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Post-prandial endothelial dysfunction is ameliorated following weight loss in obese premenopausal women

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
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Summary

Background: Endothelial dysfunction and postprandial hyperglycemia represent independent risk factors for cardiovascular diseases. Obesity is connected with endothelial impairments; however, it is unclear whether weight loss can modify endothelial function during the postprandial period. The aim of this study was to evaluate endothelial response (post-ischemic forearm blood flow, PIFBF) in a fasted state and following ingestion of 75g glucose before and after very low caloric diet (VLCD).

Material/Methods: 40 obese premenopausal women (age 39.6±7.8 years, BMI 34.3±3.2 kg/m^2) participated in 4-week very low caloric diet (VLCD, 800kcal/day). Before and after VLCD, the baseline blood flow and PIFBF were measured using a mercury strain gauge plethysmography in fasting state as well as 1 hour after ingestion of 75 g glucose.

Results: Dietary intervention resulted in a 7% weight loss ($p<0.05$) and a decrease in insulin resistance index HOMA-IR (2.44±1.25 *vs.* 1.66±0.81, $p<0.05$). Before VLCD intervention, PIFBF following oral glucose challenge decreased by 8.2±9.1 ml/min/100 g tissue, while after weight loss identical stimulus increased PIFBF by 4.2±8.9 ml/min/100 g tissue ($p<0.05$). Plasma ICAM-1 and VCAM-1 decreased by 8% and 10%, respectively, throughout the study.

Conclusions: Postprandial endothelial dysfunction is ameliorated following weight loss in obese women. This finding demonstrates the beneficial effects of weight reduction on atherosclerosis risk.

key words: endothelial dysfunction • weight loss • very low caloric diet • obesity • plethysmography

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Background

Excessive adipose tissue accumulation, especially in an abdominal region, represents a major risk factor for cardiovascular, cerebrovascular and metabolic diseases including type 2 diabetes and is connected with increased mortality [1,2]. Several candidate mechanisms have been identified connecting obesity and increased risk of atherosclerosis, such as production of pro-inflammatory cytokines, increased free fatty acid release from adipose tissue, oxidative stress and endothelial dysfunction [3,4].

Endothelial dysfunction expressed as a reduced response of the endothelium to pharmacological as well physiological stimuli contributes to elevated cardiovascular mortality, glucose intolerance, insulin resistance and type 2 diabetes [5]. Furthermore, postprandial hyperglycemia was shown to compromise endothelial function in healthy subjects, but this impairment is more pronounced in obese individuals [6] and type 2 diabetes patients [7].

Dynamic changes in endothelial function *in vivo* can be evaluated non-invasively by measurement of the forearm blood flow and its changes using a venous occlusion plethysmography method which has been extensively employed to evaluate the endothelial function in a fasted [8,9] and a postprandial state [8].

Lifestyle modifications including exercise- and diet-induced weight loss are major interventions used for obesity management. It has been shown previously that weight loss improves fasting endothelial functions in obese subjects [10–19], but the impact of weight loss on postprandial endothelial function has not been clarified.

In this study we investigated whether acute weight loss induced by very low caloric diet modifies post-prandial endothelial function in obese premenopausal women. We hypothesized that post-prandial endothelial function would be improved following the dietary intervention.

Material and Methods

Study population

Forty obese premenopausal women (age 39.6±7.8 years, BMI 34.3±3.2 kg/m^2) participated in the study. Subjects were recruited from March to September 2007 by referral from collaborating obesity units and other physicians, self-referral and through an advertisement in the local media. Obesity was defined as BMI ⩾30 kg/m^2, according to WHO criteria. All the women were physically examined by a physician prior to the beginning of the study. None of the women had a history of any chronic disease except obesity and all were free of any medication and were non-smokers. Pregnancy was excluded at the beginning of the study and the dietary intervention was targeted to start within the 2nd–3rd weeks of their individual menstrual cycle. All participants had blood pressure below 135/80 mmHg. The subjects had stable body weight for at least 3 months prior to the beginning of the study. Each participant gave written informed consent before starting the study. All aspects of the study were performed in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the Third Faculty of Medicine, Charles University (Prague, Czech Republic).

Clinical protocol

The subjects were investigated before the beginning of and after 4 weeks of a very low caloric diet. All investigations were done at 8.00 a.m. after an overnight fast in an out-patient research center. Body weight and waist and hip circumference were measured, and body composition was assessed using the multi-frequency bioimpedance method (Bodystat, Quad scan 4000, Isle of Man, UK). Coefficients of variation (CV) of fat mass and fat-free mass measurements were 1.7% and 0.8%, respectively. Blood samples for plasma analyses were collected from an indwelling polyethylene catheter inserted into the antecubital vein. After the collection, blood was processed immediately in a refrigerated centrifuge. The plasma was stored at –80°C until analysis. An oral glucose tolerance test (oGTT) was performed in 17 subjects before and after the VLCD with 75g of glucose dissolved in 250ml of tea and followed by ingestion of an additional 250 ml of water. The plasma was obtained for glucose and insulin measurements at baseline and at 1 and 2 hours after the glucose administration.

Forearm blood flow measurements

A venous occlusion plethysmography method was used according to a validated protocol [20]. Subjects were acclimatized in a quiet examination room for 30 minutes in a horizontal position. The forearm of the non-dominant limb was supported by soft padding to achieve a position slightly above the level of the heart. A mercury strain gauge of adequate length was placed around the non-dominant forearm at the point representing approximately the proximal 2/3 of the distance between the olecranon and the tip of the middle finger. The forearm circumference at this point was determined for subsequent calculations and same size mercury gauge was used for all measurements in the particular subject. The venous-occlusive cuff was placed around the arm and connected with a Rapid Cuff Inflator (Hokanson Inc., Bellevue, Washington, USA) computer-operated inflation valve. Because circulation in the hand (palmar circulation) contains multiple arterio-venous shunts that would impede the plethysmography measurements in the forearm, the hand region needed to be excluded from circulation. This was achieved using the inflatable cuff which was positioned around the wrist and inflated to a pressure of 200 mmHg throughout the whole measurement procedure. The arterial forearm blood flow (FBF) was registered by a TL400 Strain Gauge Plethysmograph (Hokanson Inc., Bellevue, Washington, USA) at baseline (pre-ischemic) and following 5 minutes of forearm ischemia. Pre-ischemic data were obtained as follows: the venous-occlusive cuff placed around the humerus was inflated to a pressure of 40mm Hg and plethysmography values were recorded for 1 second. Subsequently, the venous-occlusive cuff was deflated. This procedure was repeated 15 times with 10-second intervals between individual cuff inflations. Following baseline measurements, forearm ischemia was induced for 5 minutes by inflating the occlusive cuff to a pressure 40mmHg higher than the actual arterial pressure. At the end of this ischemic period, the cuff was rapidly deflated and post-ischemic forearm blood flow (PIFBF) measurements were performed in

the same way as described for baseline FBF (ie, venous-occlusive cuff is inflated to the pressure of 40 mmHg for 15 seconds when data are registered; procedure is repeated 15 times with 10-second breaks between every inflation).

The whole procedure consisting of measuring pre-ischemic and post-ischemic forearm blood flow was repeated 60 minutes after the ingestion of 75 g of glucose at the beginning of the study and after VLCD.

Dietary intervention

The dietary intervention consisted of 4 weeks of very low caloric diet (VLCD). The VLCD was a cocktail-based commercially available diet (Redita, Promil, Czech Republic) providing 600 kcal/day in 4–5 liquid portions per day in the form of a soup (vegetable, tomato, peas, mushroom) or as cocktails (chocolate, raspberry, cappuccino, nougat). The average macronutrient composition of this liquid diet was as follows: 30% of caloric intake delivery in proteins, 60% in carbohydrates and 10% in fats. Additionally, subjects were instructed to eat up to 200 kcal/day of vegetables. Subjects were individually followed-up each week by an obesity specialist, who reinforced dietary recommendations, gave psychological support and discussed compliance with each subject. Telephone consultations with investigators and a nutritionist were available during the whole intervention. All subjects were instructed to follow their habitual patterns of physical activity during the study. A 3-day food record (2 weekdays and 1 weekend day) was obtained from each participant and checked before the study and each week during the study. The dietary records were analyzed using a country-specific food-nutrient database (NutriDan 1.2. Mullerova D., Tychtl Z., Muller L., Brazdova Z., 2002, produced in cooperation with Danone Institute, distributed by DADI s.r.o., Plzen, Czech Republic). All the subjects finished the study, and based on follow-up interviews with the study dietitian their compliance with the diet was satisfactory.

Analytical methods

Plasma glucose was determined using a glucose-oxidase technique (Beckman Instruments, Fullerton, CA). Plasma insulin concentration was measured using an Insulin RIA kit (Immunotech, Prague, Czech Republic) (coefficient of variability 2.8% - 4%). Plasma levels of ICAM-1 and VCAM-1 were measured using a commercially available ELISA kit (R&D Systems)

Statistical analysis

Statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL). The changes in outcome variables were assessed using Student's T test. Blood flow values are presented both as non-adjusted data and after adjustment for plasma free fatty acids and insulin levels, as these were identified in a regression analysis as confounding factors, and pair-wise comparisons were performed using the F-test (General Linear Model). Correlations were analyzed using the Pearson's correlation test. The weigh-loss-induced differences in post-prandial/fasting PIFBF ratio were tested by Student's T test after angular (arcsine) transformation. The HOMA index (Homeostasis Model Assessment index) was computed following the equation: $((\text{fasting glucose}_{(\text{mmol/l})} * \text{fasting insulin}_{(\text{uIU/ml})})/22.5)$. Data are presented as mean values ±SD unless stated otherwise. A level of $p \leq 0.05$ was considered statistically significant in all tests.

Results

Anthropometric and biochemical variables

The dietary intervention resulted in a 7% weight loss during the VLCD phase. Fasting plasma glucose remained unchanged during the study while fasting plasma insulin levels and HOMA dropped by 28% and 32%, respectively, following the weight loss. Following the dietary intervention, circulating levels of ICAM and VCAM decreased by 8% and 10%, respectively. Diet-induced changes in anthropometric and biochemical variables are shown in Tables 1 and 2.

Forearm blood-flow

The basal forearm blood flow as well as fasting PIFBF remained unchanged during the VLCD intervention in the adjusted model, while the non-adjusted data show that basal fasting FBF decreased following the dietary intervention. Oral glucose load reduced PIFBF by 8.2 ml/min/100 ml tissue before the dietary intervention but increased by 4.2 ml/min/100ml tissue after the dietary intervention in the adjusted model, and similar responses were observed using non-adjusted data. The change in PIFBF (expressed either as absolute change [ΔPIFBF] or as a ratio [$\text{PIFBF}_{\text{glucose/fasted}}$]) was significantly different before (decreased) versus after weight loss (no change or increased) in non-adjusted and adjusted models, respectively. Data are summarized in Table 3.

Determinants of forearm blood flow

At the beginning of the study, the fasting basal forearm blood flow was negatively associated with adiposity and positively associated with percentage of body fat-free mass (r=-0.42 and r=0.42, respectively, both p=0.049). Insulin resistance evaluated by a HOMA-IR index was positively associated with basal FBF ($r = 0.606$, $p < 0.02$) and postprandial post-ischemic FBF was closely associated with glucose levels at the 60th minute of oGTT, after adjustment for adiposity (r=0.844, p=0.008).

Following VLCD, the postprandial PIFBF was closely associated with a HOMA-IR index (r=0.685, p=0.042), mostly due to an association with plasma levels of insulin (r=0.677, p=0.045), after adjustment for adiposity; however, no association between changes in PIFBF and changes in HOMA-IR was observed.

Discussion

In the present study we have shown that acute glucose intake decreased post-ischemic forearm blood flow (PIFBF) in obese women and that this effect can be reversed by acute weight loss. This finding of functional improvement in endothelial function is further supported by a decrease in plasma levels of endothelial adhesion molecules ICAM-1 and ICAM-1, but precise mechanisms regulating PIFBF after glucose ingestion remain to be elucidated.

It has been observed previously that glucose ingestion impairs endothelial-dependent vasodilation, as evaluated by

Table 1. Anthropometric and biochemical variables during the 4-week VLCD.

	Before VLCD	After VLCD
Weight (kg)	95.67±10.58	88.62±10.19*
Fat mass (%)	42.16±3.97	39.73±4.65^{NS}
Fat free mass (%)	57.85±3.97	60.12±4.79^{NS}
BMI (kg/m^2)	34.33±3.22	31.77±3.08*
Fasting insulin (mU/L)	10.38±5.01	7.48±3.41*
Insulin at 60 min (mU/L)	80.54±40.67^{NS}	61.24±26.25^{NS}
Insulin AUC (mU/L/120min)	7777.82±4073.05	5677.97±2030.52*
Fasting glucose (mmol/L)	5.14±0.51	5.00±0.47^{NS}
Glucose at 60 min (mmol/L)	8.78±2.32^{NS}	8.63±1.38^{NS}
Glucose AUC (mmol/L/120min)	882.23±166.94^{NS}	884.64±141.19^{NS}
HOMA index	2.44±1.25	1.66±0.81*
Free fatty acids (µmol/L)	800.51±293.68	1297.04±519.51*
Cholesterol (mmol/L)	5.14±0.90	3.90±0.66*
HDL-cholesterol (mmol/L)	1.49±0.33	1.16±0.31*
Triglycerides (mmol/L)	1.46±0.68	1.15±0.39^{NS}
Systolic BP (mg Hg)	114.60±12.48	113.89±12.43^{NS}
Diastolic BP (mg Hg)	71.75±8.89	69.37±9.89^{NS}

* $p < 0.05$ for comparison with values at the beginning of the study (NS = not statistically significant). BMI – Body Mass Index; AUC – Area Under Curve; BP – Blood Pressure; VLCD – Very Low Caloric Diet.

PIFBF, in healthy subjects [21–24] as well as in patients with impaired glucose tolerance and type 2 diabetes [25,26]. Furthermore, glucose induced expression of endothelial adhesion molecules in endothelial cells *in vitro* [27], which supports its direct role in pathogenesis of atherosclerosis. However, the impact of weight loss on post-prandial endothelial function (PIFBF) was not evaluated.

Life-style changes including dietary modification and subsequent weight loss represent a cost-effective treatment modality for obesity and are connected with a beneficial reduction in risk of atherosclerosis [28–30]. Part of this positive effect might be attributed to improvements in fasting

Table 2. Plasma levels of adhesion molecules during the 4-week VLCD.

	Before VLCD	After VLCD
ICAM-1 (ng/ml)	93.5±27.3	86.1±25.3*
VCAM-1 (ng /ml)	823.0±201.3	739.9±227.1*

* $p<0.05$ for comparison with values at the beginning of the study. VLCD – Very Low Caloric Diet; ICAM-1 – Inter-Cellular Adhesion Molecule; VCAM-1 – Vascular Cell Adhesion Molecule.

endothelial function following weight reduction in obese subjects [10–19]; however, this observation was not replicated in other studies [31,32]. Indeed, our study showed that fasting PIFBF remained unchanged during the study duration (expressed either as absolute or relative values, Table 3). These conflicting results may be ascribed to several factors including, but not limited to, the different sex and age distribution of investigated subjects or the type of interventions employed to induce weight loss. Importantly, physical exercise [33,34] and macronutrient composition of the diet have a profound impact on endothelial function [35]. It is also important to note that our subjects showed only very mild impairments in fasting PIFBF at the beginning of the study compared to healthy controls [36], and thus potential for further improvement detected by plethysmography might have been limited. Indeed, in general agreement with other authors [37–42], we observed a decrease in plasma levels of ICAM-1 and VCAM-1 following weight loss, which suggests overall improvement of endothelial function. It may be hypothesized that the endothelial dysfunction of investigated subjects in our study became clear only after a glucose load when a 16–20% drop (non-adjusted and adjusted model, respectively) in PIFBF was detected compared to a fasting state.

The present study investigated the effect of diet-induced weight loss on postprandial PIFBF in obese women. It is well-established that elevated postprandial glucose levels represent an important risk factor for cardiovascular morbidity and mortality [43] and that this association is at least partially mediated by derangements in endothelial function [44]. We suggest that the endothelium-dependent vasodilation following an oral glucose challenge is improved after an acute weight loss; however, mechanisms responsible for this improvement need to be elucidated. Our data are congruent with previously published observations, showing that fasting endothelial function (evaluated as flow-mediated dilation) improved by 22% after as soon as 1 week of low-caloric diet and continued to improve throughout the subsequent 5-month intervention [29]. Furthermore, there is indirect evidence based on plasma markers (sICAM and E-selectin) that post-prandial endothelial function is also improved following weight-loss [38].

The observed association between postprandial PIFBF and insulin sensitivity (HOMA-IR index) in our study, as well as similar associations described by other authors [10,12,45], suggests that the beneficial effects of weight reduction are mediated by increased insulin sensitivity of endothelial cells. Insulin plays a dominant role in the regulation of arterial vasodilation and blood flow, especially in the muscle.

Table 3. Fasting and post-prandial forearm blood-flow during the 4-week VLCD.

	Adjusted$_{FFA,insulin}$		Non-adjusted	
	Before VLCD	**After VLCD**	**Before VLCD**	**After VLCD**
Fasting basal FBF (ml/min/100ml tissue)	3.1±1.2	2.6±1.2	3.3±1.35	2.5±0.9*
Fasting PIFBF (ml/min/100ml tissue)	31.9±10.4	24.9±10.4*	31.1±9.7	24.0±6.7*
Fasting PIFBF (fold-change over baseline)	12.0±5.6	10.5±5.5	11.2±5.6	10.3±3.5
Postprandial basal FBF (ml/min/100ml tissue)	3.5±1.3	3.1±1.3	3.3±1.1	2.9±1.1
Postprandial PIFBF (ml/min/100ml tissue)	25.6±10.9	30.1±10.6	26.2±8.4#	25.3±8.3
Postprandial PIFBF (fold-change over baseline)	8.9±6.3	10.0±6.3	9.0±5.1	9.6±3.6
Postprandial / fasting PIFBF	0.75±0.27	1.20±0.27*	0.9±0.3	1.0±0.2*
ΔPIFBF	-8.2±9.1	4.2±8.9*	-5.3±9.1	0.8±5.5*

* $p<0.05$ for comparison with values at the beginning of the study (T-test for non-adjusted values or F-test for adjusted model (fasting insulin and FFA) in GLM); # p 0.05 for comparison with the fasting values (before oGTT). Forearm blood flow was measured during baseline fasting conditions and subsequently following 5 minutes of forearm ischemia (post-ischemic forearm blood blow, PIFBF) during fasted state or after glucose administration (postprandial state). VLCD=Very Low Caloric Diet. Values are Mean ± SD.

Additionally, glucose levels [11,13] and adiposity (particularly of the central type) [10,15,16] are other important determinants of impaired endothelial reactivity; changes in these parameters observed after the VLCD intervention might thus contribute to the observed improvements in PIFBF. These hypotheses are based only on association analysis and do not prove causality. We found no association between changes in PIFBF and changes in HOMA-IR, which supports other reports showing no association between changes in endothelial function and changes in HOMA-IR, BMI or plasma levels of insulin and pro-inflammatory markers [13,14,29,46]; however, opposite findings were also reported recently [37].

Our study provides novel insights into how weight loss might lower the risk of cardiovascular diseases, but its limitations need to be understood. First, the post-prandial PIFBF and its changes over time has not been established as a marker of endothelial dysfunction and it is unknown if and to what extent is this parameter is associated with cardiovascular diseases. Additionally, assessment of endothelial function using a different technique – flow-mediated vasodilation – was repeatedly shown to be closely related to future cardiovascular events [47]; investigating this variable in a post-prandial period thus might provide further important information. Second, post-ischemic FBF is determined predominantly by endothelium-dependent NO production; however, NO is not the only contributor to post-ischemic hyperemia, and other substances such as prostaglandins, asymmetric dimethylarginine and reactive oxygen species (ROS) might be involved [48]. ROS production is increased by elevated glucose levels and thus it may be hypothesized that the improved postprandial endothelial function observed in our study is the result of lower postprandial glucose levels following VLCD. However, glucose levels at 1 hour after the glucose ingestion (when postprandial endothelial function was assessed) were similar at the beginning of the study and after VLCD (8.9±2.2, 8.6±1.3 mmol/L, $p>0.3$). Third, the investigation of an endothelium-dependent vasodilation at different time-points assumes an equal baseline FBF [20], which is challenging to achieve in the real-life setting of a longitudinal interventional study. In fact, non-adjusted data show a minor but significant decrease in basal fasting FBF following dietary intervention, which was also observed by other authors under low-carbohydrate caloric restriction [42]. Despite the fact that this difference became non-significant in the adjusted model, we decided, for the purposes of "conservative" data analysis, to express data as fold-change differences over a baseline (non-ischemic) forearm blood flow, as previously recommended [20]. Such an approach eliminates bias that could be introduced by even minor changes in baseline FBF throughout the study.

Conclusions

In summary, our study suggests that weight loss in obese women improves postprandial endothelial function. This observation represents an additional explanation of why lifestyle changes and reduction in adiposity contribute to reduction in cardiovascular mortality. Future studies are necessary to identify the underlying mechanisms of this effect.

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