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Original Article

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Relationship between Retinal Nerve Fiber Layer Defects and Coronary Artery Calcium Score in Patients at Risk for Cardiovascular Disease

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ABSTRACT

Background: Noninvasive fundus imaging may provide useful information on blood vessels. This study investigated the relationship between localized retinal nerve fiber layer defects (RNFLDs) and vascular biomarkers.
Methods: This study included 1,316 participants without cardiovascular disease who were registered in a cardiovascular high-risk cohort. Examined vascular biomarkers included central hemodynamics, carotid-femoral pulse wave velocity (cfPWV), left ventricular hypertrophy (LVH) on electrocardiogram, and coronary artery calcium score (CACS). Fundus photography and optical coherence tomography were used to evaluate RNFLDs. The associations between RNFLDs and established high-risk cutoff points for each biomarker (central blood pressure [BP] ≥125/80 mmHg, central pulse pressure [PP] ≥50 mmHg, cfPWV ≥10 m/s, presence of LVH, and CACS ≥300) were assessed.
Results: RNFLD was identified in 394 participants (29.9%) who had higher fasting glucose level, lower renal function, and higher BP than those without RNFLDs. Additionally, central BP, central PP, cfPWV, CACS, and the percentage of subjects with LVH were higher in the RNFLD group. After adjusting for confounders, RNFLDs were not associated with LVH or an elevated central BP, central PP, or cfPWV. However, they were associated with an elevated CACS (odds ratio, 1.44; 95% confidence interval, 1.04–2.00; p=0.029).
Conclusions: Non-glaucomatous localized RNFLDs were associated with elevated CACS. Therefore, evaluating RNFLDs using fundus imaging may aid in the assessment of cardiovascular disease risk.

Trial Registration: ClinicalTrials.gov Identifier: NCT02003781

Keywords: Coronary artery disease; Heart disease risk factors; Retina; Retinal neurons; Vascular calcification

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Conflict of Interest
The authors have no financial conflicts of interest.

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INTRODUCTION

The retina, which is easily visible in noninvasive imaging techniques, undergoes a series of pathophysiological changes in response to elevated blood pressure (BP). Therefore, retinal changes may indicate target organ damage and the presence of cardiovascular disease (CVD). Retinal vascular abnormalities, including arteriolar thinning and decrease in the arteriolar-to-venular diameter ratio, have previously been associated with arterial hypertension and stroke.[1-5] However, the results have been inconsistent because of marked interindividual variability and low specificity. Additionally, some studies have suggested that information on the retinal microvasculature has limited clinical value in detecting hypertensive end-organ damage.[6] Recent studies have suggested that localized retinal nerve fiber layer defects (RNFLDs) may be associated with cerebrovascular disease,[7,10] such as stroke. However, little is known about the relationship between RNFLDs and subclinical CVD.

Several cardiovascular imaging and hemodynamic biomarkers have been used in clinical practice to predict CVD occurrence and patient prognosis. The risk of coronary artery disease increases with increasing arterial stiffness. Left ventricular hypertrophy (LVH, as evaluated by electrocardiogram [ECG]) is a predictor of stroke.[11] Additionally, central BP is a better predictor of all-cause mortality than brachial BP. Coronary artery calcium score (CACS) correlates well with traditional risk prediction models (e.g., Framingham risk score) and can refine risk estimation in patients with intermediate risk.[12] Therefore, current guidelines suggest that noninvasive tests may be beneficial for identifying target organ damage and atherosclerosis and, subsequently, determining CVD risk.[13,14] The current study investigated the association between noninvasive retinal imaging findings and various vascular biomarkers in participants with high CVD risk. More specifically, we examined whether RNFLDs are potential CVD biomarkers.

METHODS

Study participants

The Cardiovascular and Metabolic Disease Etiology Research Center – High Risk Cohort (CMERC-HI) study (ClinicalTrials.gov identifier: NCT02003781) is a prospective study designed to examine known and novel risk factors for predicting clinical outcomes in Korean patients with a high risk for CVD. The Institutional Review Board of Yonsei University approved the CMERC-HI protocol (4-2013-0581), and all participants provided written informed consent.

The inclusion criteria for the CMERC-HI cohort were as follows: high risk for CVD with hypertension (estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2 with target organ damage or eGFR ≤60 mL/min/1.73 m^2), diabetes mellitus with albuminuria, anuria with end-stage renal disease, and undergoing dialysis; relative of a young acute myocardial infarction patient (men <55 years old; women <65 years old); asymptomatic atherosclerotic CVD (abdominal aorta diameter ≥3 cm, ankle-brachial index <0.9, carotid plaque or intima-media thickness ≥0.9 mm, asymptomatic old cerebrovascular accident, or >30% stenosis in at least one major coronary artery); rheumatoid arthritis treated with methotrexate and steroids and >40 years of age; atrial fibrillation with a CHA_2DS_2-VASc score ≥1; and kidney transplant recipient (>3 months following transplant). Persons aged >20 years who met at least one of the inclusion criteria were enrolled. The exclusion criteria were as follows: history

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of acute coronary syndrome, symptomatic coronary disease, peripheral arterial disease, heart failure, life expectancy of <6 months, pregnant women, and history of contrast agent allergy (and related adverse effects). A total of 2,082 participants were enrolled between November 2013 and June 2016 at Severance Hospital in Seoul, Republic of Korea. The current study included baseline assessments of 1,316 CMERC-HI participants who underwent both coronary calcium scanning and fundus examination.

Clinical measurements and vascular biomarkers

Baseline assessments included anthropometric measurements, fasting blood sample biochemical analyses, and urinalysis. All participants also completed a standardized questionnaire regarding demographic characteristics, medical history, health behaviors, psychological conditions, and social network characteristics.

Office BP measurement was performed by a trained nurse in an examination room with participants in the sitting position. Right mid-upper arm circumferences were measured to choose the appropriate cuff. A medium-sized cuff was used if the circumference was 22–32 cm; conversely, if the circumference was >32 cm, a large-sized cuff was used. BP was measured using a validated automated device (HEM 7080-IC; Omron, Kyoto, Japan), which was programmed to measure sitting automatic BP at 5, 7, and 9 min. After positioning the participant and setting the device, a trained nurse left the participants alone in the examination room. After 5 minutes of rest, automatic BP measurements at 2-minute intervals were performed in the examination room. A trained nurse recorded BP data after 3 measurements, and the mean of the three measurements was used as the office BP.

Ambulatory BP measurements performed within 24 h were obtained every 30 minutes (Takeda TM-2430; A&D Medical, Tokyo, Japan) in an arm without an arteriovenous fistula. Day and night were defined for each patient based on the lifestyle information provided. Daily ambulatory BP readings were calculated as 24-hour, daytime, and nighttime averages. Central hemodynamic parameters were evaluated after the participants rested in the sitting position for at least 10 minutes (SphygmoCor® system; AtCor Medical, Sydney, Australia). The SphygmoCor® system uses a validated mathematical transfer function to calculate ascending aorta pressure waveforms from radial artery waveforms. Central systolic BP, diastolic BP, pulse pressure (PP), augmentation pressure, forward wave amplitude, and augmentation index (AI) were then acquired using these aortic pressure waveform analyses. A high-fidelity micromanometer (Millar Instruments, Houston, TX, USA) was used to record peripheral pressure waveforms from a radial artery, as previously reported.[15] The carotid-femoral pulse wave velocity (cfPWV) was measured using a previously validated method.[16] Briefly, ECG and carotid/femoral pulse waves were simultaneously obtained and used to calculate transit time using the foot-to-foot method. Lastly, the ECG Cornell voltage (RaV+SV3, 6 mm added for women) was measured by a trained person. The QRS duration was manually measured using a single heartbeat recorded on lead II.[11] Participants with LVH were identified using the Cornell product criteria.[17]

CACS

All coronary calcium scan examinations were performed with participants in the supine position using a 320-row CT system (Aquilion™ ONE; Toshiba Medical Systems, Tokyo, Japan). A non-enhanced prospective ECG-gated computed tomography (CT) scan was performed to measure CACS using the following system settings: rotation time, 275 ms; slice collimation, 0.5 mm; slice thickness, 3.0 mm; and tube voltage, 100 kV. An automatic tube

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current modulation (SUREExposure™ 3D; Toshiba Medical Systems Corporation, Otawara, Japan) was also used. Images were analyzed on a core workstation using dedicated software (TeraRecon version 4.4.11.82.3430.Beta; TeraRecon, Foster City, CA, USA). CACS was calculated using the Agatston method.[18)19)]

Retinal imaging

All participants underwent dilated (1% tropicamide) fundus photography and spectral-domain optical coherence tomography (OCT) on the same day. Two fundus photographs of each eye were obtained using a 45°-fundus camera (Visucam$^{NM/FA}$; Carl Zeiss Meditec, Jena, Germany). The first was centered on the optic disc, while the second was centered on the fovea. Several OCT scans were also acquired using spectral-domain OCT (Spectralis® HRA+OCT; Heidelberg Engineering GmbH, Dossenheim, Germany), including a horizontal line, vertical line, macular volume, and circular scans (3.4-mm diameter) centered on the optic disc. Volume scans were made up of 49 evenly spaced sections (120-μm spacing) across a 20°×20° macular area.

Fundus imaging assessments were performed by masked examiners who were unaware of the subjects' data. The presence of ophthalmic disease (e.g., pathologic myopia, diabetic retinopathy, optic nerve disease, and glaucoma) was determined by two retinal specialists (JYS and SHB). Poor-quality images due to media opacities were excluded from the analyses. Localized RNFLDs were detected using fundus and OCT images. Localized RNFLD was defined as a dark wedge-shaped area with a connecting optic disc border on fundus photography with a width or length of 5°–45°,[20)21)] and the RNFL contour line abruptly dipped on the RNFL thickness profile scale on spectral-domain OCT. RNFLDs associated with glaucomatous disc changes, chorioretinal scarring, retinal artery, or vein occlusion were not regarded as non-glaucomatous RNFLDs and hence were excluded.

Statistical analyses

The participants were divided into 2 groups according to the presence or absence of an RNFLD. Continuous variables are presented as mean±standard deviation, and differences between the groups were compared using a t-test. Categorical variables were expressed as number (%) and compared using a χ^2 test. Multivariate logistic analyses were used to determine the odds ratio (OR) and 95% confidence interval (CI) of elevated vascular biomarkers (central BP ≥125/80 mmHg, central PP ≥50 mmHg, cfPWV ≥10 m/s, presence of LVH, CACS ≥300) and the presence of an RNFLD. Covariates included age, sex, body mass index (BMI), diabetes history, hyperlipidemia history, eGFR, and 24-hour systolic BP average. The effects of elevated BP were minimized by examining a subgroup of patients with uncontrolled hypertension, defined as a 24-hour BP ≥135/85 mmHg. All analyses were performed using SPSS (version 23.0; IBM Corp., Armonk, NY, USA) and R statistical software (version 3.3.0; R Foundation for Statistical Computing, Vienna, Austria). All examined p-values were 2-sided, and $p<0.05$ was considered statistically significant.

RESULTS

Subject characteristics

The baseline characteristics of the study participants are summarized in **Table 1**. Among the 1,316 participants, 394 (29.9%) had RNFLD. There was no difference in age, sex, BMI, or blood lipid levels between those with and without RNFLD. The proportion of diabetic

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Table 1. Clinical characteristics according to the presence of RNFLD

Variables	No RNFLD (n=922)	RNFLD (n=394)	p-value
Age (years)	59.7±11.8	58.9±11.7	0.293
Male	419 (45.4)	174 (44.2)	0.713
BMI (kg/m^2)	25.2±3.6	25.0±3.8	0.336
Hypertension	851 (92.8)	365 (93.1)	0.934
DM	345 (37.7)	162 (41.3)	0.237
Hyperlipidemia	560 (61.1)	218 (55.8)	0.084
Antihypertensive medication	759 (82.3)	330 (83.8)	0.581
Statin	486 (52.7)	199 (50.5)	0.501
Fasting glucose (mg/dL)	109.9±26.7	115.8±38.8	0.008
BUN (mg/dL)	24.7±16.1	29.2±20.8	<0.001
Creatinine (mg/dL)	1.9±2.5	2.6±3.4	<0.001
eGFR (mL/min/1.73 m^2)	64.8±33.4	56.2±35.5	<0.001
Cholesterol (mg/dL)	171.5±36.2	173.5±35.6	0.368
Triglyceride (mg/dL)	138.2±79.5	146.9±81.4	0.089
HDL-cholesterol (mg/dL)	49.0±13.5	47.3±13.4	0.052
LDL-cholesterol (mg/dL)	94.3±29.1	95.5±29.8	0.530
Systolic BP (mmHg)	127.8±17.4	131.3±17.4	0.001
Diastolic BP (mmHg)	76.6±10.2	77.7±10.7	0.078
Urine ACR	398.8±343.3	369.6±330.1	0.159

Values are presented as mean±standard deviation or number (%).
ACR = albumin creatinine ratio; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RNFLD = retina nerve fiber layer defect.

participants did not differ between groups, but fasting glucose was higher in participants with an RNFLD than in those without. Most participants in both groups had hypertension and used antihypertensive medications. However, systolic BP was significantly higher (p=0.001) and diastolic BP tended to be higher (p=0.078) in the RNFLD group. The eGFR was lower in participants with an RNFLD (p<0.001) because both serum creatinine and blood urea nitrogen levels were higher than those in participants without an RNFLD. However, microalbumin levels did not differ between groups.

Vascular biomarkers and their association with RNFLDs

The ambulatory BP measurements and vascular biomarkers are presented in **Table 2**. All ambulatory BP measurements (24-hour BP, daytime BP, and nighttime BP) were higher in participants with RNFLD than in those participants without; however, both groups showed similar diurnal BP patterns. Examined central hemodynamic parameters (central BP and PP) were also higher in participants with RNFLD. The AI did not differ between groups, but the cfPWV was higher in participants with an RNFLD. The proportion of participants suspected of having subclinical target organ damage or at a high risk for CVD (defined as central BP ≥125/80 mmHg [p=0.001], central PP ≥50 mmHg [p=0.019], or cfPWV ≥10 m/s [p=0.011]) was higher in the RNFLD group. Additionally, LVH was detected on ECG in 11.4% of participants with RNFLD, but in only 6.0% of participants without RNFLD (p=0.001). Lastly, the mean CACS and the proportion of participants with elevated CACS (≥300) were higher in participants with RNFLD than in those without (p=0.009).

Multivariate logistic regression analysis was performed to evaluate the association between RNFLD and high cardiovascular risk, as defined using the critical point of each biomarker (**Table 3**). The presence of RNFLD was not associated with the presence of LVH, elevated central BP (≥125/80 mmHg), central PP (≥50 mmHg), or cfPWV (≥10 m/s). However, the presence of RNFLD was significantly associated with elevated CACS (≥300).

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Table 2. Differences of vascular biomarkers according to the presence of RNFLD

Variables	No RNFLD (n=922)	RNFLD (n=394)	p-value
ABPM			
24-hour systolic BP (mmHg)	128.8±14.2	134.0±15.0	<0.001
24-hour diastolic BP (mmHg)	77.5±7.9	79.7±8.7	<0.001
Daytime systolic BP (mmHg)	133.4±14.4	138.4±14.9	<0.001
Daytime diastolic BP (mmHg)	80.6±8.4	82.6±8.9	<0.001
Nighttime systolic BP (mmHg)	120.2±16.3	125.8±18.3	<0.001
Nighttime diastolic BP (mmHg)	71.9±8.7	74.3±10.2	<0.001
Dipping (%)	−9.7±8.1	−9.1±9.1	0.267
Dipping pattern			0.214
Dipper	426 (51.6)	179 (50.3)	
Non-dipper	304 (36.8)	123 (34.6)	
Reverse dipper	95 (11.5)	54 (15.2)	
Central hemodynamics			
Central systolic BP (mmHg)	118.2±18.2	122.3±19.3	<0.001
Central diastolic BP (mmHg)	75.3±10.0	76.9±10.8	0.013
Central BP ≥125/80 mmHg	268 (32.4)	155 (43.1)	0.001
Central PP (mmHg)	42.8±14.1	45.4±14.0	0.004
Central PP ≥50 mmHg	217 (26.2)	119 (33.1)	0.019
Augmentation index (%)	27.4±12.9	27.7±12.7	0.695
cfPWV (m/s)	9.1±2.2	9.4±2.3	0.012
cfPWV ≥10 m/s	212 (25.7)	119 (33.1)	0.011
LVH on ECG	55 (6.0)	45 (11.4)	0.001
CACS (AU)	194.9±455.8	324.2±815.7	0.003
CACS >300 AU	155 (16.8)	91 (23.1)	0.009

Values are presented as mean±standard deviation or number (%).
ABPM = ambulatory blood pressure monitoring; AU = Agatston units; BP = blood pressure; CACS = coronary artery calcium score; cfPWV = carotid-femoral pulse wave velocity; ECG = electrocardiogram; LVH = left ventricular hypertrophy; PP = pulse pressure; PWV = pulse wave velocity; RNFLD = retinal nerve fiber layer defect.

Additionally, participants with RNFLD had higher blood glucose levels and lower renal function than participants without RNFLD in the subgroup analysis of uncontrolled hypertension (**Table 4**). The RNFLD group had a higher CACS (202.9±455.4 vs. 300.9±685.5, p=0.046) and a higher proportion of participants with an elevated CACS (≥300) than those in the no RNFLD group (p=0.041; **Table 5**). The association between RNFLD and elevated CACS was significant in participants with uncontrolled hypertension (**Table 3**).

DISCUSSION

The current study examined the relationship between RNFLDs and various vascular biomarkers to determine whether the presence of an RNFLD could be used to indicate a high CVD risk. We found a significant association between RNFLD status and CACS in patients at risk for developing CVD. This association remained significant after adjusting for possible confounding factors, which suggests that the presence of RNFLD can be used to estimate CVD risk beyond the established biomarkers.

Table 3. Differences of vascular biomarkers according to the presence of RNFLD

Patients	Central BP ≥125/80 mmHg	Central PP ≥50 mmHg	cfPWV ≥10 m/s	LVH on ECG	CACS ≥300 AU
Total participants	1.22 (0.89–1.65)	1.08 (0.77–1.52)	1.25 (0.89–1.75)	1.43 (0.88–2.29)	1.44 (1.04–2.00)*
Uncontrolled hypertension	1.23 (0.84–1.78)	1.00 (0.66–1.51)	1.34 (0.88–2.02)	1.29 (0.75–2.18)	1.55 (1.02–2.34)*

Each model included age, sex, body mass index, fasting glucose level, estimated glomerular filtration rate, and 24-hour systolic BP as covariates.
AU = Agatston units; BP = blood pressure; CACS = coronary artery calcium score; cfPWV = carotid–femoral pulse wave velocity; ECG = electrocardiogram; LVH = left ventricular hypertrophy; PP = pulse pressure; RNFLD = retinal nerve fiber layer defect.
*p < 0.05.

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Table 4. Clinical characteristics according to the presence of RNFLD in participants with uncontrolled hypertension (n=685)

Variables	No RNFLD (n=441)	RNFLD (n=244)	p-value
Age (years)	59.7±11.8	58.6±11.7	0.250
Male	190 (43.1)	102 (41.8)	0.807
BMI (kg/m^2)	25.4±3.5	25.2±3.7	0.643
Hypertension	409 (93.2)	224 (92.2)	0.747
DM	172 (39.3)	110 (45.3)	0.150
Hyperlipidemia	263 (59.9)	135 (55.6)	0.306
Antihypertensive medication	365 (82.8)	208 (85.2)	0.464
Statin	223 (50.6)	118 (48.4)	0.636
Fasting glucose (mg/dL)	110.5±28.9	118.9±44.0	0.001
BUN (mg/dL)	26.8±18.1	32.5±22.6	0.001
Creatinine (mg/dL)	2.3±3.0	3.2±3.8	0.005
eGFR (mL/min/1.73 m^2)	61.4±36.1	50.4±36.7	<0.001
Cholesterol (mg/dL)	170.3±34.0	171.8±36.4	0.602
Triglyceride (mg/dL)	141.6±74.0	151.3±84.8	0.158
HDL-cholesterol (mg/dL)	48.0±13.2	46.2±13.3	0.131
LDL-cholesterol (mg/dL)	93.9±28.1	95.3±30.3	0.590
Systolic BP (mmHg)	133.8±17.8	135.2±17.6	0.325
Diastolic BP (mmHg)	79.2±10.5	79.0±10.7	0.829
Urine ACR	423.4±338.5	374.3±326.5	0.070

Values are presented as mean±standard deviation or number (%).
ACR = albumin creatinine ratio; BMI = body mass index; BP = blood pressure; BUN = blood urea nitrogen; CACS = coronary artery calcium score; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; RNFLD = retina nerve fiber layer defect.

Table 5. Differences of vascular biomarkers according to the presence of RNFLD in participants with uncontrolled hypertension (n=685)

Variables	No RNFLD (n=441)	RNFLD (n=244)	p-value
ABPM			
24-hour systolic BP (mmHg)	138.2±12.0	141.0±12.4	0.005
24-hour diastolic BP (mmHg)	82.4±6.8	83.2±7.9	0.187
Daytime systolic BP (mmHg)	142.6±11.9	144.9±12.6	0.018
Daytime diastolic BP (mmHg)	85.4±7.5	85.8±8.3	0.515
Nighttime systolic BP (mmHg)	129.4±15.5	133.3±16.3	0.003
Nighttime diastolic BP (mmHg)	76.7±8.0	78.0±9.3	0.050
Dipping (%)	−9.1±8.5	−8.0±9.1	0.112
Dipping pattern			0.145
Dipper	213 (48.5)	111 (45.5)	
Non-dipper	168 (38.3)	87 (35.7)	
Reverse dipper	58 (13.2)	46 (18.9)	
Central hemodynamics			
Central systolic BP (mmHg)	124.5±18.9	127.2±19.7	0.097
Central diastolic BP (mmHg)	78.0±10.4	78.9±11.3	0.278
Central BP ≥125/80 mmHg	175 (45.2)	119 (53.8)	0.050
Central PP (mmHg)	46.5±15.7	48.2±15.0	0.191
Central PP ≥50 mmHg	132 (34.1)	85 (38.5)	0.322
Augmentation index (%)	29.4±12.3	28.7±11.2	0.494
cfPWV (m/s)	9.4±2.2	9.8±2.4	0.062
cfPWV ≥10 m/s	118 (30.6)	86 (38.9)	0.047
LVH on ECG	40 (9.1)	31 (12.7)	0.173
CACS (AU)	202.9±455.4	300.9±685.5	0.046
CACS >300 AU	75 (17.0)	58 (23.8)	0.041

ABPM = ambulatory blood pressure monitoring; AU = Agatston units; BP = blood pressure; CACS, = coronary artery calcium score; cfPWV = carotid-femoral pulse wave velocity; ECG = electrocardiogram; LVH = left ventricular hypertrophy; PP = pulse pressure; PWV = pulse wave velocity; RNFLD = retinal nerve fiber layer defect.

CACS is strongly correlated with overall atherosclerotic burden and has highly reproducible results.[22)23)] Large prospective studies have shown that CACS is also associated with the risk of future cardiovascular events. The Multi-Ethnic Study of Atherosclerosis, a population-

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based study that examined individuals without CVD, found that participants with a CACS of >300 were nearly 10 times more susceptible to future coronary heart disease than those with a CACS of 0.[24] Furthermore, adding CACS to a traditional risk factor prediction model significantly improved the prediction of future coronary events.[25]

Ischemic damage to the inner retina (e.g., cotton-wool spots, diabetic endothelial dysfunction) or optic disc can result in retinal nerve fiber loss. Therefore, localized RNFLDs are sequelae to localized retinal vascular insufficiencies.[7][10][20] Furthermore, localized RNFLDs have been associated with chronic arterial hypertension in patients, and experimentally induced chronic arterial hypertension/atherosclerosis has been shown to cause localized RNFLD development in rhesus monkeys.[26] Moreover, they have also been strongly associated with increasing grades of arterial hypertension, stroke, and cerebral small vessel disease.[7][9][27] These findings all support the proposition that retinal abnormalities and coronary atherosclerosis share a common pathophysiological process, which may explain the association between an elevated CACS and the presence of RNFLDs. In the current study, participants with RNFLDs had higher BP, higher fasting glucose, and lower kidney function than those without RNFLDs. Therefore, CVD risk was higher in participants with RNFLDs. However, it should be noted that RNFLDs are not acute phenomena, but rather cumulative abnormalities that result from long-term ischemic injuries.[27] Similarly, calcium deposition in the coronary arteries is not an acute process, but rather an indicator that chronic atherosclerosis has progressed considerably.[28] Therefore, both RNFLDs and coronary artery calcium deposition reflect long-term exposure to atherosclerotic risk factors.

The presence of RNFLDs was not associated with PWV, LVH, or central BP after adjustment for other variables, which may be because BP is a major confounding factor. A multivariable logistic regression model that did not include BP as a covariate showed a significant relationship between RNFLDs and vascular biomarkers. PWV and central BP are easily influenced by BP during measurement[29][30] and do not reflect chronic atherosclerotic damage as strongly as CACS. Therefore, unlike other vascular biomarkers, RNFLD is associated with CACS independent of BP. Furthermore, this association was observed in participants with uncontrolled hypertension.

The presence of a localized RNFLD has several advantages as a biomarker for CVD compared to other retinal findings previously examined. First, localized RNFLDs do not occur in normal eyes[20]; hence, RNFLDs have higher diagnostic specificity than retinal microvascular abnormalities, which are common and highly variable among patients.[6] Therefore, a patient's risk for CVD may be overestimated by retinal microvascular abnormalities. Second, RNFLDs are easily visible on fundus color photographs, red-free photographs, and OCT images, all of which are noninvasive and widely used in clinical ophthalmology. Additionally, specialized image processing software is not required. Third, localized RNFLDs are permanent and remain visible until the surrounding retinal nerve fiber layer is lost. In contrast, cotton wool spots, retinal hemorrhages, and retinal microvascular abnormalities are generally partially or completely resolved.[31]

Our study had several limitations. Since this was a cross-sectional study, it did not provide information on causal relationships. Further investigation is required to understand why RNFLDs occur and how calcium is deposited in the coronary arteries. Moreover, considering these factors have not yet been fully elucidated, unknown confounding factors may have influenced our results. Additionally, our study population comprised participants with a high

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risk of CVD; therefore, generalizability of our findings may not be feasible. Further studies are needed to confirm the relationship between the presence of RNFLDs and long-term cardiovascular outcomes and to determine the incremental improvement in risk prediction models when RNFLD status is added. In conclusion, our results suggest that the presence of RNFLDs is an independent risk factor for elevated CACS in participants with a high risk of CVD. Additionally, retinal imaging may provide important insights into the pathogenesis of CVD. Furthermore, various combinations of retinal imaging parameters should be examined to determine how CVD risk prediction is optimized and to identify patients who may require more aggressive CVD risk-reduction therapies.

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