Germany: Longitudinal analysis of intraocular pressure in healthy eyes

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Abstract: Purpose: The knowledge of physiology of intraocular pressure (IOP) is important for the interpretation of pathophysiological alterations of IOP in glaucoma patients. Thus, the purpose of this study was a retrospective analysis of follow-up data of IOP in normal subjects in Germany. Methods: A retrospective analysis of IOP data of 112 eyes of 112 normal subjects (age: 18–81 years) of the Erlangen Glaucoma Registry (NCT00494923; ISSN 219-5008, CS-2011) was performed. Data of normal subjects with annual visits (with a number of 2–18) were analyzed. IOP was measured by Goldmann applanation tonometry at each visit in the morning. After IOP correction by the Dresdner correction table (according to the central corneal thickness, CCT), different statistical models were applied taking in account the influence of age and gender. Results: A significant influence of age and gender was observed on CCT (p < 0.001). Additionally, age affected IOP (p = 0.0018), yet, gender did not show any dependency on IOP. A significant age effect was observed on IOP_corr without differences between female and male. Quantile analysis yielded a significant change of the 0.25 percentile of IOP (p < 0.0001) and a slightly change for the 0.75 percentile of IOP (p = 0.05) over time in women. In men, a significant change was seen for the 0.5 percentile of IOP over time (p = 0.04). Conclusion: An age-dependency on CCT and IOP was observed in the German population. Additionally, gender affected CCT, yet not IOP.

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The main research topic of our group is glaucoma disease, the second leading cause of blindness in the developing countries. We investigate risk factors and pathophysiological mechanisms, which cause or are associated with glaucoma. Additionally, we work on improving the present glaucoma diagnostics and developing novel diagnostic techniques. In cooperations new therapeutic strategies for glaucoma disease were investigated. The basis for all these research work is knowledge of ocular morphology and function in healthy eyes. Thus, we perform studies with the aim of investigating ocular parameters and their physiological changes in healthy eyes.

PUBLIC INTEREST STATEMENT
Glaucoma is one of the leading causes of blindness in the developing countries. As it is known that intraocular pressure (IOP) is the main risk factor for this disease, data about its physiological change in healthy eyes are important for interpretation in disease. The study presents data of the normal cohort of the Erlangen Glaucoma Registry, a longitudinal follow-up study, starting in 1991. An influence of age on IOP was observed, yet gender did not show any dependency. Recent studies showed that IOP is dependent on central corneal thickness (CCT), thus IOP must be corrected according to CCT.1 CCT was influenced by age and gender in the present normal cohort. After IOP correction by CCT, IOP_corr was changing over time, yet no gender effect was observed. 1.Kohilaas M Effect of central corneal thickness, corneal curvature and axial length on applanation tonometry. Archives of ophthalmology 2006; 124: 471-476.
1. Introduction

Glaucoma is one of the leading causes of blindness in the developing countries (Quigley & Broman, 2006). This neurodegenerative disease proceeds in almost every patient although all therapeutic regimes have been performed (Hohberger et al., 2017). All therapies aim to lower the elevated IOP, being the main risk factor of glaucoma disease. Each single millimeter of mercury increase of IOP can enhance glaucoma progression rate at about 12–13% (Leske et al., 2003). It is important to understand the physiology of IOP in normal subjects in order to interpret the pathophysiological alterations of IOP in patients.

IOP is a steady-state equilibrium of the production of aqueous humor in the non-pigmented ciliary body and outflow via trabecular meshwork or uveoscleral. At this steady-state, IOP shows a mean of 15.5 ± 2.57 mmHg in healthy human eyes (Leydhecker et al., 1958; Schottenstein, 1989). Regulation of IOP is a complex process. As it is known that several factors influence IOP. IOP is not a “fixed” parameter (diurnal, short-term or long-term fluctuations). Circadian IOP variations were presented by Sidler-Huguenin in 1898 for the first time (Sidler-Huguenin, 1898). Up to now, several studies have been performed, investigating IOP variations (Jonas et al., 2007; Lee et al., 2010; Sit, 2014). Short-term fluctuations represent IOP changes within seconds (Jonas et al., 2007; Lee et al., 2010), whereas long-term fluctuations represent IOP changes within several visits (Asrani et al., 2000; Sit, 2014). Longitudinal studies, investigating IOP variations during lifetime, are rare in normal subjects (Astrom et al., 2014; Bonomi et al., 1998; Klein et al., 1992; Leske et al., 1997; Zhao et al., 2014). Most studies show a cross-sectional design or are population-based prevalence studies (Bonomi et al., 1998; Leske et al., 1997).

The present study aimed to investigate IOP and central corneal thickness (CCT) changes in normal subjects in Germany. Additionally, the influence of gender on IOP and CCT was investigated.

2. Material and methods

2.1. The Erlanger glaucoma registry

A retrospective analysis of 112 healthy eyes of 112 subjects of the control group of the Erlangen Glaucoma Registry (EGR; ClinicalTrials.gov Identifier: NCT00494923; ISSN 2191-5008, CS-2011 (Hohberger et al., 2017)) was done. The EGR is an observational, longitudinal follow-up study with the aim of research on risk factors for glaucoma disease and glaucoma progression. In addition to glaucoma suspects and glaucoma patients, normal subjects were included as control subjects in order to get normal follow-up data. Normal subjects did not show any eye diseases or systemic disorder with ophthalmologic involvement. In a retrospective analysis, the normal subjects of the EGR were analyzed in respect to gender variations over time. As the 112 subjects represent the control group of the EGR, these subjects received the same morphometric and functional tests as glaucoma patients. All subjects underwent a complete ophthalmologic examination, including slit-lamp biomicroscopy, funduscopy, papillometry, Spectralis Optical Coherence Tomography (Spectralis® OCT Version 1.9.10.0, Heidelberg Engineering, Heidelberg, Germany) and standard white-on-white full-field perimetry (Octopus 500, G1 protocol, Interzeag, Schlieren, Switzerland), respectively, during each visit. IOP was measured by GAT (Haag Streit, Koeniz, Switzerland, different examiners) in the morning in order to be uninfluential of circadian changes. Central corneal thickness was measured by central ultrasound pachymetry (Pachymeter SP-100, Tomey, Aichi, Japan).

Normality was defined as age-dependent ophthalmological findings and no systemic disorder with ophthalmologic involvement. In addition, data of standard white-on-white full-field perimetry had to be with <3 adjoining test points with defects p < 0.05, no adjoining test points with defects p < 0.01, and mean visual field defect (MD) < 2.8 dB. IOP was required to be ≤21 mmHg and optic nerve head had to be
healthy (stage 0), classified after Jonas (Jonas et al., 1988a, 1988b). Exclusion criteria was IOP > 21 mmHg in two repeated measurements. Retinal nerve fiber layer thickness was within normal limits (Spectralis® OCT). Data of normal subjects with ≥2 visits and ≥annual interval were analyzed (number of visits: 2–18, median observation period: 8.3 ± 5.8 years). Informed consent was received from all subjects. The study has been approved by the local ethics committee and performed according to the tenets of the Declaration of Helsinki.

2.2. Statistical analysis

Statistical analysis has been done using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Data were presented as mean ± standard deviation (SD). Data of one eye (randomly chosen) per subject were analyzed, respectively. To analyze the longitudinal data cohort, in particular, the influence of age through the different measurements, we applied a mixed model, with the specification that the measurements for individuals are repeated and therefore auto-correlated. The different models have as dependent variables: IOP, CCT and IOPcorr. The number of annual visits was set as a weight variable. Moreover, in the mixed model, we incorporate the fixed and random effects. We modelled the individual differences assuming different random intercepts for each participant. The model was corrected for gender. As a CCT dependency is known on IOP (IOPcorr) (Kohlhaas et al., 2006), data have been corrected according to the Dresdner Correction Table (Kohlhaas et al., 2006). Moreover, being in the sample-set very young individuals we applied also a Quantile analysis. The age is divided in quantiles (0.25–0.5–0.75–0.95). The changing of the different variables (IOP, CCT and IOPcorr) was focused on the various quantiles over time. In such case, the analysis was divided for female and male. As before, the number of annual visits was set as a weight variable.

3. Results

3.1. Demographic data of the German cohort

One eye per subject was included in the statistical analysis: 112 eyes of 112 subjects (66 women, 46 men). Age range was between 18 and 81 years. The follow-up period ranged between 1 and 25 years (Figure 1). A general overview can be seen in Table 1. Quantiles (0.25–0.5–0.75–0.95) represent age range for men and women of the present cohort.
3.2. Intraocular pressure (IOP) in men and women
Mean IOP was calculated for each percentile of the cohort. Additionally, the data were subdivided in respect to gender. A mean IOP of 14.86 ± 2.17 mmHg (0.25 percentile), 15.68 ± 2.72 mmHg (0.5 percentile), 14.05 ± 2.61 mmHg (0.75 percentile) and 13.72 ± 2.72 mmHg (0.95 percentile) were observed for women. In men a mean IOP of 15.38 ± 2.66 mmHg (0.25 percentile), 15.04 ± 2.29 mmHg (0.5 percentile), 14.87 ± 2.97 mmHg (0.75 percentile) and 13.67 ± 2.03 mmHg (0.75 percentile) were yielded. A significant effect of age on IOP was observed (p = 0.0018). Gender did not affect IOP (p > 0.05).

3.3. Central corneal thickness
Mean CCT was calculated for each percentile of the cohort, subdivided by gender, respectively:

A mean CCT of 549.35 ± 26.52 mm (0.25 percentile), 541.41 ± 32.71 mm (0.5 percentile), 549.86 ± 31.12 mm (0.75 percentile) and 542.30 ± 35.57 mm (0.95 percentile) were seen in women. Men yielded a mean CCT of 566.63 ± 26.19 mm (0.25 percentile), 558.92 ± 34.28 mm (0.5 percentile), 558.96 ± 47.08 mm (0.75 percentile) and 564.28 ± 25.60 mm (0.75 percentile) were observed.

Statistical analysis (mixed model with fixed and random effects) yielded a significant age dependency of CCT (p < 0.0001). Additionally, a significant gender effect on CCT was observed (p = 0.0015).

3.4. IOP\textsubscript{corr}
According to Kohlhaas et al. (2006), IOP was corrected by CCT (IOP\textsubscript{corr}). This IOP\textsubscript{corr} did not differ between women and men (p > 0.05). Yet, an age effect was observed (p = 0.02).

3.5. Quantile analysis of IOP, CCT and IOP\textsubscript{corr}
Quantile analysis for IOP, CCT and IOP\textsubscript{corr} was done over time, subdivided according to gender. The number of annual visits was sated as a weight variable. The 0.25 percentile of IOP changed significantly over time (p < 0.0001, CI: −0.09, −0.02) and the 0.75 percentile slightly significant for women (p = 0.05, CI: −0.08, 0.00, Figure 2(a)). The 0.5 quartile did show an additionally significance on IOP for men (p = 0.04, CI: −0.08, 0.00, Figure 2(b)). The remaining quartiles of IOP revealed to be unchanged over time in men and women (p > 0.05). Data can be seen in Table 2.

Quantile analysis of CCT did not show any significance over time in women and men (p > 0.05, Figure 2(b,e)).

The 0.25 percentile of IOP\textsubscript{corr} was affected by time in women (p = 0.02, CI: −0.09, −0.01), the other quantiles remained unchanged by time (p > 0.05, Figure 2(c)). Additionally, no effect of time on quantile analysis of IOP\textsubscript{corr} was observed in men (p > 0.05, Figure 2(f)).

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### Table 1. General overview of the study cohort, subdivided for gender

| Gender | Percentile | Age |
|--------|------------|-----|
| 1      | 0.25       | 42  |
| 1      | 0.5        | 53  |
| 1      | 0.75       | 61  |
| 1      | 0.95       | 69  |
| 2      | 0.25       | 40  |
| 2      | 0.5        | 57  |
| 2      | 0.75       | 68  |
| 2      | 0.95       | 77  |
4. Discussion

Measurement and analysis of IOP are essential in glaucoma disease and follow-up. Thus, the knowledge of the physiology of IOP is the basis of a correct interpretation of pathophysiological changes of IOP in glaucoma patients. As the Erlangen Glaucoma Registry is an observational, longitudinal follow-up study with standardized clinical examinations (morphology, function, IOP), a cohort of normal subjects has been and still is observed in addition to glaucoma suspects and glaucoma patients serving as a control group. The long-term IOP data of the normal subjects of the EGR showed IOP courses over a large age range (18–81 years). An age-dependency of IOP was observed in these normal eyes, yet, being unaffected by gender. CCT was affected by age and gender, respectively. IOPcorr showed an age-, yet no gender-dependent effect.

Measurement of IOP by GAT is the gold standard in IOP measurements up to now. As it is known that GAT is affected by CCT, it is necessary to “correct” the measured IOP data according to the individual CCT for each patient. The Dresdner correction table (Kohlhaas et al., 2006) is a quick and easily usable correction sheet, which is commonly used for IOP corrections according to CCT. The CCT data of the present cohort were significantly different between male and female. Additionally, CCT was linked to age-dependent changes. Our data confirm the data of the Gutenberg Health Study, the only population-based data study in Germany up to now (Elflein et al., 2014; Hoffmann et al., 2013). Men showed a significantly thicker mean CCT (555 ± 35 μm (Elflein et al., 2014), 557.3 ± 34.2 μm (Hoffmann et al., 2013)) than women (549 ± 35 μm (Elflein et al., 2014), 551.6 ± 35.2 μm (Hoffmann et al., 2013)). Ethnicity seems to be an influencing factor on CCT, as CCT of other ethnicities appeared to be lower: a mean CCT of 529 ± 39 μm was reported for the population of Reykjavik (Eysteinsson et al., 2002), 521 ± 32 μm (Tomidokoro et al., 2007) for the Asian population, 514 ± 33 μm for Indian (Nangia et al., 2010), and 508 ± 33 μm for Australian individuals (Landers et al., 2007). As most of the studies on CCT in normal subjects were cross-sectional or population-based studies, no data are available up to now regarding the potential physiological alterations of CCT in European normal subjects with a longitudinal follow-up design. The data presented are the first data on CCT in the German population with an age range of 18–81 years and a follow-up period until 18 visits. Contrary to the population-based Gutenberg Health Study the present study showed an age-dependency of CCT within the German population. CCT increased with age in men and women, contrary to the observed decrease of CCT in the Malayan (Hashemi et al., 2016) and Indian populations (Nangia et al., 2010).
Table 2. Quantile analysis for IOP, CCT and IOP_{corr} considering gender (estimates, standard deviation, 95% confidence interval, p-value)

| IOP | Parameter Estimates AGE (for Gender) | t Value | Pr > |t |
|-----|-------------------------------------|---------|------|
|     | Percentile | DF | Estimate | Standard error | 95% Confidence Limits |     |
| IOP | 0.25 | 1 | −0.02 | 0.02 | −0.06 | 0.02 | −1.20 | 0.23 |
|     | 0.50 | 1 | −0.04 | 0.02 | −0.08 | 0.00 | 2.05 | 0.04 |
|     | 0.75 | 1 | −0.11 | 0.02 | −0.06 | 0.01 | −1.20 | 0.23 |
|     | 0.95 | 1 | −0.08 | 0.02 | −0.19 | 0.03 | −1.43 | 0.16 |
| IOP | 0.25 | 1 | −0.02 | 0.02 | −0.06 | 0.02 | −1.20 | 0.23 |
|     | 0.50 | 1 | −0.04 | 0.02 | −0.08 | 0.00 | 2.05 | 0.04 |
|     | 0.75 | 1 | −0.04 | 0.02 | −0.08 | 0.00 | 2.05 | 0.04 |
|     | 0.95 | 1 | −0.07 | 0.02 | −0.17 | 0.03 | −1.37 | 0.17 |
| CCT | 0.25 | 1 | −0.08 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.50 | 1 | −0.06 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.75 | 1 | −0.06 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.95 | 1 | −0.05 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
| CCT | 0.25 | 1 | −0.08 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.50 | 1 | −0.06 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.75 | 1 | −0.06 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
|     | 0.95 | 1 | −0.05 | 0.11 | −0.25 | 0.47 | 0.61 | 0.54 |
| IOP_{corr} | 0.25 | 1 | −0.05 | 0.02 | −0.09 | 0.01 | −2.40 | 0.02 |
|     | 0.50 | 1 | −0.03 | 0.02 | −0.07 | 0.02 | −1.27 | 0.21 |
|     | 0.75 | 1 | −0.07 | 0.04 | −0.14 | 0.00 | −1.90 | 0.06 |
| IOP | Parameter Estimates AGE (for Gender1) | Parameter Estimates AGE (for Gender 2) | t Value | Pr > |t|
|-----|-------------------------------------|--------------------------------------|---------|------|--|------|-------|
|     | Percentile | DF | Estimate | Standard error | 95% Confidence Limits | t Value | Pr > |t|
|     | 0.95 | 1 | -0.07 | 0.04 | -0.15 | 0.02 | -1.55 | 0.12 |
|     | 0.25 | 1 | 0.00 | 0.02 | -0.03 | 0.03 | 0.00 | 1.00 |
|     | 0.5 | 1 | -0.03 | 0.02 | -0.06 | 0.00 | -1.72 | 0.09 |
|     | 0.75 | 1 | -0.04 | 0.02 | -0.08 | 0.00 | -1.75 | 0.08 |
|     | 0.95 | 1 | -0.06 | 0.07 | -0.20 | 0.09 | -0.80 | 0.42 |
Intraocular pressure in the normal cohort of the Erlangen Glaucoma Registry showed an age-dependency, yet unaffected by gender. Literature regarding IOP and gender are controversial up to now. The Tehran Eye Study revealed no association of IOP and gender (Hashemi et al., 2016), similar to our findings. On the contrary, a Japanese cross-sectional study reported a significantly higher IOP in men compared to women for subjects younger than 60 years (Nomura et al., 1999). IOP in the Gutenberg Health Study cohort showed a significantly decreased IOP in women ($13.9 \pm 2.5$ mmHg) compared to men ($14.1 \pm 2.7$ mmHg) (Hoehn et al., 2013). Yet, the Barbados Eye Study showed higher IOP in women than in men (Leske et al., 1997). However, all these studies are not comparable due to different study designs, different ethnicities and different tonometers (noncontact vs. GAT).

Age-dependent changes in IOP were seen in the present study. The importance of these results is strengthened as longitudinal IOP data of normal subjects are rare in the literature up to now. Most of the recent studies were cross-sectional or population-based. The Gutenberg Health Study (cross-sectional) offered lower IOP values with increasing age, however, only in women (Hoehn et al., 2013). The data of the present study confirm this finding of a decrease of IOP with age in women. Contrary, this effect was additionally observed in men in the present study. An increase of IOP with increasing age was observed in the Egna-Neumarkt Study, yet the study did not exclude glaucoma suspects, ocular hypertension and glaucoma patients (Bonomi et al., 1998). The population-based Barbados Eye Study yielded an increase of IOP about 1 mmHg per 10 years in the black population (Leske et al., 1997), going conform with data of the population-based Beaver Dam Eye Study (Klein et al., 1992). A decrease of IOP with an increase of age has been seen in the Korean population; however, IOP of women between 30 and 59 has not been affected by age (Zhao et al., 2014). Also, this study design varied from ours; a direct comparison to our data is impeded as noncontact tonometers were used with an 8 years follow-up period. There is a discrepancy of IOP data of cross-sectional and longitudinal studies. Whereas IOP seems to decrease with increasing age in a Japanese population, longitudinal analysis of IOP data with a 8-year follow-up period yielded an increase of IOP with increasing age (Nomura et al., 1999). Up to day, no data are available regarding IOP changes in a normal German population. The only comparable study was conducted in a Swedish population with a follow-up period of 21 years (3 visits with 7-year interval, tonometry: GAT) (Astrom et al., 2014). Contrary to our data, IOP did not change over the observed period. Further longitudinal studies are necessary to investigate the potential age effect on IOP in different populations.

However, our study is not without limitation. Several further factors might influence IOP, which we did not consider in the present study. Systemic parameters (e.g. blood pressure) or ocular properties (e.g. corneal curvature), which may be affected by age-dependent changes, could affect IOP additionally. As no further study is available right now, presenting longitudinal IOP data considering other systemic or ocular factors, these parameters are up for further investigations.

5. Conclusion
For the very first-time longitudinal IOP and CCT fluctuations were analyzed in a German cohort of normal subjects. Age and gender affected CCT. Additionally, an age-dependency was observed for IOP, yet is unaffected by gender.
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