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Longitudinal Effect of Bariatric Surgery on Retinal Microcirculation and Target Organ Damage: the BASTOD Study

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Keywords

Bariatric surgery · Weight loss · Retinal vessels · Pulse wave analysis · Ankle Brachial Index · Vascular stiffness

Key points

- The retinal microvascular phenotype improved during the first year after bariatric surgery, with decreased central retinal vein equivalent ($-5.1 \mu\text{m}$, $p < 0.0001$), and increased arteriole-to-venule ratio ($+0.02$, $p < 0.0001$).
- Factors associated with retinal microvascular plasticity were male sex, high baseline weight, and absence of diabetes.
- Longitudinal assessment of retinal vascular calibers may offer new insights into the pathophysiology of subclinical vascular processes.

Abstract

Purpose

Obesity is associated with increased cardiovascular risk. Bariatric surgery (BS) improves the clinical and metabolic profile. Retinal caliber changes could precede cardiovascular events. Different studies have shown an improvement in retinal caliber after BS. The aim of this study was to examine retinal caliber and other cardiovascular target organ damage before and after BS.

Materials and Methods

Monocentric, prospective cohort study at the Montpellier University Hospital. Biologic features, vessel stiffness, echocardiograph variables, and retinal caliber at baseline and 6 and 12 months were assessed in consecutive patients with class 2 or 3 obesity undergoing BS. A mixed linear model adjusted for age and sex was used.

Results

We included 88 patients (75 women). The mean (SD) age was 43 years (11) and mean (SD) baseline weight 117 (21) Kg. Mean changes in the first year after BS were $-5.1 \mu\text{m}$ in central retinal vein equivalent (CRVE) ($p < 0.0001$), $+0.02$ in arteriole-to-venule ratio (AVR) ($p < 0.0001$), -1.4 mmol/L in glycemia ($p < 0.0001$), -1.0 mg/L in natural logarithm of C-reactive protein ($p < 0.0001$), and -54.0 g in left ventricular mass ($p = 0.0005$). We observed no significant improvement in arterial stiffness markers. Predictors of improvement in CRVE were high baseline weight ($p = 0.030$), male sex ($p = 0.025$), and no diabetes history ($p = 0.047$).

Conclusion

The retinal microvascular phenotype improved during the first year after bariatric surgery, with decreased CRVE and increased AVR. Factors associated with retinal microvascular plasticity were male sex, high baseline weight, and absence of diabetes. Longitudinal assessment of retinal vascular calibers may offer new insights into the pathophysiology of subclinical vascular processes.

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Introduction

High body mass index (BMI) is strongly associated with mortality risk, especially cardiovascular (CV) mortality [1]. Various mechanisms can be evoked to explain this increase in CV risk, most being part of the metabolic syndrome: carbohydrate abnormalities, insulin resistance, and arterial hypertension [2].

In the concept of CV disease, the occurrence of preclinical target organ damage (TOD) is the main step in the management because it precedes CV events [3]. Target organs are the heart, arteries and their stiffness, kidneys, brain, and retina. The early detection of TOD could allow for adapting the therapeutic management to prevent a CV event. Bariatric surgery (BS) allows for resolution of the metabolic syndrome, diabetes, and reduces all-cause mortality, particularly that secondary to CV events [4].

Regarding retinal microvascularisation, fundus retinophotographs allow for an accurate and non-invasive analysis. Central retinal arteriolar equivalent (CRAE) narrowing and larger central retinal vein equivalent (CRVE) are associated with increased CV risk [5] and can predict mortality from coronary heart disease and stroke [6]. Larger CRVE is associated with increased BMI [7]. This finding raises the question of the reversibility of microvascular damages in patients with obesity and which patients could benefit the most from BS. Only 6 studies — with modest sample sizes ($n < 52$) — have investigated retinal caliber after BS (Appendix 1). Results are conflicting; a trend in decreased CRVE is frequently found [8–10]. CRAE and the arteriovenous ratio (AVR) tend to increase but not always [11–13]. These studies did not provide an analysis of factors improvement in the retinal microvascular profile. A study evaluating retinal microvascular changes after BS as well as changes in renal function, metabolic, and macrovascular parameters with a larger sample would better characterize the type of response and determine predictors of microvascular remodeling after BS.

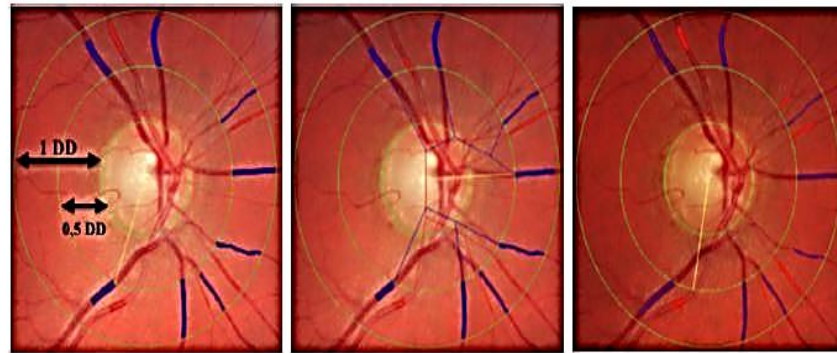
The purpose of our study was to prospectively evaluate the effect of BS on retinal microvascularisation in patients with obesity and investigate the baseline factors predicting these changes.

Methods

Design

The present study is an analysis of the bariatric surgery, arterial stiffness, and target organ damage (BASTOD) study, a prospective longitudinal single-center study with non-invasive evaluation before BS, then at 6 months and 1 year after surgery. Methodological details are provided in Supplementary material Appendix 2.

Fig. 1 IVAN software, change in vascular caliber post bariatric surgery in subject 87. Retinal vascular caliber is measured in the circle area between 0.5 and 1 disc diameter surrounding the optic disc. Areas highlighted in red indicate retinal arteriolar caliber, and areas in blue indicate retinal venular caliber. CRVE has decreased and AVR has increased between visits 1, 2, and 3. Abbreviations: DD, disc diameter; BMI, body mass index; CRVE, central retinal vein equivalent; CRAE, central retinal arteriolar equivalent; AVR, arteriole-to-venule ratio



Visit 1	Visit 2	Visit 3
BMI : 38,10	BMI : 22,64	BMI : 23,08
CRVE : 225,58	CRVE : 211,64	CRVE : 202,95
CRAE : 157,28	CRAE : 154,02	CRAE : 149,12
AVR : 0,70	AVR : 0,73	AVR : 0,73

Setting and Population

This observational study was carried out in a French university hospital. Patients were prospectively included between December 2011 and March 2016. The surgical indication and the operative method (Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy with or without preservation of the gastric antrum) were validated during a multidisciplinary meeting. All surgical procedures were performed by an experienced bariatric surgeon. Selected patients were then referred for preoperative assessment, and clinical and paraclinical data were collected. Patients included were adults from age 18 to 60 years, with World Health Organization (WHO) class 2 or 3 obesity for more than 5 years, failure of medical treatment, no hormonal causes, and no contraindication to surgery. Patients were excluded if they had uncontrolled hypertension (systolic blood pressure [BP] > 160 mmHg and diastolic [BP] > 100 mmHg), chronic kidney disease (creatinine clearance according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) < 60 ml/min/1.73 m² and/or proteinuria > 300 mg/24 h and/or hematuria on urine test strip), a history of cardiovascular disease or signs of clinical atheroma (stroke, myocardial infarction, and coronary artery disease (angina), obliterative arteritis of the lower limbs (absence of pulse, claudication), aortic aneurysm (abdominal palpation or previous imaging), and carotid murmur).

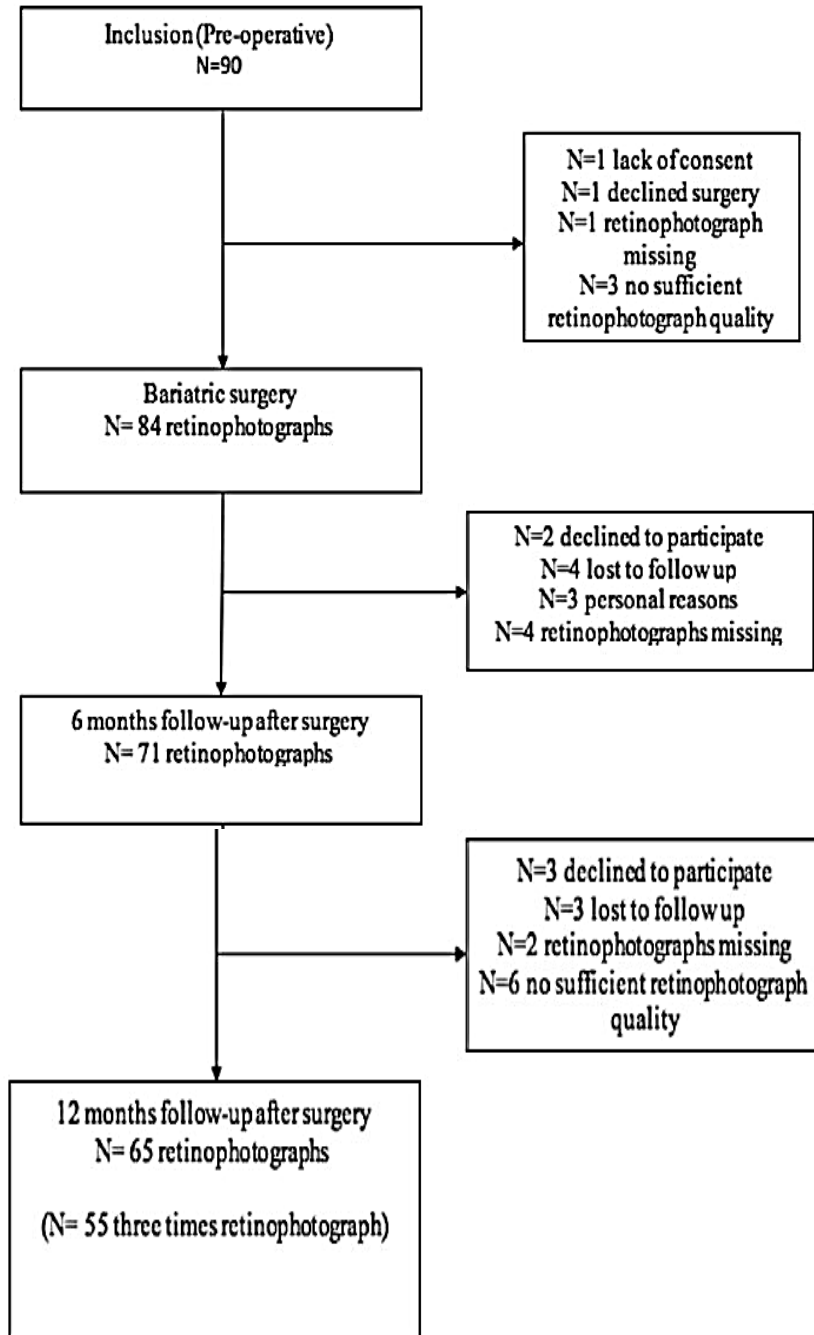
Ethics

Written informed consent was obtained for each patient in accordance with the 1995 Declaration of Helsinki. The study was approved by the medical ethics committee of the University Hospital of Montpellier and was registered at ClinicalTrials.gov (NCT01494168).

Outcomes and Measurements

Retinophotographs of both eyes were obtained by use of a nonmydriatic camera (CR5-NM45; Canon Inc., Tokyo; and TRC, Topcon Inc., Tokyo), centered on the optical disc. Retinal vascular caliber was measured with Integrative Vessel Analysis (IVAN) software according to a standardized protocol (Fig. 1).

Fig. 2 All patients underwent BS and 73 were followed up until the last visit



Patients were measured (Microbeam 04–116; Stanley Black & Decker, New Britain, CT, USA) and weighed (Model 703; CKSeca, Hamburg, Deutschland), for calculating BMI (weight/height² in kg/m²). BP and heart rate were measured. Standard blood test was performed and patients submitted a 24-h urine collection.

Echocardiography assessment of left ventricle morphology involved use of an Acuson 128 XP 10 system (Acuson, Mountain View, CA, USA). Pulse wave velocity (PWV) is the velocity of propagation, along an artery, of the pressure wave. It is directly related to the elastic modulus of the arterial wall and represents the most accessible noninvasive technique to assess arterial stiffness. The 2 velocity measures were carotid-femoral PWV and carotid-radial PWV. They

were measured with an applanation tonometer (SphygmoCor, AtCor Medical, Australia) after at least 5 min of rest and once BP had stabilized.

Statistical Analysis

Continuous variables are described with mean (standard deviation (SD)) and categorical variables with number (percentage); any missing data are indicated. Linear mixed regressions adjusted for age and sex were performed. $P < 0.05$ was considered statistically significant and all statistical tests were two-sided. Statistical analyses were performed with R 4.0.3 (Vienna, Austria).

Results

Results at Baseline (Table 1, Fig. 2)

In total, 90 patients were eligible and 88 were enrolled (one lacked consent and one declined surgery); 75 were women. The mean (SD) age was 43 (11) years and mean (SD) baseline weight 117 (21) kg. All patients underwent BS and 73 were followed up until the last visit (Fig. 2). The mean (SD) follow-up was 14.5 (2.5) months. The surgical method was Roux-en-Y gastric bypass in 4 (4%) patients, laparoscopic sleeve gastrectomy with preservation of the gastric antrum in 72 (82%) or without preservation in 12 (14%).

Effect of BS: Linear Mixed Regression (Table 2)

Mean changes during the first year after BS for retinal parameters were $-5.1 \mu\text{m}$ in CRVE ($p = 0.0005$) and $+0.02$ in AVR ($p < 0.0001$). CRAE did not significantly increase ($p = 0.32$).

Mean changes during the first year after BS for clinical variables were -48.1 kg in weight ($p < 0.0001$), -35.4 cm in waist circumference ($p < 0.0001$), and -4.0 mmHg in systolic BP ($p = 0.04$). Diastolic BP did not significantly change ($p = 0.70$).

Mean changes during the first year after BS for biological variables were -0.7% in HbA1c level ($p < 0.0001$), -4.5 in HOMA-IR ($p < 0.0001$), $-1.3 \mu\text{mol/L}$ in creatinemia ($p = 0.03$), -1.0 mg/L in ln(CRP) ($p < 0.0001$), -0.86 g/L in triglycerides level ($p < 0.0001$), and $+0.10$ g/L in high-density lipoprotein cholesterol ($p < 0.0001$). Estimated GFR and level of low-density lipoprotein (LDL) cholesterol changed without significance.

Mean changes during the first year after BS in macrovascular variables were -54.0 g in LVM ($p = 0.0005$) and -2.6% in RWT ($p = 0.002$). Central pulse BP, femoral PWV, and radial PWV did not change significantly.

Baseline Determinants of Change Over Time in Retinal Parameters (Tables 3 and 4)

The slope of CRVE over time was significantly associated with baseline weight ($p = 0.030$), waist circumference ($p = 0.017$), and absence of diabetes history ($p = 0.047$) and that of AVR over time was associated with baseline weight ($p = 0.013$). For example, a 10-kg higher

weight at inclusion was associated with greater decrease in CRVE, 1.3 $\mu\text{m}/\text{year}$. In people with diabetes, the CRVE did not decrease over time; the coefficient of the slope of the CRVE was + 3.54 and $- 5.06 \mu\text{m}/\text{year}$ for people with and without diabetes ($p = 0.047$).

We found no other significant association of potential predictors with the evolution kinetics of the retinal parameters, such as history of high BP (CRVE: $p = 0.72$; AVR: $p = 0.87$), sleep apnea syndrome (CRVE: $p = 0.50$; AVR: $p = 0.46$), diabetes for AVR (AVR: $p = 0.37$), and baseline eGFR (CRVE: $p = 0.64$; AVR: $p = 0.60$).

To find the relative contribution of factors associated with retinal microvascular changes (i.e., decrease in CRVE or increase in AVR), we performed the 2 multivariate linear mixed regressions presented in Table 3. A greater decrease slope in CRVE after BS was associated with the absence of diabetes history, obesity class 3, and male sex ($p < 0.001$, $p = 0.010$, $p = 0.025$, respectively).

Dynamic links between variations in retinal parameters and other variables were tested after BS (Appendix 2). A decrease in CRVE was correlated with an increase in eGFR ($r = - 0.29$, $p < 0.001$) and greater weight loss ($r = 0.29$, $p < 0.001$). As well, an increase in AVR was correlated with a greater weight loss ($r = - 0.21$, $p = 0.001$). We found no correlation between change in CRP level and change in CRVE ($r = 0.016$, $p = 0.81$).

Discussion

In this study of patients with obesity, we found a decrease in venous caliber (CRVE) and an increase in AVR after BS. The factors associated with decreased CRVE were pre-operative absence of diabetes and high body weight. High body weight before surgery was associated with increased AVR. Greater weight loss was associated with a greater increase in AVR and a greater decrease in CRVE. We observed no significant macrovascular changes except for a decrease in LVM and relative wall thickness.

Change in Retinal Caliber After BS

We found a decrease in the mean CRVE after BS (225.8 to 218.1 μm) at a median follow-up of 14.7 months. Some longitudinal studies have shown a significant decrease in CRVE after BS, the mean ranging from 202.9 to 197.3 μm at 6 months in 22 female patients with obesity [10], 220.5 to 214.8 μm at 10.5 months in 30 patients with obesity [9], and 223.8 to 211.9 μm at 10 months in 21 patients with obesity [8]. Our results agree with these northern European studies.

Other studies did not find a decrease in CRVE after BS: Streese et al. [13] did not find a decrease at 6 weeks (16 patients) or at 4 years (13 patients), but this result could be explained by the modest sample size. Brynskov et al. [12] did not find a decrease in 51 diabetic patients with obesity, but this observation agrees with our study because we reported that diabetic status was associated with no decrease in CRVE. The Brynskov et al. results and ours support the hypothesis of reduced retinal microvascular plasticity in people with diabetes.

Table 1 Baseline characteristics of participants (*n* = 88)

Clinical characteristics	
Age	43 (11)
Sex: male/female	13 (15)/75 (85)
Weight (kg)	117 (21)
BMI (kg/m ²)	44 (7)
Waist circumference (cm)	122 (14)
Smoking: never or past/current	61 (69)/27 (31)
BP: systolic/diastolic (mmHg)	124 (14)/69 (10)
Personal medical history	
Type 2 diabetes mellitus	24 (27)
High blood pressure	33 (38)
Hypercholesterolemia	28 (32)
Hypertriglyceridaemia	24 (27)
Biologic characteristics	
Glycemia (mmol/l)	6.5 (2.9)
Hba1c (%)	6.3 (1.4), 9
HOMA-IR (insulin resistance)	7.3 (6.8), 8
CRP (mg/l)	10 (8), 2
TG (g/l)	1.4 (0.8), 4
HDL (g/l)	0.47 (0.12), 4
LDL (g/l)	1.3 (0.3), 6
Glomerular filtration rate (ml/min/1.73 m ²)	113 (14)
Albuminuria to creatinine ratio (mg/mmol)	1.7 (3.1), 10
Microvascular features (retinal vessels)	
Central retinal artery equivalent (μm)	155 (15), 4
Central retinal vein equivalent (μm)	226 (23), 4
Arteriole-to-venule ratio	0.69 (0.06), 4
Macrovascular features	
Femoral pulse wave (m/s)	7.6 (1.8), 8
Radiale pulse wave (m/s)	8.3 (1.5), 4
Central pulse BP (mmHg)	44 (12), 1

Data are median (interquartile range) or *n* (%). If present, missing values are presented as “n”. BMI, body mass index; BP, blood pressure; Hba1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein

Our pathophysiologic hypothesis is that the decrease in CRVE after BS could be related to a decrease in CRP level even if we did not find a significant correlation between a decrease in CRVE and a decrease in CRP level, given the small number of patients. Indeed, Daien et al. [14] reported an association between CRP level and venous diameter in older people without obesity ($n = 1224$). An increase in CRVE in people with obesity is probably related to chronic inflammation after interleukin 6 (IL-6) production by adipokines stimulating CRP production [15]. This hypothesis agrees with the work of Tapp et al. [16] studying 8550 UK participants, finding a positive association between venular diameter and adiposity. In our study, the relatively small number of participants and the dispersal of values did not allow for confirming this hypothesis.

Concerning the predictors of improvement in venous caliber, we found that high pre-BS weight, class 3 (vs class 2) obesity, high waist circumference, and male sex were associated with greater slope of decrease over time in venous caliber. These factors may be predictive of other intermediate outcomes. For example, higher preoperative weight is associated with higher weight reduction and thus greater improvement in some obesity-associated comorbidities, such as dyslipidemia [17]. As for inflammation, a mediation study of the effect of metabolic parameters on the relation between pre-BS obesity class and retinal microvasculature would be of interest with a larger cohort.

The association of male sex with an improvement in venous caliber must be confirmed by other studies given the limited number of men in our study (13/88) and in other studies, obesity affecting mainly women.

We also found an increase from baseline in AVR after BS (0.69 vs 0.72), which is consistent with most studies [9, 10, 13]. Other studies did not find an increase in this ratio probably because of limited number of participants ($n = 30$ and $n = 21$) [8, 11].

We did not find an increase in CRAE after BS. This observation could be explained by a lower quality of the arteriolar caliber measurements in our study, with an inter-operator reproducibility of 0.66 ($p < 0.001$) for CRAE. In fact, the semi-automatic delineation of the arteries is complex because of not much caliber difference in color between the reddish retina and the arteries. This point underlines the reduced feasibility of measuring arteriolar caliber versus venular caliber in current practice.

Change in Biological Variables After BS

We observed an improvement in the lipid profile at 1 year after BS, with an increase in HDL level and a decrease in TG cholesterol level, which agrees with the literature [17]. We did not find a decrease in LDL cholesterol level as in the study of Cunha et al. [18], which had more than twice as many participants ($n = 229$). Our result can be explained by a reduced number of participants confirmed by the number of needed participants calculated post hoc ($n = 421$).

The improvement in the glycemic profile we noted is in accordance with the literature. In the meta-analysis of Buchwald et al., diabetes status improved or diabetes resolved in 86.6% of patients [19].

Table 2 Change in variables over time: mixed linear regression

Variable	Patients baseline	Patients 3rd visit	Beta coefficient (SE)* change per year/n	Adjusted P value*
	Mean (SEM)/n	Mean (SEM)/n		
Microvascular variables				
Central retinal vein equivalent (μm)	225.8 (2.5)/84	218.1 (2.8)/65	-5.06 (1.4)/87	0.0005
Central retinal artery equivalent (μm)	155.0 (1.7)/84	155.3 (2.1)/65	1.08 (1.08)/87	0.32
Arteriole-to-venule ratio	0.69 (0.007)/84	0.72 (0.008)/65	0.022 (0.005)/87	< 0.0001
Biologic variables				
Glycemia (mmol/l)	5.5 (0.3)/88	4.6 (1.0)/70	-1.37 (0.2)/88	< 0.0001
eGFR (ml/min/1.73 m ²)	109.4 (1.5)/88	110.6 (1.5)/71	0.44 (0.4)/88	0.30
Creatinemia ($\mu\text{mol/l}$)	65.0 (1.4)/88	64.0 (1.2)/71	-1.32 (0.6)/88	0.037
Log CRP	2.1 (0.1)/86	0.7 (0.1)/71	-1.00 (0.08)/88	< 0.0001
TG (g/l)	1.2 (0.08)/84	0.83 (0.04)/70	-0.86 (0.1)/88	< 0.0001
HDL (g/l)	0.46 (0.01)/84	0.57 (0.02)/69	0.10 (0.01)/88	< 0.0001
LDL (g/l) **	1.26 (0.03)/82	1.20 (0.04)/69	-0.03 (0.02)/88	0.21
Hba1c (%)	5.8 (0.2)/79	5.4 (0.06)/66	-0.66 (0.1)/88	< 0.0001
HOMA-IR (insulin resistance)	5.2 (0.8)/80	1.4 (0.1)/67	-4.53 (0.5)/88	< 0.0001
Log1p Albuminuria (mg/24 h)	1.7 (0.2)/68	1.7 (0.2)/41	-0.10 (0.1)/85	0.43
Log1p Albuminuria/creatinine (mg/mmol)	0.40 (0.08)/78	0.57 (0.07)/56	-0.06 (0.05)/85	0.27
Clinical variables				
Weight (kg)	111.2 (2.2)/88	82.0 (2.2)/73	-48.06 (4.5)/88	< 0.0001
BMI (kg/m ²)	42.0 (0.7)/88	31.0 (0.7)/73	-17.92 (1.8)/88	< 0.0001
Systolic BP (mmHg)	123.0 (1.5)/88	118.0 (1.8)/69	-4.04 (1.4)/88	0.003
Diastolic BP (mmHg)	67.5 (1.1)/88	69.0 (1.2)/72	0.37 (0.9)/88	0.70
Heart rate	73.0 (1.3)/88	62.0 (1.4)/62	-9.05 (1.4)/88	< 0.0001
Waist circumference (cm)	120.0 (1.5)/88	97.0 (1.8)/63	-35.41 (5.2)/88	< 0.0001
Macrovascular variables				
Left ventricular mass (g)	206.5 (6.3)/54	195.5 (6.6)/71	-54.03 (15.0)/84	0.0005
Relative wall thickness (%)	44 (1.1)/54	42 (0.9)/71	-2.6 (0.8)/84	0.002
Central pulse BP (mmHg)	44.0 (1.3)/87	45.0 (1.6)/72	1.48 (1.1)/88	0.17
Femoral pulse wave (m/s)	7.58 (0.20)/80	7.37 (0.20)/72	-0.22 (0.14)/87	0.14
Radial pulse wave (m/s)	8.34 (0.16)/84	8.23 (0.18)/72	-0.13 (0.16)/88	0.41

Characters are in bold if $p < 0.05$

*Model adjusted for sex and age at inclusion: P value, beta (time-dependent slope parameter). **A posteriori sample size calculation with a power of 90% estimated that we needed 421 participants to find a difference after BS in LDL cholesterol level. Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; Hba1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; RWT, relative wall thickness; SE, standard error; SEM, standard error of the mean; TG, triglycerides

We observed a significant decrease in creatinine level but no significant improvement in renal function (eGFR, albuminuria). In many studies, eGFR increased after BS only in patients with preoperative renal dysfunction ($< 90 \text{ mL/min}$) and remained stable when renal function was normal before BS [20]. In our study, only 4 patients had a mean eGFR $< 90 \text{ mL/min}$. The apparent discrepancy between a decrease in serum creatinine and no change in eGFR is probably due in part to the decrease in lean mass following bariatric surgery but also to the inaccuracy of serum creatinine-based formula to predict GFR in subjects with obesity [21].

Concomitant Changes in Clinical-Biological Variables and Retinal Caliber

This is the first study to investigate the relation between changes in clinico-biological variables and retinal parameters after BS. Even if eGFR did not change after BS, we observed a correlation between a decrease in CRVE and improvement in renal function. An association between CRVE and renal function had been shown in a cross-sectional observational study [19], but the longitudinal nature of our study suggests that improvement in retinal caliber over time may be associated with improved renal function. Further studies are needed to support this concept.

Table 3 Association between baseline covariates and time slope of arteriole-to-venule ratio (AVR) and central retinal vein equivalent (CRVE) ($n=87$)

Baseline variables	B coefficient of slope (SE)*	Adjusted <i>P</i> value**
CRVE		
Weight (per 10 kg)	- 1.32 (0.61)	0.030
Obesity class 3 vs 2***	- 6.00 (2.92)	0.040
Waist circumference (per 10 cm)	- 2.1 (0.86)	0.017
No diabetes history	- 8.60 (4.33)	0.047
Hypercholesterolemia history	5.76 (3.53)	0.10
AVR		
Weight (per 10 kg) ****	0.005 (0.002)	0.013
Waist circumference (per 10 cm)	0.005 (0.004)	0.103
Hypertriglyceridemia history	- 0.03 (0.02)	0.072

Characters are in bold if $p < 0.05$

*Covariate and time interaction, in $\mu\text{m}/\text{year}$. **Adjusted for age and sex. ***According World Health Organization classification, comparator = class 2. ****Obesity class 3 vs 2 was not significant. Only significant B coefficients $p < 0.20$ are presented to show the baseline covariates affecting the change in CRVE or AVR over time

Change in Macrovascular Variables

Studies have shown conflicting results regarding PWV; it has been reported to be decreased [22], unchanged [13], and even increased [23]. The most recent study published in 2021 [23] showed a paradoxical increase in arterial stiffness at 6 months after BS. In our study, PWV remained unchanged. In conclusion, the results concerning vascular stiffness after BS are discordant and physicians should interpret arterial stiffness measurements with caution.

The reduction in LVM after BS in our study (− 6.1%) is in accordance with Rider et al. [24] and Owan et al. [25] who reported a reduction of 14% and 13.6% respectively.

Strengths

The present study demonstrated decreased CRVE and increased AVR after BS. The use of a linear mixed model allowed us to consider the correlation between repeated measurements and the different evolutionary profile of individuals. This is the largest study evaluating retinal microcirculation after BS, with 88 patients versus 51 in the preceding largest study [12]. We assessed the determinants of retinal microvascular caliber changes after BS. The longitudinal nature of the study allowed us to develop pathophysiologic hypotheses based on these correlations.

Table 4 Multivariate linear mixed regressions: association between baseline covariates and time slope of CRVE and AVR ($n = 87$)

Baseline parameters	B coefficient of slope (SE)*	Adjusted <i>P</i> value
CRVE		
No diabetes history	− 10.32 (3.13)	< 0.001
Obesity class 3 vs 2**	− 7.30 (2.82)	0.010
Sex (male)	− 7.93 (3.55)	0.025
Age (per 10 years)	− 1.56 (1.20)	0.195
AVR		
Age (per 10 years)	− 3.57e-3 (5.68e-3)	0.529
Sex (male)	8.69e-3 (0.02)	0.564
Weight (per 10 kg)	− 3.19e-4 (3.24e-3)	0.922

Characters are in bold if $p < 0.05$

*Covariate and time interaction, in $\mu\text{m}/\text{year}$. **According world health classification

Limitations

Our study has some limitations, several results of the linear mixed models are significant, but some covariates measured closely related entities (weight, BMI, and waist circumference) and the magnitude of significant effect remains sometimes limited. The Spearman correlations are statistically significant but all are quite modest. Further studies are needed to confirm these correlations.

In order to keep the trend of the results, we did not decrease the significance level (set at $p < 0.05$) to account for multiple testing, which may increase the type I error rate. The significant results should therefore be interpreted in this context. In regard to our measurement instrument, we did not perform an analysis of vessel tortuosity, unlike Viljanen et al. [10] who found no change in tortuosity after BS.

We did not use optical coherence tomography angiography (OCTA), which is a very precise, rapid, and automatic measurement instrument for analyzing the retinal capillary network. Agarwal et al. [11] did use OCTA but did not observe any change in the retinal capillary network.

Lastly, the study sample size does not allow a detailed analysis of the physiological mechanism involved in the modifications of retinal microvasculature after BS.

Conclusions

Data for this cohort indicate that the retinal microvascular phenotype improved after BS, with a decrease in CRVE and increase in AVR. Predictors of retinal microvascular improvement were no diabetes history, male sex, and high baseline weight. The determinants and natural history of microvascular remodeling are still poorly understood. Our data suggest retinal vascular caliber offers new insights into the pathophysiology of subclinical vascular processes. Factors predictive of retinal microvascular improvement after BS need to be confirmed in other studies.

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Declarations

Ethics Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. **Informed Consent** Informed consent was obtained from all individual participants included in the study. **Conflict of Interest** The authors declare no competing interests.

References

1. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341(15):1097–105.
2. Must A, Spadano J, Coakley EH, et al. The disease burden associated with overweight and obesity. *JAMA*. 1999;282(16):1523–9.
3. Safar ME, Struijker-Boudier HAJ. New goals in hypertension management: target-organ protection beyond blood pressure lowering. *Drugs*. 2003;63 Spec No 1:45–7.

4. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357(8):753–61.
5. McGeechan K. Meta-analysis: retinal vessel caliber and risk for coronary heart disease. *Ann Intern Med.* 2009;151(6):404.
6. Wang JJ, Liew G, Klein R, et al. Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. *Eur Heart J.* 2007;28(16):1984–92.
7. Boillot A, Zoungas S, Mitchell P, et al. Obesity and the microvasculature: a systematic review and meta-analysis. *PLOS ONE* 2013 févr;8(2):e52708
8. Bachmayer C, Lammert A, Hasenberg T, et al. Healthy obese and post bariatric patients - metabolic and vascular patterns. *Exp Clin Endocrinol Diabetes.* 2013;121(8):483–7.
9. Lammert A, Hasenberg T, Kräupner C, et al. Improved arteriole-to-venule ratio of retinal vessels resulting from bariatric surgery. *Obesity.* 2012;20(11):2262–7.
10. Viljanen A, Soinio M, Cheung CY, et al. Effects of bariatric surgery on retinal microvascular architecture in obese patients. *Int J Obes.* 2019;43(9):1675–80.
11. Agarwal A, Saini A, Mahajan S, et al. Effect of weight loss on the retinochoroidal structural alterations among patients with exogenous obesity. *PLoS ONE.* 2020;15(7):e0235926.
12. Brynskov T, Laugesen CS, Floyd AK, et al. Thickening of inner retinal layers in the parafovea after bariatric surgery in patients with type 2 diabetes. *Acta Ophthalmol.* 2016;94(7):668–74.
13. Streese L, Königstein K, Goricki L, et al. Short- and long-term effects of bariatric surgery on vascular phenotype. *Obes Surg.* 2019;29(4):1301–8.
14. Daien V, Carriere I, Kawasaki R, et al. Retinal vascular caliber is associated with cardiovascular biomarkers of oxidative stress and inflammation: the POLA study. *PLoS ONE.* 2013;8(7):e71089.
15. Illán-Gómez F, González-Ortega M, Orea-Soler I, et al. Obesity and inflammation: change in adiponectin, C-reactive protein, tumour necrosis factor-alpha and interleukin-6 after bariatric surgery. *Obes Surg.* 2012;22(6):950–5.
16. Tapp RJ, Owen CG, Barman SA, et al. Retinal vascular tortuosity and diameter associations with adiposity and components of body composition. *Obesity (Silver Spring).* 2020;28(9):1750–60.
17. Nienov OH, Machado FD, Dias LS, et al. Effect of bariatric surgery on high-density lipoprotein (HDL) cholesterol in non-diabetic patients with severe obesity. *Obes Surg.* 2020;30(1):154–60.

18. Cunha FM, Oliveira J, Preto J, et al. The effect of bariatric surgery type on lipid profile: an age, sex, body mass index and excess weight loss matched study. *Obes Surg*. 2016;26(5):1041–7.
19. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248-256.e5.
20. Seghieri M, Vitolo E, Giannini L, et al. Determinants of glomerular filtration rate following bariatric surgery in individuals with severe, otherwise uncomplicated, obesity: an observational, prospective study. *Acta Diabetol*. 2017;54(6):593–8.
21. Fesler P, Mimran A. Estimation of glomerular filtration rate: what are the pitfalls? *Curr Hypertens Rep*. 2011;13(2):116–21.
22. Giudici A, Palombo C, Kozakova M, et al. Weight loss after bariatric surgery significantly improves carotid and cardiac function in apparently healthy people with morbid obesity. *Obes Surg*. 2020;30(10):3776–83.
23. Wang FM, Yang C, Tanaka H, et al. Increase in arterial stiffness measures after bariatric surgery. *Atherosclerosis*. 2021;320:19–23.
24. Rider OJ, Francis JM, Ali MK, et al. Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. *J Am Coll Cardiol*. 2009;54(8):718–26.
25. Owan T, Avelar E, Morley K, et al. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. *J Am Coll Cardiol*. 2011;57(6):732–9.

Appendix

Table 5

Table 5. Previous prospective studies evaluating CRVE, CRAB, AVR before and after bicuspid surgery (all non-coarcted)

Study	Region	Study site	Follow-up duration, months	Baseline age: Age, sex, BMI Mean (SD)	Statistical	Result 1	Result 2
Agarwal et al., 2010 [11]	India	20 obese patients 30 controls (as above)	3 months	Age: 33.62 (5.5) Sex: 47:21 BMI: 40.7 (10.1)	Univariate (CRVE, CRAB, AVR); Matched Wilcoxon, Wilcoxon Mantel-Haenszel or ST-CTH (P test)	No change AVR (not 0.06) No change of CRVE or CRAB	Increased CT (44.27 vs 29.10) No change PAZ, OCTA)
Baumgartner et al., 2013 [8]	Germany	21 obese patients	30 (2-6) months	Age: 46.5 (11.7) Sex - BMI: 49.6 (7.4)	Univariate; Mantel-Haenszel correlation regression	Increased CRVE (22.13 vs 21.91) no change for CRAB and AVR	No difference between MBO S and Me for CRVE, CRAB, AVR
Byrnes et al., 2016 [12]	Costa Rica	51 obese diabetes patients (31 no DM, 20 with DM)	1, 3, 6 and 12 months	Age: 46.07 Sex: 33:19 BMI: 41.06	Mixed model, symmetry correlation	Multi-variate analysis: Increased CRAB, no change for CRVE. Univariate analysis no change for CRVE, CRAB	No OCT, decreased max. thickness with peak at 6 months
Lemstra et al., 2013 [9]	Germany	38 obese patients	Pre-intervention (3.4)	Age: 45.3 (11.2) Sex: 19:11 BMI: 40.87 (4)	Univariate; Chi 2 Pearson	Increased CRAB (16.6 vs 17.59) and AVR (0.27 vs 0.41) Increased CRVE (23.03 vs 23.42)	No change for IMT
Stano et al., 2019 [13]	Switzerland	16 obese patients	6 weeks and 6 months (see 13)	Age: 44 (7) Sex: 13:3 BMI: 42.0 (4.4)	Univariate; Total mixed model; as paired measures	Baseline vs follow up: Increased CRAB (1.01 vs 1.00) (p=0.16) and IMC (1.49 vs 1.49) (p=0.99) No change for CRVE	No change for macrovascular (C-OT, M-OTV)
Vijayaraj et al., 2019 [10]	Poland	22 obese patients 13 controls (age matched)	6 months	Age: 45 (10) Sex: 23:0 BMI: 41.8 (10)	Univariate; T test and ANOVA in paired measures	Increased CRAB (1.8 vs 1.47), and AVR (0.67 vs 0.72) Increased CRVE (20.29 vs 19.3)	No change for brachial artery or total thickness

IMT, intima-media thickness (carotid); Me, metabolic syndrome; MBO S, metabolically healthy obese subjects; w, weeks; y, years

Appendix 2

Figure 3

Fig. 3 Correlation between change in clinical-biological variables and change in retinal parameters. Abbreviations: AVR, arteriole-to-venule ratio; CRVE, central retinal vein equivalent; CRAE, central retinal arteriolar equivalent

Retinal microvascular change (post BS - pre BS) :

