and taking off.

2.4. Follow-Up of Lipid Layer Thickness and Blinks. The LipiView® interferometer (Johnson & Johnson, USA), which measures the LLT (average, minimum, and max) during natural blinking in a noninvasive manner with satisfactory repeatability, was used to evaluate the LLT and blinking pattern (number of blinks, number of partial blinks, and rate of partial blinks). First, 163 normal participants were enrolled. Next, among 163 participants, LLT and blinking pattern of 56 undergoing orthokeratology treatment were followed up to 1 week and 1 month.

All measurements were made in both eyes, and data of the right eye were included for analysis in this study. Duration of measurement on LipiView was 19.1 seconds per round. In this time window, LLT (average, minimum and maximum) was calculated automatically, and the number of blinks and partial blinks were also automatically counted and displayed on the screen (Figure 1). The ambient temperature was controlled between 25 to 30°C, and relative humidity between 50% and 65%. After adjusting the position of the chin and forehead, the participants were instructed to fixate on the internal target, and the camera was then adjusted until the inferior tear meniscus area was clearly in focus. Image capture was obtained with participants blinking naturally. Reliability index (CFactor on-screen) was requested to exceed 0.7, otherwise the measurements would be repeated. The results were output as interferometric color units (ICU), which was equivalent to nanometers (nm). The LipiView® interferometer had an upper cutoff of 100 nm in the measurement of LLT.

2.5. Statistical Analysis. For data of 163 normal participants at baseline, Pearson and Spearman correlation analyses were conducted to investigate the correlation between LLT (average, min, and max) and blink pattern (number of complete blinks, number of partial blinks, and rate of partial blinks). Rate of partial blinks was calculated as follows: number of partial blinks/number of blinks. Correlation of LLT and other parameters including age, sex, spherical and

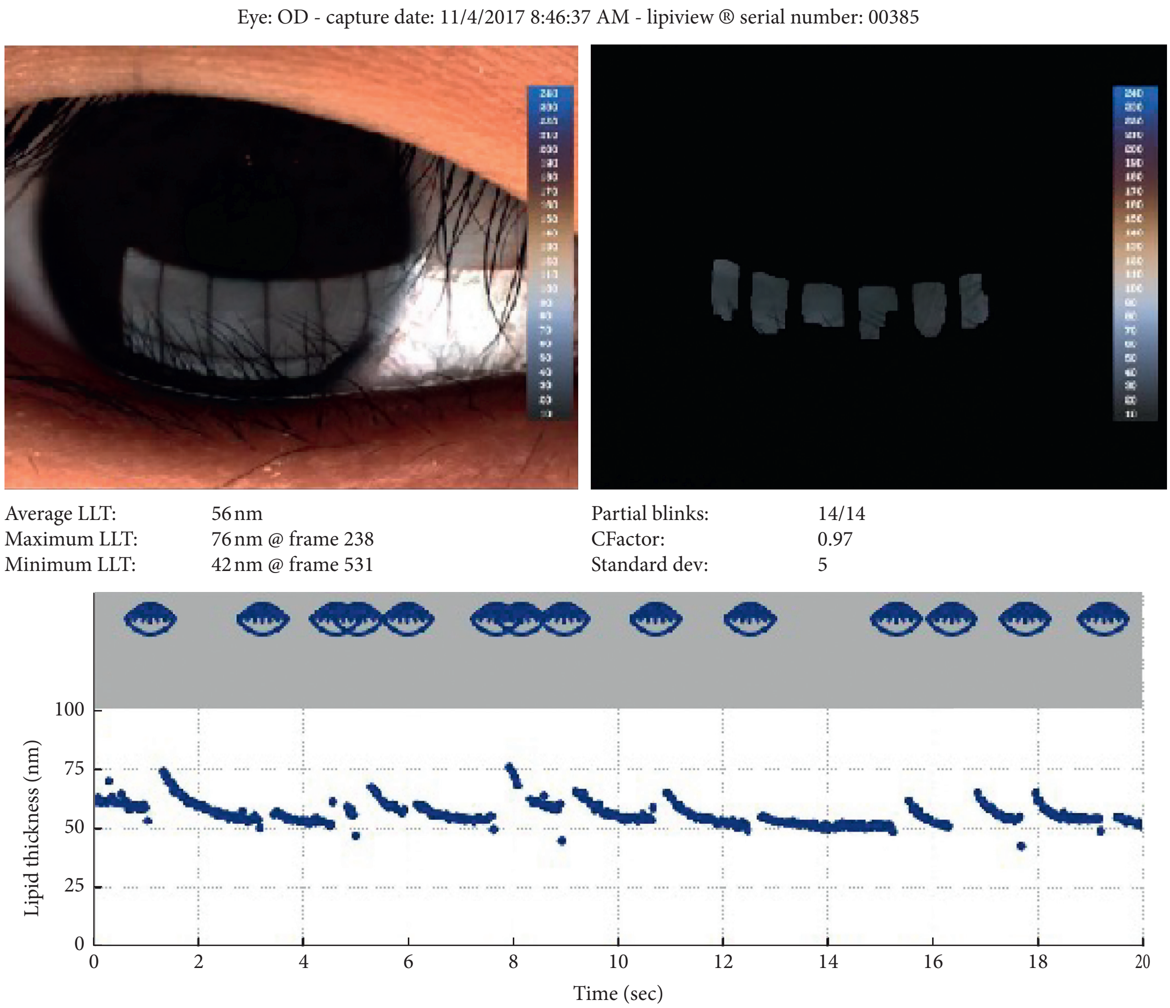

Figure 1: Display of LLT and blinking pattern on-screen of LipiView® interferometer. The result of LLT (average, minimum, and max) of a participant on the screen of LipiView. CFactor: reliability index, which needs to be above 0.7. Partial blinks: before slash is number of partial blinks, and after slash is number of all blinks during 19.1 s.

cylindrical refractive error, cylindrical axis, axial length, thinnest corneal thickness, and corneal curvature at the flat meridian (K1) and steep meridian (K2) was also analyzed.

Correlation analysis of lipid layer thickness and blinking pattern was conducted for data of 56 participants undergoing orthokeratology treatment at every follow-up. Single-factor repeated measure ANOVA was used to analyze the change in lipid layer thickness (average, minimum, and max) and blinking pattern (number of blinks, number of partial blinks, and rate of partial blinks) 1 week and 1 month after orthokeratology treatment. Repeated measure correlation (rmcorr) was used to analyze the correlation between change in lipid layer thickness and change in blinking pattern after orthokeratology treatment [18].

Statistical significance was defined as a p value < 0.05. SPSS software 22.0 (IBM Corp., Armonk, NY, USA) and *R* (4.0.2) were used.

3. Results

3.1. LLT of 163 Participants and the Correlation between LLT and Other Variables. At baseline (baseline data of participants are presented in Tables 1 and 2), the average tear LLT (average, max, and min) of 163 participants was 58.09 ± 21.66 nm ($n = 163$), 82.14 ± 20.12 nm ($n = 154$), and 46.37 ± 20.04 nm ($n = 154$), respectively.

Correlation analysis of LLT and blinking pattern is presented in Table 1. Number of partial blinks and rate of partial blinks were correlated with LLT (average, maximum, and minimum).

The results revealed that the tear LLT (average) was significantly correlated with age ($r = 0.17$, $p = 0.03$), axial length ($r = 0.18$, $p = 0.02$), thinnest corneal thickness ($r = -0.21$, $p = 0.01$), $K1$ ($r = -0.20$, $p = 0.01$), and $K2$ ($r = -0.19$, $p = 0.02$) (Table 2).

Table 1: LLT (average, minimal, and max) and blinking pattern of 163 eyes at baseline.

	LLT average (nm) 58.09 ± 21.66, $n = 163$	LLT max (nm) 82.14 ± 20.12, $n = 154$	LLT min (nm) 46.37 ± 20.04, $n = 154$
Blinks 10.13 ± 4.50, $n = 154$	$r = -0.05$, $p = 0.52$, $n = 154$	$r = -0.16$, $p = 0.84$, $n = 154$	$r = -0.15$, $p = 0.07$, $n = 154$
Partial blinks 5.55 ± 4.36, $n = 154$	$r = 0.18^*$, $p = 0.027$, $n = 154$	$r = 0.22^*$, $p = 0.006$, $n = 154$	$r = 0.19^*$, $p = 0.02$, $n = 154$
Rate of partial blinks 0.55 ± 0.33, $n = 154$	$r = 0.26^*$, $p = 0.001$, $n = 154$	$r = 0.29^*$, $p < 0.001$, $n = 154$	$r = 0.32^*$, $p < 0.001$, $n = 154$

LLT: lipid layer thickness. LLT average: average value of LLT during 19.1-second measurement. LLT max: maximum value of LLT during 19.1-second measurement. LLT min: minimum value of LLT during 19.1-second measurement. Blink: number of blinks during 19.1s. Partial blink: number of partial blinks during 19.1s. *r*: relative coefficient. P: significance. *n*: number.

Table 2: Correlation of LLT (average) and other clinical variables of 163 eyes at baseline.

		LLT average (nm)	Age (years)	Sex	Sph (D)	Cylin (D)	Axis	BCDVA (logMAR)	Axial length (mm)	*K*1 (D)	*K*2 (D)	TCT (um)
Number of cases (n)		163	163	163	155	155	106	116	157	153	154	149
Average		58.09	10.67	—	−2.86	−0.35	79.15	1.06	24.77	42.70	43.82	544.89
Standard deviation		21.66	1.89	—	1.18	0.47	83.89	0.10	0.83	1.27	1.41	28.07
Association with LLT average (nm)	*r*	—	0.17^*	−0.08	−0.00	−0.05	0.04	0.03	0.18^*	0.20^*	-0.19^*	-0.21^*
	P	—	0.03	0.33	0.97	0.53	0.66	0.76	0.02	0.02	0.02	0.01
	n	—	163	163	155	155	106	116	157	153	154	149

LLT average: average value of LLT during 19.1-second measurement. Sph: spherical power. Cylin: cylindrical power. BCDVA: best corrected distance visual acuity. *K*1: flat corneal curvature. *K*2: steep corneal curvature. TCT: thinnest corneal thickness. Blink: number of blinks during 19.1 s. Partial blink: number of partial blinks during 19.1 s. *r*: relative coefficient. *P*: significance. *n*: number.

3.2. Follow-Up of LLT and Blinking in 56 Participants after Orthokeratology Treatment. All 56 participants who underwent orthokeratology treatment showed an uneventful course, with daily uncorrected visual acuity higher than 0.8 on Snellen chart and SE being ±0.5D of plano. All 56 participants finished both the 1-week and 1-month follow-up visits. Grade one or less corneal staining was found at 1-week follow-up. No complications were observed during the 1-month follow-up.

3.2.1. Correlation between LLT and Blinking Pattern at Every Follow-Up. LLT and blinking pattern of 56 participants at every follow-up are presented in Table 3. Correlation between LLT and blinking pattern at baseline, 1 week, and 1 month was analyzed, respectively (Table 3). Correlation analysis of LLT and other clinical variables of 56 OK participants at baseline are presented in Table 4.

3.2.2. Change of LLT after Orthokeratology Treatment. ANOVA results of LLT (average, minimum, and maximum) at baseline, 1 week, and 1 month are presented in Table 5 and Figure 2.

LLT (average) significantly changed over time ($p = 0.028$), with pairwise comparison showing a significant difference between 1 week and baseline ($p = 0.017$) and between 1 month and baseline ($p = 0.025$). No statistical difference was detected between the 1-week and 1-month follow-up visits ($p = 0.699$) (Table 5, Figure 2).

LLT (minimum) also significantly changed over time ($p = 0.024$), with pairwise comparison showing a significant difference between 1 week and baseline ($p = 0.022$) and between 1 month and baseline ($p = 0.012$). No statistical difference was detected between the 1-week and 1-month follow-up visits ($p = 0.864$) (Table 5, Figure 2).

No significant change of LLT (maximum) at 1 week or 1 month was detected ($p = 0.447$) (Table 5, Figure 2).

LLT: lipid layer thickness. average: average value of LLT. min: minimum value of LLT. max: maximum value of LLT. ANOVA: single-factor repeated measure analysis of variance. LSD: LSD paired *t*-test. *n*: number. *P*: significance.

3.2.3. Change of Blinking Pattern after Orthokeratology Treatment. ANOVA results of blinking pattern (number of blinks, number of partial blinks, and rate of partial blinks) at baseline, 1 week, and 1 month are presented in Table 6 and Figure 3.

No significant change of number of blinks was detected over time ($p = 0.727$), with pairwise comparison showing no significant difference in any pair (Table 6, Figure 3).

Partial blinks significantly changed over time ($p = 0.037$), with pairwise comparison showing a significant difference between 1 week and baseline ($p = 0.012$). No statistical difference was detected between 1 month and baseline ($p = 0.417$) or between the 1-week and 1-month follow-up visits ($p = 0.094$) (Table 6, Figure 3).

Rate of partial blinks significantly changed over time ($p = 0.008$), with pairwise comparison showing a significant difference between 1 week and baseline ($p < 0.001$). No statistical difference was detected between 1 month and baseline ($p = 0.056$) or between the 1-week and 1-month follow-up visits ($p = 0.366$) (Table 6, Figure 3).

Table 3: LLT (average, minimal, and max) and blinking pattern of 56 OK eyes at baseline.

	Baseline		
	LLT average (nm) 54.29 ± 22.13, $n = 56$	LLT max (nm) 80.36 ± 20.47, $n = 56$	LLT min (nm) 42.30 ± 19.66, $n = 56$
Blinks 10.89 ± 4.79, $n = 56$	$r = -0.14$, $p = 0.45$, $n = 56$	$r = -0.10$, $p = 0.45$, $n = 56$	$r = -0.18$, $p = 0.19$, $n = 56$
Partial blinks 5.70 ± 5.06, $n = 56$	$r = 0.18$, $p = 0.19$, $n = 56$	$r = 0.13$, $p = 0.35$, $n = 56$	$r = 0.17$, $p = 0.20$, $n = 56$
Rate of partial blinks 0.51 ± 0.33, $n = 56$	$r = 0.28^*$, $p = 0.04$, $n = 56$	$r = 0.23$, $p = 0.09$, $n = 56$	$r = 0.30^*$, $p = 0.02$, $n = 56$
	1 week		
	LLT average (nm) 62.41 ± 23.08, $n = 56$	LLT max (nm) 83.86 ± 18.93, $n = 56$	LLT min (nm) 49.96 ± 22.94, $n = 56$
Blinks 11.23 ± 4.90, $n = 56$	$r = 0.25$, $p = 0.07$, $n = 56$	$r = 0.22$, $p = 0.11$, $n = 56$	$r = 0.18$, $p = 0.19$, $n = 56$
Partial blinks 7.59 ± 5.72, $n = 56$	$r = 0.45^*$, $p = 0.001$, $n = 56$	$r = 0.48^*$, $p < 0.001$, $n = 56$	$r = 0.45^*$, $p < 0.001$, $n = 56$
Rate of partial blinks 0.65 ± 0.34, $n = 56$	$r = 0.48^*$, $p < 0.001$, $n = 56$	$r = 0.54^*$, $p < 0.001$, $n = 56$	$r = 0.53^*$, $p < 0.001$, $n = 56$
	1 month		
	LLT average (nm) 61.39 ± 24.36, $n = 56$	LLT max (nm) 82.43 ± 18.98, $n = 56$	LLT min (nm) 50.57 ± 25.17, $n = 56$
Blinks 10.46 ± 4.49, $n = 54$	$r = -0.33$, $p = 0.81$, $n = 54$	$r = 0.08$, $p = 0.55$, $n = 54$	$r = -0.04$, $p = 0.77$, $n = 54$
Partial blinks 6.37 ± 4.71, $n = 54$	$r = 0.23$, $p = 0.10$, $n = 54$	$r = 0.36^*$, $p = 0.007$, $n = 54$	$r = 0.27$, $p = 0.05$, $n = 56$
Rate of partial blinks 0.60 ± 0.36, $n = 54$	$r = 0.37^*$, $p = 0.005$, $n = 54$	$r = 0.43^*$, $p = 0.001$, $n = 54$	$r = 0.44^*$, $p = 0.001$, $n = 56$

LLT: lipid layer thickness. LLT average: average value of LLT during 19.1-second measurement. LLT max: maximum value of LLT during 19.1-second measurement. LLT min: minimum value of LLT during 19.1-second measurement. Blink: number of blinks during 19.1s. Partial blink: number of partial blinks during 19.1s. *r*: relative coefficient. *P*: significance. *n*: number.

Table 4: Association of LLT average and other variables of 56 orthokeratology eyes at baseline.

		LLT average (nm)	Age (years)	Sex	Sph (D)	Cylin (D)	Axis	BCDVA logMAR	Axial length(mm)	*K*1 (D)	*K*2 (D)	TCT (um)
Number of cases (n)		56	56	56	56	56	56	56	56	56	56	56
Average		54.29	10.30	—	−2.90	−0.42	95.95	−0.02	24.82	42.77	43.91	550.79
Standard deviation		22.13	1.75	—	1.12	0.48	83.81	0.04	0.70	1.07	1.12	26.16
Association with LLT average	r	—	−0.03	−0.38*	0.07	0.06	0.34*	0.04	0.03	−0.74	−0.67	−0.21
	P	—	0.82	0.00	0.63	0.66	0.04	0.76	0.82	0.59	0.621	0.12
	n	—	56	56	56	56	37	56	56	56	56	56

LLT: lipid layer thickness. Sph: spherical power. Cylin: cylindrical power. BCDVA: best corrected distance visual acuity. *K*1: flat corneal curvature. *K*2: steep corneal curvature. TCT: thinnest corneal thickness. Blink: number of blinks during 19.5 s. Partial blink: number of partial blinks during 19.5 s.

Table 5: Short-term change of LLT (average, minimum, and max) after orthokeratology.

	n	LLT average	Standard deviation	ANOVA	Baseline (LSD)	1 week (LSD)	1 month (LSD)
LLT (average)							
Baseline	56	54.29	22.13	$p = 0.028^*$ $n = 56$	—	$P = 0.017^*$ $n = 56$	$p = 0.025^*$ $n = 56$
1 week	56	62.41	23.08		$p = 0.017^*$ $n = 56$	—	$p = 0.699$ $n = 56$
1 month	56	61.10	24.41		$p = 0.025^*$ $n = 56$	$p = 0.699$ $n = 56$	—
LLT (min)							
Baseline	56	42.30	19.66	$p = 0.024^*$ $n = 56$	—	$p = 0.022^*$ $n = 56$	$p = 0.012^*$ $n = 56$
1 week	56	49.96	22.74		$p = 0.022^*$ $n = 56$	—	$p = 0.864$ $n = 56$
1 month	56	50.57	24.94		$p = 0.012^*$ $n = 56$	$p = 0.864$ $n = 56$	—
LLT (max)							
Baseline	56	80.36	20.47	$p = 0.447$ $n = 56$	—	$p = 0.265$ $n = 56$	$p = 0.436$ $n = 56$
1 week	56	83.86	18.76		$p = 0.265$ $n = 56$	—	$p = 0.572$ $n = 56$
1 month	56	82.43	18.81		$p = 0.436$ $n = 56$	$p = 0.572$ $n = 56$	—

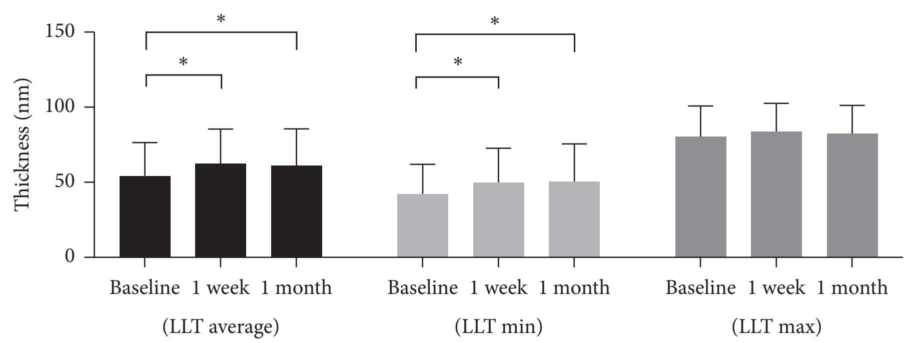

Figure 2: Lipid layer thickness (average, minimum and max) after orthokeratology lens wear. The average lipid layer thickness (average, minimum, and max) of the 56 patients at baseline, 1 week, and 1 month after orthokeratology treatment. ∗ denotes $p < 0.05$.

Table 6: Short-term change of blinking pattern after orthokeratology.

	n	Average	Standard deviation	ANOVA	Baseline(LSD)	1 week (LSD)	1 month (LSD)
Blinks							
Baseline	54	10.89	4.74	$p = 0.727$ $n = 54$	—	$p = 0.660$ $n = 54$	$p = 0.907$ $n = 54$
1 week	54	11.23	4.86		$p = 0.660$ $n = 54$	—	$p = 0.454$ $n = 54$
1 month	54	10.49	4.49		$p = 0.907$ $n = 54$	$p = 0.454$ $n = 54$	—
Partial blinks							
Baseline	54	5.70	5.01	$p = 0.037^*$ $n = 54$	—	$p = 0.012^*$ $n = 54$	$p = 0.417$ $n = 54$
1 week	54	7.59	5.67		$P = 0.012^*$ $n = 54$	—	$p = 0.094$ $n = 54$
1 month	54	6.37	4.66		$p = 0.417$ $n = 54$	$p = 0.094$ $n = 54$	—
Rate of partial blinks							
Baseline	54	0.51	0.33	$p = 0.008$ $n = 54$	—	$p < 0.001^*$ $n = 54$	$p = 0.056$ $n = 54$
1 week	54	0.65	0.33		$p < 0.001^*$ $n = 54$	—	$p = 0.366$ $n = 54$
1 month	54	0.61	0.35		$p = 0.056$ $n = 54$	$p = 0.366$ $n = 54$	—

ANOVA: single-factor repeated measure analysis of variance. LSD: LSD paired t-test. n: number. P: significance.

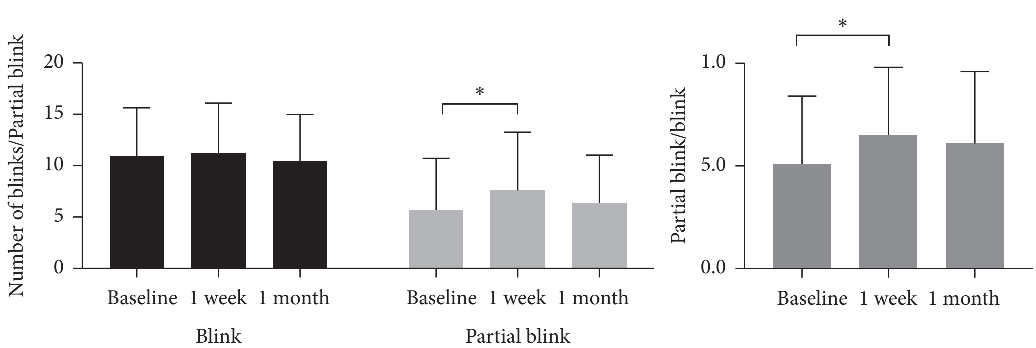

Figure 3: Blinks, partial blinks, and rate of partial blinks after orthokeratology lens wear. The number of blinks, the number of partial blinks, and rate of partial blinks of the 56 patients at baseline, 1 week, and 1 month after orthokeratology treatment. ∗ denotes $p < 0.05$.

3.2.4. Association between Change of LLT and Change of Blinking Pattern. Rmcorr analysis showed significant association between rate of partial blinks and LLT (average, minimum, and max) with $p = 0.003$, 0.001, and 0.014, respectively (Table 7).

4. Discussion

In this study, we used a noninvasive LipiView ® interferometer to observe features of the LLT in normal children and found that a number of ocular biometrics were associated with LLT. We also measured LLT in children undergoing orthokeratology treatment and found that even short-term lens wear had an impact on LLT.

LipiView has been used for dry eye evaluation in adults. However, LLT is complicated by the presence and category of dry eye, which is common among this population. A thicker LLT of 80 (20–100) nm could be found in group where 79% were diagnosed with meibomian gland dysfunction [14], while another study found that dry eye

Table 7: Correlation of change in LLT and blinking pattern after orthokeratology.

	LLT ave	LLT min	LLT max
Blink	$r = 0.04$, $p = 0.677$, $n = 56$	$r = -0.05$, $p = 0.612$, $n = 56$	$r = 0.04$, $p = 0.649$, $n = 56$
Partial blink	$r = 0.18$, $p = 0.055$, $n = 56$	$r = 0.12$, $p = 0.217$, $n = 56$	$r = 0.18$, $p = 0.055$, $n = 56$
Partial blink/blink	$r = 0.28$, $p = 0.003$, $n = 56$	$r = 0.31$, $p = 0.001$, $n = 56$	$r = 0.23$, $p = 0.014$, $n = 56$

LLT: lipid layer thickness. ave: average. min: minimum.

symptom scores were higher in participants with LLT lower than 60 nm [19]. These results were even higher than normal children in our study showing 58.09 ± 21.66 nm ($n = 163$, aged 10.7 ± 1.9 years), combining with previous study revealing different composition of lipid in meibum from varied populations [20], indicating that LLT in children needs to be evaluated with different standards.

When focusing on children and adolescents, we found that the average value of 58.09 ± 21.66 nm in our study was close to that in a previous study, being 58.1 ± 20.0 nm in asymptomatic children aged 10.8 ± 1.8 years [16]. Both studies together offered the normal range of LLT in children at age of myopia progression. Another study reported a higher average LLT of 68.7 ± 23.1 nm in elder children aged 15 years with a healthy ocular surface [17]. Combining previous studies and the current study, it is tentative to conclude that tear LLT varies in younger children, adolescents, and adults. The threshold value of LLT for the diagnosis of dry eye also needs to be differently defined at various ages.

Further analysis found that LLT was positively associated with age ($r = 0.193$, $p = 0.013$) in the present study. Although r value close to 0.2 revealed weak power of the test, when combined the facts mentioned above, it suggested age to be a factor of LLT. It is acknowledged that even 1-month-old infants already have morphologically complete meibomian glands which are distributed across the whole tarsal plates of both the upper and lower eyelids [21]. After infancy, meibomian gland loss begins, causing MG deficiency to become more prevalent into childhood and adolescence [16]. Meibomian glands decrease with age in normal subjects ranging from 4 to 98 years old [22]. However, LLT was observed to increase with age in normal children in our study. We speculate that the volume of lipid is dependent on the secretory function of every gland duct rather than the number of meibomian gland. During childhood and adolescents, potential increase in secretory function of meibomian glands might compensate for the decrease in gland tubes. The percent area of the meibomian gland acini in the eyelid was shown to be significantly higher in adolescents than in children [23]. Moreover, the composition of lipids has been shown to be related to age, suggesting another potential functional change of glands over time [20]. These above-mentioned facts helped explain the potential mechanism of positive association between LLT and age in normal children in the current study.

Our results indicated that LLT was positively correlated with axial length and negatively correlated with corneal curvatures and thinnest corneal thickness in 163 participants. However, these correlations were weak with r value near 0.2, and the correlation was no longer significant in analysis of 56 OK participants at baseline. Previous studies focusing on association of dry eye and axial length in populations with different degree of myopia also got different results [24, 25], indicating further studies are needed for clarification of correlation of LLT and other variables. It is well acknowledged that the axial length elongates and corneal flattens with age in childhood [26]; therefore, age-matched design will be necessary in studies.

Blinking helps to distribute lipid over ocular surface, being beneficial to stabilize tear film and improve dry eye disease [27], and therefore, a concerned factor in ocular surface health. Especially, in Asian population, incomplete blinks are more observed due to anatomic features of eye lids [28], which were reported to be correlated with dry eye disease [29], although the causality has not been clearly clarified. These suggested us that blinking pattern in Chinese children was an important factor of LLT. In our study, number of blinks had no significant change at 1-week or 1-month follow-up, while number of partial blinks and rate of partial blinks increased significantly after orthokeratology treatment. Ocular surface disease index and corneal sensitivity showed changes after orthokeratology in previous studies [7]. Lum et al. found a decrease in corneal sensitivity and nerve fiber density after orthokeratology lens wear [13], and these changes had already occurred after one month of orthokeratology wear [30], which could potentially change blinking pattern.

In this study, children who have undergone orthokeratology treatment showed an increase in LLT even in the short term of one week and lasted till one month. We speculated that the interaction of the orthokeratology contact lens and the ocular surface, especially between the lens edge and the tarsal plate, could have yielded an elevation in lipid secretion during blinking. In our study, rate of partial blinks was significantly correlated with LLT at every follow-up. Notably, rmcorr analysis confirmed that increase in rate of partial blinks was associated with increase of LLT (average, max, and minimum) after orthokeratology lens wear. However, being different with other studies indicating that partial blinks were associated with dry eye disease and poorer lipid layer quality [29, 31, 32], increase of rate of partial blinks in our study was companied with elevation in LLT value. Since this is a short-term observation study and advent of dry eye is a chronic process, we could not conclude that the increase in LLT was "good" sign for ocular surface health. It might be temporary, or a kind of stimulus response. Interestingly, similar 1-month change of incomplete blinking was observed after corneal refractive surgeries; however, it was accompanied with decreased LLT [33]. The mechanism under the difference change of LLT needs further study.

Considering other factors of LLT change, studies have shown that tear composition including ascorbate, sIgA, albumin, and lactate dehydrogenase changed dramatically after one night of orthokeratology lens wear, which could be an "irritation" caused by short-term orthokeratology treatment [11]. Also, composition change of tear might have influence on detection of thickness of the lipid layer. Moreover, changed corneal curvature of reshaped cornea could influence the dynamics of tear. In terms of long-term effects of orthokeratology lens wear on ocular surface, a previous study showed an insignificant decrease in tear breakup time and no change in meibomian glands after three years of overnight orthokeratology treatment [7]. These studies combined suggested that despite a short-term interruption, orthokeratology is generally safe in the long run with minimal influence on ocular surface.

There are limitations of this study. Morphology of meibomian glands was not quantitatively analyzed. Data such as refraction and corneal curvature after orthokeratology were missing. Further studies in the future will help better understand the lipid layer quality, in addition to quantity, after orthokeratology.

5. Conclusion

LLT in Chinese normal children was different with LLT in adults reported previously. Significant correlation between LLT and rate of partial blinks was found. LLT increased in children undergoing orthokeratology in the short term and the change was associated with increase in rate of partial blinks. A long-term study incorporating LLT and other tear composition parameters is needed to elucidate the long-term impact of orthokeratology on ocular surface and the underlying mechanism.

Data Availability

The datasets of the current study are available upon request from the co-first authors Li Zeng and Zhi Chen.

Ethical Approval

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Eye and ENT Hospital, Shanghai, China.

Consent

Written informed consent, after the aims and nature of the study were explained, was obtained from the participants for publication of this article and any accompanying images and data.

Disclosure

Li Zeng and Zhi Chen should be considered as equal first authors.

Conflicts of Interest

The authors declare that they have no conflicts interest.

Authors' Contributions

Li Zeng, Zhi Chen, and Xingtao Zhou were responsible for study concept and design. Li Zeng, Zhi Chen, Dan Fu, and Jiaqi Zhou carried out data collection. Li Zeng conducted analysis and interpretation of data. Li Zeng and Zhi Chen were involved in drafting and critical revision of the manuscript. Xingtao Zhou was responsible for supervision. All authors have read and approved the whole manuscript and the publication. Li Zeng and Zhi Chen contributed equally to this work.

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