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Peripheral corneal thickness and associated factors – results from the population-based German Gutenberg Health Study

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ABSTRACT.

Purpose: **Changes in peripheral corneal thickness are described in various corneal diseases such as corneal ectasia. However, few data exist describing the increase in corneal thickness from central to peripheral and reporting the normal distribution of corneal thickness in rings around the corneal centre. The aim of this study was to report these cornea characteristics and investigate associated factors in a population-based setting.**

Methods: **The Gutenberg Health Study is a prospective, population-based study examining participants in a 5-year follow-up (age range 40–80 years) using Scheimpflug imaging. Corneal thickness was assessed in each participant at the apex, as well as in the corneal centre (thinnest corneal thickness) and in rings with 2, 4, 6, 8 and 10 mm diameter around the corneal centre, and the increase in corneal thickness towards the periphery. The relationship between corneal thickness at these locations and possible associated factors was determined using linear regression models. For this purpose, general and ocular parameters were included.**

Results: **A total of 9729 participants were included in the present analysis (4874 women, age 59.2 ± 10.8 years). Multivariable analysis showed a correlation between the increase in corneal thickness in the circles from 0 to 10 mm (diameter) and the following parameters: age (B = −0.24 µm per year, $p < 0.001$); body height (B = −0.04 µm, $p = 0.005$); smoking (B = −0.72 µm, $p < 0.001$); spherical equivalent (B = −0.70 µm per dioptre, $p < 0.001$); white-to-white distance (B = −0.75 µm/mm, $p < 0.001$); mean corneal radius (B = −3.61 µm/mm, $p < 0.001$); intraocular pressure (B = −0.12 µm/mmHg, $p < 0.001$); glaucoma (B = −1.94 µm, $p < 0.001$); and pseudophakia (B = 0.89 µm, $p < 0.001$).**

Conclusion: **The results of the present study suggest that several general and ocular parameters are associated with peripheral corneal thickness. In the context of diagnosing glaucoma, a smaller increase in corneal thickness towards the periphery might be a new additional marker.**

Key words: anatomy – cornea – epidemiology – peripheral corneal thickness – population-based study

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AF, SMG, NP and AKS conceived and designed the study; AF, MN and AKS analysed the data; AF wrote the paper; SMG, JWP, MN, IS, PSW, TM, MEB, KJL, NP and AKS critically revised the manuscript; all authors read and approved the final manuscript. MN and PSW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Statistical analyses were performed by MN.

The analysis presents clinical data of a large-scale population-based cohort with ongoing follow-up examinations. This project constitutes a major scientific effort with high methodological standards and detailed guidelines for analysis and publication to ensure scientific analyses on highest level. Therefore, data are not made available for the scientific community outside the established and controlled workflows and algorithms. To meet the general idea of verification and reproducibility of scientific findings, we offer access to data at the local database in accordance with the ethics vote upon request at any time. The GHS steering committee, which comprises a member of each involved department and the coordinating PI of the Gutenberg Health Study (PSW), convenes once a month. The steering committee decides on internal and external access of researchers and use of the data and biomaterials based on a research proposal to be supplied by the researcher. Interested researchers make their requests to the coordinating PI of the Gutenberg Health Study (Philipp S. Wild; philipp.wild@unimedizin-mainz.de). More detailed contact information is available at the homepages of the GHS (www.gutenberghealthstudy.org).

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Introduction

Central and peripheral corneal thickness are important parameters giving insights into corneal health and function. Age, gender, race, environmental and genetic influences were shown to be associated with central corneal thickness (CCT) (Hoffmann et al. 2013). Furthermore, CCT is of importance for diagnosing keratoconus as well as for measuring correct intraocular pressure as part of glaucoma management (Thapa et al. 2012).

Up to date, there are scarce data investigating peripheral corneal thickness (Ma et al. 2016) and its regional distribution in relation to ocular and general parameters. Peripheral corneal thickness mapping is of particular importance in monitoring different corneal diseases such as Fuchs endothelial dystrophy (Alnawaiseh et al. 2016), corneal ectatic disease and keratoconus (Gromacki & Barr 1994). Alterations of peripheral corneal thickness in different corneal regions are essential for planning refractive surgery. Hashemi et al. (Hashemi et al. 2016) observed that increasing age is linked to a decreased central and peripheral corneal thickness. However, the association of peripheral corneal thickness with other general and ocular parameters has not been well investigated so far.

Scheimpflug imaging allows performing corneal tomography with high reliability and validity and measuring corneal thickness within a diameter of 10 mm (Chen & Lam 2007; Ho et al. 2007). A better understanding of peripheral corneal morphology and associated factors may be decisive for the choice of surgical treatment and its prognosis.

We investigated the relationship between central and peripheral corneal thickness measured with Scheimpflug tomography and ocular as well as anthropometric factors for the first time in a large population-based cohort.

Materials and Methods

Study population

The Gutenberg Health Study (GHS) is an interdisciplinary, prospective, population-based cohort study in the Rhine-Main region of Western Germany (Rhineland-Palatinate) (Wild et al. 2012). Recruitment and baseline examination were performed between 2007 and 2012 of participants aged between 35 and 74 years. After baseline examination, consecutive follow-up examinations were conducted every 5 years. At the five-year follow-up examination, study participants underwent a single examination with Scheimpflug imaging while no data are available for peripheral corneal thickness from baseline. For our analysis, subjects of the 5-year follow-up performed between 2012 and 2017 were included. All GHS participants were randomly selected from local governmental registry offices stratified by sex, age and residence (urban or rural) at baseline. Every resident has the duty to be registered in the governmental registry. The effective recruitment efficacy proportion was 55.5%.

Twelve thousand four hundred and twenty-three of the original 15 010 GHS baseline participants (82.8%) took part at the 5-year follow-up examination. Written informed consent was obtained from all study participants prior to their study entry and the GHS complies with Good Clinical Practice, Good Epidemiological Practice, and the ethical principles of the Declaration of Helsinki. The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07; original vote: 22.3.2007, latest update: 20.10.2015).

Ophthalmologic examination

Detailed ophthalmologic examination was performed in every study participant as described earlier (Höhn et al. 2015). This included testing of visual acuity and objective refraction (Humphrey® Automated refractor/Keratometer (HARK) 599™), and intraocular pressure measurement with a non-contact tonometer (NT 2000™, Nidek Co., Tokio, Japan). Scheimpflug imaging (Pentacam HR™, Oculus, Wetzlar, Germany) and optical biometry (Lenstar LS900, Haag-Streit, Bern, Switzerland) were additionally conducted (Hohn et al. 2015). The spherical equivalent was calculated by adding the spherical correction value to half the cylinder value.

Inclusion/exclusion criteria

In the present study, only participants with successful Scheimpflug imaging in the 5-year follow-up examination were included. Participants with low-quality measurements or decentration were excluded. Furthermore, participants with self-reported corneal surgery and / or self-reported severe eye injury were also excluded.

Scheimpflug imaging

Corneal and anterior segment tomography was conducted in every participant using a rotating Scheimpflug camera. This device allows a three-dimensional examination from the anterior corneal surface to the posterior lens surface. Standard operating procedures were used for performing Scheimpflug imaging to reduce examiner--depending variance. In the case of optimal alignment, corneal tomography was started while participants had to fixate a light source. During the Scheimpflug examination, 25 Scheimpflug images are captured in about 2 seconds. Quality controls of the device were checked. All corneal thickness measurements were controlled for outliers, and outliers were removed if a measurement artefact was suspected based on the raw Scheimpflug images. The following corneal parameters were included in the present analysis: corneal thickness at the apex, corneal thickness in the pupil and minimal corneal thickness (D0) and circles around the thinnest corneal thickness in a diameter of 2 mm (D2), 4 mm (D4), 6 mm (D6), 8 mm (D8) and 10 mm (D10). Furthermore, corneal thickness at 3 mm distance from the thinnest corneal position in the superior, inferior, nasal and temporal quadrant was measured.

Covariates

The following general and ocular factors were selected as covariates based on a systematic literature research (Wong et al. 2009; Hoffmann et al. 2013; Elflein et al. 2014). General parameters included gender (female), age (years), body height (m), smoking (yes) and diabetes (physician diagnosis or HbA1c-level ≥ 6.5 or antidiabetic medication). As ocular covariates, the following parameters were selected: lens status (phakia versus pseudophakia), white-to-white distance (mm), corneal curvature (mm), spherical equivalent (dioptre), intraocular pressure (mmHg) and glaucoma (yes/no). Glaucoma was defined according to a modified ISGEO classification including optic disc size-adjusted cut-off values for vertical cup-to-disc ratio (VCDR) (Höhn et al. 2018) and also minimal rim width <0.1 on optic disc photographs at baseline examination, together with FDT perimetry. At 5-year follow-up examination, glaucoma was again evaluated according to this classification and potential incident cases underwent an image side-by-side comparison to baseline optic disc photographs by two board-certified ophthalmologists. In the case of no visible change of the optic disc, these images were classified as non-glaucomatous. Prevalent cases at baseline and incident cases up to the 5-year follow-up examination were summarized as glaucoma cases in this analysis.

Statistical analysis

The main outcome measures were corneal thickness at the apex, at the pupil centre and minimal corneal thickness and corneal thickness in circles around the thinnest corneal position until a diameter of 10 mm. Descriptive statistics were computed for the main outcome measures such as absolute and relative frequencies for dichotomous parameters, mean and standard deviation for approximately normally distributed data, and median and interquartile range for the remaining variables. Linear regression models with generalized estimating equations (GEE) were used to assess associations and to account for correlations between corresponding eyes. If available, both eyes were included in the analyses. In model #1, the relationship between the different general and ocular parameters and the main outcome measures were investigated in a crude model; in model #2, a multivariable model with inclusion of all general and ocular parameters was performed to assess the association of these parameters with corneal thickness in the different locations. Slope was calculated as the slope coefficient of a linear regression of thickness measurements on measurement position. The data were analysed with R version 3.6.1 (R Core Team 2016). This is an explorative study, and no adjustment for multiple testing was carried out. Thus, P-values should be regarded as a continuous parameter reflecting the level of confidence and are therefore reported exactly. A p-value <0.001 was considered as strong association, $p < 0.05$ as likely association, $p > 0.05$ but <0.6 as inconclusive and p >= 0.6 as probably not associated.

Results

Participant characteristics

Of 15 010 subjects examined at baseline, 12 423 returned for the five-year follow-up examination and of these in 10 675 participants, Scheimpflug imaging was possible. In total, 1748 were excluded because of missing Scheimpflug measurements or reduced image quality. Furthermore, 210 were excluded because of self-reported corneal surgery and 736 because of self-reported severe eye injury. Consequently, 9729 participants were included in the present study. Baseline characteristics such as age, height, cardiovascular parameters, ocular disease and geometric parameters are presented in Table 1. Mean age at examination was 59.2 ± 10.8 years, and 50.1% (n = 4874) were female.

Descriptive central and peripheral corneal thickness

In Table 2, measurements of corneal thickness at the apex, in the pupil, centre and in the circles with 2, 4, 6, 8 and 10 mm diameters around the corneal centre (thinnest corneal thickness) are displayed stratified by age in decades. Thinnest corneal thickness was observed in the corneal centre with a constant increase of corneal thickness from the centre to the periphery. Furthermore, older persons showed thinner corneas than younger persons. The effect of increasing age on thinner corneal thickness increased towards periphery. Furthermore, central and peripheral corneal thicknesses were highest in the superior sector followed by the nasal, the inferior and the temporal sector. Figure 1 presents slopes 0–10 mm for the right and left eye, and Fig. 2 presents boxplots for corneal thickness from the corneal centre to the different locations of the corneal periphery.

Multivariable analyses

Age, sex, smoking and diabetes

In multivariable analyses, female sex was associated with decreased corneal thickness until 6 mm around the corneal centre. Higher age was associated with decreased corneal thickness at the corneal centre and in the corneal periphery.

Increased body height was associated with decreased corneal thickness from 4 mm circles until 10 mm circles around corneal centre, smoking was associated with increased corneal thickness at corneal centre and until 6 mm around the corneal centre but not in the more peripheral cornea, while diabetes showed no association at any measurement area.

Ocular parameters

Increased white-to-white distance was associated with decreased corneal thickness at the centre and until the 10 mm diameter periphery. Corneal radius was positively associated with the corneal thickness within a circle of 6 mm diameter around the centre, while at 8 mm diameter, there was no relationship, and at 10 mm circle, there was an inverse relationship. Hyperopic refractive error showed only an association with decreased corneal thickness in the circle with 10 mm diameter.

Increased ocular pressure was associated with increased corneal thickness at each location, and glaucoma was linked to decreased corneal thickness from 4 to 10 mm diameter circles, while pseudophakia was linked to increased corneal thickness from 8 to 10 mm diameter in the corneal periphery (Table 3).

Slope of corneal thickness

Multivariable analysis showed an inverse association between the corneal thickness increase from 0 to 10 mm diameter and age, height, smoking, spherical equivalent, white-to-white distance, corneal radius, intraocular pressure and glaucoma, while pseudophakia was positively associated with corneal thickness towards the periphery.

Discussion

The present study provides new data about the distribution of peripheral corneal thickness and its association

Table 1. Characteristics of the study sample (n = 9729). Data from the population-based Gutenberg Health Study (2012–2017) by sex groups. Mean ± Standard Deviation or Median and 25%/75% Quantiles.

Variable	Overall	Male	Female
Participants (n)	9729 (100%)	4855 (49.9%)	4874 (50.1%)
Age (y)	59.2 ± 10.8	59.4 ± 10.9	59.0 ± 10.7
Cardiovascular parameters			
Diabetes (yes)	9.9% (965)	12.4% (601)	7.5% (364)
Smoker (yes)	18.1% (1756)	19.1% (924)	17.1% (832)
Ocular disease			
Previous cataract surgery OD (yes)	7.8% (756)	7.4% (356)	8.3% (400)
Previous cataract surgery OS (yes)	8.1% (783)	7.6% (366)	8.6 (417)
Ocular parameters			
Visual acuity OD (logMAR)	0.00 (0.00/0.10)	0.00 (0.00/0.10)	0.00 (0.00/0.10)
Visual acuity OS (logMAR)	0.00 (0.00/0.10)	0.00 (0.00/0.10)	0.00 (0.00/0.10)
Spherical equivalent OD (dioptre)	−0.12 (−1.25/0.75)	−0.12 (−1.38/0.75)	−0.12 (−1.25/0.88)
Spherical equivalent OS (dioptre)	−0.12 (−1.25/0.75)	−0.12 (−1.38/0.75)	−0.0 (−1.25/0.88)
Intraocular pressure OD (mmHg)	14.09 ± 2.83	14.18 ± 2.94	14.00 ± 2.72
Intraocular pressure OS (mmHg)	14.24 ± 2.87	14.38 ± 2.97	14.10 ± 2.75
Mean corneal radius OD (mm)	7.76 ± 0.27	7.82 ± 0.28	7.70 ± 0.26
Mean corneal radius OS (mm)	7.76 ± 0.27	7.82 ± 0.27	7.70 ± 0.26
White-to-white OD (mm)	12.2 ± 0.4	12.3 ± 0.4	12.1 ± 0.4
White-to-white OS (mm)	12.2 ± 0.4	12.3 ± 0.5	12.1 ± 0.4
Axial length OD (mm)	23.7 ± 1.3	24.0 ± 1.2	23.5 ± 1.2
Axial length OS (mm)	23.7 ± 1.3	24.0 ± 1.3	23.4 ± 1.2

dpt = dioptre; n = number of participants, mm = millimetre; OD = right eye; OS = left eye.

Table 2. Measurements of corneal thickness in different corneal areas stratified by age groups in decades with Scheimpflug tomography. Data from the population-based Gutenberg Health Study (2012–17). Mean ± Standard Deviation.

Variable in µm	40–49 years	50–59 years	60–69 years	70–80 years	p-Value
Corneal thickness					
Apex OD	559 ± 33	559 ± 32	557 ± 32	554 ± 33	<0.001
Apex OS	560 ± 33	559 ± 33	558 ± 32	555 ± 33	<0.001
Pupil OD	558 ± 33	557 ± 32	555 ± 32	552 ± 33	<0.001
Pupil OS	558 ± 33	557 ± 33	556 ± 32	553 ± 33	<0.001
Corneal thickness: sectors					
Superior OD	666 ± 40	664 ± 40	658 ± 40	651 ± 41	<0.001
Superior OS	665 ± 39	658 ± 38	656 ± 41	650 ± 41	<0.001
Inferior OD	622 ± 36	622 ± 37	619 ± 35	611 ± 35	<0.001
Inferior OS	621 ± 37	621 ± 35	619 ± 37	613 ± 35	<0.001
Nasal OD	642 ± 37	641 ± 35	636 ± 36	627 ± 37	<0.001
Nasal OS	644 ± 37	639 ± 36	635 ± 38	629 ± 37	<0.001
Temporal OD	622 ± 35	621 ± 35	617 ± 35	609 ± 35	<0.001
Temporal OS	617 ± 37	615 ± 34	613 ± 36	608 ± 36	<0.001
Corneal thickness in circles around corneal centre					
D 0 mm OD	554 ± 33	553 ± 33	551 ± 32	547 ± 32	<0.001
D 0 mm OS	554 ± 34	553 ± 33	551 ± 32	548 ± 33	<0.001
D 2 mm OD	563 ± 33	562 ± 32	560 ± 32	557 ± 32	<0.001
D 2 mm OS	563 ± 33	562 ± 33	560 ± 32	558 ± 33	<0.001
D 4 mm OD	589 ± 33	589 ± 33	586 ± 33	583 ± 33	<0.001
D 4 mm OS	589 ± 34	589 ± 33	586 ± 33	584 ± 34	<0.001
D 6 mm OD	634 ± 36	632 ± 35	627 ± 35	621 ± 36	<0.001
D 6 mm OS	634 ± 35	632 ± 35	627 ± 35	622 ± 36	<0.001
D 8 mm OD	700 ± 40	693 ± 39	684 ± 40	676 ± 41	<0.001
D 8 mm OS	701 ± 39	693 ± 40	684 ± 40	677 ± 41	<0.001
D 10 mm OD	789 ± 49	776 ± 50	765 ± 51	758 ± 51	<0.001
D 10 mm OS	791 ± 50	777 ± 50	765 ± 51	760 ± 50	<0.001

D = Distance; OD = right eye; OS = left eye. All corneal thickness values are reported in µm.

with ocular and anthropometric parameters in a large population-based study. Our study highlights that increased age is associated with a thinner central and peripheral cornea. Furthermore, the present study provides evidence that higher intraocular pressure is associated with a thicker cornea in the centre and periphery. In contrast, glaucoma was linked to a thinner cornea at the 4 mm circle and towards the periphery independently of intraocular pressure. This new information is particularly of clinical importance as peripheral corneal thickness is important for surgical procedures like laser or refractive surgery (Doughty & Zaman 2000; Javaloy et al. 2004), glaucoma assessment (Doughty & Zaman 2000) and observation of corneal diseases such as keratoconus (Pflugfelder et al. 2002) and Fuchs endothelial dystrophy (Borboli & Colby 2002).

In our analyses, we observed that a thicker central and peripheral cornea until 6 mm was associated with male gender. These results are in line with previous reports observing thicker CCT in men (Pfeiffer et al. 2007; Elflein et al. 2014). In contrast, Hashemi et al. (2016) found no difference for corneal thickness

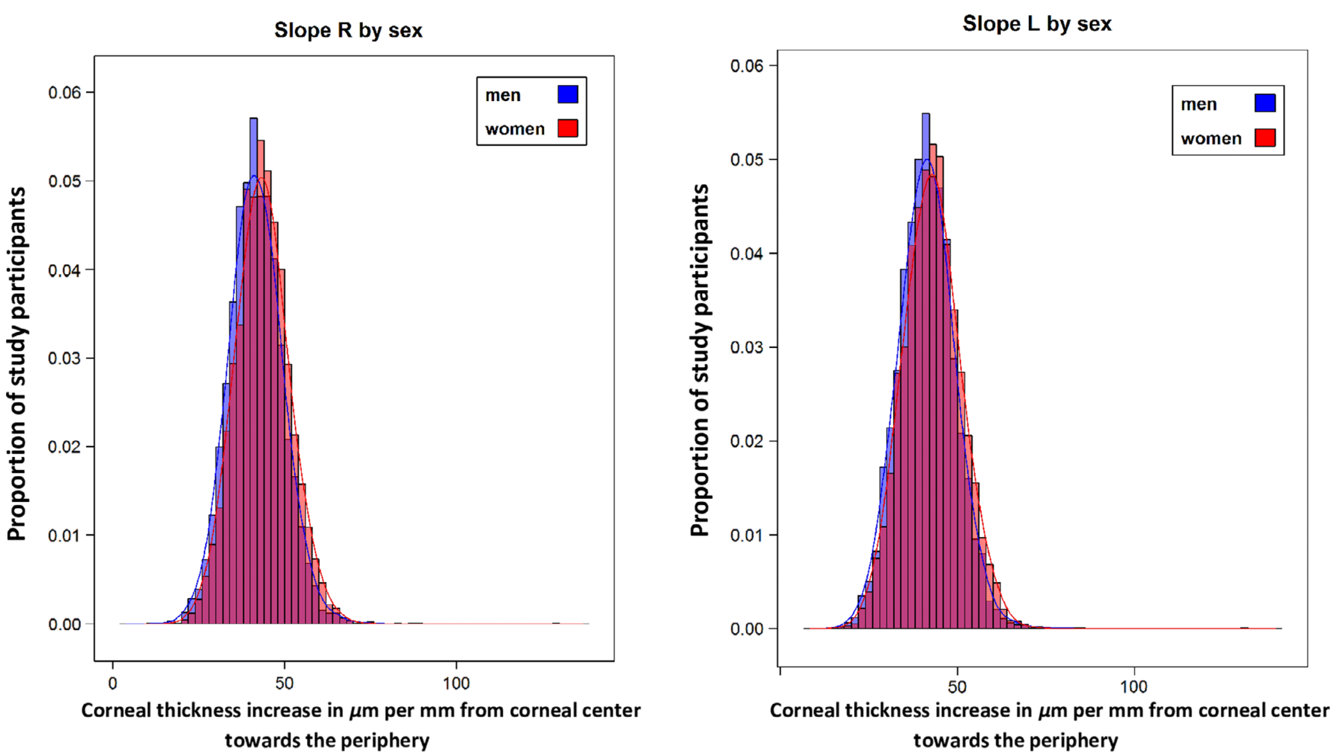

Fig. 1. Corneal thickness increases towards the periphery for the right and left eyes separately (*n* = 9729).

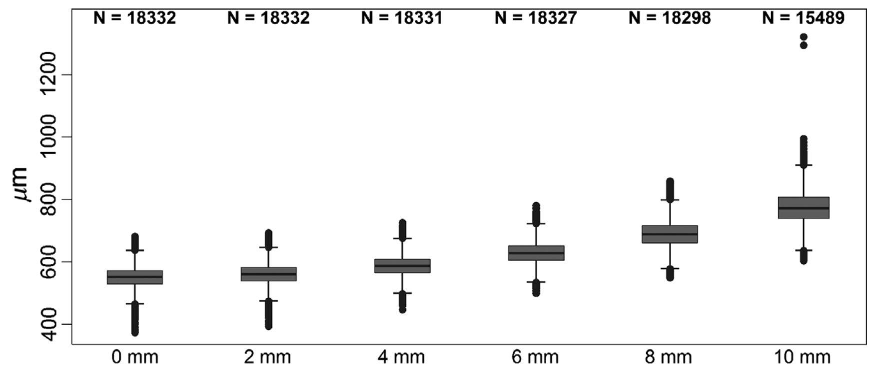

Fig. 2. Corneal thickness in micrometres of both eyes for the different circles towards the periphery.

in the apex. However, the authors reported in their multivariable model that corneal thickness in the 4 mm ring was associated with female gender showing a decreased corneal thickness compared with men (Hashemi et al. 2016). The authors speculated that this might be related to a decreased hydrating effect of oestrogen in postmenopausal women in their participants. Overall, our study highlights that gender seems to influence not only the corneal centre but also corneal periphery.

The relationship of lower central and peripheral corneal thickness with higher age is in congruence to the study by Hashemi and colleagues who observed a significant thinning in the corneal centre (1.5 µm in apical thickness) and the corneal periphery over an observation period of 5 years in participants aged 40–64 years (Hashemi et al. 2016). A relationship between thinner pericentral corneal thickness with higher age was observed in previous studies (Hashemi

Table 3. Association analyses with corneal thickness measured with Scheimpflug tomography in different corneal areas. Data from the population-based Gutenberg Health Study (2012–17) (*n* eyes = 16 698).

Parameters Multivariable analysis	D 0 mm B (CI 95%) p-value	D 2 mm B (CI 95%) p-value	D 4 mm B (CI 95%) p-value	D 6 mm B (CI 95%) p-value	D 8 mm B (CI 95%) p-value	D 10 mm B (CI 95%) p-value	Slope 0–10 mm B (CI 95%) p-value
Sex (female)	−4.14 (−5.95; −2.32) <0.001	−4.50 (−6.31; −2.68) <0.001	−4.80 (−6.65; −2.94) <0.001	−3.76 (−5.76; −1.76) <0.001	−2.09 (−4.40; 0.21) 0.075	−1.99 (−5.17; 1.19) 0.22	0.40 (−0.06; 0.86) 0.087
Age (years)	−0.26 (−0.33; −0.19) <0.001	−0.24 (−0.31; −0.17) <0.001	−0.28 (−0.35; −0.21) <0.001	−0.54 (−0.61; −0.46) <0.001	−0.96 (−1.05; −0.88) <0.001	−1.22 (−1.34; −1.11) <0.001	−0.24 (−0.25; −0.22) <0.001
Height (m)	−0.06 (−0.16; 0.04) 0.42	−0.08 (−0.18; 0.02) 0.11	−0.13 (−0.23; −0.03) 0.012	−0.18 (−0.29; −0.07) 0.001	−0.23 (−0.36; −0.11) <0.001	−0.29 (−0.46; −0.12) <0.001	−0.04 (−0.06; −0.01) 0.005
Smoking (yes)	2.33 (0.55; 4.11) 0.010	2.44 (0.65; 4.22) 0.007	2.62 (0.82; 4.43) 0.004	2.67 (0.75; 4.60) 0.007	1.33 (−0.85; 3.52) 0.23	−2.04 (−4.92; 0.84) 0.17	−0.72 (−1.14; −0.31) <0.001
Diabetes (yes)	0.04 (−2.20; 2.28) 0.97	0.27 (−1.98; 2.52) 0.81	0.96 (−1.34; 3.26) 0.41	2.24 (−0.24; 4.73) 0.077	2.71 (−0.12; 5.54) 0.060	−0.29 (−4.13; 3.55) 0.88	0.28 (−0.25; 0.82) 0.30
Refractive error (dioptre)	0.33 (−1.06; 1.73) 0.64	0.33 (−1.07; 1.72) 0.64	0.24 (−1.18; 1.65) 0.74	−0.04 (−1.55; 1.48) 0.96	−1.07 (−2.81; 0.67) 0.23	−3.15 (−5.49; −0.82) 0.008	−0.70 (−1.14; −0.31) <0.001
White-to-white distance (mm)	−3.82 (−4.90; −2.75) <0.001	−4.09 (−5.15; −3.03) <0.001	−5.31 (−6.42; −4.20) <0.001	−7.00 (−8.24; 5.75) <0.001	−9.14 (−10.6; −7.67) <0.001	−11.9 (−14.0; −9.76) <0.001	−0.75 (−1.10; −0.40) <0.001
Mean corneal radius (mm)	7.00 (3.99; 10.0) <0.001	6.70 (3.86; 9.53) <0.001	7.22 (4.75; 9.69) <0.001	7.57 (5.27; 9.87) <0.001	0.81 (−1.76; 3.37) 0.54	−18.1 (−22.1; 14.2) <0.001	−3.61 (−4.44; −2.79) <0.001
Intraocular pressure (mmHg)	2.31 (2.14; 2.48) <0.001	2.25 (2.07; 2.42) <0.001	2.28 (2.10; 2.46) <0.001	2.27 (2.08; 2.46) <0.001	2.24 (2.02; 2.45) <0.001	2.35 (2.05; 2.66) <0.001	−0.12 (−0.17; −0.08) <0.001
Glaucoma (yes)	−3.11 (−6.48; 0.26) 0.070	−3.39 (−6.79; −0.00) 0.076	−4.85 (−8.33; −1.37) 0.006	−7.24 (−11.0; −3.52) <0.001	−9.94 (−14.2; −5.68) <0.001	−15.6 (−21.4; −9.78) <0.001	−1.94 (−2.71; −1.17) <0.001
Pseudophakia (yes)	1.43 (−0.41; 3.27) 0.13	1.50 (−0.34; 3.33) 0.11	1.65 (−0.38; 3.67) 0.11	1.86 (−0.37; 4.10) 0.10	3.30 (0.89; 5.71) 0.007	7.49 (3.53; 11.5) <0.001	0.89 (0.34; 1.44) 0.001

Multivariable models with central corneal thickness (thinnest position), as well as in rings with 2, 4, 6, 8 and 10 mm diameter around corneal centre and slopes 0–10 mm as depending variable. The relationship between corneal thickness at these locations and possible associated factors was determined using linear regression models with inclusion of age, sex, height, smoking, diabetes, refractive error, white-to-white distance as surrogate parameters for corneal diameter, mean corneal radius, intraocular pressure, self-reported glaucoma and previous cataract surgery as independent parameters.

et al. 2011; Galgauskas et al. 2014) while a European study observed no association between ageing and corneal thickness in the centre and periphery (Jonuscheit & Doughty 2009). In contrast, Rüfer et al. (2007) reported a positive relationship between central corneal thickness and age. Overall, the different devices assessing central and peripheral corneal tomography used in these studies may have caused the different results. In our study, a higher age was associated with a decreased corneal thickness. Age-related changes of the cornea were also reported for different corneal layers by various studies. For the corneal epithelium, an age-related decrease of its thickness was measured in the corneal periphery while, in the corneal centre, there was no association with age (Rüfer et al. 2007). For the corneal endothelium, an age-related decrease of endothelial cells was observed (Roszkowska et al. 2004). Overall, these previously reported changes of the individual corneal layers may have contributed to the finding of the present study which found a decreased corneal thickness particularly in the corneal periphery in older persons.

When analysing the distribution of corneal thickness with respect to quadrants, the superior cornea was the thickest followed by the nasal cornea and the inferior cornea, while the cornea in the temporal quadrant was the thinnest. This distribution is in line with previous data of different authors (Ambrósio et al. 2006; Khoramnia et al. 2007; Zheng et al. 2008).

In our investigation, we could assess the relationship of a broad spectrum of non-ophthalmic parameters such as body height which was associated with a thinner cornea in the corneal periphery. In a Japanese study, the authors found associations of CCT with body weight (Tomidokoro et al. 2007). In contrast, the authors of the Beijing Eye Study found no link of CCT with body weight and body height (Zhang et al. 2008). In the Ocular Hypertension Treatment Study, the authors found a correlation between CCT with diabetes (Brandt et al. 2001) which is in contrast to our results as we did not find any association between diabetes and corneal thickness neither in the centre nor in the periphery. In agreement, an earlier investigation found no differences in absolute peripheral corneal thickness values between healthy subjects and those with diabetes. However, intraindividual difference between thinnest corneal thickness and peripheral pachymetry readings has shown significant higher values in individuals with diabetes than in healthy subjects (Ramm et al. 2020).

The current study focussed on the relationship between peripheral corneal thickness and ocular parameters. The corneal thickness at 10 mm circles showed an inverse association with a hyperopic refractive error. This effect was not present in the central cornea.

In previous reports of the population-based Central India Eye and Medical Study (Nangia et al. 2010) and the Tehran Eye Study (Hashemi et al. 2009), no association was observed between refractive error and central corneal thickness. Overall, our data can extent previous literature and provide new evidence that ocular geometry such as white-to-white distance, corneal radius and refractive error are linked to corneal thickness in the peripheral cornea. Furthermore, we observed an increased thickness of the 8 and 10 mm circle with pseudophakia. One reason for this association might be the scar after clear cornea incision. On the other hand, Wong et al. observed a higher peripheral corneal thickness after phacoemulsification with longer duration and higher cumulative energy (Wong et al. 2014). This has to be considered when interpreting our results regarding pseudophakia.

It is well known that IOP measurements are linked to CCT (Whitacre et al. 1993; Katsimpris et al. 2015; Hansen & Ehlers 1971; Ehlers et al. 1975; Doughty & Zaman 2000; Tomidokoro et al. 2007) and should be considered in diagnosis and management of patients with glaucoma and ocular hypertension. This can lead to an underestimation of IOP in patients with a thinner and overestimation in patients with thicker corneas (Whitacre et al. 1993). However, the association of peripheral corneal thickness with IOP is less known. Interestingly, we observed an association between intraocular pressure and corneal thickness in the corneal centre and periphery. Our data indicate that even peripheral corneal thickness shows a significant association with intraocular pressure which is congruent to previous studies (Whitacre et al. 1993; Katsimpris et al. 2015). Our data further show that a less increase in corneal thickness towards the periphery is particularly present in subjects with glaucoma. A recent study suggests that the pachymetry slope towards the periphery increases to a smaller amount in normal-tension glaucoma compared with controls (Pillunat et al. 2019), which is in line with our results. The pathophysiologic reasons should be further investigated in the future.

Strengths and limitations

One limitation of the present study is that the accuracy of corneal thickness measurements can vary and depend on the device used and on day time of measurement (Read & Collins 2009). Within our study, we used non-contact Scheimpflug technology for corneal thickness measurement, which was evaluated in several studies showing high reproducibility and repeatability (Barkana et al. 2005; Grewal et al. 2010) when compared to ultrasound biometry and showed an excellent repeatability particularly for the peripheral corneal zones (Xu et al. 2016). Another limitation is that Scheimpflug measurements could be slightly decentrated which could affect in some cases the measurement at the 10-mm ring position contributing to not fully measurable or falsified corneal thickness measurements at the most peripheral rings. We thus evaluated outliers of these measurements and excluded them if necessary. The major strengths of our study are the population-based sample, the large number of participants and standardized examinations and a broad range of various general and ocular parameters. The use of non-contact measurements is feasible to conduct population-based surveys. Each examination was strictly performed according to standard operating procedures. Another strength of the present analysis is the investigation of a broad spectrum of non-ophthalmic factors.

Summary

The results of the present study suggest that several general and ocular parameters are related to peripheral corneal thickness. These factors should be considered when interpreting peripheral corneal thickness, for example in the context of corneal ectasia or before refractive surgery. In the context of diagnosing glaucoma, a smaller increase in corneal thickness towards the periphery might be a new marker.

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