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Age-Related Corneal Transparency Changes Evaluated With an Alternative Method to Corneal Densitometry

Alejandra Consejo, MSc, PhD, Marta Jiménez-García, MSc,†‡ and Jos J. Rozema, MSc, PhD†‡*

Purpose: To compare densitometry distribution analysis (DDA), a platform-independent method to assess corneal transparency, with traditional corneal densitometry.

Methods: A total of 196 healthy participants aged 43.3 ± 18.0 years (range 18–79 years) were recruited for assessment. All participants were assessed using the corneal densitometry analysis add-on to the standard software of the Oculus Pentacam HR. In addition, the Scheimpflug image corresponding to the horizontal meridian of each participant was exported for further analysis. For each image, corneal pixel intensities were statistically modeled. The estimated output parameters, α and β, were compared with the corresponding densitometry values. The analysis was performed considering 3 concentric areas and 3 layers defined at fixed corneal depths. To demonstrate the platform independence of the DDA method, a randomly selected subset of 80 participants also had their eye measured with Oculus Corvis ST.

Results: α and β were found to be well correlated with densitometry, especially α (overall cornea; r = 0.89, $P < 0.001$), independent of the corneal region investigated. Changes in α, β, and corneal densitometry were correlated with age.

Conclusions: In this work, we presented the relationship of DDA with age and traditional corneal densitometry. The α and β parameters, the output of DDA, are platform independent and can be used to investigate corneal clarity objectively.

Key Words: corneal transparency, densitometry, Pentacam, Scheimpflug, statistical image analysis

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From the *Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland; †Department of Ophthalmology, Antwerp University Hospital, Edegem, Belgium; and ‡Department of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium.

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Correspondence: Alejandra Consejo, MSc, PhD, Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224, Warsaw, Poland (e-mail: alejandra.consejo@ichf.edu.pl).

Corneal transparency is of fundamental importance in the vision process. Loss of clarity in the cornea has repeatedly been associated with corneal infections,[1,2] ectatic disorders,[3,4] dystrophies,[5] ocular surgery,[6–8] and aging.[9–11] Assessing and monitoring corneal transparency is, therefore, an important part of ophthalmological examination.

In clinical practice, a standard slit-lamp examination is often performed to assess corneal clarity. However, the inherent subjectivity of the method hampers the reproducibility of the results and progression-related assessments. These limitations can be overcome by using Scheimpflug imaging. The Scheimpflug-based Oculus Pentacam, in particular, includes a so-called densitometry (DS) map analysis as an add-on to their standard software that represents the amount of backscattered light in different regions of the cornea.[9] Over the past years, DS has gained the appreciation of clinicians and researchers as an objective and automatic tool to measure corneal transparency.[1,9] However, to date, it is exclusively available to a single commercial device.

To overcome this limitation, it was recently demonstrated that an alternative method based on the statistical analysis of pixel intensity distribution may be of use in assessing corneal clarity based on optical coherence tomography[12] or Scheimpflug images.[13,14] In clinical terms, this method has been already used to assess corneal clarity changes due to keratoconus,[14,15] glaucoma,[16] and refractive surgery.[17] Because, similar to traditional DS, this novel statistical method is based on light backscattering, one would expect both methods to be correlated.

The aim of this work was to assess whether the results from this newly proposed methodology, called densitometry distribution analysis (DDA), are age dependent and comparable with those given by traditional Pentacam DS.

MATERIALS AND METHODS

Participants

This study was approved by the Antwerp University Hospital Research Ethics Committee and adhered to the tenets of the Declaration of Helsinki. All subjects gave written informed consent to participate after the nature and possible consequences of the study were explained. Participants in this study included 196 healthy adult White subjects (59% women and 41% men) aged from 18 to 79 years, 43.3 ± 18.0 years old (mean ± SD). Participants did not report a history of corneal pathology and were not using topical drops that would impair corneal function. The exclusion criteria were any corneal disease that could cause scarring, such as

infections, dystrophies, trauma, or corneal ectasia. Peripheral limbal degenerations such as arcus senilis, associated with aging, were not considered exclusion criteria. Any previous corneal or intraocular surgery was also considered grounds for exclusion. Subjects with diabetes mellitus, multiple sclerosis, or uncontrolled hypertension were also excluded. The intake of systemic medications was not considered an exclusion criterion unless the drug was known to induce corneal changes.

All participants underwent a comprehensive ophthalmologic examination, including corneal imaging using Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) of their right eye and a standardized interview. To demonstrate the platform independency of the DDA method, a subset of 80 subjects randomly selected was also measured with Corvis ST (Oculus, Wetzlar, Germany). The subset of subjects (66% women and 34% men) aged from 18 to 78 years, 42.76 ± 20.3 years old.

It is important to consider that instillation of sodium fluorescein affects the light intensity distribution of the Scheimpflug images, making them look brighter. Consequently, no sodium fluorescein was instilled before the Scheimpflug examination. The study was performed in a windowless clinical assessment room with a uniform ambient light level of 4 lux as measured by using a lux meter (ISO-Tech; RS Components, Corby, UK).

Data Analysis

The corneal DS screen is provided as an add-on to the standard software of the Pentacam Scheimpflug device. The measurement protocol takes a series of 25 images over different meridians. In the analysis, data are interpolated to create a DS map automatically. The output is expressed in grayscale units. The grayscale unit scale is calibrated by proprietary software, which defines a minimum light scatter of 0 (maximum transparency) and a maximum light scatter of 100 (minimum transparency). For consistency with the previous literature, the DS protocol was performed in a manner previously described.[9] Three concentric zones were inspected independently: the central zone of 2 mm diameter, the annulus extending from 2 to 6 mm diameter, and the one that extends from 6 to 10 mm diameter. Therefore, the overall cornea was considered over a diameter of up to 10 mm. Depth analysis was performed in 3 layers: the anterior layer (includes the anterior 120 μm), the central layer, and the posterior layer (the latter corresponds to the most posterior 60 μm of the cornea). In addition, the whole corneal depth was also considered.

In addition to extracting the DS values provided by the built-in software, the Scheimpflug images corresponding to the horizontal corneal meridian (a fixed size of 500 × 1080 pixels) were exported for further analysis. Raw Scheimpflug images (ie, without gamma correction and contrast enhancement that are applied by default by Pentacam HR software) were used. The data analysis procedure was explained in detail elsewhere[14] and consists of 2 main stages: 1) corneal segmentation and 2) statistical modeling of the pixel intensity distribution. Corneal segmentation allows selecting those pixels in the image that corresponds to the cornea, separating them from the background and other ocular components. After the corneal segmentation, a region of interest (ROI) was extracted automatically for statistical modeling. Different ROIs were delineated following the same areas and criteria described for the DS analysis for both regional and depth analyses.

Furthermore, pixels corresponding to a given ROI were grouped in a histogram according to pixel intensity. Pixel intensity indicates how bright a given pixel is. The resulting histogram was further approximated by the two-parameter distribution function that provides the best fit in the statistical analysis of the Scheimpflug light intensity distribution,[15] the Weibull probability density function. From this function, 2 parameters are extracted (α and β) to be compared with traditional DS values. In summary, parameters α and β are derived from the statistical analysis of light intensity

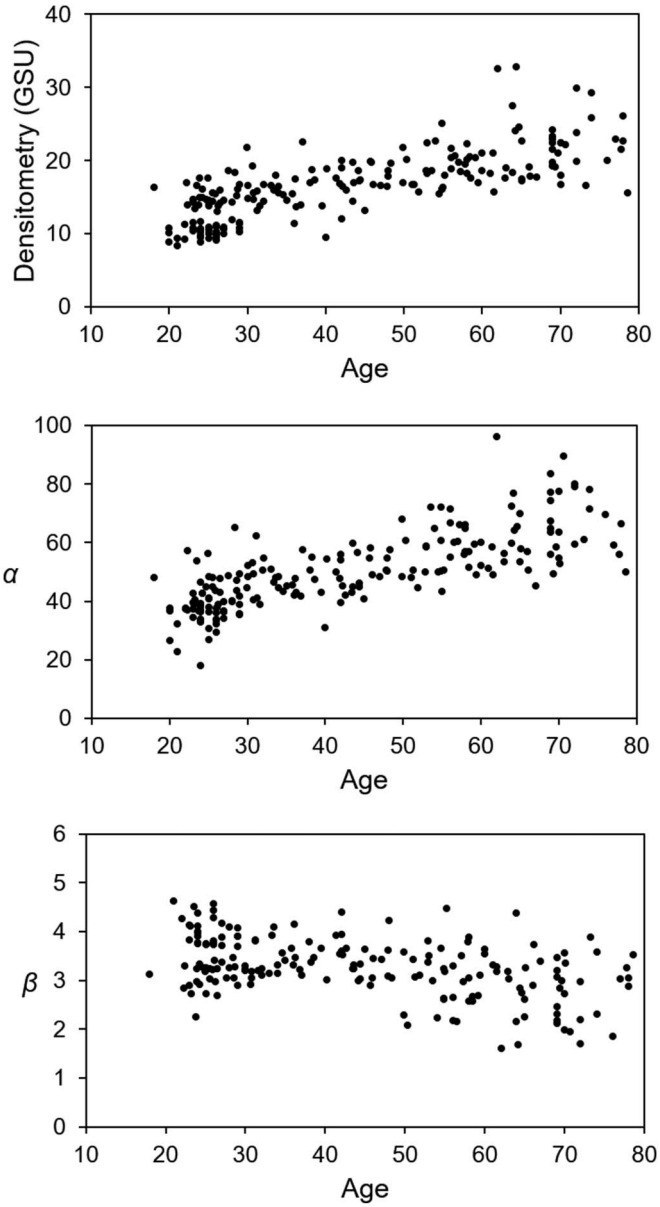

FIGURE 1. Overall densitometry, α and β (0–10 mm) plotted against age. α and β are expressed in arbitrary units.

distribution of corneal Scheimpflug images and are indirectly associated with the way light travels in the corneal tissue,[18] which in turn is related with corneal clarity.[19]

To demonstrate the platform independency of the DDA method, the data acquired from Corvis ST were used. The Corvis ST is a high-speed dynamic Scheimpflug imaging system based on mechanical stimulation of the cornea. After data acquisition with the Corvis ST, the very first image (fixed size of 200 × 576 pixels) of each measurement from each subset subject was exported for further analysis. This image corresponds to an image obtained before air stimulus, with the cornea in a static position. The same data processing procedure described for Pentacam images, and explained in detail elsewhere,[15] was applied to Corvis ST images to extract α and β parameters. Corvis ST has a smaller corneal coverage (up to 8 mm) than that of Pentacam HR (up to 12 mm) and also less resolution. Consequently, to facilitate the comparison between devices, for Corvis ST images, the overall corneal thickness was considered using the entire available horizontal dimension (ie, 576 pixels, equivalent to approximately 8 mm).

Statistical Analysis

The statistical analysis was performed using Microsoft Office Excel (Microsoft Office Professional Plus 2016; Microsoft; Redmond, WA). The normality of all sets of data was not rejected (Shapiro–Wilk test, $P > 0.05$). The Student t test, one-way ANOVA, and Pearson correlation coefficients were used to assess relationships within the continuous variables under investigation. In addition, a paired t test was applied to compare α and β parameters extracted from Pentacam HR and Corvis ST. The results were subjected to a Bonferroni correction to account for inflation. The level of significance was set to 0.05.

RESULTS

α and β in Relation to Age

Both parameters under investigation were found to be correlated with age, with the correlation of α with age [overall cornea (0–10 mm), r = 0.67, $P < 0.001$] being higher than that of β with age [overall cornea (0–10 mm), r = −0.46, $P < 0.001$].

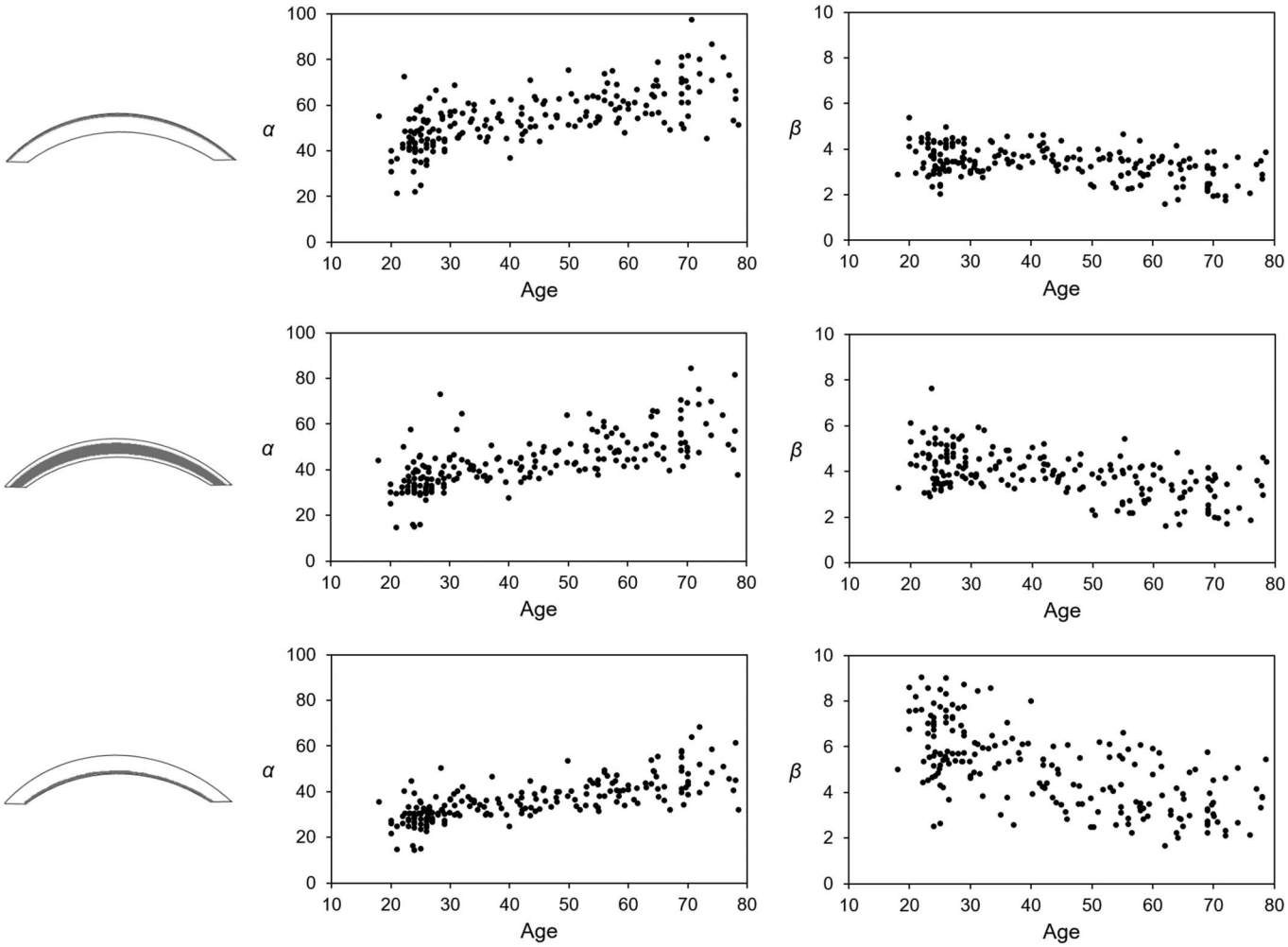

FIGURE 2. Parameters α and β based on the layer plotted against age (coverage 0–10 mm). α and β are expressed in arbitrary units.

The relationship between α, β, and DS with age in the overall cornea is displayed in Figure 1. Corneal local and layer details of α and β with age are shown in Figures 2 and 3. Age-related group means of corneal regional and layer details of α and β, along with DS, are presented in Table 1. The corresponding Pearson correlation coefficients are shown in Table 2.

There was a significantly higher proportion of women than that of men in the cohort. To adjust for this and for the effect of age on DS previously noted, a linear regression model was constructed to determine the effect of sex. The regression model was performed on all eyes' α and β values. After correction for age, there was no statistically significant influence of sex on α ($P = 0.91$) and β values ($P = 0.74$).

Correlation of α and β with DS

Both parameters under investigation were found to be correlated with DS values. The correlation of α with DS [overall cornea (0–10 mm), r = 0.89, $P < 0.001$] was higher than that of β with DS [overall cornea (0–10 mm), r = −0.60, $P < 0.001$], as shown in Figure 4. Pearson correlation coefficients of α and β with DS of different corneal regions and layers are shown in Table 3.

The relationship between α and DS, considering the whole corneal depth and a diameter of 10 mm, can be defined by the following linear equation:

$$\alpha = 2.5 \cdot DS + 7.6,$$

from which it is possible to estimate that α increases at 2.5 times the rate of DS. The goodness of fit of the relationship between α with DS was calculated by the coefficient of determination $R^2 = 0.80$, $P<0.001$. Consequently, knowing the value of α of a given cornea is possible to predict the corresponding DS, or vice versa, at 80% certainty.

The Platform Independence of the DDA Method

From the subset of 80 subjects, the average value of α calculated from Pentacam HR images, 49 ± 10 a.u., was not found to be statistically significantly different from that calculated from Corvis ST images, 49 ± 8 a.u., [paired *t*

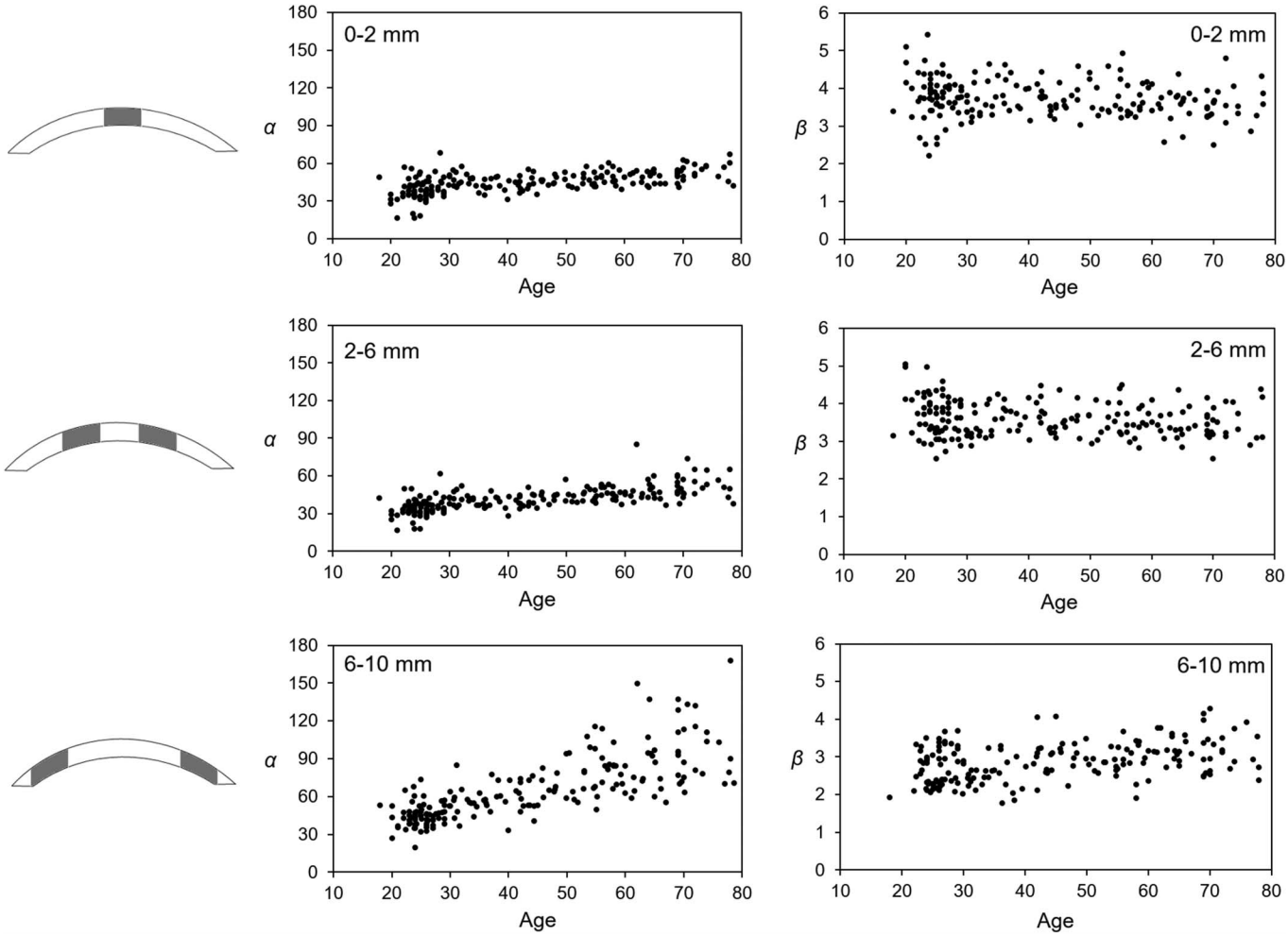

FIGURE 3. Parameters α and β based on the corneal region plotted against age in the central 2 mm (top), in the region from 2 to 6 mm (middle), and in the region from 6 to 10 mm (bottom). α and β are expressed in arbitrary units.

TABLE 1. Group Mean Values ± SD of α, β, and Corneal DS for Different Age Groups

	18–29 yrs	30–39 yrs	40–49 yrs	50–59 yrs	60–69 yrs	70–80 yrs
No. of participants	68	28	26	29	27	18
Mean age	24.9 ± 2.4	33.9 ± 2.8	44.6 ± 2.8	55.4 ± 2.5	65.2 ± 3.0	73.5 ± 3.2
Depth layers						
Anterior						
α	45 ± 10	53 ± 6	55 ± 8	60 ± 7	63 ± 9	69 ± 13
β	3.7 ±0.7	3.5 ± 0.4	3.6 ± 0.5	3.2 ±0.6	30 ± 0.6	2.8 ± 0.7
DS	18 ± 4	24 ± 5	25 ± 4	29 ± 4	32 ± 7	33 ± 6
Central						
α	35 ± 9	42 ± 7	43 ± 7	49 ± 7	52 ± 8	59 ± 13
β	4.4 ±0.9	4.2 ± 0.7	4.0 ± 0.6	3.4 ±0.8	3.2 ± 0.8	3.1 ± 0.9
DS	14 ± 3	18 ± 3	19 ± 3	22 ± 3	24 ± 5	25 ± 5
Posterior						
α	29 ± 6	35 ± 4	36 ± 5	40 ± 5	44 ± 7	48 ± 9
β	6.4 ±1.5	5.6 ± 1.3	4.5 ±1 .2	4.1 ±1.3	3.6 ± 1.2	3.5 ± 1.0
DS	10 ± 3	14 ± 3	15 ± 4	17 ± 4	19 ± 4	20 ± 4
Concentric regions						
0–2 mm						
α	39 ± 9	46 ± 5	45 ± 6	48 ± 6	49 ± 4	55 ± 6
β	3.8 ±0.6	3.8 ± 0.4	3.8 ± 0.4	3.7 ±0.5	3.5 ± 0.4	3.6 ± 0.5
DS	13 ± 3	16 ± 2	16 ± 3	17 ± 2	18 ± 2	19 ± 2
2–6 mm						
α	35 ± 7	41 ± 5	41 ± 6	45 ± 5	49 ± 10	53 ± 9
β	3.7 ±0.5	3.5 ± 0.4	3.6 ± 0.4	3.5 ±0.4	3.5 ± 0.4	3.5 ± 0.5
DS	12 ± 3	15 ± 2	15 ± 2	16 ± 1	18 ± 3	18 ± 3
6–10 mm						
α	45 ± 9	57 ± 10	63 ± 13	80 ± 17	89 ± 25	97 ± 27
β	2.7 ± 0.5	2.5 ± 0.4	3.0 ± 0.4	2.9 ± 0.4	3.2 ± 0.5	3.2 ± 0.5
DS	12 ± 3	17 ± 5	20 ± 4	24 ± 6	28 ± 9	29 ± 8
Overall						
α	39 ± 8	48 ± 5	50 ± 8	58 ± 8	62 ± 12	68 ±13
β	3.6 ± 0.5	3.4 ± 0.3	3.4 ± 0.4	3.1 ± 0.6	2.9 ± 0.6	2.8 ± 0.7
DS	13 ± 3	16 ± 2	17 ± 3	19 ± 2	21 ± 4	22 ± 4

α and β are expressed in arbitrary units, whereas DS is expressed in grayscale units.

test, $P > 0.05$/N (Bonferroni)]. Similarly, the average value of β calculated from Pentacam HR images, 3.3 ± 0.7 a.u., was not found to be statistically significantly different from that derived from Corvis ST images, 3.2 ± 0.6 a.u., [paired t test, $P > 0.05$/N (Bonferroni)]. In addition, as shown in Table 4, parameters α and β calculated from Corvis ST Scheimpflug images were found to be well correlated with traditional corneal DS, age, and α and β extracted from Pentacam HR, evidencing the platform independency of the DDA method.

TABLE 2. Pearson Correlation Between Age and α, β, and Corneal DS

	α	β	DS
Depth layers			
Anterior	0.67	−0.41	0.73
Central	0.69	−0.52	0.76
Posterior	0.73	−0.65	0.77
Concentric regions, mm			
0–2	0.56	−0.16	0.59
2–6	0.66	−0.17	0.65
6–10	0.76	−0.38	0.77
Overall	0.76	−0.45	0.75

All Pearson correlations were found to be statistically significant (all P's < 0.01).

DISCUSSION

This study compares traditional DS with DDA, a method of statistical analysis of pixel intensity distribution of corneal images.[12,14] The outcome of DDA consists of 2 parameters, α and β, that were found to be well correlated with DS, especially α (r = 0.89, $P < 0.001$).

The great advantage of α and β parameters over traditional DS is that these are platform independent. The α and β parameters have been already used as a corneal clarity marker to quantify corneal clarity in different ocular conditions based on Scheimpflug[13–15] or optical coherence tomography images.[12,16,17]

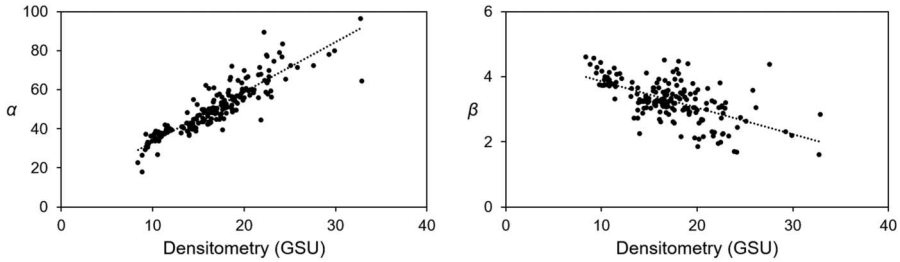

FIGURE 4. Correlation of α and β plotted against densitometry. α and β are expressed in arbitrary units, whereas DS is expressed in grayscale units.

Similar to traditional DS, α and β parameters are based on the backscattering of light. Generally speaking, light from the source reaches the object to be imaged (the cornea), which is partially backscattered toward the detector to form an image. This final image, therefore, depends on how light travels inside the cornea and how much of it is backscattered. Corneal tissue is nonhomogeneous. It comprises different elements, such as epithelial cells, keratocytes, proteoglycans, collagen fibrils, and endothelial cells.[20] The arrangement of these corneal components would cause light to travel differently within the different layers and regions, resulting in intensity differences in the final image.

One step further is to analyze the pixel intensity distribution of the final image in detail to infer tissue characteristics using a statistical model that describes pixel brightness in the cornea. Although many statistical models could be suitable for this purpose,[12] the Weibull function was chosen because it shows a smaller fit error for Scheimpflug images.[15] This model provides parameters α and β that have a physical interpretation.[18,21] In particular, β ("shape parameter") may account for the scatter density, whereas α ("scale parameter") may account for the cross section of the scattered element.[18,21] In other words, if one considers that the cornea comprises small scattering elements, β would indicate their number and α their size.

Both α and β were found to correlate with age (Figs. 1–3, Table 2), where α would increase with age (like DS), whereas β would decrease with age. However, the connection of α and β with changes in corneal tissue at the cellular level is not straightforward. It has been reported that the radius of the collagen fibrils increases with age, associated with more collagen molecules and their intermolecular spacing,[22] which relates to the observed age-dependent behavior of α and β.

α and corneal DS were found to be lowest in the central 6 mm and increased in the periphery. These observations are in agreement with the previous literature on age-related changes in DS.[9–11] However, contrary to those previous reports, we found that DS, although lower in value, was significantly changed with age in the central ring of 2 mm ($r = 0.59$, $P < 0.001$; Table 2). This could be an artifact caused by the fact that the youngest group (18–29 years) was larger in the number of individuals than the remaining age groups. However, randomly taking 30 participants from the youngest group and leaving the rest of the data, the age correlation would remain almost unchanged ($r = 0.56$, $P < 0.001$). Eliminating the youngest group from the group correlation, that is, only investigating participants older than 30 years, the relationship of central DS (0–2 mm) with age was still statistically significant ($r = 0.40$, $P < 0.001$). Similarly, if the correlation was performed in participants up to 50 years old as in the study of Garzón et al,[10] the correlation remained the same ($r = 0.45$, $P < 0.001$). Because DS values are directly derived from the Oculus software and no postprocessing was applied to them before the correlation with age, no immediate reason for the discrepancy with previous studies could be found for the central cornea (0–2 mm). When divided by layer, the anterior 120 μm showed the highest degree of backscatter, with the lowest backscatter occurring at the posterior 60 μm (Table 1), which is consistent with the literature.[9–11]

Previous studies analyzing corneal clarity based on statistically modeling the corneal light intensity distribution using α and β[12–15] chose to restrict the analysis to the stroma because it had been suggested that epithelial tissue

TABLE 3. Pearson Correlation Between Corneal Densitometry and α and β parameters

	α	β
Depth layers		
Anterior	0.79	−0.55
Central	0.79	−0.57
Posterior	0.85	−0.72
Concentric regions, mm		
0–2	0.87	−0.24
2–6	0.87	−0.35
6–10	0.87	−0.26
Overall	0.89	−0.60

All Pearson correlations were found to be statistically significant (all P's < 0.001).

TABLE 4. Pearson Correlation, for a Subset of 80 Subjects, Between α and β Parameters Calculated from Corvis ST Images and (1) Corneal DS, (2) Age, and (3) α and β Parameters Calculated from Pentacam HR Images Using the DDA

	α	β
Corvis ST* versus Pentacam HR (DS)†	0.73	−0.48
Corvis ST* versus Age	0.70	−0.41
Corvis ST* versus Pentacam HR (DDA)*	0.76	0.60

All Pearson correlations were found to be statistically significant (all P's < 0.001).
*Overall cornea measured in a region of 0 to 8 mm diameter.
†Overall cornea measured in a region of 0 to 10 mm diameter.

backscatters light differently[23] and may consequently exhibit a different intensity distribution to that of the stroma.[12] The current findings confirm this premise. In the current work, it was found that there is a statistically significant difference when comparing the anterior and central layers (for both α and β, $P < 0.001$). In addition, a statistically significant difference was also found when comparing the posterior and central layers (for both α and β, $P < 0.001$).

The DDA methodology proved to be platform independent. As indicated in Table 4, α and β parameters extracted from both Pentacam HR and Corvis ST were found to be well correlated with traditional corneal DS and age. However, DS was found to be better correlated with α and β extracted from Pentacam HR (r = 0.89 and r = −0.60, respectively, both $P < 0.001$) than with α and β extracted from Corvis ST (r = 0.73 and r = −0.48, respectively, both $P < 0.001$). These differences are justified by different image sizes and corneal coverage. Images from Pentacam HR have a larger resolution (500 × 1080 pixels) than those from Corvis ST (200 × 576 pixels), which facilitates the calculation of image-derived parameters, such as α and β. It is also important to consider the fact that the maximum corneal coverage that Corvis ST offers is approximately 8 mm diameter, and at the same time, it is not possible to freely select the desired DS corneal diameter from Pentacam HR software. Consequently, α and β parameters extracted from Corvis ST corresponding to the central 8 mm were compared with DS values corresponding to the central 10 mm. This difference in corneal coverage also clarifies why the correlations between α and β (Corvis ST) and DS were found to be smaller than those from α and β (Pentacam HR) and DS.

The repeatability of the DDA method was tested in a previous study.[15] In that earlier study, based on Scheimpflug images extracted from Corvis ST, the coefficient of variation was found to be 2.0% in α and 2.5% in β in a control subject measured 20 times.[15] Because, in the current work, α and β from Corvis ST and α and β from Pentacam HR were found to be well correlated, respectively, and taking into consideration the better quality resolution Pentacam HR offers, we would expect the repeatability of the DDA method applied to Pentacam HR images to be comparable with that previously estimated. However, it would be of interest to assess the specific repeatability of the DDA method applied to Pentacam HR images.

One of the limitations of this work is that the analysis was performed up to 10 mm, although previous DS records reported data up to 12 mm. This decision was taken to avoid the undesired border effects (strong limbal/scleral reflections) that would hamper the calculation of α and β in this area. This decision was also supported by the claim that DS data in the peripheral area (10–12 mm) should be interpreted with caution because reproducibility and repeatability in this region were the weakest.[9] The analysis of α and β was performed on a single corneal meridian (horizontal meridian), whereas DS uses 25 meridians that are interpolated to reconstruct a complete map. There is no technical limitation to follow the same procedure with α and β, and this will be addressed in future work. Although this could be seen as a limitation of the current study, the ability to extract corneal clarity measurements comparable with DS based on a single image is a major strength of DDA and of clinical value. The usefulness of a single meridian was already proven of clinical value in keratoconus detection.[14,15] In particular, the combination of α and β with traditional biomechanical parameters showed to minimize misclassifications in keratoconus detection in comparison to traditional classification methods.[14] Similarly, in previous work, it was demonstrated that it is possible to detect early keratoconus using a single Scheimpflug image (corresponding to 1 corneal "cut") by the combination of α and β parameters with central corneal thickness.

The DDA method can be useful for clinical applications where corneal clarity and corneal microstructure in vivo are of interest. In particular, besides corneal ectasia,[14,15] the recent literature has demonstrated the usefulness of extracting tissue-related parameters, such as α and β, in the investigation of corneal hypoxia,[12,13] glaucoma,[16] and corneal tissue remodeling after refractive surgery.[17]

The DDA method is time efficient. Once the images are extracted for analysis, the method takes less than 0.25 seconds to run and return the α and β parameters from each image. A complete map, composed of 25 images, would be available to the user in approximately 6 seconds.

In summary, in this work, we presented the relationship of α and β parameters with age and traditional corneal DS. α and β parameters are platform independent and can be used to investigate corneal clarity.

REFERENCES

1. Otri AM, Fares U, Al-Aqaba MA, et al. Corneal densitometry as an indicator of corneal health. *Ophthalmology.* 2012;119:501–508.
2. Orucoglu F, Talaz S, Aksu A, et al. Corneal densitometry evaluation in archipelago keratitis. *Int Ophthalmol.* 2014;34:99–102.
3. Lopes B, Ramos I, Ambrósio R Jr. Corneal densitometry in keratoconus. *Cornea.* 2014;33:1282–1286.
4. Kim BZ, Jordan CA, McGhee CN, et al. Natural history of corneal haze after corneal collagen crosslinking in keratoconus using Scheimpflug analysis. *J Cataract Refract Surg.* 2016;42:1053–1059.
5. Alnawaiseh M, Zumhagen L, Wirths G, et al. Corneal densitometry, central corneal thickness, and corneal central-to-peripheral thickness ratio in patients with Fuchs endothelial dystrophy. *Cornea.* 2016;35:358–362.
6. Rozema JJ, Trau R, Verbruggen KH, et al. Backscattered light from the cornea before and after laser-assisted subepithelial keratectomy for myopia. *J Cataract Refract Surg.* 2011;37:1648–1654.
7. Savini G, Huang J, Lombardo M, et al. Objective monitoring of corneal backward light scattering after femtosecond laser-assisted LASIK. *J Cataract Refract Surg.* 2016;32:20–25.
8. Patel SV, McLaren JW, Hodge DO, et al. The effect of corneal light scatter on vision after penetrating keratoplasty. *Am J Ophthalmol.* 2008; 146:913–919.
9. Dhubhghaill SN, Rozema JJ, Jongenelen S, et al. Normative values for corneal densitometry analysis by Scheimpflug optical assessment. *Invest Ophthalmol Vis Sci.* 2014;55:162–168.
10. Garzón N, Poyales F, Illarramendi I, et al. Corneal densitometry and its correlation with age, pachymetry, corneal curvature, and refraction. *Int Ophthalmol.* 2017;37:1263–1268.
11. Alzahrani K, Carley F, Brahma A, et al. Corneal clarity measurements in healthy volunteers across different age groups: observational study. *Medicine (Baltimore).* 2017;96:e8563.
12. Jesus DA, Iskander DR. Assessment of corneal properties based on statistical modeling of OCT speckle. *Biomed Opt Express.* 2017;8: 162–176.
13. Consejo A, Alonso-Caneiro D, Wojtkowski M, et al. Corneal tissue properties following scleral lens wear using Scheimpflug imaging. *Ophthalmic Physiol Opt.* In press. doi: 10.1111/opo.12710.

14. Consejo A, Glawdecka K, Karnowski K, et al. Corneal properties of keratoconus based on Scheimpflug light intensity distribution. *Invest Ophthalmol Vis Sci.* 2019;60:3197–3203.
15. Consejo A, Solarski J, Karnowski K, et al. Keratoconus detection based on a single Scheimpflug image. *Trans Vis Sci Techn*. 2020;9:36.
16. Iskander DR, Kostyszak MA, Jesus DA, et al. Assessing corneal speckle in optical coherence tomography: a new look at glaucomatous eyes. *Optom Vis Sci.* 2020;97:62–67.
17. Shetty R, Francis M, Shroff R, et al. Corneal biomechanical changes and tissue remodeling after SMILE and LASIK. *Invest Ophthalmol Vis Sci*. 2017;58:5703–5712.
18. Tunis AS, Czarnota GJ, Giles A, et al. Monitoring structural changes in cells with high-frequency ultrasound signal statistics. *Ultrasound Med Biol.* 2005;31:1041–1049.
19. Spadea L, Maraone G, Verboschi F, et al. Effect of corneal light scatter on vision: a review of the literature. *Int J Ophthalmol.* 2016;9:459–464.
20. Meek KM, Knupp C. Corneal structure and transparency. *Prog Retin Eye Res.* 2015;49:1–16.
21. Shankar PM, Dumane VA, Reid JM, et al. Classification of ultrasonic B-mode images of breast masses using Nakagami distribution. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2001; 48:569–580.
22. Daxer A, Misof K, Grabner B, et al. Collagen fibrils in the human corneal stroma: structure and aging. *Invest Ophthalmol Vis Sci.* 1998;39: 644–648.
23. Patel SV, Winter EJ, McLaren JW, et al. Objective measurement of backscattered light from the anterior and posterior cornea in vivo. *Invest Ophthalmol Vis Sci.* 2007;48:166–172.