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Estimated Rates of Retinal Ganglion Cell Loss with Aging

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Purpose: To evaluate the effect of aging on estimated retinal ganglion cell (RGC) counts over time in healthy eyes, obtained from a combination of structural and functional information.

Design: Longitudinal observational cohort study.

Participants: One hundred healthy eyes of 50 subjects.

Methods: Estimated RGC counts were obtained by a previously described method using standard automated perimetry sensitivity thresholds and OCT retinal nerve fiber layer thickness measurements. Linear mixed-effects models were applied to investigate the effect of aging, as well as other covariates, on rates of change in estimated RGC counts over time.

Main Outcome Measures: Rates of change in estimated RGC counts in healthy eyes.

Results: Subjects had a mean age of 49.6 ± 15.7 years at baseline (range 22.8–89.9 years) and were followed up for 3.5 ± 2.5 years. Thirty-three (66%) patients were female and 11 (22%) self-identified as Black. At baseline, the eyes had an average estimated RGC count of 1 144 010 ± 222 084 cells. After adjusting for confounding factors, the mean rate of change in estimated RGC counts was −6769 RGC/year (95% confidence interval: −10 994 to −2544 RGC/year; $P = 0.002$), or 0.6%/year. Older age and longer axial length were significantly associated with lower RGC counts at baseline.

Conclusions: A significant age-related decline in estimated RGC counts was found in healthy subjects with a combined metric integrating imaging and functional testing. The estimated mean age-related decline was remarkably similar to estimates from previous histologic studies in cadaver eyes, reinforcing the validity of the proposed combined metric and highlighting the importance of considering age when evaluating RGC count changes over time for monitoring glaucoma progression.

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Determining the effect of aging on the amount of neural tissue in the eye is important for establishing normative limits for classifying and assessing whether a certain amount of neural loss is pathologic or not. This has particular relevance in the case of glaucoma, a complex, multifactorial, progressive optic neuropathy characterized by the death of retinal ganglion cells (RGC),[1] and is the main cause of irreversible blindness in the world.[2]

Several histologic studies have attempted to investigate the relationship between age and neural tissue loss in the human eye. The effect of aging has been previously assessed through histologic analysis of the RGC somas[3–5] and their axons in the optic nerve,[5–9] with the majority of studies finding rates of RGC loss ranging between 0.3% and 0.6% per year. However, a limitation of histologic studies is their reliance on cross sectional data, which, due to the considerable variance in RGC counts among individuals, might lead to less precise estimates of the impact of aging on neural tissue loss over time.

Although obtaining longitudinal RGC counts in vivo in human eyes is still a very challenging task, the study by Harwerth et al[10] demonstrated that RGC counts could be estimated from peripapillary retinal nerve fiber layer (RNFL) thickness measurements obtained by OCT, as well as from visual field sensitivity thresholds obtained from standard automated perimetry (SAP). The authors derived empirical formulas to relate these measurements to histologic RGC counts in monkeys with different levels of neural damage caused by experimentally induced glaucoma.[10] The empirical formulas were then subsequently validated on histologic counts obtained from cadaver eyes.[11] Medeiros et al[12] proposed to combine estimates of RGC counts obtained from structural and functional sources into a single combined index of structure and function (RGC index). The motivation of the RGC index was to express the results of OCT and SAP into a common scale, allowing a combination of their results for assessing the amount of neural loss in an eye. The RGC index has been shown to improve diagnosis, staging, and detection of glaucoma progression.[13–24]

An assessment of the rate of estimated RGC loss based on the RGC index may provide a simple intuitive index to

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gauge the velocity of glaucoma progression throughout the spectrum of the disease, providing an additional tool to help clinical decision-making. However, to determine whether a specific rate is pathologic or not, it is important to have information about expected age-related losses. Therefore, the purpose of the present study was to quantify rates of estimated RGC loss with the RGC index in a cohort of healthy eyes followed over time.

Methods

This study is a secondary analysis of data obtained as part of a prospective longitudinal study to investigate visual function in glaucoma patients (Diagnostic Innovations in Glaucoma Study: Functional Impairment), conducted at the University of California, San Diego. The Institutional Review Boards of the University of California, San Diego and the University of Miami approved the protocol and data analyses. Written informed consent was obtained from all participants. The study adhered to the Health Insurance Portability and Accountability Act laws, and all study methods complied with the Declaration of Helsinki guidelines for human subject research.

Participants underwent a comprehensive ophthalmic examination at each follow-up visit. Examinations included a review of medical history, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement using Goldmann applanation tonometry, dilated funduscopic examination using a 78-diopter lens, gonioscopy, stereoscopic optic disc photography, RNFL thickness assessment with Cirrus HD-OCT (Carl Zeiss Meditec, Inc), and SAP using the Swedish Interactive Threshold Algorithm (standard 24-2; Carl Zeiss Meditec, Inc). Subjects were excluded if they presented with a best-corrected visual acuity worse than 20/40, spherical refraction outside ±5.0 diopters or cylinder correction outside 3.0 diopters, or any other ocular or systemic disease that could affect the optic nerve or the visual field.

Subjects were recruited from the general population and relatives of patients. Eyes were classified as healthy if intraocular pressure was <22 mmHg, with no history of elevated intraocular pressure, and ≥2 reliable normal visual fields at baseline, defined as a pattern standard deviation within 95% confidence limits and a Glaucoma Hemifield Test result within normal limits. Visual fields with >33% fixation losses or false-negative errors, or >15% false-positive errors, were excluded. Healthy eyes were also required to have normal-appearing optic discs on optic disc stereophotographs. Subjects were included in the analysis only if both eyes were classified as healthy and normal characteristics of visual fields and optic disc were maintained throughout the duration of the study in both eyes.

OCT

The Cirrus HD-OCT was used to measure peripapillary RNFL thickness. Retinal nerve fiber layer thickness was measured using the optic disc cube with circumpapillary thickness measurements calculated from a 3.46 mm diameter circular scan automatically placed around the optic disc. An experienced examiner who was masked to the results of other tests evaluated the HD-OCT scan quality. High-quality scans were required to have focused images from the ocular fundus, signal strength >6, and the presence of a centered circular ring around the optic disc. Scans were also excluded if segmentation errors or artifacts were present.

The RGC Index

The RGC index integrates structural and functional information from SAP and spectral-domain OCT to provide estimations of RGC counts in an individual eye. A detailed description of the index is available elsewhere.[12] The model considered the effect of aging on the axonal density and the effect of disease severity on the relationship between the neuronal and nonneuronal measurements of the RNFL thickness estimates by using OCT.[12] In brief, the rationale of the index is that measures of structure and function can be combined after they are transformed from their original scales (μm and decibels, respectively) into a common scale (estimated RGC counts). Consequently, in early damage, the OCT-derived RGC estimates will have greater weight than those obtained by SAP. However, in advanced damage, SAP estimates will carry greater weight than those considering OCT.[12] The conversion of SAP and OCT data to estimated RGC counts is based on empirical formulas derived from histologic studies in nonhuman primates that have subsequently been validated in human cohorts.[11] After the conversion to a common scale, a weighted average of structure- and function-derived estimates of RGC counts is obtained, with weights defined by severity of disease to account for the different performance of the SAP and OCT according to the stage of the disease.

Statistical Analysis

Linear mixed models were used to investigate the effects of age on estimated RGC counts obtained by the RGC index. Linear mixed models account for differences in rates of change between eyes and subjects by introducing random slopes and random intercepts.[25] The estimated number of RGCs was considered the dependent variable in the model. The variable "time" (in years) was included as a continuous predictor. The coefficient associated with the variable "time" corresponds to the estimate of age-related change in RGC counts. The best linear unbiased predictions were used to estimate individual slopes of change over time for each eye.[26–28] Linear mixed models were also used to adjust for signal strength as a confounding factor in estimating RGC counts. In addition, we also evaluated the effects of baseline variables age, race, gender, and axial length on RGC counts. For each of these variables, the model included the main effect as well as an interaction with "time." The statistical significance of the main effect term indicated the effect of the variable on baseline RGC counts (i.e., with time = 0), whereas the interaction term indicated whether there was an effect on change in RGC counts over time. To facilitate the interpretation of coefficients, the variables were centered on their respective sample means.

All statistical analyses were performed with commercially available software (Stata, version 18; StataCorp LP).

Results

The study included 100 eyes of 50 healthy subjects, followed up for an average of 3.5 ± 2.5 years. The mean age was 49.6 ± 15.7 years at baseline, ranging from 22.8 to 89.9 years. Thirty-three (66%) patients were female, and 11 (22%) self-identified as Black or African American. Table 1 summarizes the demographic and clinical characteristics of the study sample. The mean ± standard deviation global RNFL thickness was 105.0 ± 12.7 μm, and 0.16 ± 1.16 decibels for mean deviation at baseline, with an estimated RGC count at baseline calculated from the SAP and OCT parameters of 1 144 010 ± 222 084 cells. Figure 1 shows the distribution of estimated RGC counts for all participants.

Subjects had an average rate of estimated RGC loss over time of −6667 cells/year (95% confidence interval: −11 199 to −2133 cells/year; $P = 0.004$) (Table 2). Figure 2A shows

Table 1. Demographic and Clinical Characteristics of the Subjects and Eyes Included in the Study

Parameter	Healthy Subjects (100 Eyes, 50 Patients)
Baseline age, yrs	49.6 ± 15.7 (22.8-89.9)
Range	
Gender, %	33 (66%)
Female	
Race, %	
White	35 (70%)
Black	11 (22%)
Other	4 (8%)
Baseline MD, dB	0.16 ± 1.16
Baseline PSD, dB	1.53 ± 0.33
Baseline signal strength, unit	9.2 ± 1.0
Baseline axial length, mm	23.9 ± 0.9
Baseline RNFL thickness, μm	105.0 ± 12.7
Baseline estimated RGC count, cells	1 144 010 ± 222 084
Follow-up, yrs	3.5 ± 2.5

Values are shown as mean ± standard deviation unless otherwise noted.
dB = decibels; MD = mean deviation; PSD = pattern standard deviation; RGC = retinal ganglion cell; RNFL = retinal nerve fiber layer.

the distribution of slopes of change over time in estimated RGC counts, whereas Figure 2B shows the fitted slopes for the individual subjects included in the study. Of note, 5 subjects (10%) had positive RGC slopes over time due to an increase of SAP mean deviation values over time. In univariable models (Table 2), lower signal strength was associated with lower estimated RGC counts (−32 265 cells per 1 unit lower; $P < 0.001$). Older age at baseline ($\beta = -101\ 470$ cells per decade older; $P < 0.001$) and longer axial length ($\beta = -62\ 087$ cells per mm longer; $P = 0.011$) were also significantly associated with fewer RGC counts at baseline, but had no significant effect on the rate of RGC change over time. Race and gender did not significantly influence baseline estimates of RGC counts, or rates of change in RGC counts over time.

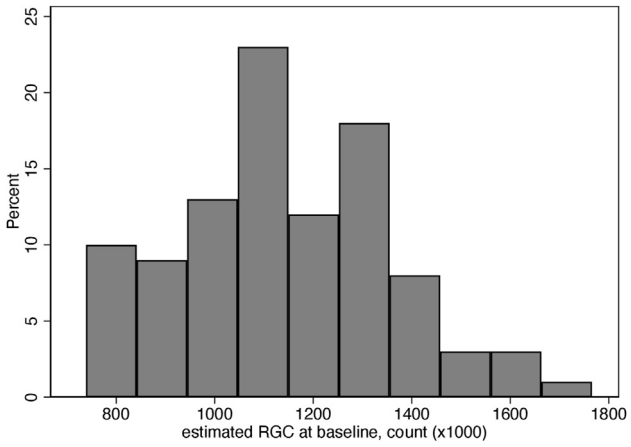

Figure 1. Histogram showing the distribution of retinal ganglion cell (RGC) counts in healthy eyes at baseline.

Table 3 shows the results of a multivariable model adjusting for the potentially confounding effect of signal strength in the estimation of RGC counts, and also including baseline age and axial length. After adjusting for these factors, the independent effect of time (i.e., normal aging) on the rate of estimated RGC loss was −6769 cells/year (95% confidence interval: −10 994 to −2544 cells/year; $P = 0.002$), or 0.6%/year, at the mean values of the covariates. Similar to the univariable model, lower signal strength was associated with lower estimates of RGC counts ($\beta = -16\ 663$ cells per unit lower; $P < 0.001$). Older age ($\beta = -91\ 128$ cells per decade older; $P < 0.001$) and a longer axial length ($\beta = -35\ 696$ cells per mm longer; $P = 0.048$) were also significantly associated with lower estimated RGC counts at baseline. We also evaluated the rates of estimated RGC loss stratified by baseline age (below or above the median baseline age of 49.7 years). The younger group presented slightly faster rates of RGC loss than the older group, although the difference was not statistically significant (−6767 cells/year versus −5801 cells/year, respectively; $P = 0.567$).

Discussion

In this study, we estimated rates of RGC loss due to aging in a cohort of healthy eyes, obtained from combining information from imaging and functional tests. Our results showed a significant age-related decline in estimated RGC counts at an average rate of 0.6% per year, which is remarkably similar to previous histologic studies in humans (Fig 3).[3–9] Our findings contribute to determining normative limits for age-related neural loss when assessing progression rates in diseases such as glaucoma. They may also help understand the impact of aging on rates of neural damage and its implications for the interpretation of clinical tests in glaucoma.

After adjusting for potentially confounding factors in a multivariable model, we found that healthy eyes lost on average −6769 cells/year in estimated RGC counts. This average age-related decline is compatible with previous estimates from histologic studies, as summarized in Table 4[3–9] and illustrated in Figure 3. For example, in a histologic study of 16 cadaver eyes, Kerrigan-Baumrind et al[5] estimated an age-related loss of 7205 cells per year, a rate very similar to the one found in our study. In another study investigating histologic axonal counts published by Balazsi et al,[6] the rate was estimated to be −5637 axons per year. In fact, most of the studies displayed in Table 4 show similar estimated rates of RGC or axonal loss with aging, with the notable exception of 2 studies.[6,8] It is possible that differences in the estimates may be derived from the use of different techniques for counting axons or RGCs, different death-to-fixation times, or variations due to small sampling. For example, in the study by Repka and Quigley,[8] which shows the most discrepant estimate, only nerves that were believed to be adequately preserved were included in the analysis, but this corresponded to a small fraction of only 19 of an initial 200 cadavers.

Table 2. Univariable Linear Mixed-Effects Models Examining the Effect of Time (Aging) and Other Clinical and Demographic Variables on Baseline and Rates of Estimated RGC Counts Over Time

	Baseline Effect			Time Effect		
Parameter	*Coefficient*	*95% CI*	P	*Coefficient*	*95% CI*	P
Time (yrs)	–	–	–	−6667	−11 199 to −2133	**0.004**
Baseline age, per decade older	−101 470	−123 076 to −79 864	**<0.001**	682	−2073 to 3438	0.627
Signal strength, per unit lower	−32 265	−43 145 to −21 384	**<0.001**	−2357	−651 to 5366	0.125
Axial length, per mm longer	−62 087	−109 857 to −14 318	**0.011**	991	−4605 to 6589	0.728
Race, Black	−40 158	−177 834 to 97 517	0.568	−823	−10 979 to 9332	0.874
Gender, female	42 032	−78 643 to 162 707	0.495	3252	−6130 to 12 636	0.497

Boldface indicates statistical significance ($P < 0.05$).
CI = confidence interval; RGC = retinal ganglion cell.

Several theories have been proposed to explain why aging leads to loss of neural tissue. A prevalent theory suggests that aging leads to changes in metabolic resources due to diminished mitochondrial efficiency.[29–31] This leads to reduced capacity to maintain intracellular ion homeostasis, decreased activity of ion pumps such as the Na+/K+-ATPase, and an increase in oxidative injury. Over time, the escalating oxidative stress is believed to culminate in damage to RGC axons, which are particularly vulnerable due to their high metabolic demands. The effect of baseline age in RGC counts found in our study is also cogent because it indicates that older age is associated with lower RGC counts in healthy eyes at baseline, with an additional effect of normal aging over time (i.e., time effect). This correlation is consistent with previous histologic studies in animals.[32] Of note, an investigation by Fortune et al[33] in rhesus monkeys found that the rate of RNFL thinning on OCT was 3 times faster than the apparent loss of optic nerve axons. The authors explained this difference by possible effects of optical degradation in the aging eye reducing the signal quality of OCT scans. In our study, we indeed observed an effect of OCT signal strength on the estimated RGC counts. Therefore, we controlled for such potentially confounding effects by incorporating signal strength in the multivariable regression model. After controlling for signal strength and other potential confounders, we found a rate of loss of 6769 cells/year with aging.

Increased axial length was also associated with lower RGC counts in our sample. The axial length has been previously shown to affect OCT measurements. Oner et al[34] observed thinner RNFL in healthy myopic eyes compared with emmetropic and hyperopic eyes. Because the formulas for estimating RGC counts use measurements of RNFL thickness, it was also important to evaluate and control for axial length in our models. We found that longer eyes had a lower number of estimated RGC counts at baseline, although we did not find a statistically significant influence of axial length on the rate of RGC loss over time. It remains to be determined whether the lower RNFL thickness (or RGC counts) seen in longer eyes corresponds to true histologic loss, or if it is primarily an artifact of the measurement techniques influenced by the altered retinal curvature and distance in myopic eyes.

We derived our estimates of RGC numbers from SAP and OCT data based on the study by Harwerth et al.[10] Their

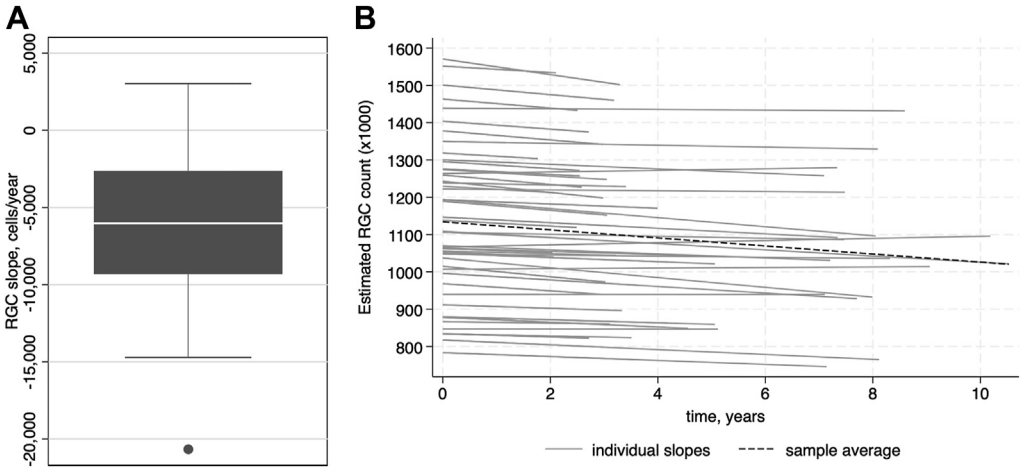

Figure 2. A, Boxplot showing the distribution of slopes of estimated retinal ganglion cell (RGC) counts over time. **B,** Fitted slopes of change in estimated RGC counts over time. The dashed line represents the sample's average trajectory. Box: median, and interquartile range (IQR); whiskers represent maximum and minimum 1.5 IQR.

Table 3. Multivariable Linear Mixed-Effects Models Investigating the Effect of Time (Aging) on Rates of Estimated Retinal Ganglion Cell Counts Over Time While Adjusting for Potentially Confounding Factors

Parameter	Coefficient	95% CI	*P* Value
Time (yrs)	−6769	−10 994 to −2544	**0.002**
Baseline age, per decade older	−91 128	−112 491 to −69 764	**<0.001**
Signal strength, per unit lower	−16 663	−25 047 to −8280	**<0.001**
Axial length, per mm longer	−35 696	−71 032 to −359	**0.048**
Intercept	1 139 467	1 102 386 to 1 176 547	**<0.001**

Boldface indicates statistical significance ($P < 0.05$).
CI = confidence interval.

research on both normal monkeys and those with laser-induced experimental glaucoma demonstrated that SAP sensitivity values can accurately estimate the histologically measured RGC counts in the retina.[10] These SAP-based estimates were found to be in close agreement with those derived from OCT RNFL thickness measurements. They observed a strong linear correlation between the number of RGC somas and axons obtained from functional and structural assessments, respectively, when accounting for retinal eccentricity and the appropriate measurement scales for neural and sensitivity losses.[10] However, the logarithmic scale used in original SAP data compresses early-stage losses while expanding the range for later stages of the disease. SAP data, acquired using logarithmic scale-based staircase procedures (decibels), is less effective at detecting small ganglion cell losses in the early stages of glaucoma. Conversely, by expanding the scale range in later stages, SAP may be more sensitive to minor changes in RGC numbers that do not produce detectable changes in RNFL thickness. Expressing functional and structural test results in the same domain allows for the potential combination of information from both tests to enhance the accuracy of estimating neural losses. However, instead of simply averaging the estimates from SAP and OCT, the RGC index employs a weighting scheme based on mean deviation values. This approach accounts for the differing performances of SAP and OCT at various stages of neural loss, ultimately increasing the accuracy of neuronal loss estimates.

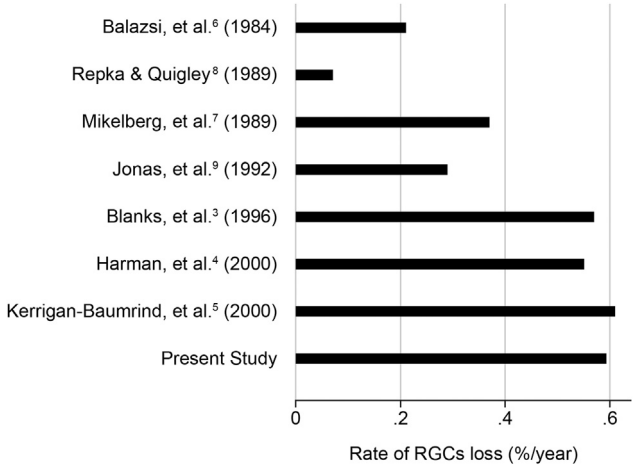

Figure 3. Comparison of the rate of estimated number of retinal ganglion cells (RGCs) loss over time in healthy eyes in the present study and in previous studies.[3–9]

Our study has limitations. Because there are no widely available techniques for quantifying RGC numbers directly in vivo, the estimates of RGC counts used in our study were obtained by using an empirical formula derived from histologic studies in monkeys. Although this approach has been applied across various human studies, definitive validation can only be achieved through direct comparison with histologic data from human eyes, which is not available. Nonetheless, the consistency of our findings with rates of RGC loss in aging reported from previous studies on cadaver eyes lends credibility to the accuracy of our estimates. Of note, a previous study by Harwerth and Quigley[11] found a good relationship between the empirical formulas to estimate RGC counts from SAP and histologic RGC counts in eyes from human cadavers. Furthermore, the utility of the RGC index as a diagnostic tool, and its effectiveness in tracking glaucoma progression, have been corroborated by multiple independent investigations, reinforcing its value in clinical settings.[17,18,20–24] Another potential limitation is the relatively short overall follow-up time. However, previous studies investigating aging effects on RNFL thickness found significant results with similar follow-up times.[35,36] Another limitation is that although our cohort covered a broad spectrum of ages, the representation of participants within each decade was somewhat limited. This makes it difficult to attempt to estimate any potential nonlinear changes in age-related loss over time. As another limitation, our sample consisted of 70% of subjects who self-identified as White, which limits the applicability of our estimations to other racial groups. Future studies should attempt to address these shortcomings by including more diverse and larger sample sizes with a wide variety of ages and longer follow-ups.

In conclusion, we found a significant age-related decline in estimated RGC counts obtained from combining information from structural and functional tests. After accounting for potentially confounding factors, the estimated age-related decline in RGC counts found in our cohort of healthy eyes was very similar to those obtained in prior histologic studies. Aging should be taken into account when assessing the clinical relevance of estimated rates of RGC loss in individual eyes.

Table 4. Summary of Estimated Rates of Axonal or RGC Loss Obtained in Previous Histologic Studies and in the Current Study

Study	Study Type	Neuronal Compartment	Number of Eyes	Number of Cells Lost Per Year	Rate of Loss
Balazsi et al,[6] 1984	Histologic	Axons	16 eyes ranging from 3.5 to 82 yrs	−5637	−0.21%/year
Repka and Quigley,[8] 1989	Histologic	Axons	19 eyes ranging from 4 to 84 yrs	−534	−0.07%/year
Mikelberg et al,[7] 1989	Histologic	Axons	12 eyes	−4909	−0.37%/year
Jonas et al,[9] 1992	Histologic	Axons	72 eyes ranging from 19 to 88 yrs	−4021	−0.29%/year
Blanks et al,[3] 1996	Histologic	Somas	12 eyes ranging from 60 to 98 yrs	−1780	−0.57%/year
Harman et al,[4] 2000	Histologic	Somas	12 eyes ranging from 16 to 77 yrs	–	−0.55%/year
Kerrigan-Baumrind et al,[5] 2000	Histologic	Axons	16 eyes ranging from 55 to 95 yrs	−7205	−0.61%/year
Estimated RGCs	Clinical	RGCs	100 eyes ranging from 22.8 to 89.9 yrs	−6769	−0.59%/year

RGC = retinal ganglion cell.

Footnotes and Disclosures

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No animal subjects were used in this study.

Author Contributions:

Conception and design: Vilasboas-Campos, Jammal, Gracitelli, Gameiro, Medeiros

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Obtained funding: Medeiros

Overall responsibility: Vilasboas-Campos, Jammal, Gracitelli, Gameiro, Costa, Medeiros

Abbreviations and Acronyms:
RGC = retinal ganglion cell; **RNFL** = retinal nerve fiber layer; **SAP** = standard automated perimetry.

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