Myopia, Axial Length and Lens Thickness: A Corneal Biomechanical Analysis of Older Children and Adolescents

Miopia, Comprimento Axial e Espessura do Cristalino: Uma Análise da Biomecânica da Córnea de Crianças mais Velhas e Adolescentes

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ABSTRACT

INTRODUCTION: Our objective was to compare the corneal biomechanics of myopes with non-myopes in a sample of Portuguese children. In addition, we sought to evaluate their habits and background as well as to assess the potential relationship of axial length and lens thickness with their corneal biomechanical properties.

METHODS: Observational cross-sectional study assessing healthy children (8 to 18 years old) conducted at a tertiary university hospital center (Centro Hospitalar Universitário do Porto, Porto, Portugal). Demographic and clinical data were retrieved from medical records and participants' and parents' interview. After this interview, ocular biometry and corneal biomechanics were assessed using ZEISS IOL Master 700 (Carl Zeiss Meditec, Jena, Germany) and Corvis ST (Oculus, Wetzlar, Germany), respectively. Linear mixed-effects models adjusting for age and gender were built to assess the relationship between corneal biomechanical properties and myopia, axial length (AL) and lens thickness (LT).

RESULTS: One hundred and fifty-six eyes (out of 78 children) were enrolled of which 100 had a spherical equivalent ≤ -0.50 and were classified as myopes. The mean±standard deviation age was 14.18±2.60 years, being significantly higher in the myopes (p=0.004). The proportion of myopes increased with age (p=0.019). LT presented a significant but weak negative correlation with intraocular pressure (r=-0.227, p=0.005). Almost half of myopes had a positive family history of myopia. Non-myopes presented a trend for a higher proportion of atopy (p=0.059) and a significantly higher proportion of dermatitis history (p=0.030). Myopia was associated with higher amplitude of whole eye movement (p<0.001). Longer AL and thinner lenses were associated with a more deformable corneal behavior.

CONCLUSION: In this sample of Portuguese children, AL and LT, but not myopic status, were related with corneal biomechanical behavior. Longitudinal studies are warranted to elucidate the role of corneal biomechanics in the screening and follow-up of ocular diseases in children.

KEYWORDS: Adolescent; Axial Length, Eye; Child; Cornea; Eye/growth & development; Lens, Crystalline; Myopia.

RESUMO

INTRODUÇÃO: O objectivo foi comparar a biomecânica corneana de míopes com não-míopes numa amostra de crianças portuguesas. Além disso, procuramos avaliar os seus hábitos e antecedentes, bem como avaliar a relação potencial do comprimento axial e da espessura do cristalino com as propriedades biomecânicas da córnea.

MÉTODOS: Estudo observacional transversal que avaliou crianças saudáveis (8 a 18 anos) realizado num centro hospitalar universitário terciário (Centro Hospitalar Universitário de Santo António, Porto, Portugal). Os dados demográficos e clínicos foram recolhidos do processo clínico e da entrevista dos participantes e dos pais. Após esta entrevista, a biometria ocular e a biomecânica da córnea foram avaliadas usando os aparelhos ZEISS IOL Master 700 (Carl Zeiss Meditec, Jena, Alemanha) e Corvis ST (Oculus, Wetzlar, Alemanha), respetivamente. Modelos lineares de efeitos mistos ajustados para idade e sexo foram construídos para avaliar a relação entre as propriedades biomecânicas da córnea e miopia, comprimento axial (CA) e espessura do cristalino (EC).

RESULTADOS: Cento e cinquenta e seis olhos (de 78 crianças) foram incluídos, dos quais 100 tinham SE ≤ -0,50 e foram classificados como míopes. A média±desvio padrão da idade foi de 14,18±2,60 anos, sendo significativamente maior nos míopes (p=0,004). A proporção de míopes aumentou com a idade (p=0,019). A EC apresentou correlação negativa significativa, porém fraca, com a pressão intraocular (r=-0,227, p=0,005). Quase metade dos míopes tinha história familiar positiva de miopia. Os não-míopes apresentaram uma tendência para uma maior proporção de atopia (p=0,059) e uma proporção significativamente maior de história de dermatite (p=0,030). A miopia associou-se a uma maior amplitude do movimento do olho (p<0,001). Comprimentos axiais mais longos e cristalinos mais finos foram associados a um comportamento corneano mais deformável.

CONCLUSÃO: Nesta amostra de crianças europeias, o CA e a EC, mas não a miopia, relacionaram-se com o comportamento biomecânico da córnea. Estudos longitudinais são necessários para elucidar o papel da biomecânica da córnea no rastreio e seguimento de doenças oculares em crianças.

PALAVRAS-CHAVE: Adolescente; Comprimento Axial do Olho; Córnea; Criança; Cristalino; Miopia; Olho/crescimento & desenvolvimento.

INTRODUCTION

Myopia is one of the most common eye disorders. It is estimated that myopia and high myopia will affect nearly 5 billion and 1 billion people, respectively, by 2050.[1] The most relevant risk factors for myopia progression are Asian ethnicity, younger age at diagnosis, parental myopia and environmental factors, mostly increased time of near work and reduced outdoor activities.[2] There are two major types of myopia, refractive and axial, with the latter being the more common in children.[2] In fact, it has been shown that axial length (AL) growth follows physical development until the age of 10 to 12 years old, being increased by myopia development at any age during that phase.3 Concurrently with AL growth, other changes in ocular metrics have been reported, including anterior chamber depth (ACD)[4] and lens thickness (LT).[4,5]

The advent of corneal visualization with Scheimpflug technology, Corvis ST, allows direct real-time visualization of corneal deformation response to an air pulse.[6] Corvis ST performs a comprehensive assessment of the cornea through cross-sectional images captured by a high-speed Scheimpflug camera. Studies enrolling adult patients have demonstrated a more deformable corneal behavior in patients with myopia.[7,8] Although, it is still not clear if the behavior contributes to myopia development or is a consequence of this condition. Some authors have already assessed the corneal biomechanical properties in children[9-12] but all those studies enrolled only Asian children. To our best knowledge, no study so far addressed the corneal biomechanics in European children. In addition, the evidence produced so far did not include some of the most recent parameters including whole eye movement (WEM), stress strain index (SSI) and stiffness parameter at first applanation (SP-A1). As aforementioned, ocular growth and myopia development produce changes in different structures of the eye. Thus, it is paramount to study other ocular biometrics and assess their relationship with biomechanics. Clinically, the potential results from these assessments can help to provide a more comprehensive study of children at risk of developing myopia.

In the present study, we aim to compare the corneal biomechanics of myopes with non-myopes in a sample of Portuguese children. In addition, we sought to evaluate their habits and background as well as to assess the potential relationship of axial length and lens thickness with their corneal biomechanical properties.

METHODS

This is an observational cross-sectional study assessing healthy children conducted at a tertiary university hospital center (Centro Hospitalar Universitário do Porto, Porto, Portugal).

STUDY PARTICIPANTS:

Consecutive subjects aged 8 to 18 years were invited to participate in the study during regular appointments at the ophthalmological outpatient clinic in 2021. Exclusion criteria were systemic autoimmune disorders known to affect the eye; systemic treatment with isotretinoin, antihistamines, antidepressants, or steroids; previous diagnosis of any ocular or palpebral disease (such as diagnosed dry eye disease, active conjunctivitis or Meibomian gland disease, but not refractive error); previous ocular surgery or trauma; use of contact lenses or any kind of eye drops. If exclusion criteria applied unilaterally, the fellow eye could be included in the study. The research adhered to the principles of the Declaration of Helsinki and its latest amendment (2013), and complied with the requirements of the institute's committee on human research.

Eligible participants were enrolled after obtaining their acceptance and written informed consent for the study and for publication from a parent or legal guardian. All data was saved and shared anonymously.

STUDY PROTOCOL:

All included subjects underwent the study evaluation between 2 and 6 pm. Demographic and clinical data were retrieved from medical records and patients' and parents' interview including subjective refraction, family history of myopia or keratoconus, personal history of atopy or neuropsychological disorders, personal habits including use of eye drop, dietary supplements, sunglasses and eye rubbing, and hours per day of reading, screen exposure and outdoor activities. To access symptomatology, we used the validated questionnaire Ocular Surface Disease Index-6 (OSDI-6).[13] We replaced question 3 "Driving or being driven at night?" with "Walking or being driven at night?". After the questionnaire, subjects were asked about feeling daily one or more of the following symptoms: eye itching, tearing, discomfort and/or dryness. Subjects were further inquired about the use of screen-equipped devices, and eye rubbing and sleeping habits. After this interview, ocular biometry and corneal biomechanics were assessed using ZEISS IOL Master 700 (Carl Zeiss Meditec, Jena, Germany) and Corvis ST (Oculus, Wetzlar, Germany), respectively.

Corvis ST (software version 1.6r2015) is a noncontact tonometer coupled with a high-speed Scheimpflug-camera (4330 frames/sec) that records the movements of the cornea in response to an air puff. The air puff forces the cornea through three main phases: an ingoing applanation phase (A1), the middle phase, the highest concavity (HC), during which cornea assumes its maximum deformation and an outgoing applanation phase (A2), after which returns to its resting state. The following parameters[14-18] will be assessed in this work:

1. For the applanation phases (A1 and A2):
   a. time (A1T/A2T, ms): time from start to A1/A2,
   b. velocity (A1V/A2V, m/s): velocity of corneal apex at A1/A2
   c. deformation amplitude (A1DA/A2DA, mm): moving distance of the corneal apex from the initial position to that at the A1T/A2T
   d. deflection length (A1DL/A2DL, mm): length of the flattened cornea at A1/A2
   e. deflection amplitude (A1DeflA/A2DeflA, mm): similar to A1DA/A2DA but without whole eye movement
   f. deflection area (A1DeflArea/A2DeflArea, mm^2): "displaced" area of the cornea in the analyzed horizontal sectional plane
   g. delta Arc length (A1dArcL/A2dArcL, mm): change in arc length from initial state to A1/A2, in a defined 7-mm zone

2. For the HC phase:
   a. time (HCT, ms)
   b. deformation amplitude (HCDA, mm)
   c. deflection length (HCDL, mm)
   d. deflection amplitude (HCDeflA)
   e. deflection area (HCDeflArea, mm^2)
   f. delta Arc length (HCdArcL)
   g. radius (Rad): Central curvature radius at the highest concavity
   h. peak distance (PD): distance between the two surrounding peaks of the cornea at the highest concavity

3. Other parameters
   a. deformation amplitude max (DAmpMax, mm)
   b. deflection amplitude max
      i. amplitude (DeflAmpMax, mm): the maximum amount of the corneal movement compensating for WEM.
      ii. time (DeflAmpMaxTime, ms): the duration of the corneal movement compensating for whole eye movement
   c. deformation amplitude ratio max (DARatioMax 1/2 mm): the ratio between the deformation amplitude at the apex and the average deformation amplitude measured at 1 or 2 mm from the center
   d. Whole Eye Movement Max
      i. Amplitude (WEMA, mm): maximum amplitude of the whole eye movement
      ii. Time (WEMT, ms): maximum time of the whole eye movement
   e. integrated inverse radius (IIR): the area under the inverse concave radius versus time curve

f. stiffness parameter at A1 (SP-A1): corneal stiffness as defined by resultant pressure divided by deflection amplitude at A1
g. stress-strain index (SSI): estimates the overall stress–strain behavior of corneal tissue

A more deformable cornea is characterized by lower time (A1T), smaller deflection length (A1DeflL) and higher velocity (A1V), at A1; higher deformation (HCDA) and deflection amplitudes (HCDeflA), and smaller PD and Rad, at HC; smaller deflection length (A2DL) and lower velocity (A2V), at A2; higher DA ratio and 1IR; lower SPA1 and SSI.[19-21] The opposite is found in stiffer and less deformable corneas.

STUDY OBJECTIVES

The primary objective of this study is to compare the corneal biomechanical parameters between myopes and non-myopes children, as defined below. As secondary objectives, we sought to compare the personal history and habits as well as the family background between the aforementioned groups and to assess the possible association between corneal biomechanical parameters and two biometric parameters, namely AL and LT.

DATA ANALYSIS

Patients were classified into two groups according to the spherical equivalent of subjective refraction: myopes if SE ≤ -0.5 diopters (D) and non-myopes otherwise. Given this was an eye-centered classification, some patients had one eye in each group; thus, the eye was considered the statistical unit for all analysis.

Categorical variables were described through absolute and relative frequencies and continuous variables through means and standard deviations (SD), or medians and interquartile range (IQR) for variables with a skewed distribution. The Kolmogorov–Smirnov test and normal probability plots were used to confirm the normal distribution of the data. A linear mixed-effects model, using patient identification number as a random effect to correct for the inclusion of both eyes of all participants, was used to test the differences among continuous variables between groups. A p for trend test was used to assess the distribution of myopia according to age class. A correlation analysis between age and spherical equivalent, axial length and lens thickness was performed using Pearson correlation coefficient. A subanalysis of LT correlation with pachymetry and intraocular pressure was also made. For interpretation, a correlation coefficient will be considered "very weak" if between 0 and ± 0.19, "weak" if between ± 0.20 and ± 0.39, "moderate" if between ± 0.40 and ± 0.59, "strong" if between ± 0.60 and ± 0.79 and "very strong" if between ± 0.80 and ± 1.0.

The potential association between myopia, axial length and lens thickness with corneal biomechanical parameters was assessed with linear mixed-effects models as aforementioned, adjusting for age and gender. A final model including the three parameters and adjusting for the same variables was also built. Statistical significance was defined as p <0.05. Analyses were performed with Stata (version 14.2).

RESULTS

For this study, 79 children were enrolled and assessed. Due to lack of collaboration to perform Corvis ST, one child was excluded from the analysis, resulting in a total sample of 156 eyes (out of 78 children), of which 100 had an SE ≤ -0.50 and were classified as myopes.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The characteristics of the sample are described in Table 1. The mean±SD age was 14.18±2.60 years, being significantly higher in the myopes (p=0.004). The proportion of myopes increased with age (p=0.019). There was no difference in gender distribution across groups, with 32 children (41.3%) being male. The myopes had a significantly higher absolute SE (p<0.001) and longer axial length (p<0.001). A significant weak negative correlation was found between SE and age (r=-0.202, p=0.017; Fig.1). No significant correlation was found between age and AL (p=0.172) or LT (p=0.634). LT presented a significant but weak negative correlation with IOP (r=-0.227, p=0.005) and very weak with AL (r=-0.173, p=0.033) and no significant correlation with pachymetry (p=0.690). Considering the intra-ocular pressure, corneal tomography and pachymetry, no differences were found between groups and all values were within the normal range.

Regarding the family and personal history, almost half of myopes had a positive family history of myopia while its proportion among non-myopes was 34% (p=0.130). The overall proportion of atopy was 30.8%, with non-myopes presenting a trend for higher proportion of atopy (p=0.059) and a significantly higher proportion of dermatitis history (p=0.030).

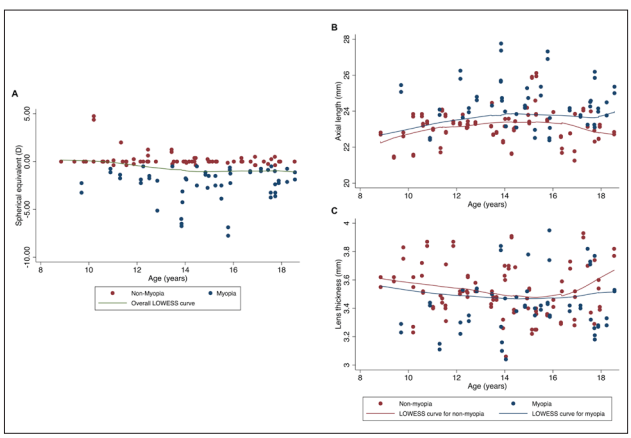

Figure 1. Locally weighted scatterplot smoothing (LOWESS) curves showing the relationship between age and spherical equivalent (A), axial length (B) and lens thickness (C). On graph A, the LOWESS curve shows represents the whole sample; on graphs B and C, the LOWESS curves for myopes and non-myopes are presented separately.

Table 1. Population characteristics.

	Myopia 56 eyes	Non-Myopia 100 eyes	*P*-value
Age (years), mean±SD	14.98±2.39	13.73±2.60	**0.004**
Age (years), n (%)			
[8, 10[	2 (3.6%)	8 (8.0%)	**0.019**
[10, 12[	4 (7.1%)	22 (22.0%)	
[12, 14[	14 (25.0%)	22 (22.0%)	
[14,16]	18 (32.1%)	24 (24.0%)	
[16,18]	18 (32.1%)	24 (24.0%)	
Male, n (%)	20 (35.7%)	44 (44%)	0.310
Spherical equivalent (D), mean±SD	-2.40±1.81	0.17±0.74	**<0.001**
Biometry			
Axial length (mm), mean±SD	24.43±1.27	23.33±1.65	**0.001**
Lens thickness (mm), mean±SD	3.42±0.20	3.52±0.18	0.988
bIOP (mmHg), mean±SD	14.35±1.84	14.0±2.03	0.226
Corneal parameters			
Kf	42.35±1.64	42.79±1.43	0.672
Ks	43.77±1.61	44.00±1.53	0.615
Km	43.04±1.58	43.38±1.44	0.810
Pachymetry	556.00±32.86	555.37±38.08	0.142
Family history			
Myopia, n (%)	26 (46.4%)	34 (34.0%)	0.130
Keratoconus, n (%)	2 (3.6%)	2 (2.0%)	0.580
Personal history of atopy, n (%)	12 (21.4%)	36 (36.0%)	0.059
Asthma, n (%)	3 (5.4%)	12 (12.0%)	0.130
Conjunctivitis, n (%)	6 (10.7%)	4 (4.0%)	0.100
Rhinitis, n (%)	7 (12.5%)	21 (21.0%)	0.180
Dermatitis, n (%)	0 (0.0%)	8 (8.0%)	**0.030**
Personal habits			
Dietary supplements, n (%)	4 (7.1%)	4 (4.0%)	0.390
Sunglasses, n (%)	8 (14.3%)	18 (18.0%)	0.550
Eye rubbing, n (%)	37 (66.1%)	69 (69%)	0.710
On-screen time (h/day), median (IQR)	6 (4.5-8)	6 (3.5-8)	0.460
Outdoor time (h/day), median (IQR)	3 (2-5.5)	3 (1-4)	0.080
Reading time (h/day), median (IQR)	2 (0-4)	1 (0-3)	0.092
Ocular surface symptoms			
OSDI score, mean±SD	4.59±4.09	5.06±3.74	0.480
Itching, n (%)	14 (25.0%)	34 (34.0%)	0.240
Tearing, n (%)	5 (8.9%)	11 (11.0%)	0.680
Discomfort/Foreign body, n (%)	3 (5.4%)	7 (7.0%)	0.690

bIOP, biomechanically-correct intraocular pressure; D, diopters; IQR, interquartile range; OSDI, Ocular Surface Disease Index; SD, standard deviation

No significant differences were found among the personal habits. Although, children with myopia presented a trend for higher values of outdoor and reading time. Fifty-three children (67.9%) reported eye rubbing as a habit.

The most prevalent eye symptom was itching, being reported by 24 (30.8%) of children. The mean±SD OSDI score was 4.90±3.86, which is considered low. No significant differences were found between groups concerning the ocular surface symptoms.

CORNEAL BIOMECHANICAL PROPERTIES

Tables 2 and 3 present three linear mixed-effects models for assessment of the effect of myopia (model 1), axial length (model 2) and lens thickness (model 3) on cornea biomechanics, when adjusted for age and gender.

Considering the myopic status, a trend for lower values of HC (ß=-0.156, *p*=0.051) and A2 (ß=-0.129, *p*=0.051) times and WEM parameters (ß=-0.023, *p*=0.068 for WEMA; ß=-0.269, *p*=0.050 for WEMT).

Positive associations were found between AL and two biomechanical parameters, namely peak distance (ß=0.025; *p*=0.041) and WEMA (ß=0.023, *p*<0.001). Other biomechanical parameters presented a negative association with AL, including A2T (ß=-0.044, *p*=0.018), A2DA (ß=-0.008, *p*=0.004), DeflAmpMaxTime (ß=-0.081, p=0.039) and WEMT (ß-0.090, *p*=0.026).

Regarding the lens, higher values of thickness were found to be associated with lower values at A1, namely time (ß-0.325, *p*=0.017), deformation (ß=-0.013, *p*=0.009) and deflection (ß=-0.016, *p*=0.001) amplitudes and deflection area (ß=-0.027, *p*=0.011). No associations were found at HC phase. Thicker lenses were associated with higher time (ß=0.511, *p*=0.004) and deflection area (ß=0.075, *p*=0.016) at A2 and higher WEMT (ß=0.861, *p*=0.010) and IIR (ß=1.046, *p*=0.047).

In the final model (Table 4) that included the three factors (myopic status, AL and LT) and that was adjusted for age and gender, thicker lenses had the same associations for A1 and A2 and longer AL had a negative association with A2DA (ß=-0.008, *p*=0.006). For the HC phase, longer AL were positively associated with PD (ß=0.025; *p*=0.041) and there was a trend for lower A2T with increasing AL (ß=-0.035, *p*=0.059). Myopic status had no significant associations at any of the three phases. Concerning the other parameters, WEMA had opposite associations with myopic status (ß=-0.034, *p*=0.009) and AL (ß=0.024, *p*<0.001); the DeflAmpMax was negatively associated with AL and thicker lenses were associated with higher time of WEM (ß=0.712, *p*=0.035).

DISCUSSION

Myopia is the most common ocular disorder globally, affecting almost one-third of the European population.[22] In the 25-29 age group, this number almost reaches 50%,[22] with a clear rising trend in recent years in this age groups and late teens. Therefore, it is paramount to assess the habits, history and ocular characteristics of children and adolescents, aiming to understand potential associations with this refractive error. Some authors[9-12] have studied the corneal biomechanics of a pediatric group before but, to our best knowledge, this is the first European study on this subject. We enrolled a representative number of healthy children and performed a comprehensive assessment of

Table 2. Linear mixed-effects models for assessment of the effect of myopia.

	Myopia 56 eyes	Non-Myopia 100 eyes	MODEL 1 Myopia ß (95% CI)	*P*-value
1st Applanation (A1)				
Time (A1T, ms)	7.687±0.286	7.649±0.301	0.059 (-0.033-0.152)	0.208
Velocity (A1V, m/s)	0.143±0.018	0.142±0.015	-0.001 (-0.006-0.004)	0.680
Deformation Amplitude (A1DA, mm)	0.134±0.010	0.134±0.010	0.001 (-0.003-0.004)	0.370
Deflection Length (A1DL, mm)	2.184±0.307	2.206±0.320	0.015 (-0.124-0.094)	0.788
Deflection Amplitude (A1DeflA, mm)	0.092±0.009	0.090±0.013	0.002 (-0.002-0.006)	0.360
Deflection Area (A1DeflArea, mm^2)	0.164±0.023	0.163±0.024	-0.001 (-0.009-0.008)	0.832
dArc Length (A1dArcL, mm)	-0.0157±0.003	-0.016±0.003	0.001 (-0.0002-0.002)	0.133
Highest concavity (HC)				
Time (HCT, ms)	17.238±0.446	17.380±0.472	-0.156 (-0.312-0.001)	0.051
Deformation Amplitude (HCDA, mm)	1.048±0.099	1.040±0.088	-0.003 (-0.033-0.026)	0.818
Deflection Length (HCDL, mm)	6.307±0.916	6.176±1.171	0.001 (-0.385-0.384)	0.997
Deflection Amplitude (HCDeflA, mm)	0.895±0.099	1.038±1.718	-0.119 (-0.585-0.347)	0.617
Deflection Area (A1DeflArea, mm^2)	3.169±0.411	3.023±0.483	0.069 (-0.082-0.220)	0.372
dArc Length (HCArcL, mm)	-0.120±.0194	-0.118±0.020	-0.002 (-0.010-0.005)	0.491
Radius (Rad, mm)	6.498±0.572	6.516±0.662	-0.016 (-0.244-0.211)	0.889
Peak Distance (PD, mm)	4.980±0.252	4.892±0.283	0.024 (-0.065-0.113)	0.596
2nd Applanation (A2)				
Time (A2T, ms)	22.252±0.416	22.380±0.350	-0.129 (-0.259-0.001)	0.051
Velocity (A2V, m/s)	-0.270±0.028	-0.252±0.110	-0.015 (-0.046-0.016)	0.344
Deformation Amplitude (A2DA, mm)	0.337±0.065	0.359±0.058	-0.011 (-0.033-0.009)	0.278
Deflection Length (A2DL, mm)	2.971±0.760	3.153±0.866	-0.193 (-0.474-0.087)	0.177
Deflection Amplitude (A2DeflL, mm)	0.111±0.022	0.111±0.020	0.001 (-0.006-0.008)	0.780
Deflection Area (A2DeflArea, mm2)	0.237±0.046	0.255±0.086	-0.016 (-0.041-0.010)	0.231
dArc Length (A2dArcL, mm)	-0.021±0.007	-0.010±0.116	-0.009 (-0.040-0.022)	0.580
Other parameters				
Deformation Amplitude Max (DAmpMax, mm)	1.048±0.099	1.040±0.088	-0.003 (-0.033-0.026)	0.818
Deflection Amplitude Max				
Amplitude (DeflAmpMax, mm)	0.914±0.123	1.314±4.311	-0.328 (-1.495-0.838)	0.581
Time (DeflAmpMaxTime, ms)	16.917±0.595	16.853±0.798	0.029 (-0.232-0.290)	0.828
Deformation Amplitude Ratio Max				
DARatioMax 1 mm	1.546±0.086	1.537±0.051	0.014 (-0.010-0.038)	0.258
DARatioMax 2 mm	4.101±0.405	4.106±0.437	-0.023 (-0.162-0.116)	0.742
Whole Eye Movement Max				
Amplitude (WEMA, mm)	0.236±0.060	0.267±0.074	-0.023 (-0.048-0.002)	0.068
Time (WEMT, ms)	21.743±0.931	22.110±0.640	-0.269 (-0.538-0.00004)	0.050
IIR	8.995±1.030	9.081±1.143	-0.022 (-0.408-0.364)	0.911
SP-A1	102.290±18.393	99.982±22.503	2.540 (-5.081-10.161)	0.514
SSI	0.909±0.124	0.949±0.170	-0.035 (-0.090-0.020)	0.213

CI, confidence interval; IIR, integrated inverse radius; SP-A1, stiffness parameter at A1; SSI, stress-strain index

their background and ocular status. We found that myopia proportion increased with age and that almost half of this group had a positive family history of myopia while non-myopes presented a higher proportion of atopy, mostly atopic dermatitis. More than two-thirds (67.9%) of children reported to eye rub and almost a third complained of eye itching. Myopes were older and had longer axial lengths. Considering the corneal biomechanics, longer axial lengths and thinner lenses were associated with a more deformable corneal behavior.

Environmental factors, such as near work, have been associated with myopia. As focused near tasks lead to blinking reduction increasing the exposition of ocular surface, we hypothesized that myopic children might have more signs and complains of dry eye disease. In this study, the OSDI score was low for both groups and no significant difference was found.

Age and parental history of myopia are known risk factors for myopia among children.[23,24] A population-based study carried out in Korea and using the Korea National Health And Nutrition Examination Survey 2016–2017 (KNHANES VII) reported a sharp increase in myopia preva-

Table 3. Linear mixed-effects models for assessment of the effect of axial length and lens thickness on corneal biomechanics.

	MODEL 2 Axial Length ß (95% CI)	*P*-value	MODEL 3 Lens Thickness ß (95% CI)	*P*-value
1st Applanation (A1)				
Time (A1T, ms)	0.006 (-0.019-0.031)	0.630	-0.325 (-0.592- -0.057)	**0.017**
Velocity (A1V, m/s)	-0.001 (-0.003-0.0002)	0.099	0.006 (-0.009-0.021)	0.443
Deformation Amplitude (A1DA, mm)	-0.0003 (-0.001-0.001)	0.533	-0.013 (-0.023- -0.003)	**0.009**
Deflection Length (A1DL, mm)	-0.017 (-0.051-0.016)	0.313	-0.147 (-0.413-0.118)	0.278
Deflection Amplitude (A1DeflA, mm)	-0.0004 (-0.002-0.001)	0.481	-0.016 (-0.025- -0.006)	**0.001**
Deflection Area (A1DeflArea, mm^2)	-0.002 (-0.005-0.0006)	0.125	-0.027 (-0.048- -0.006)	**0.011**
dArc Length (A1dArcL, mm)	0.0002 (-0.0001-0.001)	0.191	0.002 (-0.001-0.005)	0.188
Highest concavity (HD)				
Time (HCT, ms)	-0.013 (-0.062-0.037)	0.615	0.073 (-0.309-0.454)	0.709
Deformation Amplitude (HCDA, mm)	-0.002 (-0.010-0.006)	0.666	0.049 (-0.035-0.133)	0.258
Deflection Length (HCDL, mm)	-0.006 (-0.119-0.107)	0.916	-0.714 (-1.710-0.281)	0.160
Deflection Amplitude (HCDeflA, mm)	0.024 (-0.122-0.170)	0.746	1.089 (-0.033-2.212)	0.057
Deflection Area (A1DeflArea, mm^2)	0.019 (-0.023-0.060)	0.377	0.117 (-0.305-0.540)	0.586
dArc Length (HCArcL, mm)	0.001 (-0.001-0.003)	0.487	0.008 (-0.012-0.027)	0.433
Radius (Rad, mm)	0.018 (-0.048-0.084)	0.597	0.168 (-0.413-0.750)	0.570
Peak Distance (PD, mm)	0.025 (0.001-0.049)	**0.041**	0.213 (-0.036-0.462)	0.093
2nd Applanation (A2)				
Time (A2T, ms)	-0.044 (-0.080- -0.007)	**0.018**	0.511 (0.166-0.857)	**0.004**
Velocity (A2V, m/s)	0.0002 (-0.009-0.010)	0.971	0.053 (-0.022-0.129)	0.169
Deformation Amplitude (A2DA, mm)	-0.008 (-0.014- -0.003)	**0.004**	-0.027 (-0.084-0.030)	0.354
Deflection Length (A2DL, mm)	-0.073 (-0.160-0.014)	0.100	0.057 (-0.628-0.742)	0.871
Deflection Amplitude (A2DeflL, mm)	0.0001 (-0.002-0.002)	0.907	-0.002 (-0.019- -0.015)	0.802
Deflection Area (A2DeflArea, mm^2)	-0.0003 (-0.008-0.008)	0.936	0.075 (0.014-0.135)	**0.016**
dArc Length (A2dArcL, mm)	0.001 (-0.009-0.010)	0.906	0.055 (-0.022-0.131)	0.161
Other parameters				
Deformation Amplitude Max (DAmpMax, mm)	-0.002 (-0.010-0.006)	0.666	0.049 (-0.036-0.133)	0.258
Deflection Amplitude Max				
Amplitude (DeflAmpMax, mm)	0.046 (-0.320-0.412)	0.805	2.627 (-0.189-5.443)	0.068
Time (DeflAmpMaxTime, ms)	-0.081 (-0.159- -0.004)	**0.039**	0.119 (-0.521-0.761)	0.715
Deformation Amplitude Ratio Max				
DARatioMax 1 mm	-0.003 (-0.010-0.004)	0.384	0.002 (-0.059-0.062)	0.955
DARatioMax 2 mm	-0.004 (-0.042-0.034)	0.832	0.362 (-0.037-0.760)	0.075
Whole Eye Movement Max				
Amplitude (WEMA, mm)	0.023 (0.016-0.030)	**<0.001**	0.020 (-0.044-0.085)	0.538
Time (WEMT, ms)	-0.090 (-0.170- -0.011)	**0.026**	0.861 (0.207-1.516)	**0.010**
IIR	-0.069 (-0.178-0.039)	0.209	1.046 (0.012-2.079)	**0.047**
SP-A1	0.547 (-1.653-2.747)	0.626	-15.603 (-35.701-4.495)	0.128
SSI	-0.003 (-0.018-0.013)	0.718	-0.129 (-0.275-0.018)	0.085

CI, confidence interval; IIR, integrated inverse radius; SP-A1, stiffness parameter at A1; SSI, stress-strain index

lence from 15.2% at 6 years of age to 76% at 13.[23] High myopia showed a later rise, beginning to augment at 11 years old (6.8%) and reaching 20% at the age of 16.[23] Children with parental history of myopia had a 1.84-fold increased risk of this condition.[23] In KHANES VII, higher body mass index (BMI) was a risk factor for high myopia and atopic dermatitis was non-significantly associated with increased risk of myopia.[23] We found an opposite significant association regarding the latter condition. Several factors can explain this discrepancy: we are assessing a European group while the KHANES VII evaluated an Asian population; for our sample, this condition was mostly self-reported, thus we cannot exclude a recall bias despite it would likely be nondifferential; this difference occurred by chance as the proportion of atopic dermatitis in our sample is below the prevalence described in the literature.[25] In the present study, we found a non-significant trend for higher time spent on outdoor activities and reading for the myopes. Serum vitamin D is considered a biomarker of outdoor activity and its lower levels have been associated with increased risk of myopia both in children[26] and adults.[27] Thus, time spent outdoor seems to be inversely associated with the

Table 4. Linear mixed-effects model for assessment of the effect of myopia, axial length and lens thickness on corneal biomechanics.

	Myopia ß (95% CI)	*P*-value	Axial Length ß (95% CI)	*P*-value	Lens Thickness ß (95% CI)	*P*-value
1st Applanation (A1)						
Time (A1T, ms)	0.050 (-0.044-0.144)	0.298	0.002 (-0.0223-0.027)	0.870	-0.306 (-0.576- -0.035)	**0.027**
Velocity (A1V, m/s)	-0.0001 (-0.006-0.005)	0.965	-0.001 (-0.003-0.0003)	0.111	0.005 (-0.011-0.020)	0.547
Deformation Amplitude (A1DA, mm)	0.0003 (-0.003-0.004)	0.850	-0.0006 (-0.002-0.0005)	0.312	-0.013 (-0.023- -0.003)	0.009
Deflection Length (A1DL, mm)	-0.007 (-0.127-0.112)	0.908	-0.020 (-0.056-0.016)	0.279	-0.174 (-0.448-0.100)	0.213
Deflection Amplitude (A1DeflL, mm)	0.002 (-0.003-0.006)	0.450	-0.001 (-0.002-0.0003)	0.152	-0.016 (-0.026- -0.006)	**0.002**
Deflection Area (A1DeflArea, mm2)	-0.0001 (-0.009-0.009)	0.970	-0.002 (-0.005-0.0001)	0.056	-0.030 (-0.051- -0.009)	**0.005**
dArc Length (A1dArcL, mm)	0.001 (-0.0004-0.002)	0.188	0.0002 (-0.0001-0.001)	0.292	0.002 (-0.0004-0.005)	0.090
Highest concavity (HD)						
Time (HCT, ms)	-0.152 (-0.325-0.022)	0.086	-0.006 (-0.046-0.058)	0.826	0.015 (-0.409-0.380)	0.942
Deformation Amplitude (HCDA, mm)	-0.001 (-0.032-0.029)	0.930	-0.002 (-0.010-0.007)	0.700	0.047 (-0.039-0.133)	0.285
Deflection Length (HCDL, mm)	-0.050 (-0.463-0.363)	0.997	-0.014 (-0.132-0.105)	0.818	-0.756 (-1.783-0.271)	0.149
Deflection Amplitude (HCDeflL, mm)	-0.066 (-0.581-0.448)	0.801	0.051 (-0.105-0.207)	0.520	1.108 (-0.063-2.280)	0.064
Deflection Area (A1DeflArea, mm2)	0.055 (-0.100-0.211)	0.485	0.014 (-0.028-0.057)	0.501	0.151 (-0.275-0.577)	0.488
dArc Length (HCArcL, mm)	-0.003 (-0.010-0.005)	0.446	0.001 (-0.001-0.003)	0.292	0.007 (-0.012-0.027)	0.453
Radius (Rad, mm)	-0.011 (-0.253-0.230)	0.927	0.019 (-0.050-0.089)	0.588	0.183 (-0.417-0.782)	0.550
Peak Distance (PD, mm)	0.011 (-0.077-0.099)	0.809	0.025 (0.001-0.049)	**0.044**	0.235 (-0.010-0.481)	0.060
2nd Applanation (A2)						
Time (A2T, ms)	-0.076 (-0.207-0.056)	0.259	-0.035 (-0.072- -0.001)	0.059	0.442 (0.098-0.786)	**0.012**
Velocity (A2V, m/s)	-0.012 (-0.046-0.022)	0.491	0.002 (-0.00-0.013)	0.643	0.049 (-0.030-0.128)	0.228
Deformation Amplitude (A2DA, mm)	-0.007 (-0.028-0.014)	0.529	-0.008 (-0.014- -0.002)	**0.006**	-0.037 (-0.092-0.017)	0.179
Deflection Length (A2DL, mm)	-0.132 (-0.443-0.178)	0.404	-0.062 (-0.156-0.032)	0.195	0.099 (-0.806-0.609)	0.785
Deflection Amplitude (A2DeflL, mm)	0.001 (-0.007-0.009)	0.791	0.0001 (-0.002-0.002)	0.958	-0.002 (-0.019- -0.016)	0.860
Deflection Area (A2DeflArea, mm2)	-0.010 (-0.038-0.017)	0.473	0.002 (-0.006-0.010)	0.678	0.070 (0.007-0.134)	**0.029**
dArc Length (A2dArcL, mm)	-0.006 (-0.041-0.029)	0.730	0.002 (-0.008-0.013)	0.680	0.053 (-0.026-0.133)	0.189
Other parameters						
Deformation Amplitude Max (DAmpMax, mm)	-0.001 (-0.032-0.029)	0.930	-0.002 (-0.010-0.007)	0.700	0.047 (-0.039-0.133)	0.285
Deflection Amplitude Max						
Amplitude (DeflAmpMax, mm)	-0.193 (-1.484-1.098)	0.770	0.115 (-0.276-0.506)	0.564	2.643 (-0.297-5.583)	0.078
Time (DeflAmpMaxTime, ms)	0.127 (-0.152-0.406)	0.372	-0.092 (-0.174- -0.009)	**0.030**	0.090 (-0.568-0.749)	0.788
Deformation Amplitude Ratio Max						
DARatioMax 1mm	0.018 (-0.007-0.044)	0.165	-0.004 (-0.012-0.003)	0.240	0.007 (-0.056-0.070)	0.835
DARatioMax 2mm	-0.009 (-0.154-0.135)	0.900	-0.001 (-0.040-0.037)	0.941	0.357 (-0.048-0.762)	0.084
Whole Eye Movement Max						
Amplitude (WEMA, mm)	-0.034 (-0.059- -0.009)	**0.009**	0.024 (0.017-0.031)	**<0.001**	0.020 (-0.049-0.090)	0.570
Time (WEMT, ms)	-0.132 (-0.411-0.148)	0.355	-0.070 (-0.152-0.013)	0.099	0.712 (0.050-1.374)	**0.035**
IIR	0.087 (-0.316-0.489)	0.673	-0.065 (-0.177-0.048)	0.260	1.022 (-0.031-2.075)	0.057
SP-A1	1.421 (-6.689-9.530)	0.731	0.270 (-2.027-2.567)	0.818	-14.624 (-35.289-6.040)	0.165
SSI	-0.041 (-0.097-0.015)	0.153	-0.0005 (-0.016-0.015)	0.943	-0.148 (-0.296-0.010)	0.051

CI, confidence interval; IIR, integrated inverse radius; SP-A1, stiffness parameter at A1; SSI, stress-strain index

risk of myopia. We found an opposite trend which can be explained by reverse causality as those children have already been diagnosed and one of the most frequent recommended behavioral changes after a diagnosis of myopia is to increase the time spent outdoors. The second trend was also described by some authors[23,24,28] but is considered of small contribution. In fact, the association between near work-induced transient myopia (NITM) and permanent myopia is not well-stablished, even after marked and sustained, but interrupted, periods of near work. Providing rest intervals between near tasks seems to avoid the cumulative effect of NITM and decrease the probability of myopia development.[29]

In the present study, we could not find any significant association between myopia and corneal biomechanical parameters of the three main phases of acquisition. This fact might be related with definition used (SE ≤ -0.5D) that included several subjects with a low myopia and biometric parameters in the normal range. In our final model, myopia was associated with a lower amplitude of WEM which has been considered a surrogate of the biomechanical behavior of orbital soft tissue. On the other hand, increased values

of AL were associated with higher amplitude of WEM. Further studies are needed to clarify this point as this is the first work assessing WEM parameters in children. In agreement with other reports,[10,11] our results demonstrate an association between longer AL and a more deformable cornea, when adjusted for age and sex. These two factors have been shown to influence corneal biomechanical properties assessed with Ocular Response Analyzer (ORA)[10] and Corvis ST,[11] motivating us to adjust for them in all models. Tang *et al*[11] evaluated the corneal biomechanical properties of a cohort of children and their parents. They found an association between myopia and a more deformable corneal profile in both groups that is mostly mediated by AL. These facts are statistically and clinically relevant. Concerning the statistical relevance, this highlights the importance of adjusting for AL during corneal biomechanics' statistical workups. Regarding the clinical interest, it suggests a close relationship between AL and corneal biomechanics which may be of use for screening and follow-up of pediatric myopia, aiming to identify as soon as possible those at risk of developing myopia or progressing to pathologic levels. In fact, a study by Wan *et al*[12] suggested that low corneal hysteresis, assessed by ORA, was associated with axial elongation at 24 months in young myopic children not undergoing myopia control treatment, which was orthokeratology in their study. Although, most studies, as happens with the present one, have a cross-sectional design and cannot establish a causal relationship between AL and corneal biomechanics nor clarify the direction of a potential effect. Thus, further studies, mostly longitudinal enrolling pre-myopic and myopic children with and without myopia control treatments assessing ocular biometry and corneal biomechanics are warranted.

Lens thinning has been regarded as a compensatory mechanism along with corneal flattening for axial elongation during emmetropization between the ages of 8 to 10.[30] Gwiazda *et al*[5] analyzed the lens changes over 11 years of Correction of Myopia Evaluation Trial (COMET) cohort, that enrolled only myopic children, and reported that the pattern of lens thinning followed by thickening was not associated with myopic progression. In addition, the changes in lens thickness were not related with the degree of myopia but instead age seemed to be a more relevant factor for those changes.[5] These findings were supported by other studies.[4,31] Therefore, lens thickness seems to follow a U-shaped curve that may be indicative of early stretching, reaching a minimum thickness during the phase of more rapid ocular elongation.[32] This is supported by the work of Mutti *et al*[33] suggesting that these lens changes are mechanically induced by the equatorial growth of the eye during childhood. Shih *et al*[4] reported that anterior chamber depth (ACD) also changed with age, increasing from the age of 7 to 11, remaining stable thereafter. In addition, the ACD and LT alterations were also verified in emmetropic and hyperopic eyes,[4] although myopic and emmetropic presented more prominent changes than hyperopic eyes. In summary, lens thickness of children is influenced by age and axial length and by a minimal to no effect of myopia.

In the present study, the lens thickness was not different between myopes and non-myopes nor was correlated with age. The latter fact is probably due to the age of our sample as most of our participants were over 12 years old. In our final model (Table 4), changes in lens thickness were associated with alterations in corneal biomechanical behavior with thinner lenses presenting a more deformable corneal profile. These findings were independent of age, gender, axial length and myopic status. To our best knowledge, this is the first study assessing the relationship between lens thickness and corneal biomechanics. Several hypotheses can be speculated from these results: 1) patients with thinner lenses might present other ocular changes that predispose to more deformable corneal behaviors, including alterations in pachymetry and IOP; although, our results demonstrate only a weak correlation between lens thickness and the latter and none with the former; 2) lens thickness might be a surrogate of eye biomechanical as it seems to follow the changes of ocular development and to be influenced by factors, such as axial length, that will affect the final dimensions of the eye; 3) patients with thinner lenses might have a deeper ACD and vitreous cavity and less resistance from the aqueous humor, allowing more deformability of the eye. Although, all these hypotheses are all speculative and further studies are warranted to clarify this subject. Despite the previous evidence did not support an association between lens thickness and myopia progression, our results might have clinical interest in other fields, namely in glaucoma in which a more deformable corneal behavior has been demonstrated.[34,35]

This study has some limitations. First, our sample was recruited from the outpatient clinic which thwarts the representativeness as participants had already been referred to an ophthalmologist. To minimize this issue, specific selection criteria to enroll healthy participants were applied. Despite the consecutive enrollment, some patients did not show up or refused to participate and a sensitivity analysis was not performed. Most of our sample were at 12 or more years of age by which most ocular development has already occurred. This precludes direct comparisons with most of other pediatric studies that enrolled younger children. As aforementioned, this is a cross-sectional design that prevents to infer causality from our findings. The analysis of ACD and its relationship with other biometric parameters would have been of value to some of our hypothesis.

To our best knowledge, the present study is the first European study to assess the corneal biomechanics of older children and adolescents. In addition, we performed one of the most complete biomechanical assessments as we included the most recent parameters.

CONCLUSION

In this European study, the first of this kind, we enrolled a representative number of healthy children and performed a comprehensive assessment of their background and ocular status. Myopes were older and had longer axial length. Considering the corneal biomechanics, longer axial lengths

and thinner lenses were associated with a more deformable corneal behavior. Longitudinal studies enrolling children and assessing corneal biomechanics are needed to further elucidate the ocular biomechanical behavior on screening and follow-up of ocular diseases.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

AF, JH, AM, CC, PMB, PM and IB: Conception, design and interpretation of data.

AF, JH, AM, CC, DJ, PS, IN and IB: Data acquisition.

AF and JH: Statistical analysis.

AF: Drafting of manuscript.

All authors approved the version to be published.

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