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CLINICAL RESEARCH

Body Weight Loss by Very-Low-Calorie Diet Program Improves Small Artery Reactive Hyperemia in Severely Obese Patients

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Abstract
Background Endothelial dysfunction is a major underlying mechanism for the elevated cardiovascular risk associated with increased body weight. We aimed to assess the impact of weight loss induced by an intensive very-low-calorie diet (VLCD) on arterial wall function in severely obese patients (SOP).
Methods Thirty-four SOP were admitted to the metabolic ward of the hospital for a 3-week period. A VLCD characterized by a liquid diet providing 800 kcal/day was administered. The small artery reactivity to postischemic hyperemia index (saRHI), a surrogate marker of endothelial function, was assessed before and 1 week after hospital discharge. Anthropometry and biochemical parameters were also measured. Obese and non-obese age- and gender-matched groups were recruited for baseline comparisons.
Results SOP had significantly lower saRHI compared with obese and non-obese individuals. SaRHI significantly increased after the intervention in SOP (1.595±0.236 vs. 1.737±0.417, p=0.015). A significant improvement in glucose (p=0.026), systolic blood pressure (p=0.049), LDLc (p< 0.001), and inflammatory parameters was observed. Body weight loss was associated with a higher saRHI (r=−0.385, p=0.033), and it was the main determinant of saRHI variation independently of confounders (β −0.049, IC 95 % −0.091–0.008, p=0.021).
Conclusions Weight loss induced by a VLCD in SOP improved small artery reactivity, and it was associated with the amelioration of metabolic and inflammation markers. Endothelial dysfunction may be softened by body weight loss interventions and useful in the management of cardiovascular risk factors in SOP.

Keywords Very-low-calorie diet · Small artery reactive hyperemia · Severe obesity · Body weight loss · Endothelial function

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Introduction

Obesity is an increasing public health concern because of consumption of high calorie diets and reduction in daily energy expenditure [1, 2]. There is an increase of both the prevalence and severity of obesity. Data from The Spanish Society for the Study of Obesity have shown that the prevalence of morbid obesity in Spain in 2007 was 0.3 % for men and 0.9 % for women [3]. This represents a serious public health concern because severe obesity is associated with a high burden of obesity-related morbidities, which include cardiovascular diseases and an increased overall mortality. A strong body of evidence has shown that human obesity is characterized by profound alterations in the

structure and function of large- and medium-sized arteries [4]. Interestingly, weight loss induced by diet, weight-lowering drugs, or surgery has been associated with endothelial function improvement as assessed by flow-mediated dilatation (FMD) in general obese and severely obese populations [5–8]. Although the FMD technique is a popular approach to measuring medium-sized artery wall function, its clinical use has not been generalized, which is mainly due to technical requirements [9]. The measurement of small artery reactive hyperemia index (saRHI), by peripheral artery tonometry (PAT), represents a novel clinical method to assess endothelial function. Although both FMD and saRHI are considered as surrogate markers of endothelial function, recent data suggest that they measure different aspects of arterial function, with PAT technique being more representative of small artery function [10]. Small arteries not only generate peripheral resistance and are of increasing interest in the coronary circulation but also are of particular significance in chronic renal disease and cerebrovascular disease of the white matter [11].

SaRHI has been associated with the presence of major cardiovascular risk factors [9]. We have described the impact of smoking, high-density lipoprotein cholesterol (HDLc), and waist circumference on saRHI [12]. In addition, we demonstrated that high adherence to healthy lifestyle advice is related to saRHI improvement after 1-year follow-up [13].

In severely obese patients (SOP) with comorbidities, bariatric surgery induces massive body weight loss, which is paralleled by a decrease in cardiovascular risk and endothelial function improvement as assessed by FMD. Apart from the impressive impact on type-2 diabetes (T2D) [14], other alterations like hypertension, dyslipidemia, obstructive sleep apnea, and metabolic syndromes are also ameliorated [15]. Very-low-calorie diets (VLCD) (800 kcal/day) have been used in SOP to provide a fast decrease in body weight when usual hypocaloric diets or drugs have failed. The beneficial effects of weight reduction by VLCD on different cardiovascular risk factors have been reported. The improvement of endothelial function as assessed by FMD of brachial arteries has also been documented [16, 17], although there is lacking information about the small artery function in SOP after a VLCD. In this study, we examined saRHI changes in SOP after losing weight during a 3-week VLCD intervention period while admitted to the hospital's metabolic ward.

Materials and Methods

Study Design, Patients, Clinical Assessment, and Intervention

This was a prospective and interventional study. Thirty-four severely obese subjects were recruited from the very-low-calorie diet program of the Dietetics and Nutrition Unit. The inclusion criterion was severe obesity, which was defined as a body mass index higher than 40 kg/m^2 or higher than 35 kg/m^2 with associated and uncontrolled comorbidities, such as T2D, hypertension, or dyslipidemia, with previously dietary and pharmacological treatment failure. Patients with either previous cardiovascular disease, chronic renal, hepatic, pulmonary and/or neurodegenerative problems, neoplasm antecedents, or other severe chronic diseases or who were unable to follow the diet or to remain hospitalized during the study were not included. Patients were admitted to the metabolic ward of the hospital for 3 weeks. After admission, a complete physical examination including anthropometry assessment (body weight, waist circumference, and blood pressure) and biochemical and vascular studies, including saRHI, was performed. Patients were put on a VLCD of 800 kcal/day for 3 weeks. During the admission period, all patients received food and nutritional education and a daily physical activity plan was implemented. To minimize a possible direct impact of very restrictive diet on vascular reactivity, final vascular assessment was performed 1 week after hospital discharge while patients were on a usual low-calorie maintenance diet. The patients were recalled for a new clinical and biochemical assessment and the saRHI study was repeated. The patients' usual pharmacological treatment was maintained. Age- and gender-matched obese and non-obese control groups were recruited for baseline comparisons. The study was approved by the hospital's ethics and clinical investigation committee. All subjects provided written informed consent.

Very-Low-Calorie Diet Program Characteristics

The VLCD (Optifast, Nestlé HealthCare Nutrition, Iberia) was administrated as a liquid solution for four meal replacements (200 kcal per meal), providing a total of 800 kcal/day. During the 3-week intervention period, the patients remained admitted in the metabolic unit under continuous medical and nurse surveillance. During weekends, the liquid solution diet was delivered to each patient with particular instructions to follow for treatment at their homes. The macronutrient profiles of the dietary intervention were 35 % of energy as protein (70 g protein/day), 45 % as carbohydrates, and 20 % as fat. The diet contains also almost 15 g of fiber per day and all of the micronutrients suggested by the required dietary allowances. After discharge from the hospital, patients were put on a hypocaloric Mediterranean-type diet (1,300–1,500 kcal).

Small Arteries Reactive Hyperemia Index and Arterial Stiffness Measurement

SaRHI was measured using peripheral artery tonometry (PAT) technology (EndoPAT- 2000, Itamar Medical Ltd.,

Israel). Determinations were performed in a quiet room with controlled temperature (22–24 °C) after the patients had fasted for 12 h and refrained from smoking or strenuous exercise for 24 h. The patients lay in a relaxed, quiet, and evenly illuminated environment and the device measured changes in pulse waves in the digital arteries. Blood flow measurements from two fingertips, one from each hand (test and control), were compared after a stabilization period, and a second comparison pair of measurements was taken before and after 5 min of brachial ischemia in one arm (the test arm). The results were processed by specific software to calculate the post-ischemia reflex vasodilatation observed when measurements from the test arm (before and after ischemia) were compared to those from the control arm. The value obtained was termed saRHI. The variability of this technique in our laboratory was 17 %, the intraclass correlation coefficient was 0.52, and the within-subject variation was 0.19. The sample size considering 80 % power to detect a difference between means of 0.08 with a level of significance (alpha) of 0.05 (two-tailed) was calculated regarding these conditions. The sample size required was 32 participants in each study group.

Arterial stiffness, measured as AIx, was also determined during the same exploration and processed by specific software to analyze the differences in pulse wave amplitude before and after ischemia in comparison to the control arm. We then calculated the AIx adjusted to 75 beats per minute (AIx@75).

Biochemical Determinations

Standard biochemical parameters were determined via the usual methods. Glucose, total cholesterol, triglycerides, apolipoprotein B100, apolipoprotein A1, direct low-density lipoprotein cholesterol (LDLc), HDLc, high-sensitivity C-reactive protein (hs-CRP), and non-essential fatty acids (NEFA) were measured using enzymatic and immunoturbidimetric assays (Spinreact, SA, Spain, and Wako Chemicals GmbH, Germany) adapted to a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Spain). sE-Selectin, vascular cell adhesion molecule 1, glycerol, and insulin were assessed using commercial ELISA kits (R&D Systems, Spain; Mercodia, Sweden; ZenBio, USA). Insulin resistance was estimated by the homeostasis model assessment (HOMA) index, which was calculated as fasting glucose (in mmol/L) multiplied by fasting insulin (in mlU/L) divided by 22.5 [18].

Statistical Analyses

Anthropometric, biochemical, and vascular data are presented as the mean ± SD or as the median and interquartile range for continuous variables and as frequencies for categorical ones. Differences between baseline study groups were assessed using an ANOVA or Kruskall–Wallis test for continuous variables or chi-square test for categorical ones. Differences between baseline and after-intervention data were assessed using Student's *t*-test or Wilcoxon test. Pearson's correlation was used to determinate the association between body weight loss and endothelial function improvement. Differences in saRHI improvement according to body weight loss were assessed using Wilcoxon's test. A multivariate stepwise linear regression model was performed to assess the modulators of saRHI. The dependent variable was saRHI, and the independent variables were body weight loss, decreases in systolic blood pressure, glucose improvement, LDLc improvement, hs-CRP improvement, and age. Statistical tests and corresponding *p*-values were two-sided, and SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Baseline demographic, anthropometry, biochemical, and vascular characteristics of SOP compared with those of the control group are shown in Table 1. No significant differences were observed in major cardiovascular risk factors. As expected, body weight and waist circumference were higher in SOP compared with other study groups.

Anthropometry, Biochemical, and Vascular Changes After Body Weight Loss by VCLD Intervention

Figure 1 shows baseline differences in saRHI according to each study group and the differences between before and post-intervention in SOP (1.595±0.263 to 1.737±0.417, $p=0.015$). The main biochemical and clinical determinants of cardiovascular risk factors were significantly decreased after the intervention. Body weight loss after the intervention was –6.1±3.3 kg ($p<0.001$), representing a mean reduction of 5.9 % of baseline. Waist circumference decreased by 5.2± 4.1 cm ($p<0.001$).Glucose levels decreased in 7.7 % ($p=0.026$), systolic blood pressure in 4.5 % ($p=0.049$), and LDLc in 12.7 % ($p<0.001$). Consequently, the global cardiovascular risk assessed by the Framingham risk score decreased significantly (−1±2, $p=0.033$). Interestingly, the main reductions were observed in insulinemia, glycerol, and NEFA with a decrease of 28, 25, and 20 %, respectively. Moreover, HOMA index and hs-CRP were also decreased by 19 and 16 %. We also observed a significant decrease in sE-selectin concentrations (44.1±14.5 vs. 36.4±12.2 ng/ml, $p<0.001$), representing 17.5 % of change (Table 2). There were no statistical differences in saRHI improvement or metabolic and inflammation markers when diabetic and non-diabetic patients were compared. We analyzed the impaired fasting glucose individuals ($n=6$) and we did not

Table 1 Baseline characteristics of study participants according to each study group

	SOP (n=34)	OB (n=34)	NOB (n=34)
Age, years	52±13	55±7	59±5
Gender, % women	68.6	71.5	67.6
T2DM, %	42.9	40.7	35.3
Dyslipidemia, %	45.7	52.9	47.1
Hypertension, %	74.3	86.1	76.5
Smoking, %	14.3	14.3	11.8
Body weight (kg)	120±26.3	80.8±17.3[a]	71.2±7.4[b]
BMI (kgm^{-2})	45.6±7.1	31.1±5.6[a]	27.1±2.1[b]
Waist circumference, cm	131±16	101±11[a]	92±7[b]
Systolic BP (mmHg)	135±17	139±21	135±18
LDL cholesterol (mmolL^{-1})	3.16±0.96	3.46±0.97	3.48±0.84
HDL cholesterol (mmolL^{-1})	1.43±0.28	1.49±0.35	1.5±0.46
Triglycerides (mmolL^{-1})[c, d]	1.54±0.74	3.51±4.43[a]	3.27±4.87[b]
Apolipoprotein B100 (mg dL^{-1})	1.04±0.23	1.21±0.21	1.05±0.33
Glucose (mmolL^{-1})	6.42±1.74	7.43±3.49	7.35±3.45

Compared with an ANOVA test or Kruskall–Wallis test for continuous variables or chi-square test for categorical ones. Values are given as the mean ± SE, median ± interquartile range, or percentage of patients

SOP severely obese patients, *OB* obese patients, *NOB* non-obese patients

[a] P-value<0.05 between SOP and obese group (OB)

[b] P-value<0.05 between SOP and non-obese group (NOB)

[c] Kruskall–Wallis test

[d] Median ± interquartile range

observe significant differences in saRHI changes between impaired fasting glucose individuals and those with normal glucose metabolism (0.117±0.05 vs 0.135±0.03, p=0.872).

Determinants of saRHI

In univariate test analysis, the saRHI were inversely associated with body weight loss (r=−0.385, p=0.033). Moreover, changes in saRHI were correlated with changes in sE-selectin (r=0.271, p=0.043). Multivariate stepwise linear regression analyses were performed to assess the main

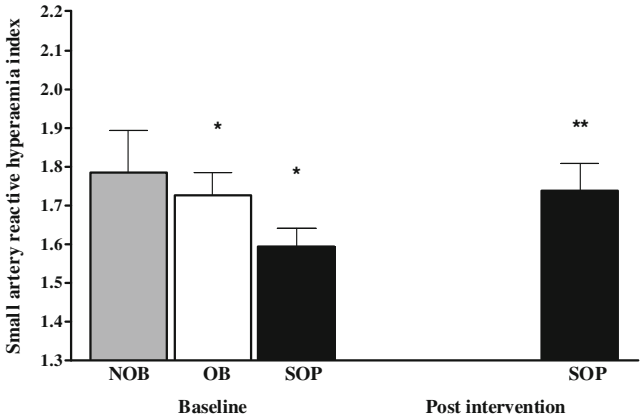

Fig. 1 Differences in saRHI according to baseline study groups and post-intervention in SOP. Baseline differences in small artery reactive hyperemia index (saRHI) according to each study group. Severely obese patients (*SOP*)=1.595±0.263; obese group (*OB*) (n=34) 1.747±0.454, p <0.05; non-obese group (*NOB*) (n=34) 1.784±0.638, p <0.05. Post-intervention differences in SOP; 1.595±0.263 to 1.737±0.417, p= 0.015. *P-value <0.05 between saRHI in SOP compared with other study groups. **P-value <0.05 between saRHI in SOP before and post-intervention. Data obtained with Kruskall–Wallis test and Wilcoxon test. Values are expressed as the median ± interquartile range

Table 2 Antrophometry, biochemical, and vascular changes after follow-up in SOP

	SOP (n=34)	P value[a]
Body weight (kg)	−6.1±3.3	<0.001
BMI (kgm^{-2})	−2.68±1.09	<0.001
Waist circumference, cm	−5.2±4.1	<0.001
Systolic BP (mmHg)	−6±2	0.049
LDL cholesterol (mmolL^{-1})	−0.44±0.57	<0.001
HDL cholesterol (mmolL^{-1})	−0.14±0.18	<0.001
Triglycerides (mmolL^{-1})[b, c]	−0.18±0.46	0.024
Apolipoprotein B100 (mg dL^{-1})	−0.13±0.16	<0.001
Glucose (mmolL^{-1})	−0.47±1.04	0.026
Insulin (mlU/L)	−5.3±5.5	0.009
HOMA-index	−1.3±2.2	0.012
NEFA (umol/L)	−158±234	0.001
Glycerol (umol/L)	−23.3±−43.3	0.004
Framingham risk score (%)	−1±2	0.033
Hs CRP (mg/L)	−1.07±2.54	0.009
E-Selectin (ng/mL)	−8.84±7.41	<0.001
VCAM (mg/mL)[b, c]	32±119	NS
saRHI	0.139±0.03	0.015
AIx@75[b, c]	1.23±0.55	NS

Values are given as the mean ± SE and/or median ± interquartile range

HOMA-index homeostasis model assessment index, *NEFA* non-essential fatty acids, *Hs-CRP* high-sensitivity C-reactive protein, *VCAM-1* vascular cell adhesion molecule 1, *saRHI* small artery reactive hyperemia index, *AIx@75* augmentation index adjusted to 75 bpm

[a] Baseline compared with after the intervention with a paired t-test or Wilcoxon test for continuous variables

[b] Wilcoxon test

[c] Median ± interquartile range

predictors of endothelial function using saRHI as a dependent variable. The independent variables included body weight loss, decreases in waist circumference, decreases in systolic blood pressure, glucose and LDLc improvement, hs-CRP improvement, and age. After adjusting for interactions, the best predictor model included body weight loss and decreases in systolic blood pressure. When this model was forced, body weight loss (β −0.049, IC 95 % −0.091−0.008, p=0.021) remained an independent predictor of saRHI. A trend of significance was observed in systolic blood pressure decrease (β −0.008, IC 95 % −0.016–0.000, p=0.06) (Fig. 2).

Discussion

This study aimed to assess the small artery reactivity by PAT in a group of SOP following a VLCD program. Our main observation was that, after the intervention period, the saRHI was significantly improved, and this reduction was inversely associated with weight loss. In fact, weight loss was the main determinant of the final saRHI according to a multivariate test. Although the impact of weight loss on endothelial function has been already documented [6, 8, 19], our results show the acute benefits of body weight loss by a liquid VLCD on small artery reactivity in SOP. This aspect is interesting because previously available data regarding endothelial function improvement after weight loss in SOP are focused on the effect of bariatric surgery [7, 20] or pharmacological interventions [8]. The impact of body weight loss by a VLCD on endothelial function has only been evaluated in overweight or obese patients with or without cardiovascular risk factors [21, 22], and these studies were performed using the brachial FMD method. We confirm these data and extend them to SOP using the PAT method.

Our data support the outcome that peripheral vascular reactivity is immediately modified after reducing body weight. By measuring the saRHI at 1 week after hospital discharge, we minimized the impact of a very restrictive intake on vascular tone.

It is difficult to define the mechanisms associated with the change in peripheral arterial reactivity observed, although it has been demonstrated that nitric oxide is the main determinant of saRHI. Previous work from our group has shown that different metabolites, including HDLc and apolipoprotein A1, are directly associated to saRHI [12]. In the present study, changes in saRHI cannot be attributed to these lipid changes because HDLc and apolipoprotein A1 were significantly reduced, reinforcing the strong impact of weight loss on vascular reactivity. In addition, we previously observed that the concentrations of sE-selectin, which is a plasma endothelial function biomarker, are inversely associated with saRHI [23]. In this study, sE-selectin decreased significantly after body weight loss by a VLCD, thereby reinforcing this association.

Changes in glucose, lipid metabolism, and inflammation parameters, secondary to body weight loss, were so generalized that it is difficult to attribute the observed effects on saRHI to a single modification. It is well known that NO bioavailability is dependent on insulin resistance and inflammatory status [24]. Accordingly, in our group of patients, a clear improvement of insulin sensitivity parameters was observed, including glycemia, insulinemia, HOMA index, and NEFA concentrations, which are considered to have a direct deleterious effect on artery wall biology. The subclinical inflammatory state of obesity has also been considered as a causal mechanism of endothelial dysfunction in this setting [25]. In this respect, the improvement in hsCRP levels after intervention has to be taken into account to explain the impact on vascular function.

Another factor associated with body weight loss was a decrease in systolic blood pressure and thus with saRHI improvement. This association was unexpected because several reports, including ours, suggest a paradoxical direct association between blood pressure and saRHI [13, 26]. Other studies have already demonstrated that low-energy diets diminish blood pressure, which is probably mediated by both insulin and norepinephrine decreases along with a reduction in the sympathetic neural system tone [27, 28]. According to these data, the Landsberg's hypothesis supports that insulin

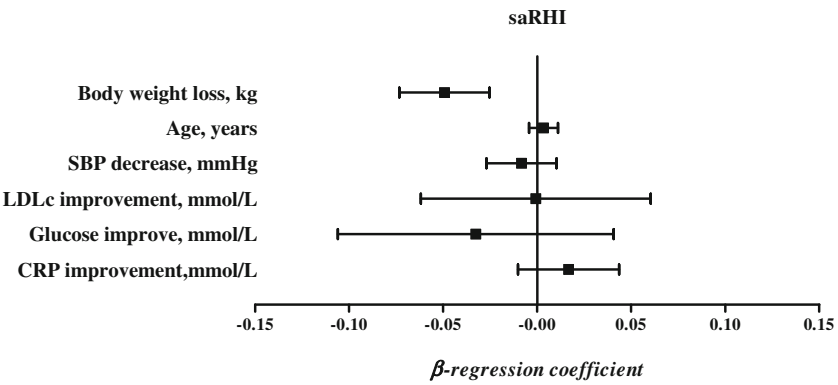

Fig. 2 Determinants of saRHI improvement in SOP. Multivariate stepwise linear regression test. Dependent variable: saRHI; independent variables: body weight loss, decreases in systolic blood pressure, glucose improvement, LDLc improvement, CRP improvement, and age. Durbin–Watson=2.345, R^2=0.499

resistance in obese subjects is a component of a complex physiologic response aimed at limiting weight gain via sympathetic stimulation which, in turn, increases systolic blood pressure and energy expenditure [29]. Interestingly, the sympathetic system seems to be one of the main determinants of small artery reactivity. Moreover, nitric oxide plays a physiological role in adipose tissue vascular bed and it is increased by body weight loss [30]. This effect could explain the better insulin sensitivity that is also observed in our study.

Our study has several limitations, and one of them is sample size. The sample size was calculated according to the saRHI determination variability. However, the type of patients included and the nature of the intervention, requiring 3 weeks of hospital admission, curtailed the recruitment numbers. Nevertheless, the prospective nature of our study and the robustness of these results lower the potential effect of this limitation. The aim of our study was to observe differences in saRHI after an acute weight loss induced by VLCD. In our unit, this type of intervention is exclusively addressed to severely obese patients who require a fast reduction on weight because of uncontrolled comorbidities such as T2D, hypertension, or dyslipidemia with previously dietary and phramacological tretament failure. For these reasons, in the present study, there are no longitudinal long-term data available. Our patients lost about 6 % of body weight, thereby remaining severely obese. Thus, we could not analyze the impact of normalizing weight on saRHI. However, we confirmed that these relatively small changes in weight were associated with clear metabolic and vascular benefits, which encourages the pursuit of any level of weight loss among obese/overweight patients. We appraised the reactivity of distal arteries as a surrogate marker of endothelial function. This measure is only homologated in USA, although PAT technique has been increasingly used, and there is an increasing amount of evidence supporting its clinical application. On the other hand, the assessment of small artery reactivity has an important value in itself.

In conclusion, body weight loss with a very-low-calorie diet program in a group of severely obese patients improves small artery reactivity, thereby suggesting an improvement in endothelial function. The determinants of this result are probably an aggregate of metabolic, inflammation, and vascular effects associated with weight loss. saRHI improvement after body weight loss by VLCD program may be of benefit on cardiovascular risk in SOP. Large and prospective studies are warranted to study the longitudinal effects of weight loss on saRHI in morbidity and mortality.

Conflict of Interest There was no funding or external support for this study. All contributing authors declare that they have no conflicts of interest.

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