tvst

Cornea & External Disease

Corneal Biomechanical Characteristics in Osteogenesis Imperfecta With Collagen Defect

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Received: June 14, 2022
Accepted: December 6, 2022
Published: January 9, 2023

Keywords: corneal biomechanical properties; corvis biomechanical index; corvis biomechanical factor; stiffness parameter at first applanation; stress-strain index; osteogenesis imperfecta

Citation: Chou CC, Shih PJ, Jou TS, Hsu MY, Chen JP, Hsu RH, Lee NC, Chien YH, Hwu WL, Wang IJ. Corneal biomechanical characteristics in osteogenesis imperfecta with collagen defect. Transl Vis Sci Technol. 2023;12(1):14, https://doi.org/10.1167/tvst.12.1.14

Purpose: To identify the characteristic corneal biomechanical properties of osteogenesis imperfecta (OI), and to compare the corneal biomechanical properties between OI and keratoconus.

Methods: We included 46 eyes of 23 patients with OI, 188 eyes of 99 keratoconus patients, and 174 eyes of 92 normal controls to compare corneal biomechanical parameters between OI corneas, keratoconus, and normal controls by using Corneal Visualization Scheimpflug Technology (Corvis ST).

Results: Patients with OI had significantly higher Corvis biomechanical index (CBI) ($P < 0.001$), higher tomographic and biomechanical index (TBI) ($P = 0.040$), lower Corvis Biomechanical Factor (CBiF) ($P = 0.034$), and lower stiffness parameter at first applanation (SP-A1) ($P < 0.001$) compared with normal controls. In contrast, OI group showed lower CBI ($P < 0.001$), lower TBI ($P < 0.001$), higher CBiF ($P < 0.001$), and higher SP-A1 ($P = 0.020$) than keratoconus group. Notably, the stress-strain index (SSI) was not significantly different between the OI and normal controls ($P = 1.000$), whereas keratoconus showed the lowest SSI compared with OI group ($P = 0.025$) and normal controls ($P < 0.001$).

Conclusions: Although the corneal structures of OI patients are less stable and easier to deform as compared to those of the control group, there is no significant difference in material stiffness observed between the OI and normal controls. In contrast, the corneas of keratoconus showed not only lower structural stability and higher deformability but also lower material stiffness compared with those of OI cornea and normal controls.

Translational Relevance: The biomechanical alterations are different between OI corneas and keratoconus.

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Introduction

Osteogenesis imperfecta (OI) is a rare inherited connective tissue disorder, with a prevalence of one in 15,000 to 20,000 births.[1] It is related to primary defects in type I procollagen and to dysregulation of type I procollagen biosynthesis.[2] Approximately 85% to 90% of OI is inherited as autosomal dominant mutations in either the *COL1A1* or *COL1A2* genes.[3,4] The *COL1A1* and *COL1A2* genes encode type I collagen.[5] Other mutations in the recessive type of OI are associated with dysfunctions in the synthesis and folding pattern of type I collagen.[2,6] Approximately 90% of the body's collagen is type I collagen, which is an important structural protein of extracellular matrices in bones and eyes.[1] Patients with OI present with major bone manifestations, including bone fracture, deformity, and growth deficiency.[5,7]

Collagen type I mutations in OI affect multiple ocular structures.[5] Blue sclera and thinner central corneal thickness (CCT) are ocular characteristics of patients with OI. Blue sclera is caused by thinning and translucence of the sclera, showing an underlying choroid color,[8] and thinner CCT results from type I collagen defects.[9] Keleş et al.[10] demonstrated topographic and tomographic features of OI corneas, including higher astigmatism, index of vertical asymmetry, index of height asymmetry, and Belin-Ambrośio Enhanced Ectasia Display (BAD) overall deviation of normality (final D) value in patients with OI. In contrast, Magalhaes et al.[11] showed no difference in the anterior and posterior corneal curvatures. Based on topographic and tomographic features, the differences between OI and keratoconus are controversial.

Corneal biomechanical changes may precede topographic and tomographic changes.[12–14] Corneal biomechanical properties rely mainly on collagen type I, the most abundant collagen type present in the corneal and scleral extracellular matrix (ECM).[15,16] Previous studies have investigated in vivo corneal biomechanics and revealed lower corneal hysteresis obtained from an Ocular Response Analyzer (Reichert Ophthalmic Instruments, Depew, NY, USA) in OI corneas.[17,18] However, there is a limited understanding on biomechanical destabilization, deformability, and material stiffness in OI corneas. In this study, we aim to identify the biomechanical differences among the corneas of OI, keratoconus, and normal controls by using the Corvis ST (Oculus, Wetzlar, Germany).

Methods

This retrospective cross-sectional study was approved by the institutional review board of the National Taiwan University Hospital. This study adhered to the tenets of the Declaration of Helsinki. Patients diagnosed with OI, keratoconus, and normal controls were recruited from the National Taiwan University Hospital between April 2017 and August 2022. We retrospectively reviewed their medical images and records. The patients in the OI group were diagnosed based on the clinical features including bone fragility, radiological findings, bone mineral density, and family history in clinics of the Department of Medical Genetics at National Taiwan University Hospital.[19] These OI patients were referred to the Department of Ophthalmology for multidisciplinary care. The keratoconus was diagnosed by stromal thinning, conical protrusion, Fleischer's ring, or Vogt's striae on slit lamp examination, and focal corneal steepening, inferior-superior curvature asymmetry, or skewing steepest radial axes above and below the horizontal meridian on topography.[20] Participants in the normal control group were healthy, without any systemic disease who presented at the ophthalmology clinic for routine ocular examinations. We excluded participants with the following criteria: a history of corneal or glaucoma surgery, corneal ulcer, Fuchs' dystrophy, granular dystrophy, pseudophakic corneal edema, Terrien's marginal degeneration, uveitis, and nonglaucomatous optic neuropathy. The participants underwent comprehensive ophthalmic examinations, including visual acuity, slit-lamp examination, intraocular pressure (IOP), CCT evaluation, and anterior segment imaging with Corvis ST and Pentacam (Oculus).

Corvis ST has enabled the assessment of dynamic corneal deformation response and in vivo corneal biomechanical properties.[21] The biomechanical corrected IOP (bIOP) was developed by using finite element simulations and obtained from Corvis ST.[22] The bIOP is least affected by corneal properties and is close to the real IOP.[22] The deformation amplitude ratio (DA ratio) at 2 mm was based on the ratio between the deformation amplitude and the distance moved by the paracentral cornea 2 mm nasally and temporally from the corneal apex. Higher DA ratio at 2 mm indicated a more deformable corneal structure. The Corvis ST measured the central radius of curvature during the concave deformation phase and calculated the area under the inverse radius versus time curve. This area was termed the integrated

radius. Higher integrated radius is an indicator of higher corneal structural deformbility.[23] Ambrósio's relational thickness to the horizontal profile (ARTh) describes the thickness profile in the temporal-nasal direction.[24] The ARTh is the ratio between the thinnest corneal thickness and pachymetric progression index. The lower the ARTh, the more deformable the corneal structure.[24] The stiffness parameter at first applanation (SP-A1) was measured by subtracting the bIOP from the adjusted air pulse pressure at first applanation and then dividing by the deflection amplitude at first applanation. The SP-A1 represents overall structural deformability of the cornea.[25] The SP-A1 level is lower in more deformable corneal structures.[24,26]

The Corvis Biomechanical Index (CBI) was developed as a composite index of corneal biomechanical status to detect abnormal corneal biomechanical stability.[24] The CBI is used to separate keratoconus,[24] subclinical keratoconus,[12] and normal eyes. The CBI is based on a logistic regression algorithm that combines different dynamic corneal response parameters obtained from Corvis ST.[24] Recently, the Corvis Biomechanical Factor (CBiF) has enabled the linear and standardized assessment of corneal biomechanics.[14] Lower CBiF and higher CBI values represent decreased corneal biomechanical stability.[14,24] The tomographic and biomechanical index (TBI) combine Scheimpflug-based corneal tomography and biomechanics to enhance ectasia detection.[27] Higher TBI values indicate decreased corneal biomechanical stability.[27] The stress-strain index (SSI) obtained from Corvis ST is based on numerical simulation and finite element analysis.[28,29] The SSI was developed for estimating the stress-strain material behavior of the cornea.[28] The SSI is independent of IOP and CCT.[28,30] Lower SSI is an indicator of lower corneal material stiffeness.[28]

The final D values computed using the BAD III version were designed to separate normal from abnormal corneas.[31] The final D values show variance from normal but are not specific for ectatic disease.[32] In addition, corneal elevation at the thinnest corneal point, average radii of curvature obtained from a 3.0 mm optical zone centered on the thinnest corneal point, and average pachymetric progression index (PPI) were measured using Pentacam. Corneal densitometry was measured under backscattered light over a 12-mm diameter area of the cornea.[33] This corneal area was divided into four concentric annuli (including 0–2 mm, 2–6 mm, 6–10 mm, and 10–12 mm from the corneal center), each of which was further subdivided into three different layers. The anterior layer comprised the superficial 120 mm, the posterior layer comprised the innermost 60 mm, and the central corneal layer was located between the two layers.[10] The output is standardized from 0 to 100 grayscale units, representing the minimum light scatter to maximum light scatter.[34]

Statistical Analysis

We performed statistical analyses using IBM SPSS (version 22.0; International Business Machines Corp., New York, NY, USA). The normality of variables was tested using the Kolmogorov-Smirnov test. We performed nonparametric tests for variables that did not pass the normality test. Continuous variables were presented as median and interquartile ranges (IQR). Categorical variables were presented as number and percentage. We analyzed demographic data between the OI, keratoconus, and normal controls using the Kruskal-Wallis test and the chi-square test for continuous and categorical variables, respectively. To analyze ocular data from both eyes between the OI, keratoconus, and normal controls, we performed generalized estimating equation models to account for inter-eye correlation.[35] Bonferroni post hoc tests were performed for pairwise comparisons. All P values were two-sided, and significance was set as $P < 0.05$.

Results

We included 46 eyes of 23 OI patients, 188 eyes of 99 keratoconus patients, and 174 eyes of 92 normal controls in this study. The genetic mutation data of OI group are presented in Table 1. The demographic characteristics of the three groups are summarized in Table 2. The median ages of the OI group, keratoconus group, and normal controls were 18.00 (IQR, 12.00–40.00), 25.00 (IQR, 22.00–29.00), and 24.50 (IQR, 18.00–30.00) years, respectively ($P = 0.282$). The numbers of males in the OI group, keratoconus group, and normal controls were 7 (30.4%), 73 (73.7%), and 42 (45.7%), respectively ($P < 0.001$). No significant difference was observed between the three groups in terms of the body mass index. Fourteen (60.9%) patients in the OI group had a history of fracture, and 12 (52.2%) were receiving intravenous bisphosphonate treatment. The ophthalmic characteristics of the three groups are summarized in Table 3. The spherical equivalent of the OI, keratoconus group, and normal controls were −1.75 (IQR, −3.25 to −0.13), and −6.75 (IQR, −10.75 to −4.25), and −6.75 (IQR, −8.50 to −3.69) diopters, respectively ($P < 0.001$). The bIOP in the OI group (17.55 mm Hg [IQR, 15.65–19.20]) was

Table 1. Mutation Characteristics in Patients with OI

ID	Inheritance	Mutated Allele 1	Mutated Allele 2
1	AR	PLOD2: c.1138C>T, p.(Arg380Cys) het	PLOD2: exon1 del het
2	NA	NA	NA
3	NA	NA	NA
4	AR	SERPINF1: c.72dupC, p.(Glu27GlyfsTer37) het	SERPINF1: c.72dupC, p.(Glu27GlyfsTer37) het
5	AR	SERPINF1: c.72dupC, p.(Glu27GlyfsTer37) het	SERPINF1: c.72dupC, p.(Glu27GlyfsTer37) het
6	NA	NA	NA
7	NA	NA	NA
8	AD	COL1A1 c.3046-1G>A het	Wild type
9	NA	NA	NA
10	AD	COL1A2: c.3355G>C, p.(Ala1119Pro) het	Wild type
11	AD	COL1A2: c.3355G>C, p.(Ala1119Pro) het	Wild type
12	AD	COL1A1: c.2775del, p.(Gly926ValfsTer182) het	Wild type
13	AR	WNT1: c.104+1G>A het	WNT1: c.105G>A, p.(Trp35Ter) het
14	NA	NA	NA
15	AD	COL1A1: c.769G>A, p.(Gly257Arg) het	Wild type
16	NA	NA	NA
17	AD	COL1A2: c.901G>A, p.(Gly301Arg) het	Wild type
18	AD	COL1A1 c.2236-49_2273del het	Wild type
19	NA	NA	NA
20	AD	COL1A1: exon 1-25 del het	Wild type
21	AD	COL1A1: c.1405C>T, p.(Arg469Ter) het	Wild type
22	AD	COL1A1: c.1405C>T, p.(Arg469Ter) het	Wild type
23	AD	COL1A1: c.2236G>T, p.(Gly746Cys) het	Wild type

AR, autosomal recessive; AD, autosomal dominant; del, deletion, dup, duplication; het, heterozygous; ID, subject identity; NA, not available.

Table 2. Demographic Characteristics of the Participants

	Control	OI	Keratoconus	*P* Value
Participants	92	23	99	
Eyes	174	46	188	
Age (y)	24.50 (18.00–30.00)	18.00 (12.00–40.00)	25.00 (22.00–29.00)	0.282
Gender*				**<0.001**
Female	50 (54.3%)	16 (69.6%)	26 (26.3%)	
Male	42 (45.7%)	7 (30.4%)	73 (73.7%)	
BMI (kg/m^2)	21.56 (19.61–25.00)	20.99 (17.66–26.59)	21.87 (19.57–24.26)	0.629
Fracture*	0 (0.0%)	14 (60.9%)	0 (0.0%)	**<0.001**

BMI, body mass index.

Data are presented as median (interquartile range) unless stated otherwise. Kruskal-Wallis test was used. Boldface indicates statistical significance.

*The χ^2 test was used.

higher than that in the control group (15.7 mm Hg [IQR, 14.50–17.20], $P = 0.031$) and keratoconus group (14.0 mm Hg [IQR, 12.40–15.20], $P < 0.001$).

The corneal biomechanical parameters obtained from the Corvis ST between the three groups are presented in Table 4. The biomechanical parameters of corneal overall structures among the three groups were compared by performing the generalized estimating equations with adjustment for age, spherical equivalent, bIOP and CCT. Patients with OI had significantly higher CBI (0.51 [IQR, 0.23–0.79] vs. 0.11 [IQR, 0.05–0.19], $P < 0.001$), higher TBI (0.44 [IQR, 0.26–

Table 3. Ocular Characteristics of the Participants

	Control	OI	Keratoconus	*P*	*P1*	*P2*	*P3*
CVA	0.90 (0.60–1.00)	0.85 (0.60, 1.00)	0.40 (0.20, 0.60)	**<0.001**	1.000	**<0.001**	**<0.001**
SE (D)	−6.75 (−8.50 to −3.69)	−1.75 (−3.25 to −0.13)	−6.75 (−10.75 to −4.25)	**<0.001**	**<0.001**	**<0.001**	**0.021**
Average K (D)	43.40 (42.48–44.36)	44.33 (43.63–45.11)	46.50 (44.25–50.75)	**<0.001**	**0.004**	**<0.001**	**<0.001**
IOP (mm Hg)	16.50 (15.00–18.00)	16.00 (14.50–18.13)	12.50 (10.50–14.00)	**<0.001**	1.000	**<0.001**	**<0.001**
bIOP (mm Hg)	15.70 (14.50–17.20)	17.55 (15.65–19.20)	14.00 (12.40–15.20)	**<0.001**	**0.031**	**<0.001**	**<0.001**

bIOP, biomechanical corrected intraocular pressure; CVA, corrected visual acuity; D, diopter; K, keratometry; SE, spherical equivalent; *P*, *P* values of the generalized estimating equations; *P1*, *P* values by Bonferroni post hoc tests between OI and control; *P2*, *P* values by Bonferroni post hoc tests between OI and keratoconus; *P3*, *P* values by Bonferroni post hoc tests between keratoconus and control.

Data are presented as median (interquartile range) unless stated otherwise. Boldface indicates statistical significance.

Table 4. Biomechanical Parameters Obtained Using Corvis ST

	Control	OI	Keratoconus	*P*	*P1*	*P2*	*P3*
CBI	0.11 (0.05–0.19)	0.51 (0.23–0.79)	0.99 (0.91–1.00)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
CBiF	6.53 (6.39–6.76)	6.02 (5.70–6.32)	4.90 (4.20–5.50)	**<0.001**	**0.034**	**<0.001**	**<0.001**
SP-A1	119.72 (108.66–130.57)	91.50 (81.47–110.61)	62.30 (47.40–79.00)	**<0.001**	**<0.001**	**0.020**	**<0.001**
ARTh	582.35 (520.85–659.43)	501.14 (426.86–552.13)	244.20 (143.80–366.30)	**<0.001**	0.468	**<0.001**	**<0.001**
DA Ratio 2 mm	4.28 (4.03–4.60)	4.62 (4.28–5.29)	6.00 (5.30–7.30)	**0.042**	1.000	0.147	0.050
Integr_Radius	8.62 (7.93–9.11)	9.40 (8.33–10.28)	12.35 (10.70–15.20)	**0.003**	1.000	0.112	**0.007**
TBI	0.21 (0.06–0.38)	0.44 (0.26–0.81)	1.00 (1.00–1.00)	**<0.001**	**0.040**	**<0.001**	**<0.001**
SSI	0.81 (0.72–0.90)	0.79 (0.63–0.98)	0.65 (0.54–0.79)	**<0.001***	1.000*	**0.025***	**<0.001***

DA Ratio 2 mm, deformation amplitude ratio at 2 mm; Integr_Radius, integrated radius; *P*, *P* values of the generalized estimating equations with adjustment for age, spherical equivalent, biomechanical corrected intraocular pressure and central corneal thickness; *P1*, *P* values by Bonferroni post hoc tests between OI and control; *P2*, *P* values by Bonferroni post hoc tests between OI and keratoconus; *P3*, *P* values by Bonferroni post hoc tests between keratoconus and control.

Data are presented as median (interquartile range). Boldface indicates statistical significance.

**P* values of the generalized estimating equations with adjustment for age.

0.81] vs. 0.21 [IQR, 0.06–0.38], $P = 0.040$), lower CBiF (6.02 [IQR, 5.70–6.32] vs. 6.53 [IQR, 6.39–6.76], $P = 0.034$), and lower SP-A1 (91.50 [IQR, 81.47–110.61] vs. 119.72 [IQR, 108.66–130.57], $P < 0.001$) compared with control group. In contrast, OI group showed lower CBI (0.51 [IQR, 0.23–0.79] vs. 0.99 [IQR, 0.91–1.00], $P < 0.001$), lower TBI (0.44 [IQR, 0.26–0.81] vs. 1.00 [IQR, 1.00–1.00], $P < 0.001$), higher

Table 5. Corneal Tomographic Parameters Measured Using Pentacam

	Control	OI	Keratoconus	*P*	*P1*	*P2*	*P3*
Corneal thickness of apex (μm)	569.00 (548.00–590.00)	500.00 (451.50–531.25)	485.50 (444.50–512.75)	**<0.001**	**<0.001**	0.136	**<0.001**
Corneal thickness at the thinnest point (μm)	564.50 (543.00–586.00)	497.00 (446.50–528.50)	477.00 (437.75–506.00)	**<0.001**	**<0.001**	0.061	**<0.001**
PPI	0.98 (0.91–1.06)	1.02 (0.90–1.13)	1.99 (1.49–3.04)	**<0.001**	0.761	**<0.001**	**<0.001**
BAD final D	0.92 (0.53–1.35)	1.67 (1.35–2.51)	7.81 (4.51–14.26)	**<0.001**	**0.027**	**<0.001**	**<0.001**
Elevation of front surface at thinnest position (μm)	3.00 (1.33–4.00)	3.00 (2.00–6.25)	18.70 (9.60–33.98)	**<0.001**	0.165	**<0.001**	**<0.001**
Elevation of back surface at thinnest position (μm)	6.00 (3.00–8.00)	6.00 (3.00–11.00)	43.00 (23.63–74.90)	**<0.001**	0.741	**<0.001**	**<0.001**
ARC (mm)	7.77 (7.60–7.93)	7.59 (7.43–7.71)	6.73 (5.84–7.32)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PRC (mm)	6.29 (6.12–6.42)	6.33 (6.18–6.43)	5.00 (4.10–5.64)	**<0.001**	1.000	**<0.001**	**<0.001**

ARC, anterior radius of curvature in the 3.0 mm zone centered on the thinnest location of the cornea; final D, overall deviation of normality; PRC, posterior radius of curvature in the 3.0 mm zone centered on the thinnest location of the cornea; *P*, *P* values of the generalized estimating equations; *P1*, *P* values by Bonferroni post hoc tests between OI and control; *P2*, *P* values by Bonferroni post hoc tests between OI and keratoconus; *P3*, *P* values by Bonferroni post hoc tests between keratoconus and control.

Data are presented as median (interquartile range) unless stated otherwise. Boldface indicates statistical significance.

Table 6. Corneal Densitometry Measured Using Pentacam

	Control	OI	Keratoconus	*P*	*P1*	*P2*	*P3*
Anterior 120 µm layer							
0–2 mm	24.20 (23.00, 26.00)	23.30 (21.58, 24.40)	25.30 (22.43, 28.15)	**<0.001**	**0.022**	**<0.001**	**0.009**
2–6 mm	21.80 (20.60, 23.03)	20.50 (19.00, 21.50)	21.80 (19.90, 23.78)	0.143	0.394	0.205	0.836
6–10 mm	20.00 (17.90, 24.00)	18.10 (15.90, 22.00)	17.80 (16.00, 19.78)	**<0.001**	1.000	0.421	**<0.001**
10–12 mm	33.60 (25.98, 40.78)	36.95 (21.78, 48.68)	26.40 (20.15, 37.35)	**0.002**	1.000	0.097	**0.006**
Total diameter	23.70 (21.08, 25.93)	22.35 (18.88, 26.03)	22.30 (20.05, 25.15)	0.196	1.000	1.000	0.233
Center layer							
0–2 mm	13.60 (13.10, 14.23)	14.90 (13.60, 16.65)	14.70 (13.90, 16.38)	**<0.001**	**0.002**	0.142	**<0.001**
2–6 mm	12.20 (11.70, 12.83)	12.95 (12.10, 14.33)	12.50 (11.80, 13.60)	**0.005**	0.169	1.000	**0.017**
6–10 mm	11.95 (10.80, 14.30)	11.40 (10.20, 14.33)	11.40 (10.70, 12.60)	**0.006**	0.894	0.241	**0.018**
10–12 mm	21.65 (17.40, 26.20)	21.25 (13.15, 27.60)	17.45 (14.68, 22.30)	0.701	1.000	1.000	1.000
Total diameter	14.00 (12.68, 15.40)	13.80 (12.65, 16.58)	13.65 (12.60, 14.78)	0.399	0.657	0.539	1.000
Posterior 60-µm layer							
0–2 mm	11.10 (10.00, 12.10)	11.85 (10.68, 12.73)	10.00 (8.20, 12.28)	0.751	1.000	1.000	1.000
2–6 mm	10.30 (9.40, 11.23)	10.70 (9.80, 11.70)	10.50 (9.10, 11.40)	0.504	1.000	1.000	1.000
6–10 mm	11.10 (9.88, 12.60)	10.60 (9.20, 12.13)	10.30 (9.20, 11.50)	0.367	0.715	1.000	0.796
10–12 mm	17.05 (14.08, 20.23)	15.95 (10.48, 20.68)	15.50 (13.30, 18.63)	0.199	1.000	1.000	0.218
Total diameter	11.80 (10.58, 13.20)	11.40 (10.05, 13.45)	11.20 (10.00, 12.50)	0.301	1.000	0.887	0.516
Total thickness							
0–2 mm	16.20 (15.50, 17.40)	16.55 (15.40, 17.60)	16.85 (15.20, 18.80)	**0.019**	1.000	**0.030**	**0.015**
2–6 mm	14.80 (13.98, 15.70)	14.75 (13.70, 15.65)	15.00 (13.80, 16.20)	0.448	1.000	1.000	0.623
6–10 mm	14.20 (12.98, 16.73)	13.30 (12.03, 15.95)	13.10 (12.03, 14.70)	**<0.001**	1.000	0.290	**0.002**
10–12 mm	24.30 (19.98, 29.00)	24.45 (14.90, 31.83)	19.95 (16.90, 25.50)	**0.003**	1.000	0.289	**0.004**
Total diameter	16.70 (14.90, 18.13)	15.70 (14.10, 18.25)	15.70 (14.23, 17.30)	0.309	1.000	0.939	0.568

P, *P* values of the generalized estimating equations; *P1*, *P* values by Bonferroni post hoc tests between OI and control; *P2*, *P* values by Bonferroni post hoc tests between OI and keratoconus; *P3*, *P* values by Bonferroni post hoc tests between keratoconus and control.

Data are presented as median (interquartile range) unless stated otherwise. Boldface indicates statistical significance.

CBiF (6.02 [IQR, 5.70–6.32] vs. 4.90 [IQR, 4.20–5.50], $P < 0.001$), and higher SP-A1 (91.50 [IQR, 81.47–110.61] vs. 62.30 [IQR, 47.40–79.00], $P = 0.020$) than keratoconus group. We further compared the corneal material stiffness, SSI, among the three groups by performing the generalized estimating equations with adjustment for age. Intriguingly, the SSI was not significantly different between the OI and normal controls (0.79 [IQR, 0.63–0.98] vs. 0.81 [IQR, 0.72–0.90], $P = 1.000$), whereas keratoconus showed the lowest SSI (0.65 [IQR, 0.54–0.79]) compared with OI group (0.79 [IQR, 0.63–0.98], $P = 0.025$) and normal controls (0.81 [IQR, 0.72–0.90], $P < 0.001$).

A comparison of corneal tomographic features using Pentacam between the three groups is summarized in Table 5. Corneal thickness at the apex and corneal thickness at the thinnest point were significantly lower in OI corneas (corneal thickness at the apex = 500.00 [IQR, 451.50–531.25]; corneal thickness at the thinnest point = 497.00 [IQR, 446.50–528.50]) compared with normal controls (corneal thickness at the apex = 569.00 [IQR, 548.00–590.00] µm, $P < 0.001$; corneal thickness at the thinnest point = 564.50 [IQR, 543.00–586.00] µm, $P < 0.001$). In contrast, no significantly different corneal thickness at the apex, and corneal thickness at the thinnest point were noted between OI and keratoconus group. Notably, no significant difference in PPI between the OI corneas and normal controls was noted (1.02 [IQR, 0.90–1.13] vs. 0.98 [IQR, 0.91–1.06], $P = 0.761$), whereas keratoconus showed highest PPI (1.99 [IQR, 1.49–3.04]) than OI corneas (1.02 [IQR, 0.90–1.13], $P < 0.001$) and normal controls (0.98 [IQR, 0.91–1.06], $P < 0.001$). OI corneas had higher BAD final D (1.67 [IQR, 1.35–2.51]) compared with normal controls (0.92 [IQR, 0.53–1.35], $P = 0.027$), whereas keratoconus showed the highest BAD final D (7.81 [IQR, 4.51–14.26]) compared with OI cornea (1.67 [IQR, 1.35–2.51], $P < 0.027$) and normal controls (0.92 [IQR, 0.53–1.35], $P < 0.001$). OI corneas showed lower anterior radius of curvature (7.59 [IQR, 7.43–7.71]) compared to those in normal controls (7.77 [IQR, 7.60–7.93] mm, $P < 0.001$). There were no significant differences in elevation of front surface at thinnest position, elevation of back surface at thinnest position, and posterior radius of curvature between the OI corneas and normal controls, whereas keratoconus showed significantly highest elevation of front surface at thinnest position, highest elevation of

back surface at thinnest position, lowest anterior radius of curvature, and lowest posterior radius of curvature compared with OI corneas and normal controls.

Corneal densitometry values measured using Pentacam are presented in Table 6. In comparison to the control group, patients with OI had significantly lower corneal densitometry in the 0 to 2 mm annuli of the anterior 120 µm layer (23.30 [IQR, 21.58–24.40] vs. 24.20 [IQR, 23.00–26.00], $P = 0.022$]), and higher corneal densitometry in the 0 to 2 mm annuli of the center layer (14.90 [IQR,13.60–16.65] vs. 13.60 [IQR,13.10–14.23], $P = 0.002$). In addition, keratoconus showed the highest corneal densitometry in the 0 to 2 mm annuli of the anterior 120 µm layer (25.30 [IQR, 22.43–28.15]) compared with the OI (23.30 [IQR, 21.58–24.40], $P < 0.001$]) and normal controls (24.20 [IQR, 23.00–26.00], $P = 0.009$]); keratoconus also showed the highest corneal densitometry in the 0 to 2 mm annuli of the total thickness (16.85 [IQR, 15.20–18.80]) compared with the OI (16.55 [IQR, 15.40–17.60], $P = 0.030$]) and normal controls (16.20 [IQR, 15.50–17.40], $P = 0.015$]).

Among patients with OI, there was no significant difference in corneal biomechanical parameters between patients with and without history of fracture (Supplementary Table S1). Furthermore, there was no significant difference in corneal biomechanical parameters between patients with and without intravenous bisphosphonate treatment (Supplementary Table S2). In addition, no significant correlation was noted between corneal biomechanical parameters and bone mineral density in patients with OI (Supplementary Table S3).

Discussion

We found different biomechanical properties between OI corneas, keratoconus, and normal controls. Our study revealed that higher values of CBI, TBI, and lower values of CBiF and SP-A1 in OI corneas than normal controls, whereas no significantly different values of SSI was found between OI and normal controls. In contrast, keratoconus showed highest values of CBI, TBI, and lowest values of CBiF, SP-A1, and SSI compared with OI corneas and normal controls.

Comparative analysis using generalized estimating equations suggested that decreased corneal structural stability in the OI corneas than normal controls as indicated by higher CBI, lower CBiF, and higher TBI values. We furthermore found higher corneal structural deformability in OI corneas than normal controls as indicated by lower SP-A1. There were limited studies about the biomechanical properties of OI corneas. In agreement with our findings, the decreased rigidity of the OI sclera was noted in previous studies.[5,36] The lower stability and higher deformability of OI corneal structures may be explained by the defective collagen type I in OI corneas. Type I collagen constitutes about 80% of the collagen in cornea[11] and contributes to corneal tensile strength.[5] Besides the overall corneal structure, we also evaluate the viscoelasticity of OI corneas. The cornea is a viscoelastic material that can be conceptualized as a combination of two mechanical components: a spring with elastic property and a shock absorber with viscous property.[37] Corneal hysteresis represents viscous properties of cornea.[37] Previous studies have demonstrated decreased corneal hysteresis obtained from the Ocular Response Analyzer in OI corneas.[17,18] Corneal material stiffness represent elastic properties of cornea.[37] We found that corneal material stiffness, SSI, was not significantly different between the control and OI corneas in this study. In contrast, keratoconus showed the lowest CBiF, SP-A1 and SSI, and highest CBI and TBI compared with OI corneas and normal controls in our study, which is consistent with previous studies.[25,38] These findings suggested that keratoconus showed lowest corneal structural stability, highest corneal deformability, and lowest corneal material stiffness compared with OI corneas and normal controls. The possible explanation for the different corneal biomechanical properties between OI and keratoconus could be the different pathogenesis between OI and keratoconus. The mutated collagen in OI mainly causes overall corneal structural alterations, in contrast to the focal and progressive corneal weakening in keratoconus.[13] Additionally, abnormal proteoglycans and proteolytic activity were noted in keratoconus.[39,40] Taken together, OI corneas have characteristic biomechanical properties.

The corneal shape depends heavily on corneal biomechanical properties.[41] Regarding tomographic characteristics in OI corneas, higher BAD final D, and lower anterior radius of curvature were noted, which is consistent with previously reported literature.[10] Intriguingly, no significantly different elevation of the front surface at the thinnest position, elevation of the back surface at the thinnest position, or the posterior radius of curvature in the OI cornea was noted in our study. In contrast, keratoconus showed higher posterior corneal elevation,[42] and higher posterior radius of curvature.[32] Furthermore, we found no difference in PPI between the OI and normal controls, whereas keratoconus showed highest PPI than OI and normal controls. Consistent with previ-

ous studies, the corneal thickness spatial profile of OI corneas showed relatively homogeneous thinning in all corneal positions,[11] whereas the corneal thickness spatial profile of keratoconus eyes showed heterogeneous thinning from the central to the peripheral cornea.[43,44] These findings are logical because the mutated collagen in OI causes generalized corneal alterations, in contrast to the focal and progressive corneal destructions in keratoconus.[13] Therefore OI corneas have characteristic biomechanical and corresponding tomographic properties.

Corneal densitometry values provide quantitative data on corneal transparency.[34] Light scattering is minimal in normal corneas.[34] Corneal transparency is influenced by several factors, including the organization of collagen fibrils[34] and density of keratocytes.[33] In comparison to the control group, OI corneas had significantly lower corneal densitometry values in the 0 to 2 mm annuli of the anterior 120 µm layer. This finding may be explained by the decreased ECM in the OI corneas. In contrast, this study and previous studies revealed that increased corneal densitometry in the 0 to 2 mm annuli of the anterior 120 µm layer in keratoconus.[45]

Careful evaluation of glaucoma risk in patients with OI is essential, because a higher risk of primary open-angle glaucoma in OI patients has been previously reported.[5,17,46] The IOP is underestimated in thinner[47] and more deformable corneas.[48] Hence, thinner and more deformable OI corneas may lead to underestimation of IOP. In our study, we noted that bIOP was higher than IOP in OI eyes. Corneal biomechanical properties may reflect whole-eye biomechanical properties.[21,49] Because the cornea and sclera have similar ECM constituents, the cornea, peripapillary sclera, and lamina cribrosa may have similar biomechanical properties.[15,50,51] Accordingly, a more deformable structure in the OI cornea may indicate more deformable peripapillary sclera and lamina cribrosa,[52] which are the main load-bearing structures of the optic disc.[21,53,54] More deformable peripapillary sclera and lamina cribrosa may affect the risk of glaucomatous optic neuropathy.[21] A genotyping study further suggested that *COL1A1* mutations in OI might cause primary open-angle glaucoma.[55]

Fractures are the most important clinical symptoms of OI[5] and impair the quality of life of patients with OI.[56] We observed that no significant different corneal biomechanical parameters between OI patients with and without fracture history. Intravenous bisphosphonates are prescribed to increase bone mineral density and decrease fracture risk in patients with OI.[57,58] However, it is unclear whether intravenous bisphosphonate therapy improves the corneal conditions in patients with OI in our study. We found no significant difference in corneal biomechanical parameters between patients with and without intravenous bisphosphonate treatment. Furthermore, no correlation was noted between bone mineral density and corneal biomechanical parameters in our study. Consistently, no correlation was noted between bone mineral density and corneal tomographic parameters in a previous study.[10] The possible explanation is that bone fragility is determined by multiple factors such as organic collagen type I and nonorganic hydroxyapatite.[59] The decreased corneal biomechanical parameters mainly reflects the defect of organic collagen type I in OI. Additionally, the secondary bone fragility from osteoporosis does not occur in cornea. Thus the corneal biomechanical parameters might not serve as a surrogate for fracture risk assessment.

This study had several limitations. First, the sample size was limited because of the rarity of OI. It is still unclear whether the OI corneas are more likely to develop the keratoconus. Second, our participants were Asian. Future studies are warranted to investigate the implications of our results in other ethnicities. Finally, deriving causal relationships was challenging because of the cross-sectional study design. Longitudinal cohort studies are warranted to elucidate the underlying pathophysiological mechanisms of OI.

In summary, our study revealed that lower structural stability and higher deformability in OI corneas than normal controls, while no significantly different corneal material stiffness was found between OI and normal controls. In contrast, keratoconus showed not only lower structural stability and higher deformability but also lower material stiffness compared with OI cornea and normal controls. The biomechanical alterations are different between OI corneas and keratoconus. Future longitudinal studies with more samples are warranted to explore whether the OI corneas more likely develop the keratoconus. This study provides a novel conceptual framework for understanding the OI corneas.

Acknowledgments

Supported by the Ministry of Science and Technology of Taiwan (MOST 110-2634-F-002-044) and the Taichung Veterans General Hospital (TCVGH-1106903B).

Disclosure: **C.C. Chou**, None; **P.J. Shih**, None; **T.S. Jou**, None; **M.Y. Hsu**, None; **J.P. Chen**, None; **R.H. Hsu**, None; **N.C. Lee**, None; **Y.H. Chien**, None; **W.L. Hwu**, None; **I.J. Wang**, None

References

1. Forlino A, Marini JC. Osteogenesis imperfecta. *Lancet*. 2016;387:1657–1671.
2. Rohrbach M, Giunta C. Recessive osteogenesis imperfecta: clinical, radiological, and molecular findings. *Am J Med Genet C Semin Med Genet*. 2012;160c:175–189.
3. Treurniet S, Burger P, Ghyczy EAE, et al. Ocular characteristics and complications in patients with osteogenesis imperfecta: a systematic review. *Acta Ophthalmol*. 2022;100:e16–e28.
4. Forlino A, Cabral WA, Barnes AM, Marini JCJNRE. New perspectives on osteogenesis imperfecta. *Nat Rev Endocrinol*. 2011;7:540–557.
5. Treurniet S, Burger P, Ghyczy EAE, et al. Ocular characteristics and complications in patients with osteogenesis imperfecta: a systematic review. *Acta Ophthalmol*. 2022;100(1):e16–e28.
6. Marini JC, Blissett AR. New genes in bone development: what's new in osteogenesis imperfecta. *J Clin Endocrinol Metab*. 2013;98:3095–3103.
7. Marini JC, Forlino A, Cabral WA, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. 2007;28:209–221.
8. Burnei G, Vlad C, Georgescu I, Gavriliu TS, Dan D. Osteogenesis imperfecta: diagnosis and treatment. *J Am Acad Orthop Surg*. 2008;16:356–366.
9. Hald JD, Folkestad L, Swan CZ, et al. Osteogenesis imperfecta and the teeth, eyes, and ears-a study of non-skeletal phenotypes in adults. *Osteoporos Int*. 2018;29:2781–2789.
10. Keleş A, Doğuizi S, Şahin NM, Koç M, Aycan Z. Anterior segment findings in patients with osteogenesis imperfecta: a case-control study. *Cornea*. 2020;39:935–939.
11. Magalhaes OA, Rohenkohl HC, de Souza LT, Schuler-Faccini L, Félix TM. Collagen I defect corneal profiles in osteogenesis imperfecta. *Cornea*. 2018;37:1561–1565.
12. Vinciguerra R, Ambrósio R, Roberts CJ, Azzolini C, Vinciguerra P. Biomechanical characterization of subclinical keratoconus without topographic or tomographic abnormalities. *J Refract Surg*. 2017;33:399–407.
13. Scarcelli G, Besner S, Pineda R, Yun SH. Biomechanical characterization of keratoconus corneas ex vivo with Brillouin microscopy. *Invest Ophthalmol Vis Sci*. 2014;55:4490–4495.
14. Flockerzi E, Vinciguerra R, Belin MW, Vinciguerra P, Ambrósio R, Seitz B. Correlation of the Corvis biomechanical factor with tomographic parameters in keratoconus. *J Cataract Refract Surg*. 2022;48:215–221.
15. Kotecha A. What biomechanical properties of the cornea are relevant for the clinician? *Surv Ophthalmol*. 2007;52(Suppl 2):S109–S114.
16. Sorushanova A, Delgado LM, Wu Z, et al. The Collagen Suprafamily: from biosynthesis to advanced biomaterial development. *Adv Mater*. 2019;31:e1801651.
17. Doolan E, O'Brien C. Abnormal corneal properties in osteogenesis imperfecta and glaucoma: a case series. *BMJ Open Ophthalmol*. 2021;6:e000684.
18. Lagrou LM, Gilbert J, Hannibal M, et al. Altered corneal biomechanical properties in children with osteogenesis imperfecta. *J AAPOS*. 2018;22:183–187.e1.
19. Lin CH, Chien YH, Peng SF, et al. Cyclic pamidronate infusion for neonatal-onset osteogenesis imperfecta. *Pediatr Neonatol*. 2014;55:306–311.
20. Hallahan KM, Sinha Roy A, Ambrosio R, Salomao M, Dupps WJ Discriminant value of custom ocular response analyzer waveform derivatives in keratoconus. *Ophthalmology*. 2014;121:459–468.
21. Qassim A, Mullany S, Abedi F, et al. Corneal stiffness parameters are predictive of structural and functional progression in glaucoma suspect eyes. *Ophthalmology*. 2021;128(7):993–1004.
22. Joda AA, Shervin MM, Kook D, Elsheikh A. Development and validation of a correction equation for Corvis tonometry. *Comput Methods Biomech Biomed Engin*. 2016;19:943–953.
23. Vinciguerra R, Romano V, Arbabi EM, et al. In vivo early corneal biomechanical changes after corneal cross-linking in patients with progressive keratoconus. *J Refract Surg*. 2017;33:840–846.
24. Vinciguerra R, Ambrosio R, Jr., Elsheikh A, et al. Detection of keratoconus with a new biomechanical index. *J Refract Surg*. 2016;32:803–810.
25. Zhang H, Eliasy A, Lopes B, et al. Stress-strain index map: a new way to represent corneal material stiffness. *Front Bioeng Biotechn*. 2021;9:640434-.
26. Roberts CJ, Mahmoud AM, Bons JP, et al. Introduction of two novel stiffness parameters and interpretation of air puff-induced biomechanical deformation parameters with a dynamic Scheimpflug analyzer. *J Refract Surg*. 2017;33:266–273.
27. Ambrósio R, Lopes BT, Faria-Correia F, et al. Integration of Scheimpflug-based corneal tomog-

raphy and biomechanical assessments for enhancing ectasia detection. *J Refract Surg*. 2017;33:434–443.
28. Eliasy A, Chen KJ, Vinciguerra R, et al. Determination of corneal biomechanical behavior in-vivo for healthy eyes using CorVis ST tonometry: stress-strain index. *Front Bioeng Biotechnol*. 2019;7:105.
29. Chu Z, Ren Q, Chen M, Cheng L, Cheng H, Cui W, Bi W, Wu J. The relationship between axial length/corneal radius of curvature ratio and stress–strain index in myopic eyeballs: using Corvis ST tonometry. *Front Bioeng Biotechnol*. 2022;10:939129.
30. Lopes BT, Bao F, Wang J, et al. Review of in-vivo characterisation of corneal biomechanics. *Med Novel Technol Devices*. 2021;11:100073.
31. Luz A, Lopes B, Salomão M, Ambrósio R. Application of corneal tomography before keratorefractive procedure for laser vision correction. *J Biophotonics*. 2016;9:445–453.
32. Belin MW, Jang HS, Borgstrom M. Keratoconus: diagnosis and staging. *Cornea*. 2022;41:1–11.
33. Ní Dhubhghaill S, Rozema JJ, Jongenelen S, Ruiz Hidalgo I, Zakaria N, Tassignon M-J. Normative values for corneal densitometry analysis by Scheimpflug optical assessment. *Invest Ophthalmol Vis Sci*. 2014;55:162–168.
34. Otri AM, Fares U, Al-Aqaba MA, Dua HS. Corneal densitometry as an indicator of corneal health. *Ophthalmology*. 2012;119:501–508.
35. Ying G-S, Maguire MG, Glynn RJ, Rosner B. Calculating sensitivity, specificity, and predictive values for correlated eye data. *Invest Ophthalmol Vis Sci*. 2020;61:29.
36. Scollo P, Snead MP, Richards AJ, Pollitt R, DeVile C. Bilateral giant retinal tears in osteogenesis imperfecta. *BMC Med Genet*. 2018;19:8.
37. Dupps WJ. Hysteresis: new mechanospeak for the ophthalmologist. *J Cataract Refract Surg*. 2007;33:1499–1501.
38. Roberts CJ, Mahmoud A, Fleming G, Ohr M, Weber P. Comparisons of novel stress-strain index and other clinical measures of corneal and ocular stiffness in normal and pathologic cohorts. *Invest Ophthalmol Vis Sci*. 2020;61:5213.
39. Ma J, Wang Y, Wei P, Jhanji V. Biomechanics and structure of the cornea: implications and association with corneal disorders. *Surv Ophthalmol*. 2018;63:851–861.
40. D'Souza S, Nair AP, Sahu GR, et al. Keratoconus patients exhibit a distinct ocular surface immune cell and inflammatory profile. *Sci Rep*. 2021;11:20891.
41. Vinciguerra R, Elsheikh A, Roberts CJ, et al. Influence of pachymetry and intraocular pressure on dynamic corneal response parameters in healthy patients. *J Refract Surg*. 2016;32:550–561.
42. Fontes BM, Ambrósio R, Jardim D, Velarde GC, Nosé W. Corneal biomechanical metrics and anterior segment parameters in mild keratoconus. *Ophthalmology*. 2010;117:673–679.
43. Ambrósio R, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. *J Cataract Refract Surg*. 2006;32:1851–1859.
44. Soiberman U, Foster JW, Jun AS, Chakravarti S. Pathophysiology of keratoconus: what do we know today. *Open Ophthalmol J*. 2017;11:252–261.
45. Koc M, Tekin K, Tekin MI, et al. An early finding of keratoconus: increase in corneal densitometry. *Cornea*. 2018;37:580–586.
46. Lyster ML, Hald JD, Rasmussen ML, Grauslund J, Folkestad L. Risk of eye diseases in osteogenesis imperfecta—A nationwide, register-based cohort study. *Bone*. 2022;154:116249.
47. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol*. 2000;44:367–408.
48. Vinciguerra R, Rehman S, Vallabh NA, et al. Corneal biomechanics and biomechanically corrected intraocular pressure in primary open-angle glaucoma, ocular hypertension and controls. *Br J Ophthalmol*. 2020;104:121.
49. Nguyen BA, Reilly MA, Roberts CJ. Biomechanical contribution of the sclera to dynamic corneal response in air-puff induced deformation in human donor eyes. *Exp Eye Res*. 2020;191:107904.
50. Marshall GE, Konstas AG, Lee WR. Collagens in ocular tissues. *Br J Ophthalmol*. 1993;77:515–524.
51. Martínez-Sánchez MI, Bolívar G, Sideroudi H, Teus MA. Effect of prostaglandin analogues on the biomechanical corneal properties in patients with open-angle glaucoma and ocular hypertension measured with dynamic Scheimpflug analyzer. *Graefes Arch Clin Exp Ophthalmol*. 2022;260:3927–3933.
52. Xu Y, Ye Y, Chen Z, et al. Corneal stiffness and modulus of normal-tension glaucoma in Chinese. *Am J Ophthalmol*. 2022;242:131–138.
53. Sigal IA, Yang H, Roberts MD, Burgoyne CF, Downs JC. IOP-induced lamina cribrosa displacement and scleral canal expansion: an analysis of factor interactions using parameterized eye-specific models. *Invest Ophthalmol Vis Sci*. 2011;52:1896–1907.

54. Boote C, Sigal IA, Grytz R, Hua Y, Nguyen TD, Girard MJA. Scleral structure and biomechanics. *Prog Retin Eye Res*. 2020;74:100773.
55. Wallace DJ, Chau FY, Santiago-Turla C, et al. Osteogenesis imperfecta and primary open angle glaucoma: genotypic analysis of a new phenotypic association. *Mol Vis*. 2014;20:1174–1181.
56. Song Y, Zhao D, Li L, et al. Health-related quality of life in children with osteogenesis imperfecta: a large-sample study. *Osteoporos Int*. 2019;30: 461–468.
57. Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. *Cochrane Database Syst Rev*. 2014:Cd005088.
58. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A*. 2014;164a:1470–1481.
59. Mamede AP, Vassalo AR, Cunha E, et al. Biomaterials from human bone—probing organic fraction removal by chemical and enzymatic methods. *RSC Adv*. 2018;8:27260–27267.