Original Article

Association between localized retinal nerve fiber layer defects in nonglaucomatous eyes and metabolic syndrome: a propensity score-matched analysis

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Background: We investigated the association between metabolic syndrome and localized retinal nerve fiber layer (RNFL) defects in nonglaucomatous subjects.

Methods: We examined 20,385 adults who visited the Health Promotion Center of Seoul St. Mary's Hospital between May 2015 and April 2016. After excluding those with known glaucoma or glaucomatous optic discs, subjects with and without localized RNFL defects were 1:5 propensity score matched. Metabolic syndrome components, including central obesity, elevated triglyceride, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure (BP), and elevated fasting glucose, were compared between two groups. We performed logistic regression to investigate the association between RNFL defects and each component of metabolic syndrome and the number of metabolic syndrome components.

Results: Subjects with RNFL defects showed higher waist-to-hip ratios, systolic BP (SBP) and diastolic BP (DBP), fasting blood glucose, and hemoglobin A1c (HbA1c) levels than did those without RNFL defects both before and after propensity score matching. The number of metabolic syndrome components was significantly greater in those with RNFL defects (1.66±1.35) than in those without (1.27±1.32, P<0.01). In multivariate logistic regression, the odds ratio (OR) of RNFL defects was significantly increased in subjects with central obesity [OR =1.53, 95% confidence interval (CI): 1.11–2.13], elevated BP (OR =1.50, 95% CI: 1.09–2.05), and an elevated fasting glucose level (OR =1.42, 95% CI: 1.03–1.97). An increased number of metabolic syndrome components was associated with a higher risk of RNFL defects.

Conclusions: Localized RNFL defects in nonglaucomatous subjects are associated with metabolic syndrome components, including central obesity, elevated BP, and an elevated fasting glucose level, suggesting that comorbid metabolic syndrome should be considered when evaluating subjects with RNFL defects.

Keywords: Retinal nerve fiber layer defect (RNFL defect); metabolic syndrome; glaucoma

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Introduction

The retinal nerve fiber layer (RNFL) contains the axons of retinal ganglion cells. Damage to the optic nerve triggers the loss of such cells, thus affecting the RNFL. Localized RNFL defects are rare in normal eyes, and are of high diagnostic utility for glaucoma (1). However, RNFL defects are not pathognomonic of glaucoma, being also evident in patients with other diseases associated with retinal vascular insufficiency, including nonarteritic anterior ischemic optic neuropathy, diabetic retinopathy, and arterial hypertension (1-3).

Localized RNFL defects have been associated with certain components of metabolic syndrome in previous studies, including obesity (4-6), cardiovascular risk factors (7), hypertension (7-10), and albuminuria in patients with type 2 diabetes (11). Metabolic syndrome is a growing epidemic estimated at 1.4 billion worldwide and rising every year (12). Metabolic syndrome is characterized by visceral obesity, dyslipidemia, hyperglycemia, and hypertension (13), all of which can trigger endothelial dysfunction and vascular insufficiency (14). We hypothesized that RNFL defects are associated with metabolic syndrome. Therefore, in this cross-sectional study, we investigated the association between metabolic syndrome and localized RNFL defects in nonglaucomatous patients. We present this article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3381/rc).

Highlight box

Key findings

- Retinal nerve fiber layer (RNFL) defects are associated with metabolic syndrome in a propensity score-matched cohort.

What is known and what is new?

- Localized RNFL defects have been associated with certain components of metabolic syndrome in previous studies, including obesity, cardiovascular risk factors, hypertension, and albuminuria in patients with type 2 diabetes.
- In this study, we found that localized RNFL defects are associated with metabolic syndrome components, including central obesity, elevated systolic/diastolic blood pressure, fasting glucose level, HbA1c, and triglyceride, and lower HDL-cholesterol. In addition, RNFL defects are associated with greater number of metabolic syndrome components.

What is the implication, and what should change now?

- We suggest that comorbid metabolic syndromes should be considered when evaluating subjects with RNFL defects.

Methods

We reviewed the data of 20,385 subjects who underwent health examinations at the Health Promotion Center of Seoul St. Mary's Hospital (a tertiary, university teaching hospital with 1,300 beds) between May 2015 and April 2016. The exclusion criteria were age <19 or >85 years, missing fundus photographs, or poor images attributable to media opacity or poor co-operation. We also excluded those who had undergone intraocular surgery and those diagnosed with glaucoma. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Seoul St. Mary's Hospital (No. KC15RISI0550), which waived the need for informed consent from the study subjects because of the retrospective nature of the work.

The health examination included anthropometric measurements, basic hematological tests (a complete blood count and blood chemistry), ophthalmic examinations [intraocular pressure (IOP) measurement via noncontact tonometry and fundus photography], a chest X-ray, an abdominal sonogram, endoscopy, and a standardized self-completed questionnaire exploring medical history. Additional examinations were available upon request. All examinations were performed by doctors, trained nurses, and medical laboratory technologists.

Anthropometric measurements were measured via the bioelectrical impedance method using an Inbody 720 device (Biospace, Seoul, Korea) with subjects wearing light clothing and no shoes. The body mass index (BMI) was the weight divided by the square of the height (kg/m^2). Waist circumference, hip circumference, the waist-to-hip ratio, skeletal muscle mass, body fat mass, and body fat amount were measured.

Blood pressure (BP) was measured using an automatic monitor (TM-2655P; P.M.S., Berkshire, UK) with subjects seated after at least 5 min of rest. Blood samples were collected from antecubital veins after overnight fasts. The samples were collected into sodium fluoride tubes for plasma glucose measurement and into serum-separating tubes for all other measurements. All samples were centrifuged within 30 min and analyzed in a central laboratory employing a Hitachi 7600 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). Fasting blood glucose levels were measured using the hexokinase method. Fasting triglyceride and total and low-density lipoprotein (LDL)

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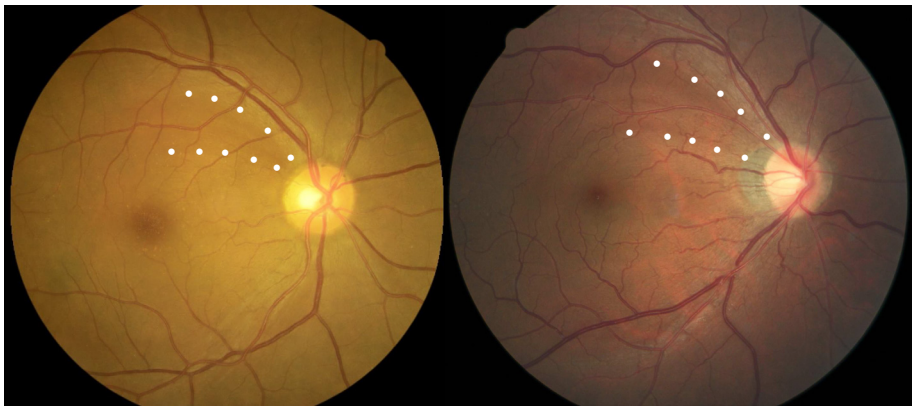

Figure 1 Localized retinal nerve fiber layer defect.

cholesterol levels were measured enzymatically; high-density lipoprotein (HDL) cholesterol levels were assayed employing selective inhibition. Hemoglobin A1c (HbA1c) was measured via high-performance liquid chromatography using the DCCT-aligned method (Tosoh-G8; Tosoh, Tokyo, Japan).

IOP was measured using a noncontact tonometer (TX-F; Canon Inc., Tokyo, Japan), and fundus photographs taken employing a nonmydriatic fundus camera (CR-DGi; Canon Inc.). The IOP was the average of three measurements on each eye; the mean IOPs of both eyes were used in our analysis. All fundus photographs were reviewed by two (independent) ophthalmologists (one glaucoma specialist and one retina specialist); any disagreement was resolved by consensus. An RNFL defect was defined as a wedge-shaped defect running toward or touching the optic disc margin for not more than 60° (*Figure 1*) (2,9,15). Eyes with multiple RNFL defects were included in the study. RNFL defects associated with significant glaucomatous optic disc changes, chorioretinal scarring, a history of uveitis, a retinal hemorrhagic lesion in those with diabetic or hypertensive retinopathy, or retinal vessel occlusion were not included in the analysis. Glaucomatous optic disc changes were defined as: (I) a vertical cup-to-disc ratio ≥0.7; (II) neuroretinal rim notching, thinning, or excavation; or (III) interocular asymmetry in vertical cup-to-disc ratio ≥0.2.

Metabolic comorbidities were identified by reference to the medical history and the health examination data. Metabolic syndrome was defined using the criteria of the International Diabetes Federation; American Heart Association; and National Heart, Lung, and Blood Institute (16,17), thus:

(I) Central obesity: waist circumference for Koreans, men ≥90 cm, women ≥85 cm (18);
(II) Elevated triglyceride level: triglycerides ≥150 mg/dL or on dyslipidemia medication;
(III) Reduced HDL cholesterol: HDL-cholesterol <40 mg/dL in men, <50 mg/dL in women;
(IV) Elevated BP: systolic BP (SBP) ≥130 mmHg, diastolic BP (DBP) ≥85 mmHg, or on antihypertensive treatment;
(V) Elevated fasting glucose: fasting glucose level ≥100 mg/dL, or on hypoglycemic treatment.

Statistical analysis

Continuous variables are presented as means ± standard deviations and were compared using the Student's *t*-test. Categorical variables are presented as frequencies (percentages) and were compared employing the Pearson chi-squared test. Propensity score-matching was performed to minimize selection bias. Propensity scores were calculated via multiple logistic regressions that considered age, sex, and IOP. Subjects with and without RNFL defects were then 1:5-matched using a greedy nearest neighbor approach without replacement. Multivariate logistic regression was used to identify associations between metabolic syndrome components and RNFL defects. A subanalysis was performed after stratification of the BP levels. All tests were two-sided, and P values <0.05 were considered statistically significant. All analyses were performed using SPSS ver. 22.0 (SPSS Inc., Chicago, IL, USA); propensity score-matching was performed using an SPSS extension program (R 2.15.0).

Results

The baseline clinical characteristics of all subjects are

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Table 1 Baseline characteristics of subjects with and without retinal nerve fiber layer defects before propensity score matching

Characteristics	Retinal nerve fiber layer defect		P value
	No (n=17,353)	Yes (n=238)	
Age (years)	47.09±10.68	51.38±10.33	<0.01
Sex (men, %)	9,763 (56.3)	152 (63.9)	0.01
Intraocular pressure (mmHg)	13.15±2.85	13.88±2.99	<0.01
Height (cm)	166.96±8.46	166.87±8.32	0.87
Weight (kg)	66.14±12.88	66.52±12.13	0.66
Body mass index (kg/m^2)	23.58±3.35	23.81±3.37	0.28
Skeletal muscle mass (kg)	26.80±6.48	27.08±6.06	0.52
Body fat mass (kg)	17.62±5.70	17.75±5.58	0.73
Body fat (%)	26.60±6.21	26.62±6.35	0.96
Waist circumference (cm)	83.38±9.40	84.25±9.37	0.15
Hip circumference (cm)	94.61±6.60	94.47±6.50	0.75
Waist to hip ratio	0.89±0.05	0.90±0.05	<0.01
Systolic blood pressure (mmHg)	118.18±13.89	122.55±14.62	<0.01
Diastolic blood pressure (mmHg)	73.81±9.72	77.06±9.50	<0.01
Pulse rate	65.83±9.76	64.75±8.57	0.09
Fasting blood glucose (mg/dL)	96.66±18.70	101.83±24.52	<0.01
HbA1c (%)	5.61±0.62	5.85±0.85	<0.01
Total cholesterol (mg/dL)	201.13±35.83	203.17±40.18	0.38
Triglyceride (mg/dL)	122.73±92.70	128.88±96.45	0.31
HDL-cholesterol (mg/dL)	55.47±13.60	54.22±11.97	0.16
LDL-cholesterol (mg/dL)	121.64±32.12	123.25±35.91	0.44

Data are presented as mean ± standard deviation or n (percentage). HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

shown in *Table 1*. After screening 20,385 subjects, 17,591 were included in the final analysis, of whom 238 (1.4%) had RNFL defects in both eyes (*Figure 2*). Those with RNFL defects were older than the others (51.38±10.33 *vs.* 47.09±10.68 years), tended to be men (63.9% *vs.* 56.3%), and evidenced a higher IOP (13.88±2.99 *vs.* 13.15±2.85 mmHg), waist-to-hip ratio (0.90±0.05 *vs.* 0.89±0.05), SBP (122.55±14.62 *vs.* 118.18±13.89 mmHg), diastolic BP (DBP) (77.06±9.50 *vs.* 73.81±9.72 mmHg), fasting blood glucose level (101.83±24.52 *vs.* 96.66±18.70 mg/dL), and HbA1c level (5.85%±0.85% *vs.* 5.61%±0.62%) than those lacking RNFL defects (*Table 1*).

After 1:5 propensity score-matching with adjustment for age, sex, and IOP, subjects with RNFL defects showed a higher BMI (23.81±3.37 *vs.* 23.13±3.16 kg/m^2), waist-to-hip ratio (0.904±0.050 *vs.* 0.895±0.048), SBP (122.55±14.62 *vs.* 119.19±14.24 mmHg), DBP (77.06±9.50 *vs.* 73.44±9.54 mmHg), fasting blood glucose level (101.83±24.52 *vs.* 97.98±21.39 mg/dL), HbA1c level (5.85%±0.85% *vs.* 5.67%±0.69%), and triglyceride level (128.88±96.45 *vs.* 112.69±75.27 mg/dL); but a lower HDL-cholesterol level (54.22±11.97 *vs.* 56.57±13.56 mg/dL) than did those lacking RNFL defects (*Table 2*).

Table 3 shows the metabolic syndrome components of those with and without RNFL defects. Subjects with RNFL defects evidenced more components (1.66±1.35) than did the others (1.27±1.32, P<0.01). Further analysis across the BP levels revealed higher risks of RNFL defects in those with a higher SBP and DBP and a lower risk in those with a lower DBP (Table S1). RNFL defects were associated with

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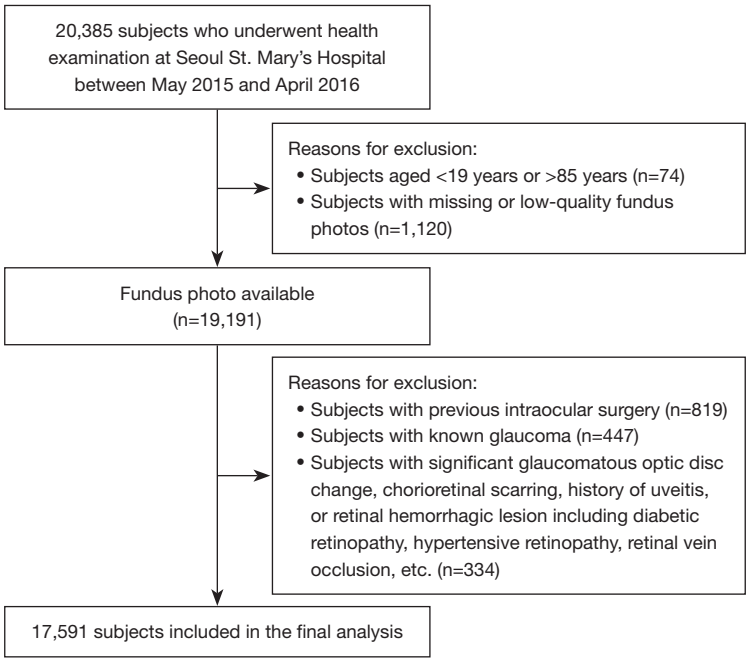

Figure 2 Selection of study subjects.

significantly more central obesity, elevated BP, and elevated triglyceride and fasting glucose levels. On multivariate logistic regression, central obesity [odds ratio (OR): 1.53, 95% confidence interval (CI): 1.11–2.13], an elevated BP (OR =1.50, 95% CI: 1.09–2.05), and an elevated fasting glucose level (OR =1.42, 95% CI: 1.03–1.97) were associated with RNFL defects (*Table 4*).

Regarding the number of metabolic syndrome components, *Figure 3* shows the percentages of subjects with and without RNFL defects by the number of metabolic syndrome components. The risk of RNFL defect increased as the number of metabolic syndrome components increased except for those with all 5 components which may be related with fewer number of subjects (*Table 5*).

Discussion

We found that localized RNFL defects were associated with metabolic syndrome in a propensity score-matched cohort. Those with such defects evidenced a greater waist circumference; SBP/DBP; and fasting blood glucose, HbA1c, and triglyceride levels; but a lower HDL-cholesterol level, than others. RNFL defects were associated with a greater number of metabolic syndrome components, central obesity, an elevated BP, and an elevated fasting glucose level.

About 1.4% of subjects had RNFL defects. In an epidemiological study using data from the Korean National Health and Nutrition Examination Survey, the prevalence of RNFL defects over 5 years [2008–2012] was 4.8%. Approximately 65.6% of such subjects lacked glaucoma (19). The cited authors reviewed both frequency-doubling perimetric data and fundus photographs. In the population-based cross-sectional Beijing Eye Study, RNFL defects were detected in color fundus photographs of 3.7% of the population (20). The differences among studies may reflect different inclusion criteria; whether glaucomatous optic discs were or were not included; and differences in ethnicity, study design, and the methods used to detect localized RNFL defects.

Localized RNFL defects are independently associated with hypertension and diabetes. However, associations with metabolic syndrome have not been investigated. Metabolic syndrome is characterized by central obesity, dyslipidemia, hyperglycemia, and hypertension, which can trigger endothelial dysfunction and vascular insufficiency, and (in turn) localized RNFL defects (14). RNFL defects can also be sequelae of retinal cotton-wool spots in those with metabolic syndrome (20,21).

We found that localized RNFL defects were associated with central obesity. Previous studies also reported that obesity (high BMI) was associated with a thinner RNFL

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Table 2 Baseline characteristics of subjects with and without retinal nerve fiber layer defects after 1:5 propensity score matching

Characteristics	Retinal nerve fiber layer defect		P value
	No (n=1,190)	Yes (n=238)	
Age (years)	51.59±10.01	51.38±10.33	0.77
Sex (men, %)	722 (60.7)	152 (63.9)	0.85
Intraocular pressure (mmHg)	13.97±2.86	13.88±2.99	0.66
Height (cm)	166.05±8.39	166.87±8.32	0.17
Weight (kg)	64.18±12.27	66.52±12.13	0.01
Body mass index (kg/m^2)	23.13±3.16	23.81±3.37	<0.01
Skeletal muscle mass (kg)	26.06±6.20	27.08±6.06	0.02
Body fat mass (kg)	16.86±5.40	17.75±5.58	0.02
Body fat (%)	26.30±6.18	26.62±6.35	0.47
Waist circumference (cm)	82.69±8.74	84.25±9.37	0.01
Hip circumference (cm)	93.22±6.45	94.47±6.50	0.01
Waist to hip ratio	0.895±0.048	0.904±0.050	0.01
Systolic blood pressure (mmHg)	119.19±14.24	122.55±14.62	<0.01
Diastolic blood pressure (mmHg)	73.44±9.54	77.06±9.50	<0.01
Pulse rate	65.15±10.10	64.75±8.57	0.57
Fasting blood glucose (mg/dL)	97.98±21.39	101.83±24.52	0.01
HbA1c (%)	5.67±0.69	5.85±0.85	<0.01
Total cholesterol (mg/dL)	200.93±36.67	203.17±40.18	0.40
Triglyceride (mg/dL)	112.69±75.27	128.88±96.45	<0.01
HDL-cholesterol (mg/dL)	56.57±13.56	54.22±11.97	0.01
LDL-cholesterol (mg/dL)	120.83±32.38	123.25±35.91	0.30

Data are presented as mean ± standard deviation or n (percentage). HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3 Association between number of metabolic syndrome components and each component of metabolic syndrome with presence of retinal nerve fiber layer defects

Metabolic syndrome	Subtypes	Retinal nerve fiber layer defect		Odds ratio (95% CI)	P value
		No (n=1,190)	Yes (n=238)		
Number of metabolic syndrome components		1.27±1.32	1.66±1.35		<0.01
Central obesity	No (n=1,068)	911 (76.6)	157 (66.0)	1 (Reference)	<0.01
	Yes (n=360)	279 (23.4)	81 (34.0)	1.69 (1.25–2.27)	
Elevated triglyceride	No (n=1,022)	866 (72.8)	156 (65.5)	1 (Reference)	0.02
	Yes (n=406)	324 (27.2)	82 (34.5)	1.41 (1.05–1.89)	
Reduced HDL cholesterol	No (n=1,210)	1014 (85.2)	196 (82.4)	1 (Reference)	0.26
	Yes (n=218)	176 (14.8)	42 (17.6)	1.24 (0.85–1.79)	
Elevated blood pressure	No (n=945)	806 (67.7)	139 (58.4)	1 (Reference)	0.01
	Yes (n=483)	384 (32.3)	99 (41.6)	1.50 (1.12–1.99)	
Elevated fasting glucose	No (n=990)	844 (70.9)	146 (61.3)	1 (Reference)	<0.01
	Yes (n=438)	346 (29.1)	92 (38.7)	1.54 (1.15–2.05)	

Data are presented as mean ± standard deviation or n (percentage). CI, confidence interval; HDL, high-density lipoprotein.

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Table 4 Multivariate logistic regression showing association between metabolic syndrome components and presence of retinal nerve fiber layer defects

Metabolic syndrome	Odds ratio	95% CI	P value
Central obesity	1.53	1.11–2.13	0.01
Elevated triglyceride	1.27	0.91–1.77	0.16
Reduced HDL cholesterol	1.06	0.71–1.58	0.77
Elevated blood pressure	1.50	1.09–2.05	0.01
Elevated fasting glucose	1.42	1.03–1.97	0.03

CI, confidence interval; HDL, high-density lipoprotein.

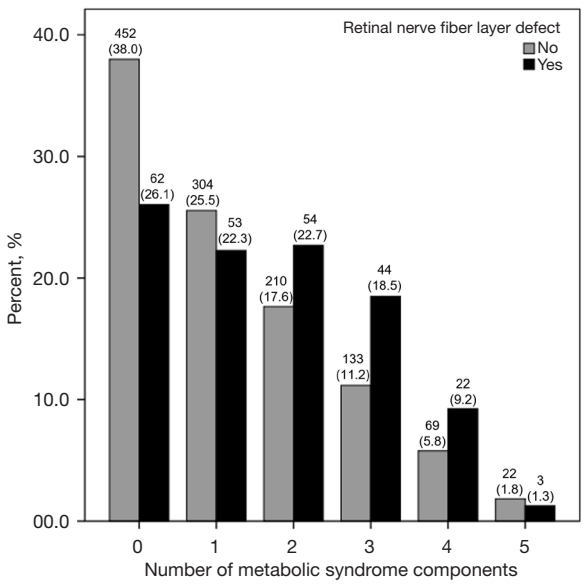

Figure 3 Number of metabolic syndrome components according to presence of retinal nerve fiber layer defect.

Table 5 Logistic regression showing association between the number of metabolic syndrome components and presence of retinal nerve fiber layer defects

Number of metabolic syndrome components	Odds ratio	95% CI	P value
0	1 (Reference)		
1	1.27	0.86–1.89	0.23
2	1.88	1.26–2.80	<0.01
3	2.41	1.57–3.72	<0.01
4	2.32	1.34–4.02	<0.01
5	0.99	0.29–3.42	0.99

CI, confidence interval.

(4-6). In a recent study, a higher BMI was associated with reduced retinal oxygen delivery and extraction in healthy subjects. It was suggested that this might reflect retinal oxidative stress and inflammation (6).

RNFL defects have been associated with hypertension (7-10). In a study of rhesus monkeys, chronic arterial hypertension and atherosclerosis triggered localized defects. The cited authors suggested that autoregulatory vasoconstriction of the superficial arterioles (caused by a high BP) triggered vessel occlusion and ischemic damage (10). In another study, localized RNFL defects were associated with a higher BP; in particular, the risk of RNFL defects increased by 13% for every 10 mmHg increase in BP (7). Similarly, in our study, localized RNFL defects were associated with a higher SBP and DBP. Those with a lower DBP were at decreased risk of localized RNFL defects. However, a U-shaped association between BP and glaucoma has been widely reported (22,23). In addition, in a study in the Netherlands, subjects with a low BP or hypertension showed thinner ganglion cell inner plexiform layers than others (24). The authors also reported that this was associated with reduced retinal blood flow, increased vascular resistance, or insufficient autoregulatory capacity. In another study, BP was not significantly associated with RNFL thickness (25), perhaps because of differences in genetic background (26), the study populations, or the methods used to evaluate RNFL thickness.

Diabetes is also linked to localized RNFL defects (1,3,19). An increased HbA1c level was associated with an increased risk of RNFL defects; it was suggested that oxidative stress, accumulation of advanced glycated end-products, and impaired retrograde axonal transport of retinal ganglion cells were in play (7).

RNFL defects were associated with higher urinary albumin excretion (a well-known marker of vascular endothelial dysfunction) in type 2 diabetics (11). The cited authors noted that the retinal blood supply was very susceptible to endothelial dysfunction (which is strongly related to autoregulation) because the retinal vasculature is controlled principally via vascular autoregulation, not autonomically.

The strengths of our study include the large size and the propensity score-matched design that minimized selection bias. Also, the diagnoses of metabolic syndrome components considered both prior diagnoses and the results of health examinations. However, we could not obtain detailed ophthalmic information such as RNFL

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thickness or visual field defects as this database did not contain such data.

Other limitations include the lack of data on spherical refraction and cylinder parameters; we could not evaluate myopic status. Myopic eyes, especially those with high myopia, exhibit RNFL thinning caused by axial elongation and are prone to RNFL defects (27,28). In addition, a recent study using UK biobank data found that myopic adults were at higher risk of incident metabolic syndrome than others (29). Thus, the fact that we did not control for myopia may have (partially) confounded the results. In addition, we included only those with localized (not diffuse) RNFL defects. Vascular dysfunction in metabolic disease may cause both types of defect. However, it is difficult to detect diffuse defects on fundus photographs. Further study using other instruments is warranted.

Furthermore, although the participants were asked whether they were on any medications, the medications and durations of use were not recorded. Certain medications may have confounded our results. Statins slightly reduced the glaucoma risk in a recent meta-analysis; statins may thus be neuroprotective (30). In addition, antihypertensive medications may affect RNFL thickness. In the Groningen Longitudinal Glaucoma Study, renin-angiotensin medications protected against glaucoma suspect conversion to disease (31). However, Chong *et al.* (32) reported that antihypertensive medications were associated with thinner RNFL and ganglion cell-inner plexiform layers in healthy Asian eyes. The effects of specific medications on RNFL thickness warrant further studies.

Conclusions

In conclusion, localized RNFL defects were associated with metabolic syndrome components, including central obesity, elevated BP, and an elevated fasting glucose level, suggesting that comorbid metabolic syndrome should be considered when evaluating subjects with RNFL defects.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board of Seoul St. Mary's Hospital (No. KC15RISI0550), which waived the need for informed consent from the study subjects because of the retrospective nature of the work.

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