ASSOCIATION BETWEEN RETINAL MICROVASCULAR CHANGES AND CAROTID INTIMA-MEDIA THICKNESS IN PATIENTS WITHOUT HYPERTENSION

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Lääketieteen tutkinto-ohjelma
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Tämän tutkimuksen tarkoituksena oli tutkia silmän verkkokalvon verisuonten paksuuksien muutoksien ja kaulavaltimoiden seinämän paksuuntumisen välistä yhteyttä potilailla, joilla ei ole verenpainetautia.

Tutkimuksessa käytettiin aineistoa Pohjois-Suomen syntymäkohortista (NFBC1966). Kokonaisuudessaan 443 ihmistä tuli mukaan tutkimukseen. Kaikilta osallistujilta otettiin silmänpohjakuvat, tutkimuksessa keskityimme oikean silmän kuviin. Lisäksi heiltä mitattiin kaulasuonten paksuus ultraäänellä. Tutkimukset tehtiin tutkittavien ollessa 46-vuotiaita. Tutkituilta otetuista silmänpohjakuvista mitattiin verkkokalvon verisuonten paksuudet, CRAE (central retinal arteriolar equivalent) ja CRAE (central retinal venular equivalent) käyttämällä puoliautomaattista tietokoneohjelmaa (IVAN). Kaulan verisuonien paksuudet (CIMT) mitattiin kaulasuonten ultraäänitutkimuksen avulla

Tutkimuksessa ei löytynyt selvää yhteyttä verkkokalvon valtimoiden tai laskimoiden halkaisijan muutosten ja kaulansuonten paksuuntumien välillä. Käänteinen assosiaatio todettiin verkkokalvon valtimoiden halkaisijan ja systolisen verenpaineen välillä *($p<0.001$, R^2 0.437)*. Samoin veren HDL-pitoisuuden sekä verkkokalvon valtimoiden halkaisijan välillä *($p=0.024$, R^2 0.104)*. Assosiaatio veren HDL-pitoisuuden ja verkkokalvon laskimoiden halkaisijan välillä myös todettiin *($p<0.001$, R^2 0.038).*

Merkittävää yhteyttä verkkokalvon verisuonten paksuuksien ja kaulavaltimoiden seinämän paksuuntumisen välillä ei löytynyt ihmisillä, joiden verenpainetaso on normaali. Kardiovaskulaarisen stressin kuten esimerkiksi kohonneen verenpaineen voidaan siis ajatella olevan riskitekijä kumpaankin. Jo aikaisemmin todettu yhteys korkeamman systolisen verenpaineen ja verkkokalvon valtimoiden kaventumisen välillä näkyi myös tässä tutkimuksessa.

Avainsanat: verkkokalvon verisuonimuutokset, kaulavaltimoiden paksuus, NFBC1966

SISÄLLYSLUETTELO

1. INTRODUCTION

The retinal blood vessels are the only vessels in human circulation which can be visualized noninvasively. Therefore, examining the retinal vasculature is a good way to examine associations between the human microcirculation and certain systemic and metabolic diseases.[1]

Several studies have shown association between metabolic syndrome and arteriolar narrowing.[2,3] For example, the Atherosclerosis Risk in Communities Study examined whether there is an association between metabolic syndrome and retinal microvascular changes in middle-aged population.[3] They showed that people with metabolic syndrome are more likely to have arteriolar narrowing than those without the disease. Yuan et al found correlation between narrower arteriolar caliber and central obesity, dyslipidaemia and high blood pressure in a Chinese population and suggested that central obesity is the main component affecting the retinal vasculature.[2] Furthermore, Saito et al showed that people with narrower arteriolar caliber are at a bigger risk of incident metabolic syndrome in future.[4] Several studies have also found association between metabolic syndrome and wider venular caliber.[2,3,5] In the Atherosclerosis Risk in Communities venular dilatation was seen in people with larger waist circumference and higher triglyceride and glucose levels.[3] Kawasaki et al examined Japanese population in the Funagata study and their findings supported the other studies.[5]

Changes in retinal arterioles have also been associated with diabetes.[6] Broe et al found connection between narrow arteriolar calibers and incidence of nephropathy in future.[6] They suggested that changes in arterioles could be used as a biomarkers of early diabetic neuropathy and retinopathy. Da Silva et al found that people with diabetes have larger retinal venule diameter than people without diabetes.[7] The study also showed that there is a linear regression between the degree of venodilatation and blood glucose level as well as the estimated duration of diabetes. The Blue Mountain Study supported the relationship between wider venular caliber and diabetes.[8] The Multi-Ethnic Study of Atherosclerosis (MESA) also supported the fact that wider retinal venules are associated with diabetic retinopathy.[9] Also the prediabetes stages (increased fasting glucose or impaired glucose tolerance) have been found to be associated with retinal venular dilatation.[8,9] Also Broe at al found that dilatation in venules can be used as a biomarker of early diabetic neuropathy, nephropathy and retinopathy in people with type 1 diabetes.[6] Both narrow arteriolar caliber and wider venular caliber are also associated with diabetic peripheral neuropathy and diabetic retinopathy.

Ikram et al studied the relationship between retinal microvascular changes and risk of atherosclerosis in the Rotterdam Study.[10] Arteriolar narrowing was associated with intimal thickening, medial hyperplasia, hyalinization and sclerosis. The study found association between larger venular diameters and atherosclerosis, aortic calcifications, carotid plaque score, higher total cholesterol level, lower HDL level, higher waist-to-hip ratio and higher leucocyte level.

Torres et al found association between hypertension and retinal microvascular changes.[11] They also studied the association between carotid intima-media thickness (IMT) and retinal arteriolar and venular diameter in patients with hypertension. They found that carotid IMT is significantly and independently associated with retinal microvascular changes (arteriolar narrowing and venular dilatation). Notable is also that carotid IMT is found to be a marker of cardiovascular risk in hypertensive patients with coronary heart disease.[12]

This study examined whether there was an association between retinal microvascular changes and the carotid intima-media thickness in patients without hypertension.

2. METHODS

2.1. Study population - The Northern Finland Birth Cohort

This study used the data from the Northern Finland Birth Cohort, NFBC1966, which is a longitudinal birth cohort. The data has been collected by using health care records, questionnaires, and clinical examinations since antenatal period (24th gestational week). All participants were born in 1966. Total of 12231 children were born in this cohort.

The NFBC Eye Study was carried out with the participants of the NFBC 1966 Study. The data for this study was collected when the participants were 46-48 years of age.Total of 3070 persons participated in the eye-screening group and the study protocol has been described in detail elsewhere.[13] There were 520 patients with retinal vessel diameter measurements, carotid IMT measurements and blood cholesterol levels. Furthermore, participants using blood pressure medications were excluded as well as patients with measured hypertension, systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg After exclusions the study population consisted of 443 participants. (Figure 1)

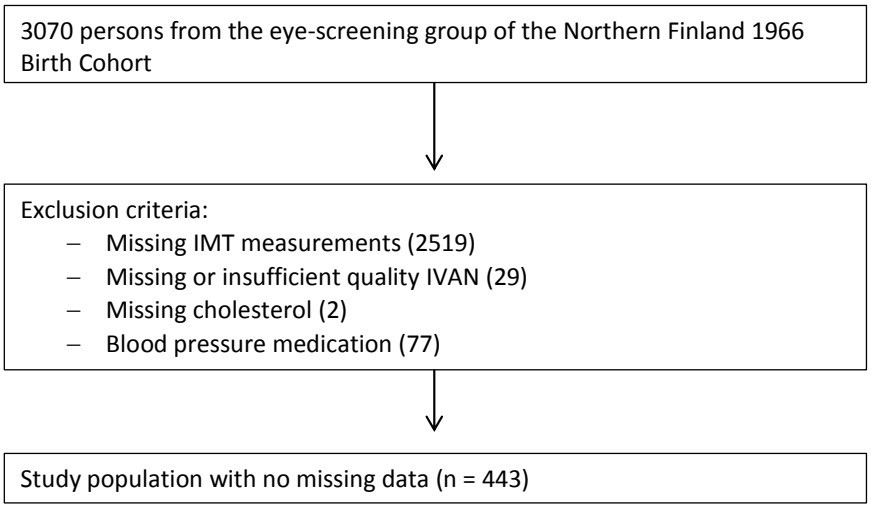

Figure 1. Selection criteria of the study population

2.2. Fundus images

Digital fundus images were taken with a Canon CF-60 UVi fundus camera with a Canon EOS 1 D MK II, 8-Mpixel Digital SLR CMOS camera (Canon Inc., Tokyo, Japan). The pictures were processed with Neacapture software (Neagen Oy, Oulu, Finland) and Adobe Photoshop CS (Adobe Systems Inc., San Jose, CA, USA). Digitized retinal photographs of each participant was analyzed by a single grader, masked to participants' characteristics. All the retinal photographs were taken from the right eye of the participants. Analyzing of retinal vascular diameters was performed with a semiautomated computer-assisted image program (IVAN, University of Wisconsin, Madison, Wisconsin, USA). The software detects the optic disc and divides the image into three zones. Zone A is within 0.5-disc diameter from the optic disc margin. Zone B is 0.5-1.0-optic disc diameter away and zone C 1.0-2,0-disc diameter away. After detecting the optic disc and the zones, vessels are traced. IVAN software then calculates the retinal vessel calibers and represents them as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE). Measurements are based on the biggest six arterioles and six venules, which are situated in zones B and C. The grader has the chance to make corrections if the program has selected wrong vessel type. At the end the software creates three summary variables: the projected caliber size of the central retinal artery (CRAE), the projected caliber size of central vein (CVRE) and the ratio of the two variables (arteriovenous ratio [AVR]).[14]

There were three graders all masked to participant's characteristics and the intragrader variability was 4.5% for CRAE and 3.7% for CRVE and the intergrader variability 3.7 % for CRAE and 3.0% for CRVE.

2.3. Carotid ultrasound and echocardiography

To evaluate the possibility of subclinical early state atherosclerosis, carotid intima-media thickness was measured from carotid ultrasound. The measurements were taken by experienced cardiologist, using the General Electric Vivid E9 device with a 9L-D 2.4/10.0 MHz linear tranducer for vascular imaging (GE Health Medical, Horten, Norway). All measurements followed the guidelines of the American Society of Echocardiography.[15]

2.4. Other measurements

The mean arterial pressure was determined after measuring systolic and diastolic blood pressure. If systolic blood pressure after three measurements was ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg, they were considered as hypertensive participants as well as those who used blood pressure medication. Diabetes status was defined as use of diabetic medication or reported having diabetes in the questionnaire. Participants with serum fasting glucose level greater than or equal to 7.0mmol/l or 2-hour-plasma glucose greater than or equal to 11.1 mmol/l in oral glucose tolerance test were considered as diabetic. The body mass index (BMI) was determined after measuring height and weight. The cigarette smoking status and prior cardiovascular diseases were determined with a questionnaire. Total cholesterol, LDL, HDL, and triglyceride levels were determined with fasting blood samples.

2.5. Statistical analysis

The statistical analyses were performed with IBM SPSS-statistics version 24 (IBM Corporation, Chicago, IL, USA). Retinal vascular diameters (CRAE and CRVE) were analysed as continuous variables. Correlations between variables were tested with Pearson's correlation coefficient. Multiple linear regression was used to analyze the association between retinal vascular calibers and intima-media thickness. The regression models were adjusted for gender, systolic blood pressure, total cholesterol, HDL and triglyceride, and the second set of models additionally with the fellow vascular caliber.

3. RESULTS

Characteristics of the study participants are shown in the **Table 1**. The study included 443 people, 186 males and 257 females. The mean body mass index of the participants was 26.1 (SD 4.4) and 53 % (n=235) of the participants were currently smoking or had smoked at some

point of their lives. Mean systolic blood pressure was 124.8 (SD 14.9) mmHg and mean diastolic blood pressure was 83.6 (SD 9.6) mmHg. Only 3.2% (n=14) had been diagnosed with diabetes and 5.4% (n=24) had prior cardiovascular disease. Mean total cholesterol was 5.3 (SD 0.9) mmol/l LDL-cholesterol 3.4 (SD 0.9) mmol/l, HDL-cholesterol 1.6 (SD 0.4) mmol/l and triglycerides 1.1 (SD 0.6) mmol/l.

Table 1. Characteristics of the study subjects [mean (SD) or n (%)]

Characteristics	Patients (n=443)
Sex (male)	186 (42.0)
BMI	26.1 (4.4)
Current or ex smoker	235 (53.0)
Systolic blood pressure (mmHg)	124.9 (14.9)
Diastolic blood pressure (mmHg)	83.6 (9.6)
Diabetes	14 (3.2)
Prior cardiovascular disease	24 (5.4)
Total cholesterol (mmol/l)	5.3 (0.9)
HDL cholesterol (mmol/l)	1.6 (0.4)
LDL-cholesterol (mmol/l)	3.4 (0.9)
Triglyceride (mmol/l)	1.1 (0.6)

Retinal venular and arteriolar diameter measurements, carotid ultrasound measurements (IMT and carotid plaque), systolic blood pressure are shown in **Table 2**. The mean arteriolar diameter was 140.5 (SD 13.7) μm and the mean venular diameter was 213.2 (SD 18.5) μm. Both measurements were slightly larger in male population. The mean systolic blood pressure was 124.9 (SD 14.9) mmHg for all, but higher in men (130.4 (SD 13.4) mmHg) than in women (121 (SD 14.6) mmHg). The same trend is shown in the carotid IMT measurements. The mean carotid IMT in the whole study was 0.60 (SD 0.08) mm; 0.63 (SD 0.09) mm in males and 0.58 (SD 0.07) mm in females. 14.9 % (n= 66) of the study population had carotid plaques: 21.5 % (n=40) of the males and 10.1 % (n=26) of the females.

Table 2. Retinal calibers and carotid ultrasound measurements, stratified by sex [mean (SD) or n

(%)].The results of each measurement are shown in percentiles (25^{th}, 50^{th}, 75^{th}).

Measurement	All patients (n = 443)	Male (n = 186)	Female (n = 257)
Arteriolar diameter (μm)	140.5 (13.7)	141.1 (12.8)	140.2 (14.4)
25th percentile	131.2	132.3	130.5
50th percentile	140.2	139.8	140.4
75th percentile	149.1	149.6	148.6
Venular diameter (μm)	213.2 (18.5)	214.1 (17.2)	212.5 (19.4)
25th percentile	200.7	202.7	199.9
50th percentile	212.9	214.3	212.6
75th percentile	223.4	223.8	222.6
Systolic blood pressure (mmHg)	124.9 (14.9)	130.4 (13.4)	121 (14.6)
25th percentile	114.3	122.0	111.0
50th percentile	124.3	128.2	120.0
75th percentile	134.0	139.7	128.3
Mean carotid IMT (mm)	0.60 (0.08)	0.63 (0.09)	0.58 (0.07)
25th percentile	0.55	0.56	0.54
50th percentile	0.58	0.60	0.57
75th percentile	0.64	0.68	0.62
Carotid Plaque	66 (14.9)	40 (21.5)	26 (10.1)

Quartiles of carotid IMT and retinal arteriolar and venular calibers (Panels A and C) are shown in **Figure 2**. Carotid IMT was weakely associated with retinal arteriolar caliber ($p=0.025$), but not with venular caliber ($p=0.72$). Quartiles of systolic blood pressure and retinal calibers were also compared (Panels B and D). There was an inverse association between systolic blood pressure and retinal arteriolar caliber ($p<0.001$), but not with systolic blood pressure and venular caliber ($p=0.55$).

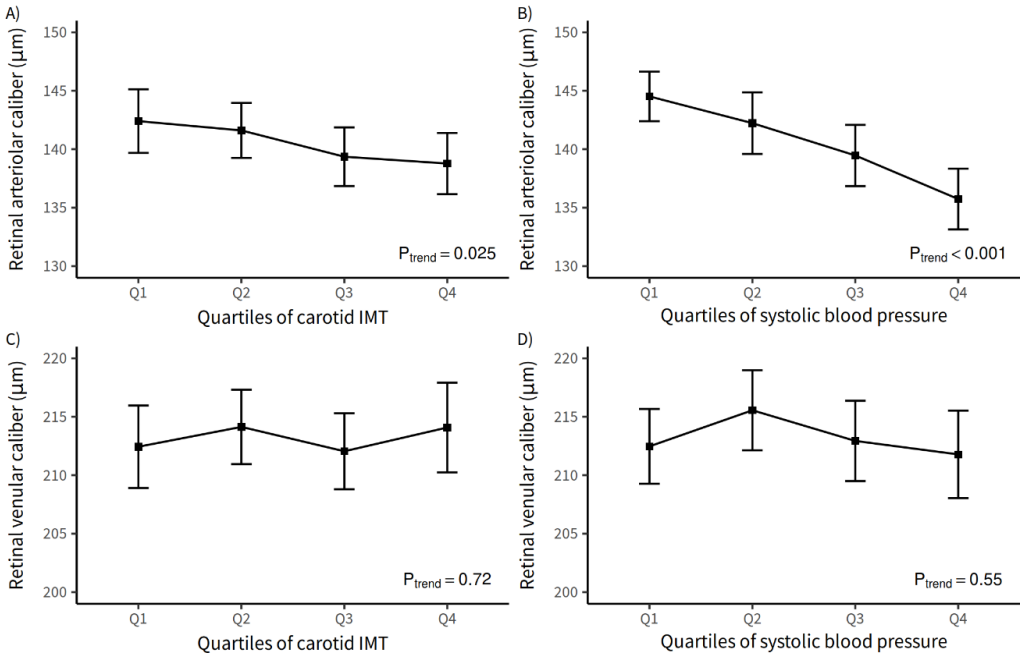

Figure 2. The quartiles of carotid IMT and retinal arteriolar and venular calibers.

Table 3 shows correlation analysis. Retinal arteriolar or venular calibers did not correlate with carotid IMT (R= -0.09, p=0.063) and (R=0.03, p=0.606), respectively. There was inverse association between systolic blood pressure and arteriolar caliber (R= -0.27, p<0.001) and HDL cholesterol and retinal venular caliber (R= -0.15, p=0.002).

Table 3. Pearson's correlation coefficients between retinal arteriolar and venular caliber and sex, systolic blood pressure, total and HDL cholesterol, prior cardiovascular disease, intima-media thickness and carotid plaque for people with no blood pressure medication (n = 425).

Variable	Retinal arteriolar caliber	P value	Retinal venular caliber	P value
Sex (male)	0.03	0.494	0.04	0.360
Systolic	**-0.27**	**<0.001**	-0.05	0.339
Total cholesterol	0.02	0.616	0.06	0.220
HDL cholesterol	-0.08	0.103	**-0.15**	**0.002**
Triglyceride	-0.04	0.394	0.03	0.571
Previous cardiovascular disease	-0.01	0.773	-0.01	0.830
Intima-media thickness	-0.09	0.063	0.03	0.606
Carotid plaque	-0.05	0.289	0.07	0.164

Multiple linear regression models of carotid IMT on retinal arteriolar caliber are shown in **Table 4**. Model 1 was adjusted by sex, systolic blood pressure, total and HDL cholesterol and triglyceride levels. There was no association between carotid IMT and retinal arteriolar

caliber (p=0.166). Inverse association was found between retinal arteriolar caliber and systolic blood pressure (p<0.001) and HDL cholesterol levels (p=0.024), but neither systolic blood pressure nor HDL cholesterol did not explain the changes in arteriolar caliber (R^2=0.104). Model 2 was adjusted additionally by retinal venular caliber and there was no association between arteriolar caliber and carotid IMT (p=0.057). Systolic blood pressure and arteriolar caliber were still associated (p<0.001), but there was no longer association between HDL cholesterol and arteriolar caliber (p=0.963). Retinal venular and arteriolar calibers were also associated (p<0.001). In model 2 the variables explained the changes in the arteriolar caliber slightly better (R^2=0.437)

Table 4. Multiple linear regression models of carotid IMT onretinal arteriolar caliber

	Model 1		Model 2	
Characteristics	β (95% CI)	P value	β (95% CI)	P value
Carotid IMT (mm)	-10.67 (-25.81 to 4.46)	0.166	-11.65 (-23.66 to 0.36)	0.057
Sex (male)	2.69 (-0.26 to 5.64)	0.074	3.12 (0.78 to 5.46)	0.009
Systolic blood pressure (mmHg)	**-0.27 (-0.36 to -0.18)**	**<0.001**	**-0.24 (-0.31 to -0.17)**	**<0.001**
Total cholesterol (mmol/l)	1.08 (-0.42 to 2.58)	0.156	0.05 (-1.15 to 1.25)	0.933
HDL cholesterol (mmol/l)	**-4.56 (-8.52 to -0.60)**	**0.024**	-0.08 (-3.27 to 3.11)	0.963
Triglyceride (mmol/l)	-1.68 (-4.07 to 0.72)	0.170	-0.61 (-2.52 to 1.30)	0.529
Retinal venular caliber (μm)	-	-	**0.44 (0.38 to 0.49)**	**<0.001**
	R2 = 0.104		R2 = 0.437	

Model 1 adjusted by sex, systolic blood pressure, total and HDL cholesterol and triglyceride. Model 2 adjusted additionally by retinal venular caliber.

Table 5 demonstrates the multiple linear regression models of carotid IMT on retinal venular caliber. Model 1 was adjusted by sex, systolic blood pressure, total and HDL cholesterol and triglycerides. Carotid IMT was not associated with venular caliber (p=0.835). Venular caliber and total cholesterol level were associated with each other (p=0.027). There was also an inverse association between venular caliber and HDL levels (p<0.001) but the variables explained only a small proportion of the changes in retinal venular caliber (R^2=0.038). Model 2 was adjusted additionally by retinal arteriolar caliber. There was no association between carotid IMT and venular caliber (p=0.186). After the additional adjustment the association between total cholesterol level and retinal venular caliber was no longer there (p=0.09). There were associations between retinal venular caliber and systolic blood pressure (p=0.003) and HDL cholesterol level (p=0.005) and retinal arteriolar caliber (p<0.001). The variables

explained changes in the retinal venular caliber more in model 2 than in model 1, but the proportion was still quite small (R^2=0.396).

Table 5. Multiple linear regression models of carotid IMT on retinal venular caliber

	Model 1		Model 2	
Characteristics	β (95% CI)	P value	β (95% CI)	P value
Carotid IMT (mm)	2.24 (-18.89 to 23.37)	0.835	11.33 (-5.47 to 28.12)	0.186
Sex (male)	-0.99 (-5.11 to 3.13)	0.637	-3.28 (-6.56 to 0.00)	0.050
Systolic blood pressure (mmHg)	-0.07 (-0.20 to 0.05)	0.238	**0.16 (0.06 to 0.26)**	**0.003**
Total cholesterol (mmol/l)	**2.36 (0.27 to 4.46)**	**0.027**	1.44 (-0.22 to 3.11)	0.090
HDL cholesterol (mmol/l)	**-10.27 (-15.80 to -4.74)**	**<0.001**	**-6.38 (-10.79 to -1.97)**	**0.005**
Triglyceride (mmol/l)	-2.44 (-5.79 to 0.91)	0.152	-1.01 (-3.67 to 1.65)	0.455
Retinal arteriolar caliber (μm)	-	-	**0.85 (0.75 to 0.96)**	**<0.001**
	R^2 = 0.038		R^2 = 0.396	

Model 1 adjusted for sex, systolic blood pressure, total and HDL cholesterol and triglyceride. Model 2 was adjusted additionally by retinal arteriolar caliber.

4. DISCUSSION

We studied the association between carotid IMT and retinal arteriolar (CRAE) and venular caliber (CRVE) in a normotensive population. We used data from a population-based cohort of middle-aged Caucasians. Our results showed that carotid IMT and retinal vascular calibers did not correlate. Similar results were found in linear regression analysis. Our results showed inverse association between retinal arteriolar caliber and systolic blood pressure and HDL cholesterol level. The data was adjusted for sex, systolic blood pressure, total and HDL cholesterol and triglyceride in order to avoid confounding factors.

Previously Torres et al studied the association between retinal microvascular changes in 173 subjects with hypertension.[11] In their cross-sectional study they found an independent and significant association between carotid IMT and retinal arteriolar caliber (adjusted beta -0.245, p=0.001) and retinal venular caliber (adjusted beta 0.191, p=0.009) after adjustment for age, gender, systolic blood pressure, total and HDL cholesterol, prior cardiovascular disease, carotid plaque and retinal fellow vessel. Yang et al also studied the relationship between retinal microvascular caliber and carotid IMT.[16] Their study was a community-based longitudinal study having similar results as Torres et al.: narrower retinal arteriolar caliber was associated with thicker carotid IMT. However, association in Yang's study was weaker

than in Torres's study. Torres et al included people aged between 18 and 80 years, mean 57.8 (±11.7) years. Yang et al studied population aged 40 years or more, mean 59.7 (± 11.0) years. In our study such an association was not found. Torres at al found association also between carotid IMT and retinal venular caliber, but Yang et al did not found an association in their study population, which is comparable to our results. The main reason for differences could be diversity in the study population, since we excluded hypertensive subjects and focused on normotensive population. Both other studies included hypertensive people and Torres et al simply focused on patients with hypertension. In our study in multivariate analysis systolic blood pressure was main determinant, therefore, it seems that blood pressure level is common denominator for both CRAE and IMT.

Van Hecke at al studied association between retinal microvascular abnormalities and large artery endothelial dysfunction and intima-media thickness in the Hoorn Study.[17] They had total of 256 participants aged 60-85 years in their cross-sectional population based study. They included people with normal glucose metabolism, impaired glucose metabolism and type II diabetics. They also had both normotensive and hypertensive people in their sample. The mean systolic blood pressure in the no retinal abnormality group was 143 (±18) mmHg and any retinal abnormality group had the mean systolic pressure of 153 (±) 23 mmHg. They found that retinal venular dilatation was associated with increased IMT [standardized beta value (95% confidence interval), 0.14 (0.005-0.25)], but after multivariable adjustment for cardiovascular risk factors the association was lost. Exclusion of patients using medication for hypertension did not change the result. Our results are in line with theirs, no significant association between carotid IMT and retinal vessel diameters were not found. This might indicate that retinal microvascular changes are not a good predictor for subclinical atherosclerosis in people without significant risk for cardiovascular diseases.

Li L. et al studied the association between retinal microvascular abnormalities (RMA) and carotid atherosclerosis lesions in Chinese patients with type 2 diabetes.[18] RMA was defined as retinal arteriosclerosis or diabetic retinopathy. They found an independent association between RMAs and greater carotid IMT suggesting that there is an association between cardiovascular diseases and retinal microvascular changes. Song et al also found that greater carotid IMT values were associated with the presence of vascular retinopathy.[19] Their study included 179 people. The sample was divided into groups based on their results from a fundoscopic examination: normal retinal artery, diabetic retinopathy, retinal artery occlusion, retinal vein occlusion and hypertensive retinopathy. Their results showed that people with

vascular retinopathy were more likely to have greater carotid IMT values compared to normal subjects, the relative risk of vascular retinopathy was almost 2.8. Therefore, they stated that vascular retinopathy should not be treated as an independent disease but as a good predictor for identifying asymptomatic carotid artery atherosclerosis. Henderson et al studied the association of hypertensive retinal microvascular changes and neurologic and cardiovascular complications.[20] Hypertension was found associated with retinal arterio-venous nicking, focal arteriolar narrowing and generalized arteriolar narrowing. This is supported by our results since the retinal arteriolar caliber and systolic blood pressure were inversely associated in current study. On the other hand, our study population did not include hypertensive patients and the proportion of subjects with prior cardiovascular diseases or diabetes was low. Hypertension is known to be one of the biggest risk factors of cardiovascular diseases. Naseh at al studied the relation between carotid IMT and hypertension.[21] They found that carotid IMT was greater in patients with hypertension than healthy individuals. Taken together, since hypertension causes retinal microvascular changes and increased carotid IMT, our results in normotensive individuals seems logical, they did not have association between retinal vasculature changes and carotid IMT.

Marin-Sanabria et al also studied patients with vascular retinopathy to find out whether microvascular retinopathy could be an indicator for high risk for stroke or other cardiovascular diseases.[22] Their study included 480 patients and were also divided into groups based on their retinal vascular status. They found that patients with retinal arteriolar occlusion and diabetic retinopathy have statistically significantly greater carotid IMT than patients in other groups. It is commonly known that hypertension is a risk for retinal vascular changes as well as sclerosis in carotid arteries and therefore greater carotid IMT.[11,23] Furthermore Konstantinidis et al concluded that signs of hypertensive retinopathy could be prognostic in giving information on the risk of target organ damage and therefore retinal vascular imaging might be useful in the management of hypertension.[23] Consequently, our results are partially in line with these studies since we only studied people without hypertension. Wang et al studied the role of retinal vascular changes (venular dilatation or arteriolar narrowing) in predicting coronary heart disease (CHD) and stroke mortality.[24] They found an association between narrower retinal arterioles and CHD mortality in women and men aged 43-69. Furthermore, venular dilation in their study was associated with CHD mortality only in men aged 43-69 and these associations were not found in people older than 70 years. Similar results showing that changes in retinal vessels calibers may predict risk of clinical coronary

heart disease have been found in several studies.[25-27] Hereby the association between retinal vascular changes, carotid artery sclerosis and coronary heart disease could be an interesting topic for future studies.

Strengths in our study are large and well-characterized population-based sample. NFBC provides a homogenous population in terms of age, ethnicity and living environment. As all the participants were part of the Northern Finland Birth Cohort 1966, they have been well monitored for several years. Standardized measurements were gathered for this well-documented cohort for refraction, other eye variables, biometry and anthropometric measurements and potential eye diseases, such as glaucoma were excluded after careful documentation.[13] The homogenous study population is also one the limitations of this study if the results and measurements are used for other ethnic groups. Our study was a cross-sectional study which also causes some limitations. In cross-sectional study it is difficult to determine if there is causality between different values or only correlation. Another limitation is that time between the retinal imaging and the carotid ultrasound and the other measurements may have been several months. Our large sample size should although decrease this error quite well.

In conclusion, there was no association between retinal microvascular changes and carotid IMT in normotensive population suggesting that cardiovascular stress, like hypertension is a risk factor for both. However, previously shown association between higher systolic blood pressure and retinal arteriolar narrowing was observed also in our study.

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