Is retinal vasculature change associated with risk of obesity? Longitudinal cohort study in Japanese adults: The Funagata study

Koko Saito[1], Yusuke Tanabe[1], Ryo Kawasaki[1,2,3]*, Makoto Daimon[4], Toshihide Oizumi[4], Takeo Kato[4], Sumio Kawata[5], Takamasa Kayama[5], Hidetoshi Yamashita[1]

ABSTRACT

Aims/Introduction: To examine the association between baseline retinal vessel caliber change and prevalence, and 5-year incidence of obesity in the adult Japanese population of the Funagata study.

Materials and Methods: Of 900 individuals (age ≥ 35 years) who underwent systemic and retinal examinations in the Funagata study during 2000–2002, 584 (64.8%) were not obese as defined by body mass index (BMI) ≥ 25 kg/m^2, and considered at risk of incident obesity. In 2005–2007, 454 patients returned for 5-year follow-up examination (52.9%). Incidence of overweight was defined as subjects who were not overweight at baseline examination (BMI < 23 kg/m^2), but overweight (BMI ≥ 23 to <25 kg/m^2) at follow up, and that of obesity as subjects who were not obese at baseline examination (BMI < 25 kg/m^2), but obese (BMI ≥ 25 kg/m^2) at follow up.

Results: The prevalence of obesity at baseline was 35.1% (316/900); there was a cross-sectional association between wider retinal venular diameters and obesity (adjusted odds ratio [OR] per +1 standard deviation (SD) change: 1.18; 95% confidence interval [CI]: 1.02–1.35) after adjusting for age and sex. Cumulative incidence of obesity between baseline and 5-year follow up was 10.6% (32/303). Although the risk of incident overweight or obesity was higher in persons with wider retinal venular caliber, there were no statistically significant associations between baseline venular caliber and 5-year incidence of obesity.

Conclusions: Although we found significant cross-sectional associations of retinal venodilation with the prevalence of overweight, we could not confirm that retinal venodilation preceded the development of obesity in this population. **(J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00086.x, 2011)**

KEY WORDS: Epidemiological study, Obesity, Retinal vessel caliber

INTRODUCTION

Overweight and obesity are common health conditions and their prevalence is increasing globally[1–3]. Excess weight is well-known to be associated with an increased risk of diabetes, hypertension, dyslipidemia and cardiovascular disease, and recent studies have reported that it might also be a risk factor for microvascular disease[4–6], including retinal vasculature[7,8]. Although many studies have investigated the risk factors associated with the development of obesity[9–12], to predict the risk factors of developing obesity remains challenging.

[1]Department of Ophthalmology and Visual Science, Yamagata University Faculty of Medicine, Yamagata, Japan, [2]Centre for Eye Research Australia, University of Melbourne, Melbourne, [3]Clinical Research Excellence in Science in Diabetes, St Vincent's Hospital, Melbourne, Vic., Australia, [4]Department of Neurology, Haematology, Metabolism, Endocrinology, and Diabetology, Yamagata University Faculty of Medicine, and [5]Metabolic and Degenerative Diseases Research Center, Advanced Molecular Epidemiology Institute, Yamagata University, Yamagata, Japan
*Corresponding author. Ryo Kawasaki Tel.: +81-23-628-5374 Fax: +81-23-628-5374
E-mail address: ryok@med.id.yamagata-u.ac.jp
Received 13 August 2010; revised 23 October 2010; accepted 1 November 2010

Population-based studies have shown that retinal vascular changes are associated with the subsequent development of systemic diseases, such as diabetes[13,14] and hypertension[15–19]. Researchers have hypothesized that retinal microvascular changes might be antecedent of developing obesity based on experimental and clinical observations[4,20,21]. For example, in the Blue Mountains Eye Study (BMES), retinal vessel diameters were not only associated with the prevalence of higher body mass index (BMI), but also with an increased risk of incident obesity[22].

However, it is unclear whether the association observed in Caucasian populations is consistently observed in other racial/ethnic groups, because the level of obesity is known to be highly dependent on race/ethnicity[23]. For example, it was reported that Asian populations have a different degree of association between obesity and cardiovascular diseases compared with Caucasian populations[24]. Therefore, we aimed to examine the association between retinal vessel caliber and prevalence, and 5-year incidence of obesity and overweight in an adult Japanese population of the Funagata study.

MATERIALS AND METHODS

Study Population

The Funagata study is a population-based study examining the risk factors and complications of diabetes in adult Japanese aged 35 years or older[25–27]. The study population and research methodology has been described elsewhere[28]. Written consent was obtained from all study participants, and the study was carried out according to the recommendations of the Declaration of Helsinki and approved by the Ethics Committee of the Yamagata University Faculty of Medicine, Yamagata, Japan.

In 2000–2002, 1786 subjects underwent systemic and retinal examinations (baseline examinations); 900 (50.4%) of these subjects underwent an assessment for obesity or overweight and had quality fundus photographs taken for the measurement of retinal vessels, and were included in an analysis of the association between retinal vessel caliber and the prevalence of obesity. Of these, 584 subjects were not obese. In 2005–2007, 454 (52.9%) subjects returned for a follow-up examination and were included in the current analysis of the association between retinal vessel caliber and 5-year incidence of obesity.

Assessments of Retinal Vessel Caliber

All fundus photographs were taken using a 45° non-mydriatic fundus camera (CR5-NM45; Canon, Tokyo, Japan; and TRC; Topcon, Tokyo, Japan). The arteriolar and venular diameters were assessed at the Fundus Reading Center (Center for Vision Research, University of Sydney, Sydney, Australia) using semi-automated computer-assisted imaging software (developed by the University of Wisconsin, Madison, WI, USA). Details of image preparation and grading protocol have been described previously.[28] In brief, a single field fundus photograph of the right eye was examined for retinal vessel caliber measurement. Magnification percentage was calculated based on resolution of images. Then a trained grader identified all arterioles and venules crossing through the circular zone between half of the optic disc diameter and one optic disc diameter from the optic disc margin. The software automatically measured and calculated the caliber of arterioles and venules separately. These measurements were summarized using the modified Parr–Hubbard formula[29] as the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE), respectively.

Assessment of Systemic Characteristics

At the baseline examinations, serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels, as well as plasma glucose concentration, were measured in fasting blood samples. BMI was calculated as weight (kg) divided by the square of the height (m). Waist and hip circumferences were measured in all subjects in a relaxed standing position wearing underclothes only by specially trained observers. Waist circumference was measured to the nearest 1 cm at the level of the umbilicus. Hip circumference was measured to the nearest 1 cm at the level of the greatest girth. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Body fat percentage was measured by bioelectrical impedance analysis (TBF-101; Tanita, Tokyo, Japan).

Definition of Obese and Overweight

The definition of obese and overweight in the present study were based on BMI criteria for Asians by the regional office for the Western Pacific Region of WHO (WRPRO criteria, 2000)[30] and the guideline proposed by the Japan Society for the study of Obesity[31]; the BMI cut-off value was BMI $\geq$ 23 kg/m^2, but <25 kg/m^2 for overweight and BMI $\geq$ 25 kg/m^2 for obese. *Incidence of overweight* was defined as not overweight or obese at baseline examinations, but overweight or obese at follow up, and *incidence of obesity* was defined as not obese at baseline examinations, but obese at follow up.

We also used two definitions of central obesity based on the 2006 International Diabetes Federation (IDF) definition and its updated definition as follows: (i) waist circumference cut-off values of ≥85 cm for men and ≥90 cm for women; and (ii) waist circumference cut-off values of ≥90 cm for men and ≥80 cm for women. *Incidence of central obesity* was defined as no central obesity at baseline examinations, but central obesity at follow up.

High WHR was defined as >0.90 for men and >0.85 for women according to the WHO definition of metabolic syndrome[32]. *Incidence of increased WHR* was defined as the absence of high WHR at baseline examinations, but its presence at follow up. A high body fat percentage was defined as ≥25% for men and ≥30% for women from a report on Japanese subjects[33]. *Incidence of increased body fat percentage* was defined as the absence of high body fat percentage at baseline examinations, but its presence at follow up.

Statistical Analysis

Statistical analysis software SPSS 14.0 (SPSS, Chicago, IL, USA) was used for data analysis. We compared baseline characteristics between subjects who were included in this analysis and those who were lost to follow up. We compared clinical characteristics between overweight or obese subjects and non-overweight subjects by Student's *t*-test or Mann–Whitney *U*-test, and a χ^2-test as appropriate. To examine whether retinal vessel caliber were associated with measures of obesity, multiple logistic regression analysis was carried out to estimate the odds ratios (OR) of outcomes (i.e. overweight, obesity, high WHR and high body fat percentage) per standard deviation (SD) change in retinal vessel caliber after initial adjustment for age and gender, and then additional adjustment for smoking status, mean arterial blood pressure (MABP; calculated as [MABP] = [1/3 × SBP] + [2/3 × DBP], where SBP = systolic blood pressure and DBP = diastolic blood pressure), serum total cholesterol, triglycerides and fasting plasma glucose. CRAE and CRVE were simultaneously included in the multivariate models as independent variables as recommended[34]. *P*-values <0.05 were considered statistically significant.

RESULTS

Cross-sectional Association of Retinal Vessel Caliber and Measures of Obesity

A comparison of baseline characteristics between subjects who were included in the present study is given in Table 1. Significant differences were observed for age, SBP, height, bodyweight, BMI, waist and hip circumferences, fasting plasma glucose, and smoking status.

Cross-sectional associations between baseline retinal vessel calibers and measures of obesity are given in Table 2. Of the 900 subjects, 316 (35.1%) and 202 (22.4%) were obese and overweight, respectively. Subjects with wider retinal venular caliber were more likely to be obese (OR per 1 SD increase in CRVE: 1.16; 95% CI 1.01–1.33; $P = 0.04$) and overweight (OR per 1 SD increase in CRVE: 1.22; 95% CI 1.07–1.39; $P = 0.003$). This association remained significant after adjustment for age and sex. However, in a multivariable-adjusted model, wider retinal venular caliber was not significantly associated with the prevalence of overweight (OR per 1 SD increase in CRVE: 1.17; 95% CI 0.98–1.41; $P = 0.087$) or obesity (OR per 1 SD increase in CRVE: 1.16; 95% CI 0.96–1.41; $P = 0.127$). Wider retinal venular caliber was significantly associated with high WHR (OR per 1 SD increase in CRVE: 1.25; 95% CI 1.03–1.51; $P = 0.023$) and central obesity according to the 2006 IDF definition (OR per 1 SD increase in CRVE: 1.40; 95% CI 1.09–1.78; $P = 0.007$) or the updated IDF definition (OR per 1 SD increase in CRVE: 1.39; 95% CI 1.13–1.71; $P = 0.002$) even after fully adjusted. The prevalence of high body fat percentage was not associated with either retinal arteriolar or venular caliber.

Cross-sectional associations between baseline retinal vessel calibers and measures of obesity stratified by sex are shown in Table 3. Female subjects with narrower retinal arteriolar caliber were less likely to be overweight (OR per 1 SD decrease in CRAE: 0.84; 95% CI 0.70–0.99; $P = 0.048$), and subjects with wider retinal venular caliber were more likely to be obese (OR per 1 SD increase in CRVE: 1.21; 95% CI 1.01–1.46; $P = 0.04$) or overweight (OR per 1 SD increase in CRVE: 1.29; 95% CI 1.09–1.54; $P = 0.003$) after adjusting for age.

Longitudinal Association between Retinal Vessel Caliber and Incidence of Obesity

Comparison of clinical characteristic between subjects who returned for follow-up examination and those who were lost to follow-up is given in Table 1. Subjects who returned for the

Table 1 | Baseline and 5-year follow-up characteristics of the study subjects

Clinical characteristics	Included* (*n* = 900)	Excluded (*n* = 886)	*P*-value	Non-overweight† and obesity subjects at baseline examinations (*n* = 382): Returned to follow-up visit (*n* = 198)	Lost to follow-up visit (*n* = 184)	*P*-value
	Mean ± standard deviation			Mean ± standard deviation		
Age (years)	58.5 ± 11.7	63.4 ± 12.2	<0.001	56.1 ± 11.1	59.6 ± 13.4	0.006
Systolic blood pressure (mmHg)	126.3 ± 16.9	128.8 ± 16.9	<0.001	120.4 ± 15.5	123.9 ± 16.7	0.024
Diastolic blood pressure (mmHg)	75.6 ± 10.1	76.2 ± 9.9	0.246	72.2 ± 9.5	73.2 ± 10.4	0.289
Height (cm)	156.1 ± 8.7	153.6 ± 10.9	<0.001	156.3 ± 8.4	155.5 ± 8.3	0.415
Bodyweight (kg)	58.5 ± 10.6	56.0 ± 10.6	<0.001	51.5 ± 6.9	50.4 ± 7.0	0.12
Body mass index (kg/m^2)	23.9 ± 3.4	23.6 ± 3.6	0.028	21.0 ± 1.6	20.7 ± 1.7	0.255
Waist circumference (cm)	79.0 ± 9.5	77.5 ± 9.3	0.001	72.0 ± 6.5	72.6 ± 7.6	0.587
Hip circumference (cm)	92.9 ± 6.5	91.4 ± 6.2	<0.001	88.4 ± 4.3	88.2 ± 4.8	0.608
Waist-to-hip ratio	0.85 ± 0.07	0.85 ± 0.07	0.429	0.81 ± 0.59	0.82 ± 0.06	0.294
Body fat percentage (%)	25.4 ± 7.2	25.0 ± 8.1	0.212	21.3 ± 5.0	20.3 ± 5.3	0.199
Serum total cholesterol (mg/dL)	201.0 ± 33.0	202.3 ± 34.4	0.404	198.2 ± 34.3	194.0 ± 32.2	0.282
High-density lipoprotein cholesterol (mg/dL)	58.6 ± 14.3	58.3 ± 14.8	0.65	62.9 ± 13.6	63.7 ± 13.8	0.413
Triglycerides (mg/dL)	117.0 ± 133.8	121.2 ± 115.4	0.47	96.4 ± 64.2	90.7 ± 45.4	0.814
	Median (interquartile range)			Median (interquartile range)		
Fasting plasma glucose (mg/dL)	92 (87, 101)	94 (88, 101)	0.009	89 (85, 94)	91 (86, 98)	0.009
	n (%)			*n* (%)		
Males	388 (43.1)	397 (44.8)	0.47	77 (38.9)	80 (43.5)	0.265
Current smoker	167 (18.8)	148 (16.9)	0.029	37 (18.8)	46 (25.7)	0.444
Past smoker	135 (15.2)	102 (11.6)		28 (14.2)	22 (12.3)	
Never smoked	586 (66.0)	627 (71.5)		132 (67.0)	111 (62.0)	

*Data of body mass index and retinal vessel diameters were available. †Overweight was defined as a body mass index ≥ 23 kg/m^2 but <25 kg/m^2.

Table 2 | Associations between retinal vessel calibers and various indices of the prevalence of obesity in the Funagata study population

Indices of obesity	*n*	Affected (%)	Odds ratio (95% confidence interval)					
			Crude	*P*-value	Age and sex adjusted	*P*-value	Multivariable-adjusted*	*P*-value
Per 1 SD decrease in central retinal artery equivalent								
Obesity (BMI ≥ 25 kg/m^2)	900	316 (35.1)	0.99 (0.85–1.14)		0.98 (0.85–1.12)		0.99 (0.82–1.20)	
Overweight and obesity (BMI ≥ 23 kg/m^2)	900	518 (57.6)	0.92 (0.81–1.05)		0.90 (0.79–1.03)		0.93 (0.77–1.12)	
High waist hip ratio (WHR > 0.90 for men, >0.85 for women)	883	308 (34.9)	1.07 (0.93–1.23)		0.98 (0.85–1.14)		1.08 (0.89–1.31)	
Central obesity (2006 IDF definition; 85 cm for men, ≥90 cm for women)	883	197 (22.3)	0.97 (0.82–1.13)		0.93 (0.77–1.11)		1.10 (0.87–1.40)	
Central obesity (updated IDF definition; ≥90 cm for men, ≥80 cm for women)	883	242 (27.4)	1.00 (0.86–1.16)		0.95 (0.81–1.10)		1.09 (0.89–1.33)	
High body fat percentage (≥25% for men, ≥30% for women)	901	324 (36.0)	1.02 (0.89–1.17)		1.02 (0.89–1.17)		1.07 (0.89–1.29)	
Per 1 SD increase of central retinal vein equivalent								
Obesity (BMI ≥ 25 kg/m^2)	900	316 (35.1)	**1.16 (1.01–1.33)**	0.04	**1.18 (1.02–1.35)**	0.024	1.16 (0.96–1.41)	
Overweight and obesity (BMI ≥ 23 kg/m^2)	900	518 (57.6)	**1.22 (1.07–1.39)**	0.003	**1.24 (1.08–1.42)**	0.002	1.17 (0.98–1.41)	
High waist-to-hip ratio (WHR > 0.90 for men, >0.85 for women)	883	308 (34.9)	1.13 (0.98–1.30)		**1.21 (1.04–1.40)**	0.011	**1.25 (1.03–1.51)**	0.023
Central obesity (2006 IDF definition; ≥85 cm for men, ≥90 cm or women)	883	197 (22.3)	**1.37 (1.16–1.62)**	<0.001	**1.34 (1.12–1.61)**	0.002	**1.40 (1.09–1.78)**	0.007
Central obesity (updated IDF definition; ≥90 cm for men, ≥80 cm for women)	883	242 (27.4)	**1.22 (1.05–1.42)**	0.011	**1.32 (1.13–1.54)**	0.001	**1.39 (1.13–1.71)**	0.002
High body fat percentage (≥25% for men, ≥30% for women)	901	324 (36.0)	1.11 (0.96–1.27)		1.15 (0.99–1.32)		1.17 (0.97–1.41)	

BMI, body mass index; IDF, International Diabetes Federation; WHR, waist-to-hip ratio. *Multivariable-adjusted model: adjusted for age, sex, smoking status, mean arterial blood pressure, total plasma cholesterol, triglycerides and fasting plasma glucose.

Table 3 | Associations between retinal vessel calibers and various indices of the prevalence of obesity in the Funagata study population by sex

Indices of obesity	*n*	Affected (%)	Odds ratio (95% confidence interval)				
			Crude	*P*-value	Age adjusted	*P*-value	Multivariable-adjusted*
Per 1 SD decrease in central retinal artery equivalent							
Male							
Obesity (BMI ≥ 25 kg/m^2)	388	134 (34.5)	0.93 (0.75–1.16)		0.96 (0.77–1.20)		1.06 (0.78–1.44)
Overweight and obesity (BMI ≥ 23 kg/m^2)	388	231 (59.5)	0.96 (0.78–1.18)		0.98 (0.79–1.21)		1.02 (0.75–1.38)
Female							
Obesity (BMI ≥ 25 kg/m^2)	512	182 (35.5)	1.03 (0.86–1.23)		0.96 (0.80–1.15)		1.04 (0.81–1.32)
Overweight and obesity (BMI ≥ 23 kg/m^2)	512	287 (56.1)	0.89 (0.75–1.06)		**0.84 (0.70–0.99)**	0.048	0.86 (0.67–1.09)
Per 1 SD increase of central retinal vein equivalent							
Male							
Obesity (BMI ≥ 25 kg/m^2)	388	134 (34.5)	1.16 (0.93–1.45)		1.13 (0.90–1.41)		1.07 (0.78–1.48)
Overweight and obesity (BMI ≥ 23 kg/m^2)	388	231 (59.5)	1.10 (0.89–1.37)		1.08 (0.87–1.34)		1.04 (0.77–1.41)
Female							
Obesity (BMI ≥ 25 kg/m^2)	512	182 (35.5)	1.15 (0.96–1.37)		**1.21 (1.01–1.46)**	0.04	1.24 (0.98–1.58)
Overweight and obesity (BMI ≥ 23 kg/m^2)	512	287 (56.1)	**1.29 (1.09–1.54)**	0.003	**1.35 (1.13–1.62)**	0.001	1.26 (0.99–1.59)

BMI, body mass index. *Multivariable-adjusted model: adjusted for age, sex, smoking status, mean arterial blood pressure, total plasma cholesterol, triglycerides and fasting plasma glucose.

follow-up examination were significantly younger (56.1 *vs* 59.6 years; $P = 0.006$), had lower SBP (120.4 *vs* 123.9 mmHg; $P = 0.024$), and had lower fasting plasma glucose (89 *vs* 91 mg/dL; $P = 0.009$). The associations between baseline retinal vessel caliber and incidence of overweight or obesity are given in Table 4. Although narrower retinal arteriolar and wider venular

Table 4 | Associations between retinal vessel diameters and various indices of incident obesity in the Funagata study population

Indices of obesity	*n*	Affected (%)	Odds ratio (95% confidence interval)		
			Crude	Age and sex adjusted	Multivariable-adjusted*
Per 1 SD decrease of central retinal artery equivalent					
Obesity (BMI ≥ 25 kg/m^2)	303	32 (10.6)	0.99 (0.68–1.42)	0.97 (0.67–1.41)	1.21 (0.74–2.00)
Overweight and obesity (BMI ≥ 23 kg/m^2)	198	30 (15.2)	0.89 (0.61–1.31)	0.89 (0.59–1.32)	1.04 (0.59–1.84)
High waist hip ratio (WHR > 0.90 for men, >0.85 for women)	322	125 (38.8)	1.06 (0.85–1.33)	1.03 (0.82–1.30)	1.20 (0.89–1.61)
Central obesity (2006 IDF definition; ≥85 cm for men, ≥90 cm for women)	368	45 (12.2)	1.05 (0.77–1.43)	0.97 (0.70–1.34)	0.86 (0.56–1.33)
Central obesity (updated IDF definition; ≥90 cm for men, ≥80 cm for women)	351	63 (17.9)	0.99 (0.76–1.31)	0.99 (0.74–1.31)	1.00 (0.70–1.43)
High body fat percentage (≥25% for men, ≥30% for women)	305	44 (14.4)	0.91 (0.66–1.25)	0.94 (0.68–1.31)	0.93 (0.60–1.42)
Per 1 SD increase in central retinal vein equivalent					
Obesity (BMI ≥ 25 kg/m^2)	303	32 (10.6)	1.25 (0.87–1.81)	1.25 (0.86–1.82)	1.37 (0.85–2.23)
Overweight and obesity (BMI ≥ 23 kg/m^2)	198	30 (15.2)	1.34 (0.90–2.01)	1.37 (0.91–2.16)	1.39 (0.78–2.49)
High waist-to-hip ratio (WHR > 0.90 for men, >0.85 for women)	322	125 (38.8)	1.15 (0.92–1.44)	1.19 (0.95–1.51)	1.29 (0.95–1.74)
Central obesity (2006 IDF definition; ≥85 cm for men, ≥90 cm for women)	368	45 (12.2)	0.92 (0.67–1.25)	0.92 (0.66–1.27)	0.75 (0.49–1.16)
Central obesity (updated IDF definition; ≥90 cm for men, ≥80 cm for women)	351	63 (17.9)	0.99 (0.76–1.30)	1.07 (0.81–1.41)	1.00 (0.70–1.43)
High body fat percentage (≥25% for men, ≥30% for women)	305	44 (14.4)	1.10 (0.80–1.51)	1.10 (0.80–1.51)	1.04 (0.69–1.58)

*Multivariable-adjusted model: adjusted for age, sex, smoking status, mean arterial blood pressure, total plasma cholesterol, triglycerides and fasting plasma glucose. BMI, body mass index; IDF, International Diabetes Federation; WHR, waist-to-hip ratio.

Table 5 | Associations between retinal vessel diameters and various indices of incident obesity in the Funagata study population by sex

Indices of obesity	*n*	Affected (%)	Odds ratio (95% confidence interval)					
			Crude	*P*-value	Age adjusted	*P*-value	Multivariable-adjusted*	*P*-value
Per 1 SD decrease in central retinal artery equivalent								
Male								
Obesity (BMI ≥ 25 kg/m^2)	130	15 (11.5)	1.02 (0.57–1.81)		1.01 (0.56–1.81)		0.98 (0.44–2.18)	
Overweight and obesity (BMI ≥ 23 kg/m^2)	77	11 (14.3)	1.19 (0.61–2.33)		1.36 (0.6–2.73)		1.40 (0.54, 3.63)	
Female								
Obesity (BMI ≥ 25 kg/m^2)	173	17 (9.82)	0.94 (0.58–1.53)		0.94 (0.57–1.54)		1.48 (0.76–2.86)	
Overweight and obesity (BMI ≥ 23 kg/m^2)	121	19 (15.7)	0.76 (0.46–1.25)		0.69 (0.41–1.16)		0.73 (0.33–1.59)	
Per 1 SD increase of central retinal vein equivalent								
Male								
Obesity (BMI ≥ 25 kg/m^2)	130	15 (11.5)	0.91 (0.51–1.64)		0.91 (0.51–1.65)		0.82 (0.38–1.74)	
Overweight and obesity (BMI ≥ 23 kg/m^2)	77	11 (14.3)	0.86 (0.43–1.75)		0.82 (0.42–1.63)		1.13 (0.44–2.91)	
Female								
Obesity (BMI ≥ 25 kg/m^2)	173	17 (9.82)	1.56 (0.95–2.56)		1.56 (0.94–2.57)		**2.10 (1.08–4.06)**	0.028
Overweight and obesity (BMI ≥ 23 kg/m^2)	121	19 (15.7)	**1.71 (1.01–2.86)**	0.043	**1.86 (1.07–3.24)**	0.027	1.81 (0.85–3.85)	

BMI, body mass index. *Multivariable-adjusted model: adjusted for age, sex, smoking status, mean arterial blood pressure, total plasma cholesterol, triglycerides and fasting plasma glucose.

caliber seems to have higher odds of incident obesity (point estimated of adjusted OR per 1 SD decrease in CRAE and per 1 SD increase in CRVE: 1.21 and 1.37, respectively) and overweight (point estimated of adjusted OR per 1SD decrease in CRAE and per 1SD increase in CRVE: 1.04 and 1.39, respectively), these associations were not statistically significant.

The associations between baseline retinal vessel caliber and incidence of overweight or obesity by sex are given in Table 5. Female subjects with wider retinal venular caliber had a twofold higher risk of incident obesity over 5 years (OR per 1 SD increase in CRVE: 2.10; 95% CI 1.08–4.06; $P = 0.028$) after fully adjusted for potential confounding factors, and there was a significant association with incident overweight (OR per 1 SD increase in CRVE: 1.71; 95% CI 1.01–2.86; $P = 0.043$).

DISCUSSION

In this adult Japanese population, we confirmed positive cross-sectional associations between retinal venular dilation and overweight subjects, and between high WHR and central obesity, independent of age and sex. The association between retinal venular dilation and high WHR was significant after multivariate adjustment for smoking, blood pressure, lipids and fasting plasma glucose, whereas it was attenuated for overweight and obesity. Previous population-based studies mainly on Caucasian populations including the BMES[22], Rotterdam Study[21] and ARIC Study[8] showed positive cross-sectional associations between wider retinal venular caliber and obesity defined by greater waist circumference[8], WHR[21] and BMI[22,35]. Our previous study also found that wider retinal caliber was related to metabolic syndrome, mainly driven by large waist circumference[7]. In the present study, we confirmed that our findings of cross-sectional associations were consistent with previous studies on Western populations.

The BMES[22] reported a positive longitudinal association between wider venular caliber at baseline examinations and incidence of obesity. In the present study, however, we did not observe this longitudinal association in a Japanese adult cohort. We have no clear explanation for this discrepancy. One possible explanation is the difference in clinical profile of obesity measures between different races/ethnicities; for example, it has been reported that Asians have a higher body fat percentage even at lower a BMI than Caucasians[36–38]. Other studies reported that the risk of cardiovascular disease or diabetes is increased at lower BMI cut-offs in Asian populations than in Caucasian populations[38,39]. Thus, the association between wider venular dilation and incident obesity might vary between racial/ethnic groups. Indeed, the mean BMI was 23.9 ± 3.4 kg/m^2 in the present study, whereas it was 26.1 ± 4.6 kg/m^2 in BMES. Another possible explanation is that the incidences of obesity and overweight in the present study were relatively low. Also, the 5-year follow-up period might have been too short to detect longitudinal associations between retinal vessel caliber and the incidence of obesity in a Japanese population.

Interestingly, we also found a longitudinal association between wider venular dilation and incident obesity in female subjects only. It has been reported that there is a gender difference in the associations between anthropometric indices of obesity and blood pressure[40], and that BMI might be better than waist circumference for defining metabolic syndrome in Japanese women[41]. The present study suggested that there might be a gender difference in the association of retinal venular change and obesity. Further studies are warranted to investigate whether this gender difference in longitudinal association is because of the difference in the cut-off for obesity measures between genders or if it is caused by other mechanisms,

Given that we only observed a cross-sectional association between retinal venodilation and obesity, and there was no longitudinal association, we speculate that retinal venodilation might be secondary to overweight or obesity and not a precedent of developing obesity. The reason for the association between obesity and wider retinal venular caliber is still not fully understood. It is speculated that both obesity and a wider retinal venular caliber share the same risk factors, such as inflammation[21]. An increase in the total blood volume in obese individuals[42] is also considered to cause wider venular caliber[22].

A key strength of the present study is its standardized assessment of obesity and retinal vessel calibers. The measurement of retinal vessel calibers was carried out at the Fundus Reading Center, Center for Vision Research, University of Melbourne, where BMES grading was also carried out. The present study had several limitations. At baseline examinations, there were differences in clinical characteristics between the included and excluded subjects. The follow-up rate was 52.9% at the second examination. In addition, there were also differences in clinical characteristics between those subjects who returned for follow up and those who were lost to follow up. Therefore, the study sample might have been influenced by selection bias even after adjustment for characteristics. Second, retinal vessel calibers or measures of obesity were defined based on a single examination. This might have resulted in measurement error, which we assume occurred at random and did not alter the results of our analysis.

In summary, we found that individuals with wider retinal venular caliber were more likely to have central obesity or a high WHR, and our findings confirmed the association reported in Western populations[8,21–23]. However, we could not confirm a longitudinal association between baseline retinal vessel calibers and the 5-year incidence of obesity. Our findings suggest that retinal venular dilation might share pathophysiology or same risk characteristics as obesity, but it is not predictive of obesity in adult Japanese populations.

ACKNOWLEDGEMENTS

This study was supported by the 21st century Centre of Excellence (COE) program #F03 ('Molecular Epidemiological Study utilizing the Regional Characteristics,' Yamagata University) and by a Grant in Aid from the Global COE program #F03 ('Formation of an international network for education and research of molecular epidemiology', Yamagata University) of the Japanese Society for the Promotion of Science, Japan. No potential conflicts of interest relevant to this study were reported.

REFERENCES

1. Berghofer A, Pischon T, Reinhold T, *et al.* Obesity prevalence from a European perspective: a systematic review. *BMC Public Health* 2008; 8: 200.
2. Flegal KM, Carroll MD, Ogden CL, *et al.* Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002; 288: 1723–1727.

3. Must A, Spadano J, Coakley EH, *et al.* The disease burden associated with overweight and obesity. *JAMA* 1999; 282: 1523–1529.
4. de Jongh RT, Serne EH, IJzerman RG, *et al.* Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. *Circulation* 2004; 109: 2529–2535.
5. de Jongh RT, Serne EH, IJzerman RG, *et al.* Impaired local microvascular vasodilatory effects of insulin and reduced skin microvascular vasomotion in obese women. *Microvasc Res* 2008; 75: 256–262.
6. Jonk AM, Houben AJ, de Jongh RT, *et al.* Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. *Physiology (Bethesda)* 2007; 22: 252–260.
7. Kawasaki R, Tielsch JM, Wang JJ, *et al.* The metabolic syndrome and retinal microvascular signs in a Japanese population: the Funagata study. *Br J Ophthalmol* 2008; 92: 161–166.
8. Wong TY, Duncan BB, Golden SH, *et al.* Associations between the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. *Invest Ophthalmol Vis Sci* 2004; 45: 2949–2954.
9. Fox CS, Pencina MJ, D'Agostino RB, *et al.* Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med* 2008; 168: 587–592.
10. Snyder EE, Walts B, Pérusse L, *et al.* The human obesity gene map: the 2003 update. *Obes Res* 2004; 12: 369–439.
11. Tataranni PA, Harper IT, Snitker S, *et al.* Body weight gain in free-living Pima Indians: effect of energy intake vs expenditure. *Int J Obes Relat Metab Disord* 2003; 27: 1578–1583.
12. Zurlo F, Ferraro RT, Fontvielle AM, *et al.* Spontaneous physical activity and obesity: cross-sectional and longitudinal studies in Pima Indians. *Am J Physiol* 1992; 263: E296–E300.
13. Klein R, Klein BE, Moss SE, *et al.* The relationship of retinopathy in persons without diabetes to the 15-year incidence of diabetes and hypertension: Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2006; 104: 98–107.
14. Wong TY, Mohamed Q, Klein R, *et al.* Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes? *Br J Ophthalmol* 2006; 90: 301–303.
15. Leung H, Wang JJ, Rochtchina E, *et al.* Relationships between age, blood pressure, and retinal vessel diameters in an older population. *Invest Ophthalmol Vis Sci* 2003; 44: 2900–2904.
16. Wang JJ, Mitchell P, Leung H, *et al.* Hypertensive retinal vessel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension* 2003; 42: 534–541.
17. Wong TY, Hubbard LD, Klein R, *et al.* Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol* 2002; 86: 1007–1013.
18. Wong TY, Klein R, Klein BE, *et al.* Retinal vessel diameters and their associations with age and blood pressure. *Invest Ophthalmol Vis Sci* 2003; 44: 4644–4650.
19. Wong TY, Klein R, Sharrett AR, *et al.* Retinal arteriolar diameter and risk for hypertension. *Ann Intern Med* 2004; 140: 248–255.
20. Hayashi K, Kanda T, Homma K, *et al.* Altered renal microvascular response in Zucker obese rats. *Metabolism* 2002; 51: 1553–1561.
21. Ikram MK, de Jong FJ, Vingerling JR, *et al.* Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study *Invest Ophthalmol Vis Sci* 2004; 45: 2129–2134.
22. Wang JJ, Taylor B, Wong TY, *et al.* Retinal vessel diameters and obesity: a population-based study in older persons. *Obesity* 2006; 14: 206–214.
23. Ogden CL, Carroll MD, Curtin LR, *et al.* Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; 295: 1549–1555.
24. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157–163.
25. Daimon M, Oizumi T, Saitoh T, *et al.* Funagata study. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese Population: the Funagata study. *Diabetes Care* 2003; 26: 2015–2020.
26. Kameda W, Daimon M, Oizumi T, *et al.* Association of decrease in serum dehydroepiandrosterone sulfate levels with the progression to type 2 diabetes in men of a Japanese population: the Funagata Study. *Metabolism* 2005; 54: 669–676.
27. Sekikawa A, Tominaga M, Takahashi K, *et al.* Prevalence of diabetes and impaired glucose tolerance in Funagata area, Japan. *Diabetes Care* 1993; 16: 570–574.
28. Kawasaki R, Wang JJ, Rochtchina E, *et al.* Cardiovascular risk factors and retinal microvascular signs in an adult Japanese population: the Funagata Study. *Ophthalmology* 2006; 113: 1378–1384.
29. Hubbard LD, Brothers RJ, King WN, *et al.* Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 1999; 106: 2269–2280.
30. WHO/IASO/IOTF. *The Asia-Pacific Perspective: Redefining Obesity and its Treatment*. Sydney: Health Communications Australia Pty Ltd, 2000.
31. The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66:987–992.
32. World Health Organization (1999). *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Organization; (pub. no. WHO/NCD/NCS/99.2). Website: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf.
33. Miyatake N, Takenami S, Kawasaki Y, *et al.* Clinical evaluation of body fat percentage in 11,833 Japanese measured by air displacement plethysmograph. *Intern Med* 2005; 44: 702–705.

34. Liew G, Sharrett AR, Kronmal R, *et al.* Measurement of retinal vascular caliber: issues and alternatives to using the arteriole to venule ratio. *Invest Ophthalmol Vis Sci* 2007; 48: 52–57.
35. Wong TY, Islam FM, Klein R, *et al.* Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (MESA). *Invest Ophthalmol Vis Sci* 2006; 47: 2341–2350.
36. Deurenberg-Yap M, Schmidt G, van Staveren WA, *et al.* The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. *Int J Obes Relat Metab Disord* 2000; 24: 1011–1017.
37. He M, Tan KC, Li ET, *et al.* Body fat determination by dual energy X-ray absorptiometry and its relation to body mass index and waist circumference in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 2001; 25: 748–752.
38. Ko GT, Chan JC, Cockram CS, *et al.* Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 1999; 23: 1136–1142.
39. Deurenberg-Yap M, Chew SK, Lin VF, *et al.* Relationships between indices of obesity and its co-morbidities in multi-ethnic Singapore. *Int J Obes Relat Metab Disord* 2001; 25: 1554–1562.
40. Sakurai M, Miura K, Takamura T, *et al.* Gender diffrences in the association between anthoropometric indices of obesity and blood pressure in Japanese. *Hypertens Res* 2006; 29: 75–80.
41. Sakurai M, Takamura T, Miura K, *et al.* BMI may be better than waist circumference for defining metabolic syndorome in Japanese women. *Diabetes Care* 2008; 31: e12.
42. Oren S, Grossman E, Frohlich ED. Arterial and venous compliance in obese and nonobese subjects. *Am J Cardiol* 1996; 77: 665–667.