Associations between metabolic syndrome and syndrome components and retinal microvascular signs in a rural Chinese population: the Handan Eye Study

Short title: Metabolic syndrome and retinal vessels

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Abstract

Background: Our purpose was to determine the relationship of metabolic syndrome (MetS) and its components with retinal microvascular abnormalities in a rural Chinese population.

Methods: The Handan Eye Study, a population-based survey, recruited 6830 (90.4% of eligible) rural Chinese ≥ 30 years of age. A diagnosis of metabolic syndrome was based on the International Diabetes Federation definition. Retinal microvascular signs and arteriolar and venular diameters were assessed from fundus photographs by graders who were trained at the Retinal Vascular Imaging Centre, University of Melbourne.

Results: After adjusting for age, gender, and smoking status, 5519 participants with MetS, or with the specific components of large waist circumference, elevated blood pressure (BP), or elevated fasting blood glucose (FG) were more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, enhanced arteriolar wall reflex, and generalized retinal arteriolar narrowing than those without the MetS or the corresponding component. Individuals with elevated triglycerides were significantly more likely to have arteriovenous nicking and retinopathy.

Conclusion: These results show that individual components of the MetS are associated with different retinal microvascular signs and with changes in retinal arteriolar and venular diameters.

Keywords: diabetes mellitus, hypertension, metabolic syndrome, retinal arteriolar diameter, retinal microvascular signs, retinal venular diameter

Introduction

Metabolic syndrome (MetS), a concurrence of disturbed glucose and insulin metabolism, obesity, abdominal fat distribution, mild dyslipidemia, and hypertension, is important because of its association with subsequent development of diabetes mellitus (DM) and cardiovascular disease [1,2]. MetS is known to be associated with pathological changes in blood vessels, and in addition to large-vessel disease there is increasing evidence that the MetS, like DM, may also impact the microvasculature [3,4]. Studies have examined the relationship of the MetS with retinal microvascular changes [5-7], and individual components of the MetS are associated with various retinal microvascular changes: narrower retinal arteriolar diameter has been associated with hypertension (HTN) [8-12], and wider venular diameter with diabetes [12] dyslipidemia [12-14] and obesity [12,14]. It has not been determined, however, if the microvascular changes are associated with the pathogenesis of the disorder, or are a manifestation of the disorders, or both [2].

Few studies have focused on individuals in China and in particular rural China. A study by Yuan et al [15] that included 869 Chinese subjects reported that retinal arteriolar narrowing and retinal venular dilatation were associated with MetS. The Beijing Eye Study, a population-based cross-sectional cohort study that included 4439 subjects for rural and urban Beijing found that retinal vascular abnormalities in Chinese adults increase with age, are more common in those living in rural areas, and are associated with a self-reported diagnosis of HTN [16]. In Chinese populations, individuals with MetS are three to 10 times more likely to develop cardiovascular disease [17]. However, it is still unclear whether such associations are also present in rural populations of Chinese adults.

Investigation of the relationship between MetS and the only visible vessel signs, namely retinal microvascular signs, may be helpful to evaluate the severity of MetS and predict its development. Thus, the purpose of this study is to determine the association of MetS and its

components with retinal microvascular abnormalities in a rural Chinese population.

Methods

Study population

The Handan Eye Study (HES) was designed to provide population-based estimates of the prevalence of eye disorders in rural adult Chinese. Details of the study design, sampling plan, population, and methods have been reported previously [18,19]. A total of 7557 residents in Yongnian County, Handan, Hebei Province, China were identified as eligible and invited to participate. Of these, 6830 (90.4% of those eligible) received examinations [18]. Of the 6830 who participated, 6648 (97.3% of 6830) had retinal photographs of sufficient quality and appropriate field definition so that retinal vessel diameters could be measured, and of these 6477 (94.8%) had retinal photographs with adequate quality for grading retinal microvascular signs including arteriolar wall signs (focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar wall reflex) and the presence of retinopathy lesions. There were 5572 (81.6% of 6830) who had blood collected for measurement of serum fasting glucose (FG) and lipids (total cholesterol [TC], total triglycerides [TG], low density lipoprotein [LDL] cholesterol, and high density lipoprotein [HDL] cholesterol. In total, 5519 (80.8% of 6830) participants had complete data, i.e., retinal vessel diameters, retinal microvascular signs, and blood collection.

The Beijing Tongren Hospital Ethics Committee approved the study protocol. Written informed consent was obtained from all participants examined in the hospital, in village sites, and at home. All study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects.

Data collection

All participants received a standardized examination. Anthropometric measurements were taken with each subject wearing light clothing and without shoes. Body mass index (BMI)

was calculated as weight (kg) divided by height (m) squared. Waist circumference was measured at the level of the umbilicus in cm. Blood samples were collected between 7:00 and 9:00 a.m. after at least an 8-h overnight fast. Sterile vacuum tubes with and without ethylenediaminetetraacetic acid (EDTA) were used, and centrifugation was done within 3 h of blood collection. Serum analysis was performed in the laboratory of Handan Central Hospital (quality control of the laboratory was certified and monitored yearly by Ministry of Health, China). Blood pressure was taken with the participant seated and after 5 minutes of rest. Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured with a digital automatic blood pressure monitor [20]. Blood pressure was measured on 2 occasions 5 minutes apart. If the blood pressures differed by more than 10 mm Hg systolic and/or 5 mm Hg diastolic, a third measurement was taken. The blood pressure of the individual was then taken as the mean of the two closest readings. Data regarding education, smoking, and alcohol consumption were obtained with a standardized questionnaire [18].

Definition of MetS

Among others, both the International Diabetes Federation (IDF) [21] and the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATPIII) [22] have established unique criteria for defining the MetS. Although we adopted the IDF definition of MetS in the current study, we repeated the analyses utilizing the NCEP-ATPIII definition of MetS and found comparable results (data not shown). According to the IDF definition, a person was considered to have MetS if they had central obesity (defined by ethnicity- and gender-specific waist circumference) plus any two of four additional factors: 1) TG level $\geq$ 1.7 mmol/L (150 mg/L), 2) HDL cholesterol < 1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women or participant was being treated for lipid abnormalities, 3) systolic blood pressure (SBP) $\geq$ 130 mm Hg or diastolic blood pressure

(DBP) ≥ 85 mm Hg at examinations or participant prior diagnosis of HTN and was receiving treatment, and 4) FG ≥ 5.6 mmol/L (100 mg/dL) or participant had a prior diagnosis of type 2 diabetes. We used the IDF ethnicity-specific definitions of central obesity for Chinese (men ≥ 90 cm and women ≥ 80 cm).

Assessment for retinal microvascular signs

The procedures for retinal photography and the grading of retinal microvascular signs are described in detail elsewhere [18]. Stereoscopic photographs of Early Treatment of Diabetic Retinopathy Study (ETDRS) Standard Field 1 (centered on the disc), and a non-stereoscopic photograph of Standard Field 2 (centered on the fovea) were taken of each eye by trained and certified photographers using a nonmydriatic retinal camera. (The TOPCON TRC-NW6S/7S [Topcon, Tokyo, Japan] was used at the beginning of the study, and then the Canon CR-DGi with a 20D SLR back [Canon, Tokyo, Japan] was used for the majority of subjects.) Photographs (3072 × 2048 pixels at 72 dpi) were graded for retinal microvascular signs and retinal vessel diameters by a single grader who was trained at the Retinal Vascular Imaging Centre, University of Melbourne. Grading was performed in a masked fashion following standardized protocols [11]. Retinal microvascular signs assessed included retinal arteriolar wall signs (focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar wall reflex), retinopathy lesions (microaneurysms, retinal hemorrhages and exudates) and arteriolar/venular diameters. Focal arteriolar narrowing was assessed in arterioles at least one half-disc diameter away from the optic disc margin and was graded as absent, questionable, mild, or severe. Arteriovenous nicking was defined as a decrease in venular width on both sides of the crossing by an arteriole above the venule and was graded as absent, questionable, mild, moderate, or severe [11]. Enhanced arteriolar wall reflex was assessed by comparing

the central light reflex on major retinal arteriolar walls with standard slides with regard to the width, density, and consistency of the reflex [23]. The level of retinal microvascular signs was based on the grading of the worse eye. If an eye was ungradable, the scores for the other eye were used. Retinal arteriolar and venular diameters were determined using a computer program to assist in making manual measurements as described previously [24]. Details of the digital image preparation are described elsewhere [18]. A trained grader, blinded to participant characteristics, performed all vessel measurements on the optic disc-centered image of the right eye of each participant. If the right eye image was not available or was upgradeable because of poor quality or ocular pathologic features, or if there were fewer than 6 large arterioles or fewer than 6 large venules measurable in the right eye image, the left eye image was graded. All arterioles and venules coursing through a zone between 0.5 to 1 disc diameters away from the optic disc margin were measured, and the average arteriolar and venular caliber of the eye was summarized as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively.

Statistical analysis

The Mann–Whitney U test was used to compare continuous variables, and the chi-square test was used to compare categorical variables of demographic characteristics. Multiple logistic regression models were used to determine the likelihood (odds ratio [OR]) of having each retinal microvascular sign by the presence versus absence of MetS and its components, after control for age, gender, and smoking status. MetS using the IDF and NCEP-ATPIII definitions, and each of the 5 components were categorized as binary independent variables (present or absent). Retinal microvascular signs were categorized as binary dependent variables (present versus absent). The association between the prevalence of retinal microvascular signs and number of metabolic syndrome components were performed by the

chi-square test. Multiple linear regression models were used to estimate mean differences (mm) in CRAE and CRVE between those with and without the MetS or its components, and were adjusted for age, gender, and smoking status. In analyses, the reference group was persons without the MetS or the corresponding component. We also estimated the ORs or mean differences in vessel diameter, for associations with each additional MetS component increase in the same subject, and persons who have four or more MetS components versus persons without any MetS components. Following the recommendation by Liew et al [25], models for CRVE were also adjusted for CRAE, and vice versa. Lastly, we performed Pearson correlation analyses to assess continuous associations between MetS components and CRAE and CRVE. All data were analyzed using Stata for Windows version 9.0 (Stata Corp, College Station, TX). A value of P <0.05 was considered to indicate statistical significance.

Results

Overall, participants had a mean ± standard deviation (SD) age of 52.0 ± 11.3 years, and were predominantly female (55.7%). The demographic characteristics of the study population according to the presence or absence of MetS are shown in **Table 1**. Briefly, persons with MetS were significantly older, and less likely to be male or smoke, compared to those without MetS (p <0.05 for all).

The associations between MetS or individual MetS components and various retinal microvascular signs, adjusted for age, gender, and smoking status are summarized in **Table 2**. Independent of age, gender, and smoking status, individuals with the MetS had a higher risk of exhibiting every retinal microvascular sign assessed. Additionally, as illustrated in **Figure 1**, the prevalence of each retinal microvascular sign, except generalized venular dilatation, was higher with an increasing number of syndrome components. The risk of many retinal microvascular signs was also higher in the presence of individual MetS components, including an elevated waist circumference, high BP, high FG, and high TG (**Table 2)**. For

instance, after adjusting for age, gender, and smoking status, the risk of arteriovenous nicking, focal arteriolar narrowing, enhanced retinal arteriolar reflex, and retinopathy was significantly higher in persons with a large waist circumference than in persons with a smaller waist circumference. Furthermore, persons with highTG levels were significantly more likely to have arteriovenous nicking and retinopathy, persons with high FG levels were significantly more likely to have an enhanced retinal arteriolar reflex and retinopathy, and those with high BP levels were significantly more likely to exhibit all retinal microvascular signs.

After adjusting for age, gender, and smoking status, CRAE was found to be significantly decreased in subjects with MetS, with an estimated difference of -3.60 μm (**Table 3**). Furthermore, CRAE was significantly decreased in persons with a large waist circumference, lower HDL cholesterol levels, higher BP, and higher FG levels, but was significantly increased in persons with high TG levels. After adjusting for age, gender, and smoking status no significant association was observed for CRVE and MetS ($p > 0.05$). However, CRVE was significantly decreased in persons with a large waist circumference, lower HDL cholesterol levels, and higher BP, but was significantly increased in persons with high TG and FG.

Finally, according to the correlation analyses presented in Table 4, nearly all the MetS components were significantly ($p<0.001$), albeit modestly (absolute Pearson correlation coefficient range 0.049 to 0.222) correlated with CRAE and CRVE. As the only exception, fasting glucose was not significantly correlated with CRVE.

Discussion

Because MetS has a major impact on the microvasculature and since retinal capillaries are the only area of the microvascular system that can be directly examined, establishing associations between MetS and retinal microvascular signs is clinically relevant. In this rural Chinese population, the risks of arteriovenous nicking, focal arteriolar narrowing, enhanced arteriolar wall reflex, retinopathy, and smaller retinal arteriolar diameter were significantly higher in participants with MetS, even after control for age, gender, and smoking status. These findings were consistent with those reported in studies carried out in Japan [5], the United States [7,8,9,12,26], Australia [10,12], and the Netherlands [14]. Additionally, we reported that the presence of individual MetS components, including an elevated BP, waist circumference, TG, and fasting plasma glucose, was associated with increased risk of the various retinal microvascular signs. Our results suggest that individuals with MetS, as well as those who do not meet the criteria for MetS but who have elevated levels of one or two MetS components are at risk of detrimental changes at the microvascular level.

Retinopathy, which includes microaneurysms, retinal hemorrhages, and soft exudates, is a well-known complication of DM and HTN and is pathologically associated with a breakdown of the blood-retinal barrier. The Atherosclerosis Risk in Communities Study [27] and the Cardiovascular Health Study [28] reported that retinal arteriolar abnormalities are related to generalized arteriolosclerosis, which is caused by elevated BP. Data from the Funagata study also indicated that retinal arteriolar narrowing was associated with an increased risk of HTN in Japanese persons [29]. In agreement, the results of the current study found that retinopathy, focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar wall reflex were all strongly associated with an elevated BP level. Moreover, a key

finding of the current study is that a deterioration of the retinal microvasculature does not only occur among individuals with MetS, but also those who do not meet the criteria for MetS but who have elevated levels of one or two MetS components. These findings question the clinical utility of the MetS diagnosis over a diagnosis of any one of the individual MetS components.In another study performed in Japan, Saito et al [30], found that narrower retinal arterial diameters and wider venular diameters were associated with a higher prevalence of MetS.

The prevalence of MetS in males and females in the present study was 17.7% and 36.7%, respectively, which is higher than reported in other studies [5,7]. In our study, central obesity emerged as the most prevalent MetS risk factor, being present in 42.3% of males and 70.5% of females. An elevated BP was the second most prevalent MetS risk factor in our sample, affecting 54.8% of males and 55.0% of females. Both central obesity and high BP were more prevalent in our study population as compared with other Chinese studies [31-33]. This diference may explain the notably high prevalence of MetS in our study. Interestingly, it has been reported that obesity was a predictors of a wider retinal venular diameter independent of HTN, diabetes, lipid levels, and smoking status [34].

Our data revealed some associations between individual MetS components and CRVE that were inconsistent with those of prior reports. Higher TG and higher FG levels were associated with retinal venular dilatation, which is consistent with some previous studies [35],For instance, a larger waist circumference and higher BP were associated with venular narrowing. However, in the multi-ethnic study of atherosclerosis (MESA) report [12], a larger waist was associated with venular dilatation. Additionally, the ARIC study along with numerous other population-based studies demonstrated that an elevated BP had little effect on venular caliber [8,14,36,26,37]. Interestingly, data from the Blue Mountains Eye study indicated that after adjusting for age and gender, wider retinal venular caliber was associated

with an increased incidence of diabetes and impaired FG [38]. Further, we could not reproduce the findings of the Funagata [5] and ARIC [26] studies, which illustrated that persons with four or more MetS components had a decreased venular diameter by comparison to those without any MetS components. The inconsistency of these findings remains unexplained and requires further study.

Several limitations to this study warrant mention. Although the response rate was high (90.4% of eligible), a relatively large percentage of persons (18.4%) did not have blood samples collected, thus there may be selection bias of the studied sample. Furthermore, the binocular fundus photograph was graded for analysis of retinal microvascular signs, but for CRAE and CRVE diameters, we analyzed only 1 nonmydriatic fundus photograph from each subject. Although there is a good correlation between right and left eyes for retinal vessel diameter [10], this may have led to an underestimation of the prevalence of retinal vascular caliber abnormalities. In addition, the prevalence of severe focal arteriolar narrowing and enhanced arteriolar wall reflex in this sample were very low. Indeed, we found no cases with severe focal arteriolar narrowing and enhanced arteriolar wall reflex in persons with four or more MetS components. Accordingly, analysis of these factors was not possible. However, we have no reasons to believe these would substantially alter the associations reported. Since the definition of MetS used in the current study is one of several internationally used definitions, direct comparison to similar studies which may have used a different definition is difficult. Reliability of vessel caliber measurements may be influenced by factors such as refraction, lighting, and image quality. However, the repeatability of measured changes was not examined in this study, which may contribute to the inconsistencies noted between different studies. Lastly, the cross-sectional design makes interpretation regarding causality difficult.

Conclusions

In conclusion, this is the first study to report associations between MetS and individual components with different retinal microvascular signs and with CRAE and CRVE diameters in a rural Chinese population. These results add further evidence of the association between MetS and its individual components and risk of retinopathy.

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Date collection; Provision of materials, patients or resources; Literature search

Ke Yang: Analysis and interpretation; writing the article; Critical revision of the article; Literature search

Feng Hua Wang: Conception and design; Critical revision of the article; Provision of materials, patients or resources

Yuan Bo Liang: Conception and design; Final approval of the article; administrative, technical or logistic support

Yi Peng: Analysis and interpretation; Date collection; Statistical expertise

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Tien Yin Wong: Conception and design; Analysis and interpretation; Critical revision of the article; Final approval of the article; Statistical expertise; Administrative, technical or logistic support

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Figure Legend

Figure 1. Prevalence of retinal microvascular signs according to number of metabolic syndrome components.

Table 1. Demographic characteristics of participants with or without metabolic syndrome as defined by the International Diabetes Federation (IDF) criteria

	Metabolic syndrome		*p*-value
	Present (n = 1562)	Absent (n = 3957)	
Age (years)	54.75 ± 10.74	50.87 ± 11.74	<0.001
Gender (% male)	27.78	50.87	<0.001
Smoking (%)			<0.001
Current smoker	14.41	30.54	
Ever smoker	3.43	5.15	
Never smoker	82.16	64.31	
Systolic blood pressure (mm Hg)	151.21 ± 20.89	134.78 ± 20.97	<0.001
Diastolic blood pressure (mm Hg)	83.14 ± 12.30	75.62 ±11.40	<0.001
Height (cm)	159.57 ± 8.27	161.87 ± 8.45	<0.001
Weight (kg)	67.90 ± 11.86	62.60 ± 10.06	<0.001
Body mass index (kg/m^2)	26.59 ± 3.76	23.89 ± 3.41	<0.001
Total cholesterol (mmol/L)	4.89 ± 1.04	4.50 ± 0.90	<0.001
Triglyceride (mmol/L)	2.24 ± 1.36	1.23 ± 0.74	<0.001
HDL cholesterol (mmol/L)	1.14 ± 0.24	1.33 ± 0.28	<0.001
Fasting plasma glucose (mmol/L)	6.31 ± 2.02	5.58 ± 0.98	<0.001

HDL, high-density lipoprotein.

Data presented are mean ± standard deviation (SD) unless otherwise stated.

Table 2. Association of metabolic syndrome with retinal microvascular signs

		Large waist		High triglycerides		Low HDL cholesterol		High blood pressure		High fasting glucose		Metabolic Syndrome	
		Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Retinopathy	Prevalence (%)	17.13	13.53	18.87	14.45	16.15	15.46	22.03	9.64	44.61	13.81	22.63	13.01
	OR (95% CI)	1.33 (1.12, 1.57)*	-	1.33 (1.14, 1.56)*	-	1.14 (0.97, 1.34)	-	2.17 (1.83, 2.56)*	-	4.55 (3.6, 5.75)*	-	1.96 (1.68, 2.28)*	-
Arteriovenous Nicking	Prevalence (%)	11.37	7.55	11.65	9.16	10.45	9.53	13.37	6.54	10.98	9.81	13.8	8.34
	OR (95% CI)	1.43 (1.16, 1.77)*	-	1.25 (1.03, 1.52)*	-	1.15 (0.94, 1.39)	-	1.56 (1.28, 1.90)*	-	0.95 (0.66, 1.36)	-	1.76 (1.46, 2.12)*	-
Focal Arteriolar Narrowing	Prevalence (%)	0.37	0.24	0.39	0.29	0.45	0.24	0.61	0.04	0.3	0.32	0.66	0.18
	OR (95% CI)	1.43 (1.16, 1.77)*	-	1.3 (0.48, 3.54)	-	1.78 (0.66, 4.81)	-	18.5 (2.37, 144.74)*	-	0.88 (0.11, 6.72)	-	3.67 (1.39, 9.65)*	-
Enhanced Arteriolar Wall	Prevalence (%)	1.93	0.53	1.75	1.23	1.73	1.17	2.4	0.4	3.96	1.21	2.65	0.88
Reflex	OR (95% CI)	2.75 (1.41, 5.37)*	-	1.35 (0.83, 2.17)	-	1.31 (0.81, 2.1)	-	4.55 (2.35, 8.78)*	-	2.7 (1.46, 5.01)*	-	3.06 (1.93, 4.85)*	-
Generalized Arteriolar	Prevalence (%)	21.44	17.77	18.16	20.74	20.64	19.62	27.21	13.25	23.57	19.78	23.83	18.53
Narrowing	OR (95% CI)	1.32 (1.13, 1.53)*	-	0.84 (0.72, 0.98)*	-	1.13 (0.97, 1.30)	-	2.56 (2.19, 2.99)*	-	1.18 (0.89, 1.57)	-	1.38 (1.19, 1.59)*	-
Generalized Venular	Prevalence (%)	20.37	19.42	15.7	21.74	20.22	19.87	21.57	18.53	18.86	20.07	20.14	19.95
Dilatation	OR (95% CI)	1.01 (0.86, 1.17)	-	0.67 (0.57, 0.78)*	-	0.96 (0.83, 1.11)	-	1.28 (1.1, 1.49)*	-	0.93 (0.69, 1.26)	-	1.01 (0.87, 1.18)	-
Severe focal arteriolar	Prevalence (%)	0.37	0.24	0.39	0.29	0.45	0.24	0.61	0.04	0.28	0.32	0.66	0.18
narrowing	OR (95% CI)	1.3 (0.43, 3.95)	-	1.29 (0.48, 3.52)	-	1.77 (0.66, 4.78)	-	20.18 (2.56, 159)*	-	0.78 (0.1, 5.97)	-	3.67 (1.39, 9.65)*	-
Moderate to severe	Prevalence (%)	11.37	7.55	11.65	9.16	10.45	9.53	13.37	6.54	11.58	9.76	13.8	8.34
arteriovenous nicking	OR (95% CI)	1.46 (1.18, 1.81)*	-	1.25 (1.03, 1.52)*	-	1.14 (0.94, 1.39)	-	1.64 (1.34, 2.01)*	-	0.96 (0.68, 1.36)	-	1.76 (1.46, 2.12)*	-
Severe enhanced arteriolar	Prevalence (%)	1.93	0.53	1.75	1.23	1.73	1.17	2.4	0.4	4.51	1.16	2.65	0.88
wall reflex	OR (95% CI)	2.8 (1.43, 5.51)*	-	1.29 (0.8, 2.09)	-	1.29 (0.8, 2.08)	-	5.06 (2.58, 9.92)*	-	3.11 (1.75, 5.54)*	-	3.06 (1.93, 4.85)*	-

OR, odds ratio; CI, confidence interval, HDL, high-density lipoprotein.

ORs were adjusted for age, gender, and smoking status.

*Indicates a significant association

Table 3. Mean difference in retinal vessel measurements by presence of metabolic syndrome components

		CRAE (μm)			CRVE (μm)		
		Mean	Mean difference (95% CI)	Adjusted mean difference (95% CI)	Mean	Mean difference (95% CI)	Adjusted mean difference (95% CI)
Large waist	Present	153.9	-5.29 (-5.92, -4.67)*	-5.47 (-6.11, -4.83)*	237.04	-3.7 (-4.66, -2.75)*	-3.63 (-4.61, -2.66)*
	Absent	159.2	-		240.74		
High triglyceride	Present	157.5	2.12 (1.46, 2.79)*	2.36 (1.7, 3.02)*	243.24	6.67 (5.66, 7.69)*	6.81 (5.81, 7.82)*
	Absent	155.4			236.57		
Low HDL cholesterol	Present	154.5	-2.4 (-3.02, -1.79)*	-2.98 (-3.61, -2.36)*	236.69	-2.89 (-3.82, -1.95)*	-2.41 (-3.36, -1.46)*
	Absent	156.9			239.57		
High blood pressure	Present	151.8	-8.15 (-8.73, -7.56)*	-7.96 (-8.57, -7.35)*	236.93	-3.02 (-3.93, -2.1)*	-3.21 (-4.16, -2.26)*
	Absent	159.9			239.95		

High fasting glucose			-2.28 (-3.43, -1.12)*	-1.36 (-2.56, -0.16)*			
	Present	153.9			242.52	4.3 (2.38, 6.22)*	4.47 (2.58, 6.37)*
	Absent	156.1			238.22		
Metabolic syndrome			-3.97 (-4.62, -3.31)*	-3.60 (-4.29, -2.92)*			
	Present	153.1			238.37	-0.17 (-1.18, 0.85)	0.2 (-0.85, 1.25)
	Absent	157.1			238.53		

CI, confidence interval; HDL, high-density lipoprotein; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent.

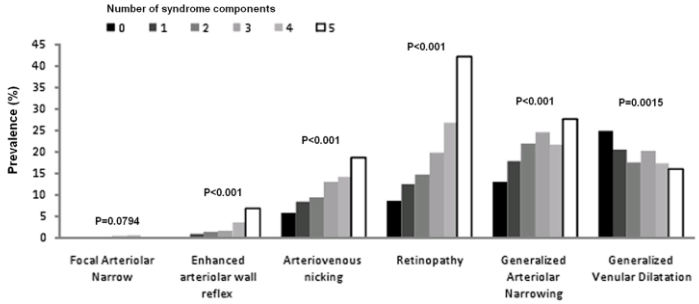
Adjusted mean difference indicates the estimated mean difference with adjustments for age, gender, and smoking status; for CRAE, the adjusted mean difference were also adjusted for CRVE and vice versa.

Table 4: Correlation between MetS components and measures of arteriolar and venular diameter.

	CRAE		CRVE	
	Pearson correlation coefficient	P-value	Pearson correlation coefficient	P-value
Waistline	-0.143	<0.001	-0.056	<0.001
Triglycerides	0.057	<0.001	0.105	<0.001
HDL cholesterol	0.072	<0.001	0.059	<0.001
SBP	0.049	<0.001	0.114	<0.001
DBP	-0.222	<0.001	-0.065	<0.001
Fasting glucose	-0.151	<0.001	-0.008	0.574

CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent

Figure 1


Number of syndrome components
0
1
2
3
4
5
Prevalence (%)
45
40
35
30
25
20
15
10
5
0
P=0.0794
P<0.001
P<0.001
P<0.001
P<0.001
P=0.0015
Focal Arteriolar Narrow
Enhanced arteriolar wall reflex
Arteriovenous nicking
Retinopathy
Generalized Arteriolar Narrowing
Generalized Venular Dilatation

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