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Age related change on the waist of the nerve fiber layer in the optic nerve head

Åldersförändring av midjan på nervfiberlagret i synnervshuvudet

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Populärvetenskaplig sammanfattning

Glaukom (grön starr), innefattar en samling sjukdomar som ger en fortskridande förtvining av synnerven, som yttrar sig kliniskt som synfunktionsrubbningar inledningsvis, och kan obehandlad leda till blindhet.

Prevalensen är cirka 2% över 40 år. Sjukdomen är betydligt vanligare hos äldre, över 75 år är prevalensen 5%. Prognosen, i och med den globalt åldrande befolkningen, är att den kommer att bli allt vanligare.

Glaukom debuterar smygande, och först när en stor del av synfältet har försvunnit märks det för patienten att synen har blivit sämre. Hjärnan har en förmåga att korrigera för blinda områden, och det gör att symtomdebuten dröjer, och då även att behandlingen inte sätts in i tid. Skadan på synnerven är permanent, och behandling syftar endast till att minska eller i bästa fall bromsa skadorna på synnerven. Att glaukom ofta upptäcks sent, och att 50% går runt utan diagnos är således ett problem.

Glaukomdiagnostiken och uppföljning vilar idag på tre ben:

1. Mätning av ögats tryck, vilket är viktigt för att monitorera den trycksänkande behandlingen.
2. Mätning av synfältet med datorstödd perimetri, en funktionell skattning.
3. Bedömning av synnervshuvudet och näthinnans nervfiberlager.

Det viktigaste för att skatta förlusten av nervfibrer är idag att göra en funktionell skattning av synfältet. Detta är dock en tidskrävande metod med bristande precision.

OCT, optisk koherenstomografi, är en ny metod för att avbilda näthinnan och synnerven. Den är snabbare och är enklare än att göra en funktionell skattning av synfältet. Läkaren tar endast ett par bilder av ögat, som kan analyseras med hjälp av AI, och därigenom få en uppskattning av förtviningen av synnerven.

I skrivande stund saknas dock referensvärden på området, och alla mätvärden i sjukvården måste alltid jämföras med den friska normalpopulationen. Härvidlag råder avsaknad av underlag, varför denna studie har sjösatts, som syftar till att undersöka hur tjockleken på näthinnan avtar som en funktion av ålder.

Abstract

Background: Glaucoma is a group of diseases with chronic progressive optic nerve neuropathy. Glaucoma leads to visual field defects and morphological changes to the optic nerve head (ONH). Current methods used in managing glaucoma are time-consuming and some methods are difficult to quantify the results of.

Optic coherence tomography (OCT), Heidelberg Retina tomography (HRT) and the scanning laser polarimetry (GDx-ECG) are currently available for clinicians to image the Optic nerve head (ONH). The problem is that consensus has not been reached on how to use these tools in managing glaucoma patients.

Purpose: To determine whether the reduction of the waist of the nerve fibre layer occurs as a function of age without pathological changes in the nerve fibre layer. Further, to provide reference data on thickness of the nerve fiber layer waist for the follow-up of glaucoma patients

Methods: Totally 16 subjects were recruited and evenly divided into 4 age groups of [30 39], [40 49], [50 59], [60 69] years. In each subject 6 volumes were captured by OCT, 3 per eye, resulting in a total of 96 volumes. Pigment epithelium central limit-Inner limit of the retina Minimal distance (PIMD) in 500 equally separated angles in the frontal plane of the ONH was calculated by analyzing OCT-images with AI software developed by a research group at Uppsala University. Mean PIMD was calculated for each volume, each eye, each subject and then each group. Left eye was randomly selected for data analysis.

Results: The 95% confidence intervals for the mean PIMD in the 4 age groups were 373.0 ± 61.8, 358.5 ± 23.8, 332.9 ± 50.1 and 336.0 ± 23.3 μm respectively. Linear regression analysis showed a percentage loss of mean PIMD per decade of 2.5%. However, there was not statistically significant among groups, likely due to the small amount of enrolled subjects.

Conclusion: There is a trend of age related non-glaucomatous loss on the waist of the nerve fiber layer in ONH. The high variation between individuals regarding PIMD suggests that further studies with larger sample sizes should be conducted.

Background

Glaucoma is a heterogenous group of different diseases with chronic progressive optic nerve neuropathy. It is characterised by morphological changes in the optic nerve head (ONH) and the retinal nerve fibre layer in a characteristic fashion that correlates with Retinal ganglion cell death (RGC) and acquired visual defects [1].

Epidemiology

Glaucoma is the most common cause of irreversible blindness in the world [2,5].

Risk factors are older age, elevated intraocular pressure, ethnic background, a positive family history and high myopia (+3D). Intraocular pressure is the only modifiable risk factor among these, progression of glaucoma normally stops if the pressure is lowered with 30-50%. [3-4]

The overall prevalence of glaucoma is 2 %. The prevalence, however, varies with age and ethnicity. The global prevalence of glaucoma for the population aged 40-80 years is 3.5%. The highest prevalence of POAG is found in Africa at 4.20%. PACG is most prevalent in Asia at 1.09%. Given the aging population and chronic nature of glaucoma, the prognosis is that the affected patients aged 40-80 years will increase from 76.0 million in 2020 to 111.8 million affected in 2040. [3-4]

Classification

There are several ways of classifying glaucoma[6]:

Time: acute glaucoma (within 48 hours) and chronic glaucoma (in this study, focus will be on chronic glaucoma).

Intraocular pressure: Hypertensive glaucoma or normotensive glaucoma

Etiology: Primary and secondary glaucoma.

Gonioscopy: Primary open-angle glaucoma (POAG) or Primary angle-closure glaucoma (PACG). This definition is referring to the anterior chamber angle, which is being determined by the Iris and the cornea's size and shape. In PACG, the outflow of aqueous humour is partially or completely obstructed.

Age at diagnosis: Childhood and juvenile glaucoma.

Anatomy and pathophysiology

Aqueous humour outflow occurs primarily through the trabecular meshwork. The trabecular meshwork consists of three components, the uveal, corneoscleral meshwork and the juxtacanalicular tissue, which forms the inner wall of Schlemm's canal. After passing these three components, the fluid is in the Schlemm's canal and it is further drained by the episcleral venous system.

The ciliary body increases the outflow of aqueous humour by contracting its longitudinal muscles, and thereby pulling on the scleral spur, which is a protrusion of the sclera into the anterior chamber, this opens up the trabecular meshwork.

The other route of egress is through the ciliary body face and iris root into the suprachoroidal space, this is a pressure independent mechanism.

Imbalance in production and outflow may give rise to increased intraocular pressure.

Aqueous humour is made from plasma that leaks from fenestrated capillaries in the non-pigmented epithelium of the ciliary body. It is transported to the posterior chamber through either one of these methods: Active transport, ultrafiltration (pressure dependent) and diffusion. Through either one of these mechanisms for transport, most proteins are filtered out, so that the aqueous humour remains transparent.

The retina has three major cell types. Photoreceptor cells (rods and cones), bipolar cells and retinal ganglion cells (RGC). The RGCs later become the optic nerve. The fovea contains 50% of these RGCs [15], and the density of RGSs diminishes, the farther out from the ONH.

The axons from the peripheral RGCs travel deep in the neuroretina and make up the peripheral parts of the ONH. The central RGCs travel superficially in the neuroretina and make up the central parts of the ONH.

The anatomy of the optic disc

The ONH (sometimes called the optic disc) consists of the neuroretinal rim (in the picture below the area between the gray circle and the black circle), which surrounds the optic cup. Glaucomatous injuries lead to a characteristic widening of the cup (cupping) in the ONH, this is due to loss of RGCs, whose axons make up the neuroretinal rim.
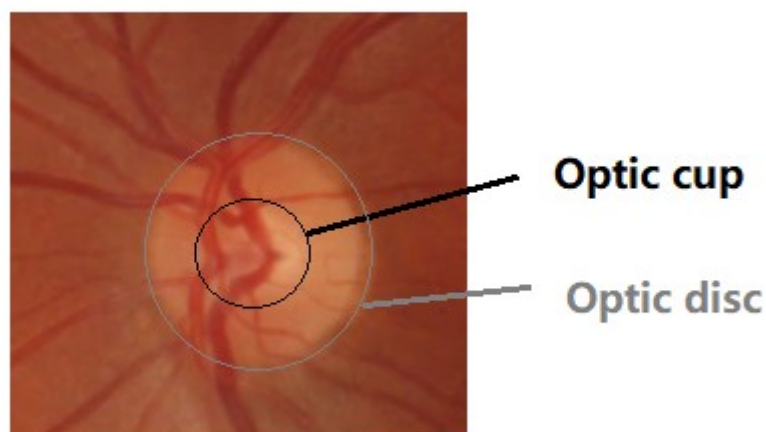

Figure 1: Anatomy of the ONH

Damage to the optic nerve fibres takes place at the lamina cribrosa (the frontier between the intraocular compartment and the retro-laminar compartment [16]), a structure shaped like a mesh, consisting of a multilayered network of collagen fibers. The exact mechanism of axonal cell death is not completely known, but in cases with increased IOP, it can in part be

explained by the mechanical pressure. The pressure difference posteriorly of the lamina cribrosa and anteriorly of the lamina cribrosa causes strain and stress on this structure [17].

The lamina cribrosa becomes compressed, deformed and remodelled, which impedes orthograde and retrograde axonal transport within the optic-nerve fibers[18-20].**Glaucoma and IOP**

The intraocular pressure (IOP) in the population is normally distributed with a slight right skew. The mean IOP in healthy normal populations is estimated at 15-16 mmHg. The standard deviation is 3.0 mmHg, implying that an IOP greater than 6.0 mmHg above the mean is to be considered an elevated IOP. [7-8].

The risk of acquiring glaucoma for those with IOP measurements of 26 mmHg is estimated to be 12 times greater, than for those with IOP within the normal range. [9]. In the light of this, the importance of lowering an elevated IOP can not be overstated.

Treatment of IOP with pharmacological interventions and surgery

Treatment of an elevated IOP reduces the risk of progression of glaucoma. A study has shown that a 25% decrease of IOP from baseline (mean untreated IOP 20.6 mmHg) reduced the risk of progression by 50%. Risk of progression decreased 10% with each mmHg IOP reduction from baseline to the first follow-up visit [10]. It has to be mentioned that the disease progression rates varied substantially between individual patients, and therefore a successful treatment can not be guaranteed in one given case.

Surgery has a place in reducing the IOP, and the IOP decreases even more than with conventional medications, such as eye drops. However, the patients who receive surgery develop more side effects, and undesired conditions (such as endophthalmitis and cataract) in the long run, suggesting that eye drops should remain the first-line treatment. [11-13].

Management of glaucoma

Pressure

Measuring the IOP, Tonometry is the one most frequently used, and it is based on the relationship between the intraocular pressure and the force necessary to deform the natural shape of the cornea by a given amount of force.

Gonioscopy is an important part of the comprehensive adult eye examination and essential for evaluating patients suspected of having, or who do have glaucoma.

The purpose of gonioscopy is to inspect the anterior chamber angle. Thus, gonioscopy differentiates between open-angle glaucoma and closed-angle glaucoma. Closed-angle glaucoma implies that there is an anatomic obstruction, impeding the natural flow of Aqueous humour.

Optic nerve head and retinal nerve fibre layer

Clinical examination

An indirect slit lamp ophthalmoscopy is often used to evaluate the ONH. The indirect slit lamp ophthalmoscopy has several advantages over the traditional direct slit lamp ophthalmoscopy; Since it is binocular, it grants the examiner three-dimensional vision. Also, it is more comfortable and allows for taking photographs, which is of crucial importance, when it comes to evaluating the appearance of the ONH over time.

The anatomic structures that are being assessed are the neuroretinal rim, which consists mainly of nerve fibres, but also some glial cells. When assessing the neuroretinal rim, signs of retinal ganglion cells (RGN) axon loss are looked for, by noting the evenness and the color of the neuroretinal rim. Also a more distinct way of observing it is looking for thinning of the rim, generally or focally. Hereat the 'ISNT' rule is applied, meaning that in a non-pathological optic disc, the inferior side of the rim is greater than the superior side of the rim, and so on. In a pathological optic disc, these proportions may be awry.

Other phenomena that are associated with glaucoma are: Parapapillary atrophy, disc hemorrhage, and splint hemorrhages.

When it comes to comparing perimetry and clinical examination: In the great majority of cases, progression was found first by perimetry. [10].

Visual field tests and their weaknesses

Visual field test is done using perimetry, most commonly using Goldmann perimetry. The purpose is to decipher whether visual field defects, scotomas are prevalent or not. These time-consuming methods are in part dependent on the examiner's skill and the patient's compliance, which is undesirable. The principle of the Goldmann perimetry is to show bright stimulus on a white background, the most commonly used form is the kinetic perimetry where the stimulus is being moved from the periphery to the point of fixation. In static perimetry, when stimulus is being shown in a different fashion; rather than moving from the periphery centrally, the stimulus is shown directly in the area of interest, and the method has the potential of discovering visual defects earlier than the kinetic variant. [21]

Impairment of the visual field often arises in the most 20-30 central degrees of the visual field, typically nasally of the blind spot. The parts of the visual fields that remain intact are typically the central and temporal parts. [22, 23].

Reproducible, but slightly varying within the area, visual field defects, scotomas, are reliable and clear signs of glaucoma, especially when congruent with pathological changes in the ONH and or the nerve fibre layer. This method is rather sensitive and provides high specificity in regards to glaucoma, however multiple studies have reported observations of RNFL and or ONH prior to detection of visual field changes. Detection of statistically significant Humphrey 24-2 visual defects have been shown to reflect a 25-35% loss of RGCs

[24], implying that the loss of RGCs occurs prior to it being possible to detect visual field defects, using gold standard perimetry methods. In the light of this, it is necessary to develop a method for diagnosing and monitoring glaucoma, which is focused on detecting RGC loss instead, since earlier detection enables earlier treatment and a better outcome.

Optic coherence tomography

Optic coherence tomography (OCT) is an imaging instrument, among several others, such as the Heidelberg Retina tomography (HRT) and the Scanning laser polarimetry (GDx-ECG).

It is a non-invasive method, based on interferometry, that generates 2D or 3D images of the posterior structures of the eye, using backscattering of low coherent broad bandwidth radiation. Low coherence interferometry is used to measure the echo time delay and intensity of backscattering [14]. The echo time delay and intensity of the back scattering are compared to a reflectance from a known path length and time delay.

OCT is already extensively being used in monitoring glaucoma, by examining different parameters associated with glaucomatous changes in the ONH and the peripapillary retinal nerve fibre layer. Software has been developed to yield all the measurements and geometrical relationships of interest, in a quick, predictable, and precise way. The problem today is that there is no consensus regarding which structures to measure and how to decipher the geometrical variables, and also putting this in a broader context; What exactly is pathological and what is not. As of now, changes over time can be analysed, but deciding, just from a single OCT-scan, if glaucoma is prevalent or not, is precarious.

Aims

To determine whether the reduction of the waist of the nerve fibre layer occurs as a function of age without pathological changes in the nerve fibre layer.

To discuss the use of OCT in managing and diagnosing glaucoma.

Methods

Subjects

16 subjects were recruited. Following exclusion criterias for participating in the study were:

1. Known pathology in the retinal nerve fiber layer.

2. First-grade relatives with glaucoma.

3. High myopia (defined as -5D).

OCT imaging

Each optic nerve head was imaged using a DRI OCT Triton™ machine, and the protocol 6x6 mm 3D disc cube was used, in acquiring the images. During the capture of the images the subjects were told to keep the eyes still and focus on a green symbol in the periphery of the field of view, in order to get the right angle, and to attain images of high quality without notches.

Procedure

The images were captured in a dimmed room, to maximize the dilation of the pupil. The subjects who had an appointment for retinopathy screening were dilated with both tropicamide and phenylephrine, the other subjects were not, since they had to have preserved near-sight vision in their profession.

The registered volumes were exported as amira-files, and were anonymized and coded, and then analysed in a program developed by a research group at Uppsala University. The software provided measurements (PIMD-values) of the waist of the RNFL in the ONH, in each of the 500 angles. The mean PIMD was calculated for each volume, each eye, each subject and lastly each group.

Experimental design

The optic nerve head was imaged in 8 men and 8 women in 4 age groups, 30-39, 40-49, 50-59 and 60-69 years, with two from each gender in each group. Both the right and the left eye was imaged, with three volumes per eye.

Statistical analysis

Analysis of variance was carried through to see whether there was a difference between age groups, and to compare it with the difference between subjects within the same group. Since there was a difference between age groups, a regression analysis was carried through, under the assumption that there was a linear relationship between age in the population and thickness of the waist of the NFL in ONH, which is imaged in 500 angels in the frontal plane, these 500 angels constitute a volume of the ONH.

Ethics

This study is a part of a larger study that has been approved be the Swedish Ethical Review Authority. The enrolled subjects were informed and subsequently gave their written consent to participate. The PIMD-values were stored in a locked hutch which only the writer of this study and his supervisor had access to.

Results

Subjects characteristics

Images of good quality were obtained from 16 subjects. The subjects were in part diabetes patients with retinopathy screening on the agenda, being offered to without any economic compensation participate in a study. The Covid-19-situation necessitated that subjects could be recruited from the working force at the department of ophthalmology at Uppsala University Hospital.

For the statistical analysis, it was decided randomly that the PIMD of the left eye was to be analysed.

ANOVA analysis

To establish the sources of variation among subjects and volumes an analysis of variance with a nested (hierarchal) mixed model was performed. The model proposes that each PIMD-2π measurement (x_{ijk}) is a sum of the population PIMD-2π mean (μ), the random variation among groups (Ai), subjects ($B_{j(i)}$), and volumes ($\varepsilon_{k(ij)}$).

$$x_{ijk} = \mu + A_i + B_{j(i)} + \varepsilon_{k(ij)} \qquad\qquad \text{Eq. 1}$$

The ANOVA analysis was performed with BMDP8V (BMDP Statistical Software Inc., Los Angeles). The dependent variable was PIMD-2π. The independent variables were subjects and volumes. The fixed variable was groups.

Estimation of normal loss rate of mean PIMD

Scatter plot of mean PIMD as a function of age showed a negative trend. The y-axis represents the mean PIMD-2π of the left eye. The x-axis shows age. In the equation for the linear regression model (Fig. 5), the rate constant was -1.0, which represents a loss rate of -1.0 μm/year in non-glaucomatous subjects. The estimated loss rate in percent per year is thus 0.25% (-1.0 ÷ 397.1). The percentage loss per decade is thus 2.5

Table 1. Sources of variation in estimates of PIMD-2π in non-glaucomatous eyes

Source of variation	Estimated variance (μm^2)	Degrees of freedom (d.f.)
Subjects	643.8	12
Volumes	273.7	32

The analysis found that the variation among volumes was 3 times lower than the variation among subjects. ANOVA shows that there is no difference of mean PIMD among age groups (F-test statistic = 1.98 ($F_{3:12:0.95}$ = 4.47). The mean PIMD-2π for each age group is presented in Table 5.

Table 2. Average PIMD-2π for each age group.

Group	Age (years)	Mean PIMD (μm) $\pm$ CI(0.95)
1	30-39	373.0 ± 61.8 (CI 95%)
2	40-49	358.5 ± 23.8 (CI 95%)
3	50-59	332.9 ± 50.1 (CI 95%)
4	60-69	336.0 ± 23.3 (CI 95%)

Fig. 2. Measurements from 16 subjects plotted in a scatter diagram with linear regression equation. Mean PIMD-2π (y-axis, μm) as a function of medians of the age groups (x-axis, years).
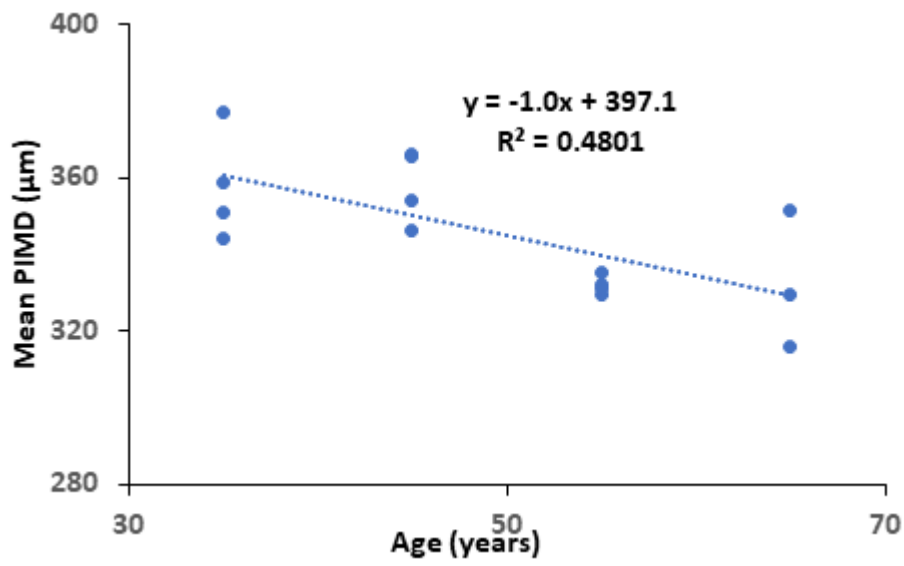
Discussion

Recruitment of subjects

The original plan was to recruit healthy subjects, without previously known pathological changes in the neuroretinal rim of the optic disc and without heredity for glaucoma and without high myopia (-5D). Then, Uppsala University Hospital implemented new guidelines, stating that no healthy subjects may enter the hospital for the purpose of participating in a study.

Instead, diabetic patients who had an appointment for retinopathy screening were offered to take part in the study. The criterias were updated to "no retinopathy", in addition to the previous three criterias.

In conjunction with this, the decision was made to not follow the original idea that patients/subjects were to be recruited consecutively to each of the 4 age intervals. Simply because the share of patients who were eligible was too small, and enforcing the idea with consecutive recruitment to each of the four age intervals, would further significantly diminish that share.

To elaborate on the consequences of this, I find it necessary to explain the rationale for the concept of consecutive recruitment: In this study a DRI OCT Triton™ was used in imaging the ONH, and the quality of the images is in part dependent upon the examiner. It is reasonable to assume that one's skills using the DRI OCT Triton™ improves as the study proceeds. This has the implications that if all the subjects were recruited chronologically, that the quality of the images would improve with age. This is in other words to be considered a possible confounding factor.

The fact that 50% of the subjects were diabetic patients, and 50% of the subjects were health practitioners at the eye care unit complicates the situation, although there was not a single group that had only subjects with diabetes, this has not been investigated thoroughly. If one group has three subjects with diabetes, and one without. This might impact the result; There might be a correlation between diabetes and an altered PIMD in the population, that has not been observed or written about in a scientific report yet.

Furthermore, the health practitioners' pupils were not dilated. This could possibly lower the image quality, although they became subject to the same scrutiny.

Sample size

Given the amount of time set aside for gathering data, the sample size had to be small, which is a pronounced weakness when it comes to the statistical analysis. The confidence interval is inversely related to the sample size; The smaller the sample size the greater the confidence interval.

The ideal difference between the mean age of the groups would be 10, but given the sample size that might not be the case in this study.

In the results, the linear regression (Fig. 5.) suggests a decrease of Mean-PIMD as a function of Age, but in (Table 5.) it is shown that there is no statistically significant reduction of the PIMD between the groups, meaning that the confidence intervals of the groups overlap one another.

A potential use for the data gathered in this study is that it may be incorporated into a larger study, and may contribute to more statistical power to another study, getting us closer to the goal of reaching a consensus regarding which morphometric measurement to use in the follow-up of glaucoma patients.

PIMD-variability

When measuring PIMD, a great variation is expected when comparing age groups, individuals and even when comparing the right with the left eye in the same individual. However, what is not expected is variation in PIMD in the same eye, in other words, a more than moderately differing PIMD stemming from the same eye is not expected. In this study three volumes per eye was captured, and when the results crystallized, a large variation (Table. 4) could be observed.

There are a few explanations for this. The first explanation, and the most likely one, is that the image quality became subject to variation. When the images were captured the subject was asked to keep the eye still, and if movement of the eye was observed, or if the picture displayed signs of a moving eye, in other words, notches in the newly captured image, the image was deleted. This process, scrutinizing the image quality, could have been more rigorous, and also if the subjects would have been recruited consecutively as originally planned, this effect would have been minimized, as the biggest intra-individual variation was seen in the first recruited subjects. Another possible explanation is that the ONH pigment epithelium central limit (OPCL) had to be manually determined in each volume, which is associated with potential minor errors. The third explanation, least likely, would be that the software developed by the research group would have been afflicted by flaws in the algorithms. This can probably be ruled out, since the same software has been used before, and

has produced reliable and trustworthy results before, confirmed by manual calculations of the PIMD.

This high variability complicates the notion that OCT could be used in managing glaucoma patients: One has to be absolutely certain that the supposedly decreased PIMD-value is due to an actual decrease in the RNFL-thickness, and not hinged upon the image quality, or due to the OPCL manually being incorrectly determined. If guidelines could be brought about, and consensus could be reached, that could help create a more standardized method of gathering and analysing RNFL-thickness. The more practitioners that use the same method, the easier it will be to compare results and gain statistical power, which would be the next step in getting us closer to using OCT in glaucoma follow-up. In the light of this, the high variation between individuals regarding PIMD does not support the idea that OCT could be used in diagnosing glaucoma, but when done right, it could be helpful in managing already diagnosed patients

Decrease of PIMD as a function of age

In the results, the linear regression (Fig. 5.) suggests a decrease of Mean-PIMD as a function of Age, but in (Table 5.) it is shown that there is no statistically significant reduction of the PIMD between the groups, meaning that the confidence intervals of the groups overlap one another.

However since the linear regression suggesting a 2.5% decrease of Mean-PIMD per decade, is somewhat congruent to similar studies, it is reasonable to assume that there is a certain decrease of the mean-PIMD as a function of age. This substantiates the idea that when comparing a patient's mean-PIMD with references, it has to be age-stratified.

However, even with age-stratification, the greatly varying PIMD-values between individuals in the same age-group challenges the idea that OCT could be useful in determining the diagnosis of glaucoma. In other words, the reference range for what a non-pathological PIMD is would need to be great, even with age-stratification. If a patient had a thick RNFL, before the patient was afflicted with glaucoma, that would mean that glaucoma-associated damage to the retina would occur long before the patient's PIMD would be thin enough to be classified as a pathologically short PIMD.

Rather, OCT should instead, against the background of its potential to accurately generate PIMD-values, be used in follow-up in already diagnosed patients.

Potential use in patients without symptoms

In several studies, it has been noted that the loss of RGCs precedes visual field defects. This leads one to think that it could be useful in the diagnosis of glaucoma, but without symptoms, the only way to know if glaucoma is prevalent, is to perform an OCT. This poses a problem:

The earlier the diagnosis of glaucoma, the better, but without symptoms the patients will stay at home. In other words the ONH has to be imaged, even when glaucoma is not suspected. And the information gathered from the image cannot determine the diagnosis of glaucoma, since the inter-individual variance is so great. Rather, the piece of information (PIMD) will be used at the supposed next appointment, and a comparison will be performed. Only the comparison can yield information on the state of the potential development of glaucoma. This means that the use in this case would be a form of screening, and the idea of implementing OCT as a screening method, when it is not extensively used in the healthcare system already is farfetched. However in patient groups with heredity for glaucoma or with multiple risk factors it could at least be considered in the future.

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