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ORIGINAL ARTICLE

Short-term weight loss reverses obesity-induced microvascular endothelial dysfunction

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Abstract Obesity is one of the major risk factors for cardiovascular diseases and its prevalence is increasing in all age groups, with the biggest impact observed in middle-aged and older adults. A critical mechanism by which obesity promotes vascular pathologies in these patients involves impairment of endothelial function. While endothelial dysfunction in large vessels promotes atherogenesis, obesity-induced microvascular endothelial dysfunction impairs organ perfusion and thereby is causally related to the pathogenesis of ischemic heart disease, chronic kidney disease, intermittent claudication, exercise intolerance, and exacerbates cognitive decline in aging. Reduction of weight via calorie-based diet and exercise in animal models of obesity results in significant improvement of endothelial function both in large vessels and in the microcirculation, primarily due to attenuation of oxidative stress and inflammation. Clinical data on the protective effects of weight loss on endothelial function is limited to studies of flow-mediated dilation assessed in brachial arteries. Currently, there is no guideline on testing the effects of different weight management strategies on microvascular endothelial function in obese patients. Here, we provide proof-of-concept that weight loss-induced improvement of microvascular endothelial function can be reliably assessed in the setting of a geriatric outpatient clinic using a fast, reproducible, non-invasive method: laser speckle contrast imaging-based measurement of endothelium-dependent microvascular responses during post-occlusive reactive hyperemia tests. Our study also provides initial evidence that short-term weight loss induced by consumption of a low-carbohydrate low-calorie diet can reverse microvascular endothelial dysfunction associated with obesity.

Keywords Weight loss · Obesity · Endothelial function · Aging

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Introduction

Obesity is national and global epidemic among older adults (Ogden et al. 2006, 2015). According to recent statistics, over 35% of the US population are considered obese and over 69% are considered either overweight or obese (Flegal et al. 2012). Among these, the rates of obesity are significantly higher in middle age (40–59 years of age, 40.2%) and older adults (> 60 years of age, 37%) than in younger adults (20–39 years of age, 32.3%) (Ogden et al. 2015). Recent data indicate that obesity is associated with high financial burden, and only in the USA the per capita medical costs associated with obesity have increased from $2741 in 2005 to $6899 in 2011 (Tremmel et al. 2017).

The literature is replete with evidence that obesity accelerates the aging processes (Baur et al. 2006; Bernier et al. 2016; Mattison et al. 2014; Minor et al. 2011; Pearson et al. 2008a, b) resulting in decreased life expectancy both in humans and laboratory animals (Abdelaal et al. 2017; Bailey-Downs et al. 2013; Ozanne and Hales 2004; Tucsek et al. 2014a). In many cases, such a dramatic decrease in lifespan is attributed to co-morbidities that accompany obesity in middle age, which are then carried into the advanced age. In addition to its adverse effects on metabolism, the musculoskeletal system, systemic inflammatory processes, sleep apnea, carcinogenesis, and mental illness, obesity is known to exert multifaceted deleterious effects on vascular health. Obesity is a critical risk factor for atherosclerotic cardiovascular and cerebrovascular diseases (Hubert et al. 1983) and also significantly contributes to the development of other risk factors for cardiovascular disease including hypertension, hypercholesterolemia and type 2 diabetes (Din-Dzietham et al. 2007; Hubert et al. 1983). A critical mechanism by which obesity promotes vascular pathologies involves impairment of endothelial function (Steinberg et al. 1996). There is substantial evidence from clinical (Perticone et al. 2001) and pre-clinical (Galili et al. 2007; Pearson et al. 2008a; Tucsek et al. 2014a; Ungvari et al. 2010a, 2011) studies demonstrating that obesity impairs bioavailability of NO by promoting oxidative stress in endothelial cells.

It is increasingly recognized that obesity is also a significant risk factor for microvascular disease, promoting both adverse structural and functional alterations in the microcirculation in a variety of tissues, including heart, brain, kidneys, lungs, adipose tissue, and skeletal muscle (Sorop et al. 2017). These microvascular pathological changes involve inflammatory processes, metabolic alterations, impaired barrier and transport functions. Importantly, obesity-induced global impairment of endothelium-mediated dilation of resistance arterioles impairs organ perfusion and thereby is causally related to the pathogenesis of ischemic heart disease, heart failure, pulmonary hypertension, chronic kidney disease, intermittent claudication and exercise intolerance. Recently, the view has emerged that obesity also promotes cognitive decline (Elias et al. 2003; Elias et al. 2005; Roriz-Cruz et al. 2007; Whitmer et al. 2008), at least in part, due to its adverse effects on the cerebral microcirculation (Alosco et al. 2012; Kim et al. 2012; Letra and Sena 2017; Li et al. 2013; Tucsek et al. 2014a; Tucsek et al. 2014b).

Successful approach to weight management in obese people includes evidence-based lifestyle modification approaches (diet, physical activity, and/or behavior change therapies), pharmacological treatments and bariatric surgery (American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2014; Yumuk et al. 2015). It is predicted that these weight loss strategies may confer microvascular protection in obese patients, contributing to the prevention of a wide range of diseases, from hypertension to vascular cognitive impairment. To test this prediction, it is essential to evaluate the effects of different weight loss approaches on microvascular endothelial function in various patient populations. Despite its clinical importance, there is no guideline on testing the impact of weight loss on microvascular endothelial function in obese patients.

In this case report study, we tested the hypothesis that weight loss-induced improvement of microvascular endothelial function in the setting of a geriatric outpatient clinic can be assessed using a fast, repeatable, and non-invasive method: laser speckle contrast imaging-based measurement of endothelium-dependent microvascular responses during post-occlusive reactive hyperemia tests (Barcelos et al. 2017; Cordovil et al. 2012). As proof-of-concept, we report the assessment of the effects of short-term, voluntary weight loss achieved by consumption of a low-carbohydrate low-calorie diet on microvascular endothelial function in a middle-aged man.

Methods

Study participant

This study has been performed under an approved Institutional Review Board protocol in the Translational

Geroscience Laboratory, Reynolds Oklahoma Center on Aging, Department of Geriatric Medicine, at the University of Oklahoma Health Sciences Center. A study participant (45 years of age, male, Caucasian) was enrolled into current study with a BMI of 31.8 (obesity class 1), history of controlled arterial hypertension, and hypercholesterolemia before starting a voluntary weight loss program based on a low-carbohydrate low-calorie diet (1200 cal/day) for 30 days. The study participant was taking lisinopril (10 mg/day p.o.) and rosuvastatin (10 mg/day p.o.), did not smoke and conducted a sedentary lifestyle throughout the study period. A complete blood metabolic panel was performed prior to and after the weight loss program.

Assessment of microvascular endothelial function

To assess microvascular endothelial function, a post-occlusive reactive hyperemia tests were performed after a 10-min rest with the patient being in a temperature-controlled room (22 ± 1 °C). Blood pressure was measured on the left arm prior the microvascular testing. Reactivity of microvessels was evaluated using a laser speckle contrast imaging system equipped with a 785 nm wavelength laser (Perimed PSI System, Perimed, J rf lla, Sweden). The left hand was placed on a black background mat, the distance from the imaging camera was set to 20 cm and the sampling rate was set to 19 images/second. Occlusion was performed via a sphygmomanometer cuff (Welch Allyn, Skaneateles Falls, NY, USA) inflated to 220 mmHg for 3 min on the upper arm, above the antecubital fossa (Fig. 1). Skin temperature was measured from a distance of less than 10 mm with a non-contact, laser-based thermometer (Thermoworks TW2, Thermoworks, American Fork, UT, USA) after removal of the occlusion cuff on the back of hands, and on the last phalanx of the middle finger. Recordings were analyzed offline with the manufacturer's software (PIMSoft, Pedimed, J rf lla, Sweden), and normalized microvascular perfusion units were measured. Two measurement areas were selected on the middle finger avoiding skin pigmentation, visible veins, skin irritation, and wounds. Two regions of interest (10 mm in diameter each) were selected above the nail bed and above the first phalanx of middle finger. A 30-s average of basal perfusion was considered the baseline perfusion. Perfusion during occlusion was also evaluated to assess the minimal perfusion rate. Images were recorded for 3 min after release of occlusion and maximal perfusion, the time-perfusion integral of the reactive hyperemia were evaluated. Reactive hyperemia was calculated based on relative changes of maximal perfusion over the baseline perfusion. We have also calculated the acute reperfusion rate based on the perfusion characteristics during the first 4 s after the arterial cuff deflation in the nail beds. Assessment of microvascular endothelial function was performed on four consecutive days before and after the weight loss program.

Statistical analysis

Data were analyzed by two-tailed t test. A p value less than 0.05 was considered statistically significant. Data are expressed as mean ± S.E.M.

Results

The low-carbohydrate low-calorie diet-based weight loss program resulted in a significant reduction in body mass of 14 kg (from 103 to 89 kg) and improvement of BMI index from 31.8 (obesity class 1) to 27.5 (overweight) over the period of 30 days. This weight loss was accompanied by improved cholesterol, HDL, LDL, and triglycerides plasma levels (Table 1).

No differences in skin temperature were detected during the endothelial function measurements before and after weight loss (32.7 ± 5.8 °C vs 30.2 ± 2.4 °C, $p = 0.33$), indicating that temperature differences did not confound the functional measurements of endothelial function. After weight loss, a trend toward improved endothelial function was discernible, as measured by post-occlusive reactive hyperemia using laser speckle contrast imaging in the skin (Fig. 2a). In addition, we have assessed the reperfusion of the microvasculature in the nail beds over the first 4 s after the arterial cuff deflation. Our data showed that weight loss also tended to improve reperfusion rate (Fig. 2b).

Discussion

In the present study, we have utilized a Laser Speckle Contrast Imaging (LSCI)-based method to assess microvascular endothelial function. There are several advantages of this approach. LSCI is a non-invasive, non-contact, and fast technique for measuring microvascular blood perfusion. The protocol used is also significantly

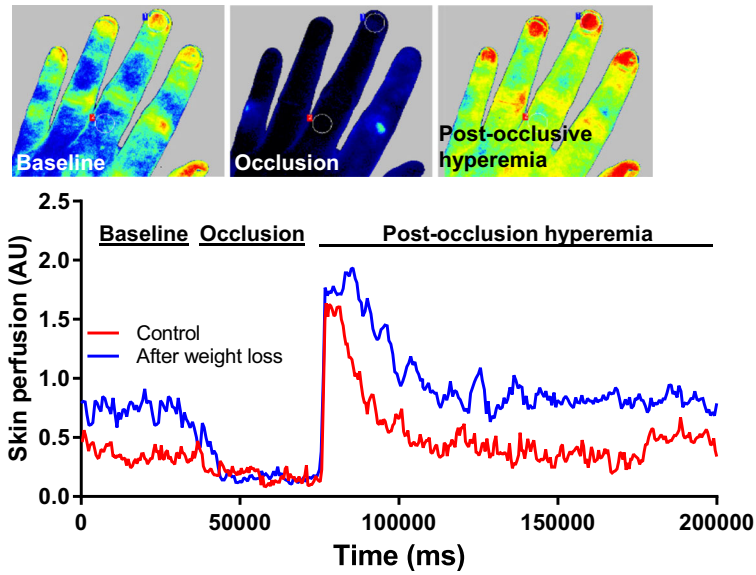

Fig. 1 Assessment of changes in skin perfusion and microvascular endothelial function induced by short-term weight loss using laser speckle contrast imaging. To assess microvascular endothelial function, we have occluded the blood flow to the hand using arterial cuff inflated to 220 mmHg for 3 min and measured changes in skin reactive hyperemia (arbitrary units) during post-occlusion test

easier to implement than measurement of brachial arterial flow in FMD studies, particularly in the setting of a geriatric outpatient clinic. Our study lays the foundation for further studies on larger cohorts of geriatric patients on different weight loss programs. Ongoing studies will also compare flow-mediated dilation (FMD) in the brachial artery and the LSCI-based microvascular perfusion data to demonstrate how endothelial functional changes in the macro- and microvasculature correlate.

Abundant preclinical data demonstrate that obesity induces microvascular endothelial dysfunction in animal models (Elmarakby and Imig 2010; Erdei et al. 2006; Henderson et al. 2004; Lynch et al. 2013; Park et al. 2012; Sweazea et al. 2010; Tarantini et al. 2018; Ungvari et al. 2010a; Ungvari et al. 2011) and that these effects are exacerbated in aging (Tucsek et al. 2014b). The available clinical data agrees with the preclinical findings, showing that even moderate obesity is associated with significant endothelial dysfunction in humans (Mohler et al. 2013; Romero-Corral et al. 2010; Williams et al. 2005). This view is also supported by ex vivo data demonstrating impaired acetylcholine-induced endothelium-dependent relaxation in subcutaneous arterioles isolated from obese subjects compared to lean individuals (Grassi et al. 2010). On the basis of these observations and the known role of endothelial dysfunction in the pathogenesis of age-related vascular diseases (Ungvari et al. 2010b), it has been predicted that weight loss in obese individuals should confer important cardiovascular benefits. Our results show that short-term significant weight loss in middle-aged obese man (reduction of BMI from 31.8 to 27.5) improves microvascular endothelial function, extending the findings of previous studies assessing FMD in brachial arteries (Bigornia et al. 2010; Joris et al. 2015; Romero-Corral et al. 2010; Rudofsky et al. 2011; Williams et al. 2005). For example, 16 weeks of combined aerobic/resistance training and diet-induced weight loss was shown to improve endothelial function in overweight and obese women (Cotie et al. 2014). Similar findings were reported by other investigators as well (Bigornia et al. 2010). Importantly, the benefits of weight loss seem to be manifested as early as 1 week after initiation of dietary intervention that resulted in a ~4% reduction of BMI (Mavri et al. 2011). Improvement in FMD induced by weight loss in obese subjects have been attributed to a decline in circulating inflammatory mediators/adipokines, blood pressure and insulin (Williams et al. 2005). We predict that the abovementioned factors would improve microvascular endothelial function as well. Interestingly, some clinical studies have reported mixed results on the effects of weight loss on endothelial function in human subjects. For example, no significant improvement in endothelial function was found in a 2-year prospective study in humans after significant weight loss achieved by either a low-carbohydrate or a low-fat diet (Mohler et al. 2013). A recent meta-analysis concluded that the protective effects of weight loss on flow-mediated vasodilation of the brachial artery may depend on subject characteristics, type of weight-loss

Table 1 Changes in the blood metabolic panel in case study participant before and after weight loss program

	Before weight loss	After weight loss
Body mass (kg)	103	89*
BMI	31.8	27.5*
Systolic blood pressure (mmHg)	128	122
Diastolic blood pressure (mmHg)	84	78
Cholesterol, < 200 mg/dL	259	189*
HDL, 40–59 mg/dL	52	61*
LDL Calculated, < 100 mg/dL	169	100*
Non-HDL cholesterol, < 130 mg/dL	207	128*
Triglyceride, < 150 mg/dL	191	141*
Albumin, 3.5–5.2 g/dL	4.8	4.9
Alkaline phosphatase, 34–132 U/L	66	58
ALT, 0–41 U/L	74	23
Anion GAP, 0–16 mmol/L	13	16
AST, 0–40 U/L	30	14
Bilirubin total, 0.0–1.2 mg/dL	0.6	0.6
Bun, 6–20 mg/dL	15	18
Calcium, 8.4–10.4 mg/dL	10.1	10.2
Chloride, 98–107 mmol/L	98	102
CO2, 22–29 mmol/L	29	26
Creatinine, 0.60–1.30 mg/dL	1.06	1.02
GFR, African American, ≥ 60 mL/min/1.73 m^2	> 60	> 60
GFR, ≥ 60 mL/min/1.73 m^2	> 60	> 60
Glucose, 74–106 mg/dL	85	89
Potassium, 3.5–5.1 mmol/L	4.3	4.1
Total protein, 6.4–8.3 g/dL	7.4	7.1
Sodium, 136–145 mmol/L	140	144
Hematocrit, 39.0–50.0%	45.4	44.8
Hemoglobin, 13.1–17.2 g/dL	15.7	15.3
Lymphocyte absolute, 1.00–4.80 K/uL	2.10	1.94
Lymphocytes, 24–44%	28	28
MCH, 27.0–35.0 pg	30.5	30.8
MCHC, 32.0–36.0 g/dL	34.6	34.2
MCV, 81.0–101.0 fL	88.2	90.1
Monocyte absolute, 0.00–0.80 K/uL	0.72	0.64
Monocytes, 0–10%	10	9
Neutrophil absolute, 1.80–7.70 K/uL	4.57	4.14
Neutrophils, 36–78%	61	60
Platelets, 150–450 K/uL	297	281
RBC, 4.20–5.60 M/uL	5.15	4.97
RDW, 11.0–16.0%	12.8	13.2
RDW-STDEV, 37.0–54.0 fL	41.4	43.6
WBC, 4.5–11.0 K/uL	7.5	7.0

HDL, high-density lipoprotein; *LDL*, low-density lipoprotein; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *BUN*, blood urea nitrogen; CO_2, carbon dioxide; *GFR*, glomerular filtration rate; *MCH*, mean corpuscular hemoglobin; *MCHC*; mean corpuscular hemoglobin concentration; *MCV*, mean corpuscular volume; *RBC*, red blood cells; *RDW*, red cell distribution width; *STDEV*, standard deviation; *WBC*, white blood cells. *sign indicates values that were improved with the weight loss

treatment, and dietary composition. In general, weight loss-mediated endothelial protection tends to be more pronounced when participants have coexisting obesity-related morbidities or when subjects receive low-fat

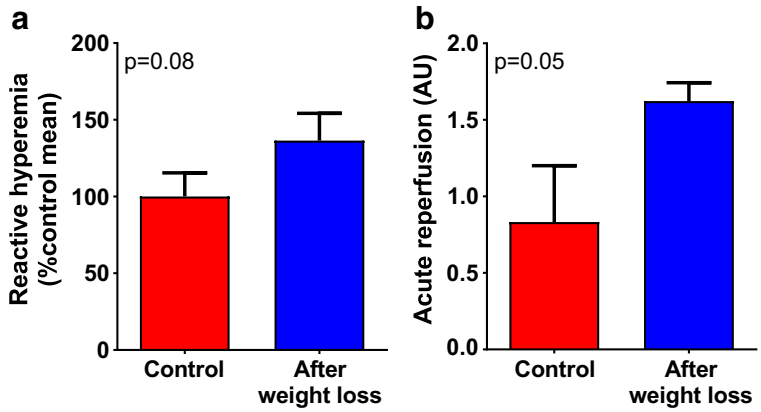

Fig. 2 Demonstration of improved microvascular endothelial function and acute reperfusion induced by short-term weight loss in a middle-aged obese man using laser speckle contrast imaging. **a** Changes in reactive hyperemia during post-occlusion test before and after weight loss. **b** Changes in acute reperfusion rate (see "Methods" section). Data presented are mean ± SEM

diets or weight-reduction regimens including exercise therapy or weight-loss medication (Joris et al. 2015). Future studies should determine how these factors influence microvascular endothelial function.

Previous studies demonstrate a beneficial effect of weight reduction on central arterial function in obese subjects. For example, low-calorie diet-induced weight reduction in obese middle-aged men, who were similar to the study participant reported here (age, ~ 45 years; BMI, ~ 30 kg/m^2), resulted in a significant improvement of central arterial distensibility (carotid arterial compliance significantly increased and b-stiffness index and aortic pulse-wave velocity significantly decreased) (Miyaki et al. 2009). Our data also suggest that weight loss may result in the improvement of vascular stiffness, evidenced by a faster reperfusion of superficial arteries of the hand during the first 4 s after the arterial cuff deflation.

Taken together, our study provides proof-of-concept that weight loss-induced improvement of microvascular endothelial function can be reliably assessed in the setting of a geriatric outpatient clinic using LSCI-based measurement of endothelium-dependent microvascular responses during post-occlusive reactive hyperemia tests. Our study also provides initial evidence that short-term weight loss induced by consumption of a low-carbohydrate low-calorie diet can reverse microvascular endothelial dysfunction associated with obesity.

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