Glucose Tolerance Levels and Circumpapillary Retinal Nerve Fiber Layer Thickness in a General Japanese Population: The Hisayama Study

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• PURPOSE: To investigate the relationship between glucose tolerance levels and the circumpapillary retinal nerve fiber layer thickness (cpRNFLT) in a general Japanese population.

• DESIGN: Population-based, cross-sectional study.

• METHODS: In 2012 and 2013, a total of 2809 Japanese community dwellers aged 40–79 years in the Hisayama Study underwent eye examinations including cpRNFLT measurement with spectral domain optical coherence tomography. Of these, 1324 subjects (578 men and 746 women) were enrolled. Glucose tolerance levels were determined by a 75-g oral glucose tolerance test. We conducted an analysis of covariance to estimate the mean values of cpRNFLT according to the subjects' glucose intolerance status.

• RESULTS: The subjects with prediabetes or with diabetes mellitus had significantly lower age- and sex-adjusted mean cpRNFLT values than those with normal glucose tolerance ($P = .04$ and $P = .0004$, respectively). The age- and sex-adjusted mean values of cpRNFLT decreased significantly with elevating fasting plasma glucose and 2-hour postload glucose levels (all P for trend $< .05$). These associations were substantially unchanged after adjustment for potential confounding factors. The coexistence of poorer glucose tolerance and higher intraocular pressure levels was additively associated with thinner cpRNFLT.

• CONCLUSIONS: Our analyses revealed that poorer glucose tolerance was significantly associated with the reduction of cpRNFLT in a Japanese general population, suggesting that the loss of neural tissue in the eye begins at the prediabetic stage, and that hyperglycemia may play a role in the reduction of cpRNFLT. (Am J Ophthalmol 2019;205:140–146. © 2019 Elsevier Inc. All rights reserved.)

GLAUCOMA IS A MAJOR PUBLIC HEALTH PROBLEM and is the leading cause of blindness and visual loss worldwide.[1] The global burden of glaucoma is expected to increase, in part because of the continuing increases in the human lifespan and the number of elderly people.[2] Spectral-domain optical coherence tomography (OCT) has shown a high level of accuracy in the detection of early alterations in the optic disc and retinal structure.[3–5] We can now detect early retinal nerve change more easily by means of OCT, and OCT is useful to elucidate the mechanisms of glaucoma.

Diabetes mellitus has been acknowledged to be a risk factor for glaucoma, as shown by many population-based studies and a meta-analysis.[6–8] However, the mechanisms underlying the association between diabetes mellitus and glaucoma are not yet known. Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) detected by OCT is known to indicate early glaucomatous damage, including visual field defects.[9,10] Early recognition of the subtle changes in the retinas of diabetic eyes is important to prevent vision loss resulting from glaucoma, and therefore it is of clinical value to clarify the influence of poorer glucose tolerance or hyperglycemia on the cpRNFLT. We investigated the relationship between glucose tolerance levels and cpRNFLT in a general Japanese population.

SUBJECTS AND METHODS

• ETHICAL CONSIDERATIONS: This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research, and it was carried out in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from all subjects.

• STUDY POPULATION: The Hisayama Study is an ongoing, long-term cohort study on cardiovascular disease

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and its risk factors in the town of Hisayama, Japan,[11,12] which is adjacent to the Fukuoka metropolitan area in southern Japan. As a part of the overall study, an epidemiologic study of eye disease among residents of the town has been underway since 1998.[13] In 2012 and 2013, 2809 Hisayama residents 40–79 years of age (participation rate 69.6%) consented to participate and underwent an ophthalmic examination for the present study. Of these, 2174 subjects underwent an OCT examination, and 642 subjects were excluded from the study for the following reasons: the use of topical intraocular pressure (IOP)–lowering medications (n = 83), diabetic retinopathy (n = 39), no available data for a 75-g oral glucose tolerance test (n =1 60), motion artifact and segmentation errors in cpRNFLT measurement (n = 356), poor quality scans (n = 80), and missing axial length values (n = 132). A final total of 1324 subjects (578 men and 746 women) were enrolled in the present study.

• **MEASUREMENTS OF CPRNFLT AND OPHTHALMIC PARAMETERS:** Each subject underwent a comprehensive ophthalmic examination as described elsewhere.[13] The IOP was measured 3 consecutive times with a noncontact tonometer using automatic air puff control on the center of the cornea (Nidek P530; Nidek, Gamagori, Japan). Axial length measurements were performed with noncontact partial coherence laser interferometry (IOL Master; Carl Zeiss, Hennigsdorf, Germany). Imaging was performed using a spectral-domain OCT instrument, i.e., a 3D OCT-1 Maestro (Topcon, Tokyo) that provides an OCT scan (6-mm^2 scan disc protocol). The principles of OCT have been well described.[3,14]

The cpRNFLT was measured along a 360° path for 4 quadrants of the optic disc. A circular circumpapillary scan taking a 3.4-mm diameter centered on the optic disc was performed to calculate the cpRNFLT value. The thicknesses of the cpRNFLT at 1024 points obtained by the Topcon 3D OCT were converted to the mean of the cpRNFLT thicknesses. Image quality values <30 (as recommended by the manufacturer) were excluded from the analyses.

• **CLINICAL EVALUATION AND LABORATORY MEASUREMENTS:** Blood samples were collected from an antecubital vein of each subject after an overnight fast of ≥12 hours. After the fasting blood specimen was obtained, an oral glucose tolerance test was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical, Shimizu, Japan). Plasma glucose levels were determined by the hexokinase method. Hemoglobin A1c (HbA1c) levels were measured by a high-pressure lipid chromatographic assay. The glucose tolerance status was defined based on the 1998 World Health Organization criteria[15] as follows. Normal glucose tolerance was defined as a fasting plasma glucose value <6.1 mmol/L and 2-hour postload glucose <7.8 mmol/L; for impaired fasting glycemia, fasting plasma glucose 6.1–6.9 mmol/L and 2-hour postload glucose <7.8 mmol/L; for impaired glucose tolerance, fasting plasma glucose <7.0 mmol/L and 2-hour postload glucose 7.8–11.0 mmol/L; and for diabetes mellitus, fasting plasma glucose ≥7.0 mmol/L and/or 2-hour postload glucose ≥11.1 mmol/L.

The subjects who were being treated with antidiabetes medications were included in the diabetes group irrespective of their glucose levels. Prediabetes was defined as either impaired fasting glycemia or impaired glucose tolerance. We also divided the fasting plasma glucose and 2-hour postload glucose levels into 4 categories: for fasting plasma glucose, <5.6, 5.6–6.0, 6.1–6.9, and ≥7.0 mmol/L; for 2-hour postload glucose, <6.7, 6.7–7.7, 7.8–11.0, and ≥11.1 mmol/L. HbA1c levels were categorized into 4 categories: <5.4%, 5.5–5.6%, 5.7–6.4%, and ≥6.5%. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically.

Each subject's blood pressure was measured 3 times after the subject had rested for ≥5 minutes in a sitting position. The average of the 3 measurements was used for the analysis. The subject's body height and weight were measured in light clothing without shoes, and the body mass index (BMI) was calculated (as kg/m^2). Information on exercise during leisure time, smoking habit, and alcohol intake was obtained using a standard questionnaire.[16] The questionnaire was administered to each subject before the initiation of this study and was checked by trained interviewers at the screening. Smoking habit and alcohol intake were classified into either current habitual use or no habitual use.

• **STATISTICAL ANALYSES:** The SAS software package (version 9.4; SAS, Cary, NC, USA) was used to perform all statistical analyses. The unadjusted mean values and the frequencies of risk factors across the categories were tested by a linear regression analysis and a logistic regression analysis, respectively. We estimated the age- and sex-adjusted or multivariable-adjusted mean values of cpRNFLT in each category by performing an analysis of covariance. A multiple regression analysis was conducted as the test of trends in adjusted mean values of cpRNFLT across the categories. In the multivariable-adjusted analysis, the following confounding factors for cpRNFLT were included: age, sex, systolic blood pressure (SBP), the current use of antihypertensive medication, total cholesterol, HDL cholesterol, current use of lipid-lowering medication, BMI, smoking habit, alcohol intake, regular exercise, IOP, axial length, disc area, and image quality, where age, SBP, BMI, total cholesterol, HDL cholesterol, IOP, axial length, disc area, and image quality were treated as continuous variables, and the others were treated as categorical variables coded as either 1 or 0 depending on the presence or absence of the factor.[17–21] The categorical variable of IOP was stratified by the median value. A 2-tailed value of $P < .05$ was considered statistically significant.

RESULTS

TABLE 1 PROVIDES THE UNADJUSTED MEAN VALUES OR FREquencies of possible relevant factors of cpRNFLT by glucose tolerance levels. The mean values of age, SBP, diastolic blood pressure, fasting and 2-hour postload plasma glucose, HbA1c, total cholesterol, BMI, and the frequencies of male gender, use of antihypertensive medication, lipid-lowering medication, and regular exercise all increased significantly with poorer glucose tolerance levels, whereas the mean values of total cholesterol, HDL cholesterol, axial length, and image quality fell significantly with poorer glucose tolerance levels (all P values $< .05$).

Table 2 shows the age- and sex-adjusted and multivariable-adjusted mean values of cpRNFLT according to glucose tolerance levels. The age- and sex-adjusted mean cpRNFLT decreased significantly with poorer glucose tolerance levels ($P = .0002$ for trend). The subjects with prediabetes or diabetes mellitus had significantly lower cpRNFLT values compared with the subjects with normal glucose tolerance ($P = .04$ and $P = .0004$, respectively). These associations remained unchanged after adjustment for potential confounding factors (i.e., age, sex, SBP, current use of antihypertensive medication, BMI, total cholesterol, HDL cholesterol, current use of lipid-lowering medication, smoking habit, alcohol intake, regular exercise, IOP, axial length, disc area and image quality; $P = .002$ for trend). In women, the multivariable-adjusted mean values of cpRNFLT decreased significantly with poorer glucose tolerance levels ($P = .01$ for trend). In men, this trend was substantially the same but was not significant ($P = .06$ for trend). There was no evidence of heterogeneity in the association between the sexes (P for heterogeneity $= .25$).

The associations between fasting plasma glucose and 2-hour postload glucose, HbA1c level, and the cpRNFLT are shown in Table 3. The age- and sex-adjusted cpRNFLT values increased significantly with elevating fasting plasma glucose, 2-hour postload glucose, and HbA1c levels ($P < .05$ for trend). These associations were substantially unchanged even after adjustment for potentially confounding factors, although the P value for the HbA1c levels failed to reach significance.

We examined the combined influence of glucose tolerance levels and the IOP levels on the risk of thinning of cpRNFLT (Figure). The coexistence of poorer glucose tolerance and higher IOP levels was significantly associated with thinner cpRNFLT, without evidence of a significant interaction (P for interaction $= .74$).

DISCUSSION

THE RESULTS OF OUR ANALYSES DEMONSTRATED THAT IN A general Japanese population, prediabetes and diabetes were significantly associated with thinner cpRNFLT after adjusting for potentially confounding factors. Increased levels of fasting and 2-hour plasma glucose levels and HbA1c were also associated with a reduction of the cpRNFLT. Intriguingly, the coexistence of poorer glucose tolerance and higher IOP level was additively associated with thinner cpRNFLT. These findings suggest that hyperglycemia—particularly when accompanied by higher IOP levels—is a risk factor for a decreased cpRNFLT. Our findings highlight the importance of the prevention and early management of poorer glucose tolerance toward reducing the risk of thinning of the cpRNFLT and subsequent visual field defects.

Several hospital-based case-control studies have assessed the association between diabetes and the cpRNFLT. In a case-control study conducted in China, the cpRNFLT values at the optic discs in patients with type 1 diabetes mellitus were significantly lower than those in the control group.[22] This finding is in accordance with ours. Oshitari and associates[23] showed that the mean cpRNFLT values in diabetic patients without diabetic retinopathy were thinner than those in the control group, but the difference was not significant. The results of the Singapore Chinese Eye Study also failed to reveal a significant association between the serum glucose level and the cpRNFLT after multivariable adjustments.[24] The reason for this discrepancy may be related to the small sample size (<1000 participants) and the inaccurate measurements of serum glucose levels (nonfasting serum sampling). Recently, Lamparter and associates[25] showed a correlation between cpRNFLT and axial length but not between cpRNFLT and HbA1c or diabetes, in a population-based study. These conflicting results may be related to a difference in the characteristics of study participants (their study had a lower frequency of female participants than our study), methodology (they did not use high-quality images derived from OCT), or race.[26] As a result of these differences, the correlations between cpRNFLT and HbA1c or diabetes were not highlighted as significant in the earlier study. Additional large-scale investigations would be helpful for clarifying the association between glucose tolerance levels and the cpRNFLT.

We also considered the potential influence of undiagnosed glaucoma subjects. The numbers of undiagnosed glaucoma participants were 5 (0.7%) in the normal group, 5 (1.3%) in the prediabetes group, and 1 (0.6%) in the diabetes group (P for trend $= .77$). We therefore performed an additional sensitivity analysis after excluding these 11 subjects with undiagnosed glaucoma. However, the significant association remained unchanged (Supplemental Table 1; Supplemental Material available at AJO.com). There was no major influence of undiagnosed glaucoma on this association.

The precise mechanisms underlying the association between glucose tolerance levels and cpRNFLT are poorly understood, but some mechanisms have been proposed. Chronic inflammation plays a role in this progression of

TABLE 1. Characteristics of the Subjects According to Glucose Tolerance Status

Variable	Normal (n = 749)	Prediabetes (n = 392)	Diabetes (n = 183)	*P* for Trend
Age (y)	58 ± 10	64 ± 8	65 ± 9	<.0001
Men (%)	37.9	46.9	60.1	<.0001
Systolic blood pressure (mm Hg)	124 ± 18	131 ± 17	137 ± 18	<.0001
Diastolic blood pressure (mm Hg)	75 ± 11	78 ± 10	80 ± 12	<.0001
Current use of antihypertensive medication (%)	19.4	37.2	59.6	<.0001
Fasting plasma glucose level (mmol/L)	5.3 ± 0.4	5.9 ± 0.5	7.2 ± 1.4	<.0001
2-hour postload plasma glucose level (mmol/L)	6.0 ± 1.0	8.3 ± 1.3	13.2 ± 3.9	<.0001
Hemoglobin A1c (%)	5.5 ± 0.3	5.7 ± 0.3	6.5 ± 0.9	<.0001
Total cholesterol (mmol/L)	5.32 ± 0.87	5.37 ± 0.90	5.07 ± 0.94	.02
HDL cholesterol (mmol/L)	1.74 ± 0.43	1.64 ± 0.44	1.52 ± 0.42	<.0001
Current use of lipid-lowering medication (%)	15.4	21.9	38.3	<.0001
Body mass index (kg/m^2)	22.3 ± 2.9	23.6 ± 3.2	25.0 ± 4.3	<.0001
Smoking habit (%)	17.2	12.5	20.8	.89
Alcohol intake (%)	55.4	53.6	61.2	.36
Regular exercise (%)	15.9	15.1	21.3	.19
Intraocular pressure (mm Hg)	13.9 ± 2.4	13.8 ± 2.4	14.1 ± 2.8	.49
Axial length (mm)	23.9 ± 1.3	23.7 ± 1.2	23.7 ± 1.2	.01
Disc area (mm^2)	2.21 ± 0.4	2.23 ± 0.4	2.24 ± 0.4	.27
Image quality	46 ± 6	45 ± 7	44 ± 7	.001

Values are mean ± standard deviation or percentages.
HDL = high-density lipoprotein.

TABLE 2. Age- and Sex-Adjusted and Multivariable-Adjusted Mean Circumpapillary Retinal Nerve Fiber Layer Thickness According to Glucose Tolerance Status

		Age- and Sex-Adjusted				Multivariable-Adjusted[a]			
Glucose Tolerance Status	n	cpRFNL, μm	95% CI	*P* Value	*P* for Trend	cpRFNL, μm	95% CI	*P* Value	*P* for Trend
Overall									
Normal	749	102.3	101.4–103.2	Reference	.0002	102.1	101.3–102.9	Reference	.002
Prediabetes	392	100.6	99.4–101.8	.04		100.6	99.4–101.7	.03	
Diabetes	183	98.5	96.7–100.4	.0004		99.3	97.3–101.0	.004	
Men									
Normal	284	100.3	98.8–101.7	Reference	.049	100.2	98.9–101.6	Reference	.06
Prediabetes	184	100.5	98.7–102.3	.82		100.5	98.8–102.1	.83	
Diabetes	110	97.0	94.7–99.3	.02		97.2	95.0–99.4	.03	
Women									
Normal	465	103.7	102.6–104.8	Reference	.001	103.5	102.5–104.6	Reference	.01
Prediabetes	208	100.5	98.9–102.2	.003		100.4	98.9–102.0	.002	
Diabetes	73	99.9	97.1–102.8	.02		101.2	98.5–103.9	.12	

CI = confidence interval; cpRNFL = circumpapillary retinal nerve fiber layer thickness.
[a]Multivariable adjustment was performed for age, sex, systolic blood pressure, current use of antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, current use of lipid-lowering medication, body mass index, smoking habit, alcohol intake, regular exercise, intraocular pressure, axial length, disc area, and image quality.

neurodegenerative effects. Hyperglycemia has been reported to induce inflammatory cytokines, such as interleukin (IL)-1, IL-6, and interferon gamma (IFNγ).[27,28] These inflammatory cytokines can activate microglia, which increase in number, translocate through the retina, and become the producers of inflammatory and apoptotic molecules. In their morphometric analysis of retinal cross-sections, Martin and associates[29] reported that diabetic mice had 20–25% fewer cells in the ganglion cell layer than age-matched control mice. In addition, the number of apoptotic cells in the ganglion cell layer was increased in the diabetic mice compared with control mice.

TABLE 3. Age- and Sex-Adjusted and Multivariable-Adjusted Mean Circumpapillary Retinal Nerve Fiber Layer Thickness According to Plasma Glucose or Hemoglobin A1c Levels

		Age- and Sex-Adjusted				Multivariable-Adjusted[a]			
	n	cpRFNL, μm	95% CI	*P* Value	*P* for Trend	cpRFNL, μm	95% CI	*P* Value	*P* for Trend
Fasting Plasma Glucose Level (mmol/L)									
<5.6	569	102.4	101.4–103.4	Reference	.001	102.2	101.3–103.2	Reference	.01
5.6–6.0	422	100.9	99.8–102.1	.06		101.0	99.9–102.1	.10	
6.1–6.9	227	99.9	98.3–101.5	.01		99.9	98.4–101.4	.01	
≥7.0	106	99.1	96.7–101.4	.01		99.7	97.6–102.0	.06	
2-Hour Postload Plasma Glucose Level (mmol/L)									
<6.7	541	102.1	101.0–103.2	Reference	.001	102.1	101.1–103.1	Reference	.004
6.7–7.7	306	102.4	101.0–103.8	.74		101.7	100.5–103.0	.60	
7.8–11.0	341	100.0	98.7–101.3	.02		100.2	99.0–101.4	.02	
≥11.1	126	98.5	96.5–100.6	.003		99.4	97.4–101.3	.02	
Hemoglobin A1c Level (%)									
<5.4	427	101.6	100.4–102.8	Reference	.06	101.7	100.6–102.8	Reference	.14
5.5–5.6	318	102.4	101.0–103.7	.41		101.9	100.6–103.1	.84	
5.7–6.4	495	100.6	99.5–101.7	.23		100.6	99.6–101.6	.18	
≥6.5	84	99.1	96.4–101.7	.09		100.3	97.9–102.8	.34	

CI = confidence interval; cpRNFL = circumpapillary retinal nerve fiber layer thickness.

[a]Multivariable adjustment was performed for age, sex, systolic blood pressure, current use of antihypertensive medication, total cholesterol, high-density lipoprotein cholesterol, current use of lipid-lowering medication, body mass index, smoking habit, alcohol intake, regular exercise, intraocular pressure, axial length, disc area, and image quality.

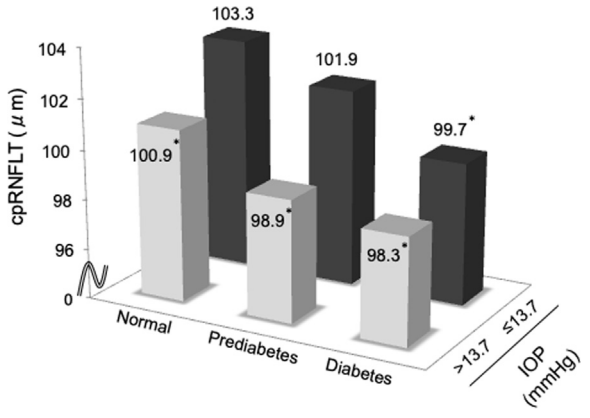

FIGURE. Multivariable-adjusted mean cpRNFLT according to glucose tolerance status and intraocular pressure levels. Adjusted for age, sex, SBP, current use of antihypertensive medication, total cholesterol, HDL cholesterol, current use of lipid-lowering medication, BMI, smoking habit, alcohol intake, regular exercise, disc area, and image quality. *$P < .05$ vs. the reference group (normal glucose tolerance and lower level of IOP). *P* for heterogeneity = .74. cpRNFLT = circumpapillary retinal nerve fiber layer thickness; IOP = intraocular pressure.

Zhang and associates[30] focused on the diabetes-induced impairment of retrograde axonal transport in streptozotocin-diabetic rats, and they reported that an accumulation of harmful glycoproteins and a disintegrated messenger system in neurons reduced the retrograde axonal transport. Moreover, Mammo and associates[31] reported that the nerve fiber layer thickness was strongly correlated with the radial peripapillary capillary (RPC) density determined by speckle variance OCT angiography. They noted that nutritional demands of retinal ganglion cell axons (which are likely to be partially satisfied by RPCs[32–35]) and structural changes to RPCs are involved in the pathogenesis of glaucoma.[36] High-glucose status may have effects on this particular structural change of RPCs by changing the vascular permeability, and this may result in the reduction of the cpRNFLT. Based on our present findings, these mechanisms may exist in the prediabetes stage, and they may lead to a reduction of cpRNFLT before diabetes mellitus.

The strengths of our study are the population-based design, the large sample size, and the use of an oral glucose tolerance test for the diagnosis of diabetes. Nevertheless, there is a potential limitation that should be noted. First, our findings were based on a single measurement of plasma glucose. This limitation might have led to a misclassification of glucose tolerance status and might have weakened the association, biasing the results toward the null hypothesis. Therefore the true association could be even stronger than is apparent. Second, this was a cross-sectional study, and the interpretation of the causal relationship between poorer glucose tolerance and the cpRNFLT was limited. However, we believe that the poorer glucose tolerance

affects the cpRNFLT, because the cpRNFLT itself is unlikely to modify the glucose level. Lastly, 436 patients were excluded because of motion artifact and segmentation errors (n = 356) and poor-quality scans (n = 80). During OCT measurement, it is necessary to fix the target for 2 seconds. It is difficult to get a good-quality image of OCT in a population-based study. Compared with the other participants, those with poor-quality OCT scans had significantly higher age, fasting plasma glucose levels, 2-hour postload plasma glucose levels, HbA1c, and frequencies of current use of antihypertensive medication (Supplemental Table 2; Supplemental Material available at AJO.com). In the analysis including the subjects with poor-quality scans (n = 80), the significant association remained unchanged (Supplemental Table 3; Supplemental Material available at AJO.com). Moreover, after adjustment for image quality as a confounding factor in the multivariable analysis, we found that the association remained significant. Therefore, the exclusion of poor cpRNFLT measurement does not change the conclusion.

In conclusion, our results showed that an increased plasma glucose level was significantly associated with the reduction of cpRNFLT in a Japanese general population. These findings suggest that (1) the loss of neural tissue in the eye begins at the prediabetic stage, and (2) that hyperglycemia may play a role in the reduction of cpRNFLT. In addition, subjects with both poorer glucose tolerance and elevated IOP are likely to have a decreased cpRNFLT, because higher IOP is a known risk factor for thinning of the cpRNFLT and the development of glaucoma.[21] Therefore, it is useful to pay attention to IOP levels in subjects with poorer glucose tolerance.

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REFERENCES

1. Bourne RRA, Jonas JB, Flaxman SR, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990–2010. *Br J Ophthalmol* 2014;98(5):629–638.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;121(11):2081–2090.
3. Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science* 1991;254(5035):1178–1181.
4. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. *Arch Ophthalmol* 1995;113(3):325–332.
5. Akashi A, Kanamori A, Ueda K, Inoue Y, Yamada Y, Nakamura M. The ability of SD-OCT to differentiate early glaucoma with high myopia from highly myopic controls and nonhighly myopic controls. *Invest Ophthalmol Vis Sci* 2015;56(11):6573–6580.
6. Mitchell P, Smith W, Chey T, Healey PR. Open-angle glaucoma and diabetes: the Blue Mountains Eye Study, Australia. *Ophthalmology* 1997;104(4):712–718.
7. Chopra V, Varma R, Francis BA, et al. Los Angeles Latino Eye Study Group. Type 2 diabetes mellitus and the risk of open-angle glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology* 2008;115(2):227–232.
8. Zhao D, Cho J, Kim MH, Friedman DS, Guallar E. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. *Ophthalmology* 2015;122(1):72–78.
9. Lin SC, Singh K, Jampel HD, et al. Optic nerve head and retinal nerve fiber layer analysis: a report by the American Academy of Ophthalmology. *Ophthalmology* 2007;114(10):1937–1949.
10. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography (OCT) macular and peripapillary retinal nerve fiber layer measurements and automated visual fields. *Am J Ophthalmol* 2004;138(2):218–225.
11. Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 1966;21:64–89.
12. Ohmura T, Ueda K, Kiyohara Y, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia* 1993;36(11):1198–1203.
13. Oshima Y, Ishibashi T, Murata T, Tahara Y, Kiyohara Y, Kubota T. Prevalence of age-related maculopathy in a representative Japanese population: the Hisayama Study. *Br J Ophthalmol* 2001;85(10):1153–1157.
14. Schuman JS, Hee MR, Arya AV, et al. Optical coherence tomography: a new tool for glaucoma diagnosis. *Curr Opin Ophthalmol* 1995;6(2):89–95.
15. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 1998;15(7):539–553.
16. Hirakawa Y, Ninomiya T, Mukai N, et al. Association between glucose tolerance level and cancer death in a general Japanese population: the Hisayama Study. *Am J Epidemiol* 2012;176(10):856–864.

17. Abe H, Shirakashi M, Tsutsumi T, et al; Tajimi Study Group. Laser scanning tomography of optic discs of the normal Japanese population in a population-based setting. *Ophthalmology* 2009;116(2):223–230.
18. Wu R-Y, Wong T-Y, Zheng Y-F, et al. Influence of refractive error on optic disc topographic parameters: the Singapore Malay Eye Study. *Am J Ophthalmol* 2011;152(1):81–86.
19. Bourne RR, Foster PJ, Bunce C, et al. The morphology of the optic nerve head in the Singaporean Chinese population (the Tanjong Pagar study): part 2–biometric and systemic associations. *Br J Ophthalmol* 2008;92(3):310–314.
20. Zheng Y, Cheung CYL, Wong TY, Mitchell P, Aung T. Influence of height,weight, and body mass index on optic disc parameters. *Invest Ophthalmol VisSci* 2010;51(6):2998–3002.
21. Mauschitz MM, Bonnemaijer PWM, Diers K, et al. Systemic and ocular determinants of peripapillary retinal nerve fiber layer thickness measurements in the European Eye Epidemiology (E3) Population. *Ophthalmology* 2018;125(10): 1526–1536.
22. Chen Y, Li J, Yan Y, Shen X. Diabetic macular morphology changes may occur in the early stage of diabetes. *BMC Ophthalmol* 2016;16:12.
23. Oshitari T, Hanawa K, Adachi-Usami E. Changes of macular and RNFL thicknesses measured by Stratus OCT in patients with early stage diabetes. *Eye* 2009;23(4):884–888.
24. Cheung CY, Chen D, Wong TY, et al. Determinants of quantitative optic nerve measurements using spectral domain optical coherence tomography in a population-based sample of non-glaucomatous subjects. *Invest Ophthalmol Vis Sci* 2011; 52(13):9629–9635.
25. Lamparter J, Schmidtmann I, Schuster AK, et al. Association of ocular, cardiovascular, morphometric and lifestyle parmeters with retinal nerve fibre layer thickness. *PLoS One* 2018;13(5):e0197682.
26. Girkin CA, McGwin G Jr, Sinai MJ, et al. Variation in optic nerve and macular structure with age and race with spectral-domain optical coherence tomography. *Ophthalmology* 2011; 118(12):2403–2408.
27. Krady JK, Basu A, Allen CM, et al. Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. *Diabetes* 2005;54(5):1559–1565.
28. Liou GI. Diabetic retinopathy: role of inflammation and potential therapies for anti-inflammation. *World J Diabetes* 2010;1(1):12–18.
29. Martin PM, Roon P, Van Ells TK, Ganapathy V, Smith SB. Death of retinal neurons in streptozotocin-induced diabetic mice. *Invest Ophthalmol Vis Sci* 2004;45(9):3330–3336.
30. Zhang L, Ino-ue M, Dong K, Yamamoto M. Retrograde axonal transport impairment of large- and medium-sized retinal ganglion cells in diabetic rat. *Curr Eye Res* 2000; 20(2):131–136.
31. Mammo Z, Heisler M, Balaratnasingam C, et al. Quantitative optical coherence tomography angiography of radial peripapillary capillaries in glaucoma, glaucoma suspect, and normal eyes. *Am J Ophthalmol* 2016;170:41–49.
32. Yu PK, Cringle SJ, Yu DY. Correlation between the radial peripapillary capillaries and the retinal nerve fibre layer in the normal human retina. *Exp Eye Res* 2014;129:83–92.
33. Henkind P. Symposium on glaucoma: Joint Meeting with The National Society for the Prevention of Blindness. New observations on the radial peripapillary capillaries. *Invest Ophthalmol* 1967;6(2):103–108.
34. Scoles D, Gray DC, Hunter JJ, et al. In-vivo imaging of retinal nerve fiber layer vasculature: Imaging histology comparison. *BMC Ophthalmol* 2009;9:9.
35. Yu PK, Balaratnasingam C, Xu J, et al. Label-free density measurements of radial peripapillary capillaries in the human retina. *PLoS One* 2015;10(8):e0135151.
36. Kornzweig AL, Eliasoph I, Feldstein M. Selective atrophy of the radial peripapillary capillaries in chronic glaucoma. *Arch Ophthalmol* 1968;80(6):696–702.