

# Endothelial Function in Obese Patients Treated with Bariatric Surgery

This article was published in the following Dove Press journal:  
*Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*

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**Purpose:** Bariatric surgery (BS) is becoming an increasingly frequent treatment option especially in people with morbid obesity, demonstrating that it is able to reduce total mortality and cardiovascular (CV) risk. Despite endothelial dysfunction is an essential requisite contributing to atherosclerosis and predicting CV events, only some studies have investigated the effects of BS on endothelial function with controversial results. In this study, the effects of weight loss on endothelial function were investigated in obese patients after BS and compared with patients after medical nutrition treatment (MNT).

**Patients and Methods:** Seventeen obese patients who underwent BS procedures (9 adjustable gastric bands, 3 gastric by-passes and 5 biliopancreatic diversions) were included in the study and compared with 18 obese individuals who underwent MNT. Endothelial function was investigated by flow-mediated dilation (FMD) of the brachial artery. Also, carotid intima-media thickness (c-IMT) was measured as a marker of subclinical atherosclerosis.

**Results:** At the end of follow-up, the mean weight loss was 18.8% in the BS group and 7.0% in the MNT group. After treatment, FMD significantly decreased in the BS group (mean  $\pm$  SD before:  $9.0 \pm 4.7$ ; after:  $6.1 \pm 2.9\%$ ;  $P=0.04$ ); however, no significant change was observed in the MNT group (before:  $9.4 \pm 5.8$ ; after:  $8.3 \pm 5.3$ ;  $P=0.41$ ). The modification of endothelial function was negatively correlated with c-IMT change in the BS group ( $r=-0.63$ ;  $P<0.007$ ).

**Conclusion:** A significant endothelial dysfunction occurred following BS but not after MNT. Furthermore, the decline of endothelial function observed in the BS group might have contributed to atherosclerosis.

**Keywords:** obesity, endothelial function, bariatric surgery, medical nutrition therapy

## Introduction

Obesity is a multifactorial disease that develops following a sufficiently prolonged period of time in which energy intake exceeds energy expenditure. Parallel to progressive urbanization, the prevalence of overweight/obesity is continuously rising<sup>1</sup> even among children and adolescents.<sup>2</sup> Therefore, obesity represents a real emergency in the Western world due to its association with many health problems among which reduced life expectancy,<sup>3</sup> compromised quality of life,<sup>4</sup> increased metabolic complications such as diabetes and cardiovascular (CV) morbidity and mortality.<sup>5</sup> The global burden of obesity is also associated with high costs and represents a serious threat to the sustainability of health systems.<sup>6</sup> Therefore, both effective preventive strategies and treatment approaches are urgently needed. At present, the gold standard for the treatment of obesity is medical nutrition treatment (MNT), based on a cognitive behavioral approach aimed at changing lifestyle with appropriate dietary habits and an adequate level of physical activity.<sup>7</sup> However, the

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MNT is often followed by frequent regain of weight loss especially in people with morbid obesity. In the latter cases, bariatric surgery (BS) is becoming an increasingly frequent treatment option. Despite its costs and possible side effects, BS is now acknowledged to be a relatively safe treatment that is more effective than MNT at least in terms of the amount of weight loss.<sup>8</sup> Although a large body of epidemiological evidence suggests the association between obesity and CV morbidity and mortality, it has not been definitively established that reducing body weight is associated with significant prevention of these outcomes, especially in the case of MNT. However, there is some evidence that BS reduces both CV mortality and CV events.<sup>8,9</sup> All conditions, including obesity, that are associated with increased CV risk are characterized by endothelial dysfunction<sup>10</sup> which is an established requisite condition for atherosclerosis.<sup>11</sup> Currently, the reference method for in-vivo investigation of endothelial function consists in measuring the ability of dilating the brachial artery after the stimulus of both hypoxia and increasing blood flow, namely flow-mediated dilation (FMD).<sup>12</sup> A large body of evidence has demonstrated that low FMD strongly predicts CV events.<sup>13</sup> To date, only few studies have investigated the effects of BS on endothelial function in terms of FMD demonstrating in general that FMD improves after BS.<sup>14</sup> However, some controversial results have also been reported and some studies have failed to confirm these conclusions.<sup>15–17</sup> Therefore, in this present study, we investigated the consequences of weight loss on endothelial function, measured as FMD, in obese patients with available data after BS who were compared with obese patients after MNT.

## Materials and Methods

### Participants

Seventeen obese patients were included in the study among those with available data who underwent BS procedures in the period from 2007 to 2012 at the Surgical Oncology Unit and at the Minimally Invasive Surgery Unit of the Policlinico “P. Giaccone” University Hospital in Palermo (Italy). Different BS procedures were performed according to SICOB guidelines:<sup>18</sup> 9 adjustable gastric banding (GB) procedures, 3 gastric by-passes (GBP) and 5 biliopancreatic diversions (BPD). These patients were compared with a group of 18 obese patients who in the same period were referred to the Laboratory of Metabolism and Clinical Nutrition of the Dipartimento Biomedico di Medicina

Interna e Specialistica (DIBIMIS; University of Palermo, Italy) for medical nutritional treatment (MNT) of obesity consisting in a hypocaloric diet [20 kcal/kg body weight of which: 55% carbohydrates, 25% fats (20% saturated, 65% monounsaturated and 15% polyunsaturated fats) and 20% proteins; the daily intakes of fibers and cholesterol were 30 g and  $\leq 250$  mg, respectively. No supplementation of vitamins, antioxidants or minerals was prescribed and general advice aiming at increasing the habitual level of physical activity. For both BS and MNT patients, inclusion criteria were age of 18–65 years, body mass index (BMI; body weight/height<sup>2</sup>)  $\geq 28.0$  kg/m<sup>2</sup> for MNT patients and  $\geq 35.0$  kg/m<sup>2</sup> for BS patients. Exclusion criteria were major complications following BS and significant comorbidities, including heart failure, coronary heart disease, stroke, chronic kidney disease, liver cirrhosis, chronic respiratory failure and diabetes under medical treatment (with the exclusion of metformin), pregnancy and lactation, lack of release of informed consent.

All participants were examined before (0–1 month) and after BS (6–24 months) or MNT (3–18 months). The assignment of the medical intervention was not at the discretion of the investigators and measurements performed were part of clinical procedures of the center. The institutional Ethics Committee (“Palermo 1” of the Policlinico “P. Giaccone” University Hospital) approved the study protocol. All participants accepted informed consent form.

### Anthropometric Measurements

All measurements were performed in the morning, after overnight fasting. Height and body weight were measured with subjects lightly dressed and without shoes. Fat mass (FM %) and fat-free mass (FFM, kg) body composition were measured by the Bioelectrical Impedance Analysis method (BIA-103, RJL, Detroit, MI, USA/Akern, Florence, Italy) following the manufacturer’s equations, as elsewhere described.<sup>19</sup> Body circumference (waist circumference) was measured at the umbilical level as a surrogate measure of visceral adipose tissue.

### Cardiovascular Measurement

Echographic scans of both extracranial carotid artery walls were performed with a high-resolution ultrasound 10-MHz linear array transducer (Sonoline G50; Siemens, Germany); the best longitudinal ultrasound scan was stored on digital support. Measurements of intima-media thickness (c-IMT) were later accomplished. The end-diastolic c-IMT of the far wall of right and left common carotid arteries was measured

as elsewhere described.<sup>20</sup> The mean value between both carotid c-IMT was calculated according to guidelines.<sup>21</sup> A trained operator performed all the ultrasonographic measurements. A 12-lead electrocardiogram was performed for each participant and the main parameters were obtained automatically using an integrated auto-diagnostic software (Esaote; Firenze, Italy); furthermore, the corrected QT interval for heart rate (QTc) was also evaluated.

## Endothelial Function

The endothelial function was evaluated through FMD measurement of the brachial artery. A high-resolution ultrasound linear probe (10 MHz, Sonoline G50; Siemens, Germany) was used. A stereotactic clamp with micrometer alignment (EDI Progetti e Sviluppo; Pisa, Italy) immobilized the probe during the test to guarantee image reliability. A sphygmomanometer was cuffed at 220–250 mmHg 2 cm below the antecubital fossa for 300 s to occlude the artery and establish reactive hyperemia. Twenty minutes later FMD measurement, 300 µg of sublingual glyceryl-trinitrate (GTN) was administered to evaluate endothelium-independent dilation. A real-time computed video-analysis of B-mode ultrasound images (FMD Studio; Institute of Physiology CNR; Pisa, Italy) recorded the brachial artery diameter variations. The diameter is detected with subpixel precision with a rate of 25 frames per second. The brachial artery diameters were represented on a graphical interface over a time scale of 9 min. The mean of the measures obtained during the first minute set the baseline vessel size. Both FMD and GTN were calculated as the maximum percentage increase of brachial artery diameter over baseline. These procedures are explained elsewhere.<sup>10,22</sup> All the FMD tests were performed by the same operator. A trained operator who was blinded to the participant's treatment classification performed all the ultrasonographic measurements. Our intra-observer coefficient of variation for FMD is 2.9%.

## Laboratory Analysis

All participants underwent blood sampling in the morning, after overnight fasting. Fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (Tg) and uric acid concentrations were measured using standard clinical chemistry methods (Glucose HK UV; Tot. cholesterol Mod P/D; HDL cholesterol gen 3 mod P/917; Triglycerides; Uric acid MOD P/917; Roche Diagnostics; Monza, Italy). Friedewald's equation was used to determine low-density lipoprotein (LDL) cholesterol serum.<sup>23</sup>

## Statistical Analysis

Data are reported as mean values  $\pm$  SD or as prevalence. The independent samples Student's *t*-test was used to compare the two groups; otherwise, Pearson's  $\chi^2$  test was used when appropriate. The effect of BS and MNT was assessed by paired samples Student's *t*-test. The simple linear regression coefficient *r* was calculated to study the correlations among variables. A two-tailed *P* value  $<0.05$  was considered significant. All analyses were performed with Systat (Windows version 11.0; San Jose, CA, USA).

## Results

A total of 35 patients (17 undergoing BS and 18 undergoing MNT) were selected. The demographic and clinical characteristics of the 2 groups are shown in Tables 1 and 2. The length of follow-up of the BS group was higher than that of the MNT group ( $P < 0.001$ ). The MNT group was older than the BS group ( $P = 0.01$ ), the BS group showed higher BMI ( $P < 0.001$ ), body weight ( $P < 0.001$ ), waist circumference ( $P < 0.001$ ) and FFM-kg ( $P < 0.001$ ) than the MNT group. The blood concentrations of FPG ( $P < 0.05$ ), TC ( $P < 0.05$ ) and LDL cholesterol ( $P < 0.05$ ) were higher in the MNT group than in the BS group. At the end of follow-up, the mean weight loss was 18.8% in the BS group and 7.0% in the MNT group. Pre-treatment FMD was not different between the groups ( $P = \text{NS}$ ); however, after treatment, FMD was significantly reduced in the BS group ( $P = 0.04$ ),

**Table 1** Characteristics of the Studied Groups

	<b>Bariatric Surgery</b> n = 17	<b>MNT</b> n = 18	<b>P<sup>a</sup></b>
Gender (males/females)	4/13	3/15	0.61
Age (years)	39.8 $\pm$ 10.4	48.7 $\pm$ 9.3	0.01
Smokers (%)	4 (23.5)	1 (5.6)	0.13
Type 2 diabetes (%)	2 (11.8)	0 (0)	0.13
Hypertension (%)	4 (23.5)	3 (16.7)	0.61
Participants on anti-diabetics (%)			
Metformin (%)	2 (11.8)	0 (0)	0.13
Participants on anti-hypertensives (%)			0.25
Diuretics (%)	1 (5.9)	0	
Beta-blockers (%)	3 (17.6)	0	
ACEI or ARBS (%)	3 (17.6)	0	
CCA (%)	3 (17.6)	0	

**Notes:** Data shown as mean  $\pm$  SD or n (%). <sup>a</sup>Student's *t*-test or  $\chi^2$  when appropriate.

**Abbreviations:** ACEI, angiotensin-converting enzyme inhibitors; ARBS, angiotensin receptor blockers; CCA, calcium channel antagonists; MNT, medical nutrition treatment.

**Table 2** Changes in Clinical and Physical Measurements After Surgical or Medical Treatment

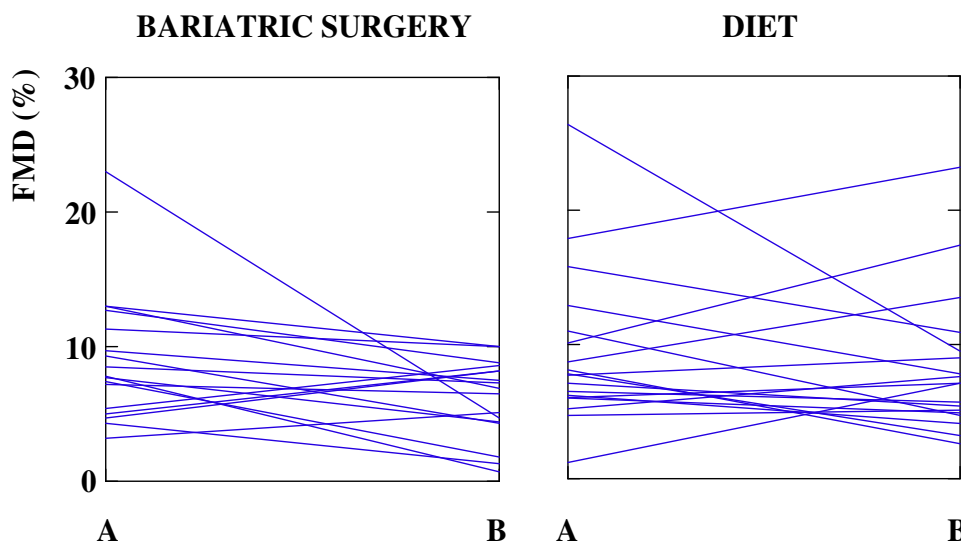
	Bariatric Surgery (n = 17)		P <sup>a</sup>	Diet (n = 18)		P <sup>a</sup>
	Before	After		Before	After	
Follow-up (months)		16 ± 8			9 ± 3*	
Body weight (kg)	137.0 ± 36.8	111.2 ± 29.5	< 0.001	92.0 ± 18.0*	85.6 ± 16.7	< 0.001
BMI (kg/m <sup>2</sup> )	50.4 ± 11.5	40.8 ± 8.8	< 0.001	35.4 ± 6.3*	33.0 ± 6.0	< 0.001
Waist circumference (cm)	139 ± 23	124 ± 20	< 0.001	109 ± 14*	105 ± 13	0.002
FM (%)	42.5 ± 4.8	39.9 ± 6.6	0.03	42.5 ± 8.3	40.4 ± 8.4	0.04
FFM (kg)	74.4 ± 17.2	64.3 ± 12.3	<0.001	56.1 ± 10.4*	51.0 ± 11.1	<0.001
Systolic BP (mm Hg)	134 ± 15	128 ± 12	0.19	131 ± 17	117 ± 10	0.01
Diastolic BP (mm Hg)	85 ± 11	84 ± 8	0.66	82 ± 10	77 ± 10	0.06
Heart rate (beats/min)	73 ± 10	67 ± 9	0.02	73 ± 8	67 ± 9	0.01
QTc interval (ms)	396 ± 17	400 ± 18	0.40	397 ± 16	391 ± 16	0.26
<b>Blood measurements:</b>						
Glucose (mg/dL)	89 ± 13	91 ± 9	0.85	103 ± 17**	94 ± 9	0.12
Cholesterol (mg/dL)	193 ± 40	191 ± 51	0.76	234 ± 49**	230 ± 55	0.57
HDL-cholesterol (mg/dL)	48 ± 12	53 ± 14	0.01	53 ± 16	51 ± 15	0.17
LDL-cholesterol (mg/dL)	117 ± 34	118 ± 42	0.72	149 ± 43**	155 ± 49	0.34
Triglycerides (mg/dL)	134 ± 48	99 ± 42	< 0.001	135 ± 54	122 ± 48	0.13
Uric acid (mg/dL)	5.1 ± 1.0	5.0 ± 0.9	0.38	4.8 ± 1.5	4.4 ± 1.3	0.55
Red blood cells (millions/mm <sup>3</sup> )	5.01 ± 0.42	4.65 ± 0.51	0.02	4.79 ± 0.49	4.75 ± 0.32	0.74
White blood cells (cells/mm <sup>3</sup> )	7765 ± 3820	7173 ± 1907	0.02	7864 ± 1595	7018 ± 1405	0.02
Hematocrit (%)	41.0 ± 3.7	40.2 ± 5.7	0.04	41.8 ± 2.5	41.3 ± 2.4	0.59
Carotid IMT (mm)	0.68 ± 0.22	0.70 ± 0.20	0.65	0.61 ± 0.16	0.63 ± 0.14	0.41
FMD (%)	9.0 ± 4.7	6.1 ± 2.9	0.04	9.4 ± 5.8	8.3 ± 5.3	0.41
GTN (%)	20.1 ± 7.4	22.2 ± 6.6	0.31	23.8 ± 5.1	23.1 ± 5.7	0.63

**Notes:** Data shown as mean ± SD. <sup>a</sup>Paired Student's t-test. \*P< 0.001 vs before bariatric surgery; \*\*P< 0.05 vs before bariatric surgery.

**Abbreviations:** BMI, body mass index; BP, blood pressure; FFM, fat-free mass; FM, fat mass; FMD, flow-mediated dilation of the brachial artery; GTN, glyceryl-trinitrate dilation of the brachial artery; HDL, high-density lipoproteins; IMT, intima-media thickness; LDL, low-density lipoproteins.

whereas no significant change was observed in the MNT group (P= 0.41) (Table 2 and Figure 1). Contrary to the average trend of FMD in the BS group, four patients of this

group (2 GBP and 2 BPD) exhibited a significant increase of FMD following the surgical procedure. Both studied groups had similar values of GTN and c-IMT. The change in

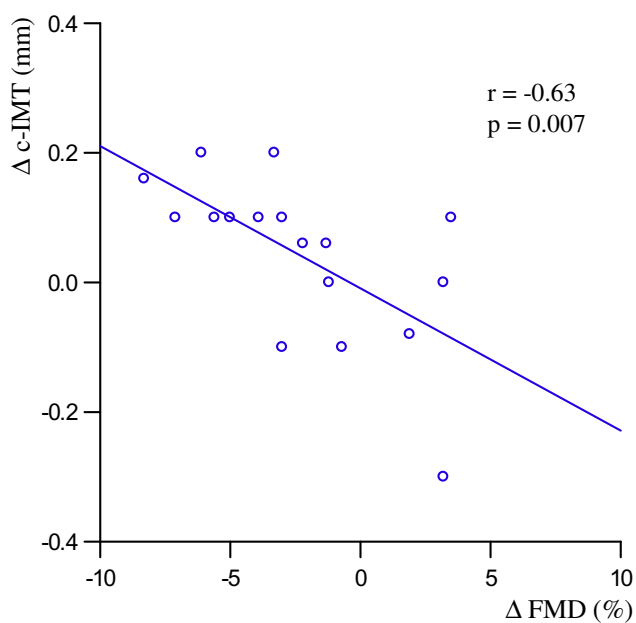


**Figure 1** Endothelial function (FMD) before (A) and after (B) surgical or dietary treatment in each patient.

endothelial function ( $\Delta$  FMD) was negatively correlated with c-IMT change ( $\Delta$  c-IMT) in the BS group ( $r = -0.63$ ;  $P < 0.007$ ; Figures 1 and 2).

## Discussion

In this study, a significant endothelial dysfunction, measured as FMD, generally occurred following BS to treat obesity. On the contrary, the FMD in obese patients did not change after MNT. Furthermore, the decline of endothelial function that we observed in the BS group might have contributed to atherosclerosis, as suggested by the significant inverse correlation between the change of FMD and that of carotid IMT. Our results generally disagree with the few available data according to which endothelial function improves following BS,<sup>14</sup> even though not sufficiently robust methods probably supported much of this evidence (Table 3). Williams et al observed a significant improvement in FMD following BS, but their study included only 8 patients undergoing GB, with a short-term follow-up of 6 months.<sup>24</sup> Another study by Saleh et al reported that FMD improved considerably following GBP in 47 individuals;<sup>25</sup> nevertheless, this study did not include a control group, the follow-up duration was just 10 months and the post-surgery FMD reached a very high value (18.9%) that is uncommon in clinical practice. Similar data were provided by Nerla et al who found that the FMD increased shortly after (3 months) surgical procedure.<sup>26</sup> In agreement with previous studies, Tschoner et al reported that



**Figure 2** Correlation between the change of endothelial function ( $\Delta$  FMD) and the change of carotid IMT ( $\Delta$  c-IMT) in patients treated with bariatric surgery.

BS was associated with an improved FMD in 52 individuals 5 years after the surgical procedure (mostly GBP);<sup>27</sup> however, no control group was included and the FMD was measured in a non-described subgroup of 36 patients. Bigornia et al demonstrated that FMD increased following weight loss but, unfortunately, they included both patients undergoing BS and MNT in the same cohort so that it was not possible to clearly demonstrate the efficacy of surgery.<sup>28</sup> Interestingly, Tarzia et al recently demonstrated, in a cohort of obese individuals undergoing BS, that the improvement in FMD first observed at 3 months was maintained even after follow-up at 4 years;<sup>29</sup> however, of the original sample of 50 patients, only 19 agreed to continue the long-term follow-up; thus, data regarding the remaining part of the cohort are missing. Furthermore, consistent with these results, three studies described a significant increase of FMD after the intervention.<sup>30–32</sup> These findings are supported in part by a meta-analysis, performed including 8 studies (269 patients) and that demonstrated an improvement of FMD after surgical treatment.<sup>14</sup> On the contrary, two studies investigating the role of BS in mediating the FMD response have not reported any change in follow-up at 1, 6 and 12 months after treatment.<sup>15,16</sup> Furthermore, Flores et al observed no improvement in endothelial function in a cohort of 33 individuals with obesity undergoing BS.<sup>17</sup>

Interestingly, there is no clear evidence that intentional weight loss with MNT in overweight or obese people is associated with a reduction in CV mortality risk.<sup>33</sup> Surprisingly, some epidemiologic studies have paradoxically shown that weight loss is associated with an increased incidence of cardiovascular events,<sup>34</sup> even in subjects who were overweight or obese at baseline.<sup>35,36</sup> On the contrary, despite some methodological limitations, it has been demonstrated, especially from the Swedish cohort of the SOS study, that bariatric surgery is associated with a significant reduction in the risk of both CV events and mortality.<sup>37</sup> Compromised endothelial function has been associated with unfavorable CV risk as well as with increased overall mortality risk.<sup>38</sup> Therefore, our results seem to be in agreement with an increased health risk at least in the nearly 2-year period following the surgical treatment of obesity. Interestingly, it should be observed that in the SOS cohort the benefits of BS became evident about 6 years after surgery, while in the first months a small but significant increase in fatal CV events was observed compared to the control group. On the other hand, CV events are a consequence of progressive vascular disease that develops over time, so it seems plausible that

Table 3 Studies That Investigated Endothelial Function in Patients Treated with Bariatric Surgery

Study	Cases (n)	Controls (n)	BMI (kg/m <sup>2</sup> )	Inclusion Criteria	Exclusion Criteria	Procedure	Exam	FMD (%)		Follow-Up
								Before Surgery	After Surgery	
Williams et al, <sup>24</sup> 2005	8	9	52.2 (50.3–55.9); median (IQR)	–	Cigarette smoking, diabetes, CKD	GB	FMD GTN	5.3 (3.8–7.0)	10.2 (7.6–13.3) (P = 0.01)	6 months
Surrin et al, <sup>30</sup> 2009	37	–	42.4 ± 3.9	BMI > 40.0 or >35.0 + comorbidities	Diabetes, hypertension, CVD, secondary obesity lipid lowering or antipsychotic medication, alcohol > 20 g/day	GBP (n=8) or GB (n=29)	FMD GTN c-IMT	5.8 ± 3.2	9.0 ± 2.9 (P < 0.001)	18 months
Lind et al, <sup>15</sup> 2009	19	19 (without obesity)	43.8 ± 3.1 cases 23.1 ± 2.0 controls	Caucasian individuals	ND	GBP	FMD PWV	7.9 ± 6.4	8.5 ± 6.2 (1 month) 9.3 ± 5.9 (1 year) (P = NS vs pre-surgical procedure)	1 year
Bigornia et al, <sup>28</sup> 2010	43 (17 BS + 26 diet)	–	45 ± 9	–	CKD, CHF, stroke	GBP or GB	FMD GTN	6.8 ± 4.2 (cases with weight loss n = 29, of which n = 17 BS)	10.0 ± 4.7 (P = 0.013 vs cases with no weight loss)	1 year
Brethauer et al, <sup>16</sup> 2011	15	–	48.1 ± 5.3	BMI > 40.0 or > 35.0 + comorbidities; age (18–75 years)	Diabetes, OSAS, Hypertension	GBP	FMD GTN	2.6 ± 2.0 (GTN 20.5 ± 6.7)	4.4 ± 3.4 (P = 0.21) (GTN 23.6 ± 6.4) (P = 0.047)	6 months
Saleh et al, <sup>25</sup> 2012	47	–	47.1 ± 5.5	BMI > 40.0, age (18–65 years)	Diabetes, use of thyroid hormones, CKD, CHF, atrial fibrillation	GBP	FMD GTN c-IMT	7.4 ± 5.8	18.9 ± 7.4 (P < 0.001)	10 months
Nerlia et al, <sup>26</sup> 2012	50	20 (no on diet)	47.1 ± 8.4	–	CKD, inflammatory bowel diseases, asthma, alcohol use disorder	GBP (n=47) or BPD (n=3)	FMD GTN	5.9 ± 2.7	8.8 ± 2.4 (P < 0.01)	3 months

Tschoner et al, <sup>27</sup> 2013	52 (36 assessed for FMD)	—	43.6 ± 4.9	BMI > 40.0 or >35.0 + comorbidities	Diabetes, CKD, hypertension, acute or chronic liver diseases, alcohol use disorder	GBP (n=42) or GB (n=10)	FMD c-IMT	5.2 ± 3.3	6.6 ± 3.4 (P= 0.001)	5 years
Flores et al, <sup>17</sup> 2014	33	—	45	Age 18–65 years, BMI >40.0 or >35.0 + comorbidities, normal renal function, hypertension on <3 medications	Secondary hypertension or established CVD	GBP (n=18) or sleeve gastrectomy (n=15)	FMD	9 ± 7	8 ± 6 (P= NS vs pre-surgical procedure)	1 year
Tromba et al, <sup>31</sup> 2017	45	—	44.3 ± 4.6	BMI >30.0–57.7	Diabetes and CVD	Sleeve gastrectomy	FMD c-IMT	3 (median value)	10 (median value, both at 3 and 6 months) (P= 0.001 3 months vs baseline; P= NS 6 months vs 3 months)	6 months
Tarzia et al, <sup>29</sup> 2017	19	—	47.7 ± 6.2	—	CKD, inflammatory bowel diseases, asthma, alcohol use disorder	GBP (n=18) or BPD (n=1)	FMD c-IMT	6.4 ± 2.8	9.5 ± 2.6 (3 months; P< 0.01) 8.2 ± 1.7 (4 years; P< 0.05) (overall P< 0.01)	4 years
de Assunção Machado et al, <sup>32</sup> 2018	56 (28 with OSAS and 28 without OSAS)	—	41.6 ± 3 (no OSAS) 43.2 ± 5.5 (OSAS)	Age ≥ 16 years, BMI > 40.0 or BMI >35.0 + comorbidities, with or without OSAS	Hyperthyroidism (TSH <0.01), neoplasms or immunosuppressive diseases, Cushing's syndrome or chronic use of corticosteroids, COPD, diabetic nephropathy, RA, diabetes, smokers, normal endothelial function	GBP	FMD GTN	3.4 ± 2.9 (no OSAS) 3.2 ± 2.2 (OSAS)	14.8 ± 4.6 (no OSAS) 11.1 ± 3.6 (OSAS) (P<0.001)	6 months

**Abbreviations:** BMI, body mass index; BPD, biliopancreatic diversion; CKD, chronic kidney disease; CHF, chronic heart failure; c-IMT, carotid intima-media thickness; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FMD, flow-mediated dilation; GB, adjustable gastric banding; GBP, gastric by-pass; GTN, glyceryl-trinitrate dilation of the brachial artery; ND, not determined; NS, not significant; OSAS, obstructive sleep apnea syndrome; PWV, pulse-wave velocity; RA, rheumatoid arthritis.

removing obesity-related risk factors takes a few years before reducing CV risk. We do not have a clear explanation for our results. Dietary factors and antioxidants in particular might have an important role in endothelial function. Antioxidants are, in fact, key factors in counteracting reactive oxygen species whose activation reduces endothelial nitric oxide bioavailability<sup>39</sup> and, therefore, normal endothelial function.<sup>40</sup> Nutritional deficiencies occur quite frequently following BS,<sup>41</sup> so, we cannot exclude that a paucity of micronutrients and antioxidants due either to reduced dietary intake or to post-surgery malabsorption may contribute to endothelial dysfunction. Should this be true, it would provide further evidence that nutritional deficiencies need to be promptly identified and treated after BS. In agreement with our results, a recent study observed that individuals undergoing GBP exhibited increased concentrations of several markers of both inflammation and oxidative stress even after 12 months of follow-up, in spite of vitamin supplementation.<sup>42</sup> Similar results were reported by Dadalt et al who observed both a significant decrease in antioxidant concentrations and high levels of inflammatory markers after GBP; they were also able to demonstrate that these values began to improve 2 years after surgery.<sup>43</sup> The average length of follow-up of the BS group was less than 2 years (16 months), so our findings may be due to a premature evaluation, before any improvement could be observed. Interestingly, the 4 cases of BS group in which we found improved FMD had a longer follow-up (18, 23, 23, 25 months). Furthermore, these 4 patients in whom endothelial function improved after BS underwent malabsorptive surgical procedures (2 GBP and 2 BPD). On the contrary, patients of the BS group that exhibited a decrease in FMD (n= 13) in most cases underwent GB (n= 9), a restrictive rather than malabsorptive procedure. Therefore, only about 30% of patients who did not obtain an improvement of endothelial function underwent a malabsorptive intervention. Despite the limited number of patients included in this study that do not allow subgroup analysis, our results might be at least in part explained by the fact that according to different studies endocrine, incretin-mediated effects characterize malabsorptive procedures and they probably induce favorable effects on endothelial function independently of weight loss.<sup>44</sup> Even more recently, it was reported in rats and in man that Roux-en-Y gastric bypass reverses obesity-induced endothelial dysfunction via GLP-1-mediated weight-independent mechanisms.<sup>45</sup> Unlike BS, MNT did not induce any change in FMD.

Noteworthy, before undergoing the procedure, neither the BS nor MNT group exhibited endothelial dysfunction. In fact, the pre-treatment mean FMD could be considered in the normal range; therefore, it seems plausible that the beneficial effects of MNT on endothelial function occur when FMD is markedly impaired or with specific nutritional treatments.<sup>22</sup>

This study has some important limitations. First, the number of patients enrolled is too small and does not allow definitive conclusions. Second, the two study groups differed for some physical characteristics such as age and the degree of obesity, two well-known factors that may influence endothelial function. Furthermore, the individual length of follow-up varied greatly between participants and groups, it was shorter in the MNT group than in the BS group. Also, the BS group was too heterogeneous according to the different types of surgical procedures, and this was another possible confounding factor. Indeed, we did not record any indicator of habitual physical activity, a well-known factor that may potentially influence endothelial function. Finally, we did not measure other biomarkers of oxidative stress or inflammation, vitamins and antioxidant concentrations; their evaluation might have allowed an in-depth interpretation of results. However, our study has also some points of strength. The presence of a control group allowed considering specific aspects of BS. The procedure used to measure FMD is more reliable and accurate than those used in the majority of other studies on this subject in past years; furthermore, a single operator performed all measurements of FMD and this contributed to enhancing the reproducibility of the results. There are many potential confounders when measuring FMD. These include dieting before/after surgery. In addition, ketosis may acutely influence FMD and it may easily occur in patients with morbid obesity; the different measurement techniques (especially those used in past years) may have significant reproducibility problems and the change in arm diameter may allow better measurements after surgery. Our study has the merit of having standardized all these factors at the best of current possibilities. Furthermore, despite a certain heterogeneity regarding follow-up length, the mean duration was one of the longest in studies available in the literature.

## Conclusion

Bariatric surgery is a safe and effective treatment for successful management of diabetes and obesity. However, there are still uncertainties about clinical outcomes that need to be

fully elucidated. Indeed, medical complications could follow BS, even after a long time, that might be potentially harmful and may require adequate nutritional follow-up. Therefore, in order to attain a better understanding of BS implications, well-controlled trials, with follow-up longer than 5 years, to assess specific issues in groups of accurately enrolled homogeneous individuals are warranted.

## Data Sharing Statement

The datasets analyzed in this study are available from the corresponding author Silvio Buscemi upon reasonable request.

## Ethics Approval and Consent to Participate

The study protocol was approved by the institutional Ethics Committee (“Palermo 1” of the Policlinico “P. Giaccone” University Hospital) and each participant signed a written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. SB took also the general responsibility and supervised the study project.

## Disclosure

The authors report no conflicts of interest in this work.

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