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Effects of Bariatric Surgery on Human Small Artery Function

Evidence for Reduction in Perivascular Adipocyte Inflammation, and the Restoration of Normal Anticontractile Activity Despite Persistent Obesity

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Objectives The aim of this study was to investigate the effects of bariatric surgery on small artery function and the mechanisms underlying this.

Background In lean healthy humans, perivascular adipose tissue (PVAT) exerts an anticontractile effect on adjacent small arteries, but this is lost in obesity-associated conditions such as the metabolic syndrome and type II diabetes where there is evidence of adipocyte inflammation and increased oxidative stress.

Methods Segments of small subcutaneous artery and perivascular fat were harvested from severely obese individuals before (n = 20) and 6 months after bariatric surgery (n = 15). Small artery contractile function was examined in vitro with wire myography, and perivascular adipose tissue (PVAT) morphology was assessed with immunohistochemistry.

Results The anticontractile activity of PVAT was lost in obese patients before surgery when compared with healthy volunteers and was restored 6 months after bariatric surgery. In vitro protocols with superoxide dismutase and catalase rescued PVAT anticontractile function in tissue from obese individuals before surgery. The improvement in anticontractile function after surgery was accompanied by improvements in insulin sensitivity, serum glycemic indexes, inflammatory cytokines, adipokine profile, and systolic blood pressure together with increased PVAT adiponectin and nitric oxide bioavailability and reduced macrophage infiltration and inflammation. These changes were observed despite the patients remaining severely obese.

Conclusions Bariatric surgery and its attendant improvements in weight, blood pressure, inflammation, and metabolism collectively reverse the obesity-induced alteration to PVAT anticontractile function. This reversal is attributable to reductions in local adipose inflammation and oxidative stress with improved adiponectin and nitric oxide bioavailability. (J Am Coll Cardiol 2013;62:128–35) © 2013 by the American College of Cardiology Foundation

Obesity has become a global public heath challenge affecting almost one-half billion adults (1) and an estimated 40 million children (2). Large artery disease is very common in obese patients and manifests clinically as myocardial infarction, stroke, and hypertension (3). Small artery disease is also common in obesity and contributes to the development of hypertension and microvascular disease due to changes in peripheral resistance and local autoregulation (4). Historically, the small artery dysfunction in obesity has been attributed to damage to the endothelium (5), most notably to generation and release of nitric oxide (NO) (6). More recently, however, appreciation has grown for an additional mechanism by which vascular damage occurs in obesity; the function of fat surrounding arteries, or perivascular adipose tissue (PVAT). The PVAT surrounds the majority of blood

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vessels in the body and, in addition to adipocytes, contains inflammatory cells, stem cells, and microvasculature. In health, PVAT modulates the contractile tone of adjacent small arteries by secreting vasodilatory molecules. These adipose-derived vasodilators act independently of the endothelium and include adiponectin (7), NO (7), hydrogen sulfide (8), and palmitic acid methyl ester (9). In 2009, we performed the first human small artery study of PVAT and showed that subcutaneous gluteal PVAT from lean healthy individuals reduced adrenergic constriction in adjacent arteries, an "anticontractile" effect. However, in patients with metabolic syndrome the vasodilatory effect of the PVAT was entirely lost, due to dual processes of adipose tissue hypoxia and inflammation, both of which are established sequelae of obesity in fat depots (7). More recently, we have seen that macrophage activation in adipose tissue contributes to the attenuation in PVAT anticontractile effect (10).

Bariatric surgery has been performed for nearly 60 years and is established as the most effective clinical intervention to achieve both significant and sustained weight-loss in severely obese individuals. There are 3 types of bariatric surgical procedures: restrictive, malabsorptive, and combined operations (11). Gastric bypass surgery is a combination of restriction and malabsorption and has been shown to achieve a significantly higher degree of weight loss than restrictive bariatric surgery (12).

Bariatric surgery also dramatically improves cardiovascular risk profiles in obese patients and reduces overall mortality (13,14). The mechanisms that underlie these cardiovascular improvements remain unclear, however. In the present study we investigated the effects of bariatric surgery achieved by the gastric bypass method on the vasodilatory properties of PVAT. We report amelioration of inflammation in PVAT with complete restoration of anticontractile activity as a consequence of improved adiponectin and NO bioavailability, despite persisting obesity.

Methods

Study population. Patients with severe obesity (body mass index [BMI] >35 kg/m^2) who were awaiting gastric bypass surgery (n = 15) and lean healthy volunteers (n = 7) were recruited after full informed written consent in accord with local research ethics committee approval. All participants provided a fasting venous blood sample for the measurement of inflammatory markers and adipokines.

The study participants also provided gluteal subcutaneous fat samples (1.5 × 1.5 × 1.5 cm) by undergoing a surgical biopsy under local anesthesia (7). The sample was immediately processed in 3 sections. One part was stored for immunohistology, the second was snap-frozen for estimation of NO levels, and the remainder was used to harvest small subcutaneous arteries with micro-dissection.

Blood pressure was recorded as a mean of 3 recordings measured with a semi-automated machine (OMRON 705CP, White Medical, Clifton-Upon-Dunsmore, United Kingdom), whereas the participants were seated at rest for 15 min.

Further measurements including BMI and waist circumference were also recorded.

The obese patients were invited to return for a follow-up assessment, including a biopsy, 6 months after bariatric surgery.

Abbreviations and Acronyms

AdipoR1 = adiponectin receptor 1
BMI = body mass index
hsCRP = high-sensitivity C-reactive protein
NO = nitric oxide
PVAT = perivascular adipose tissue
TNF = tumor necrosis factor

Biochemical analyses. High-sensitivity C-reactive protein (hs-CRP) was measured in serum by an in-house, antibody sandwich enzyme-linked immunoadsorbent assay technique with anti-human CRP antibodies, calibrators, and controls from Abcam (Cambridge, United Kingdom). Interleukin-6, tumor necrosis factor (TNF)-α, adiponectin, leptin, and resistin were measured in serum, and E-selectin was measured in plasma, all with DuoSet ELISA development kits from R&D Systems (Abingdon, United Kingdom).

Wire myography. One section of the gluteal fat biopsy was placed in chilled physiological saline solution (composition in mmol/l: sodium chloride 118, potassium chloride 3.4, magnesium sulphate 1.2, calcium chloride 1, sodium bicarbonate 25, glucose 11, potassium orthophosphate 1.2) and oxygenated. The dissection dish was placed on ice during microdissection to preserve the integrity of the tissue, whereas arterial segments 250 to 350 μm in diameter were harvested, 1 segment with PVAT intact, and the adjacent segment devoid of PVAT. Both segments came from the same artery.

Endothelium denuded vessels were mounted on 40-μm wires and studied with wire myography (Danish MyoTech, Aarhus, Denmark).

The mounted vessel segments were oxygenated and maintained at a temperature of 37°C before vessel diameter and wall tension was normalized as previously described (7,15). Vessels were challenged with a 60-mmol/l high-potassium physiological saline solution to establish viability and baseline constriction.

Each vessel segment was stimulated with cumulative doses of norepinephrine (Sigma-Aldrich, Dorset, United Kingdom) at the following doses: 10^{-9}; 10^{-8}; 3×10^{-8}; 10^{-7}; 3×10^{-7}; 5×10^{-7}; 10^{-6}; 2×10^{-6}; 3×10^{-6}; 5×10^{-6}; 10^{-5}; 2×10^{-5}; and 3×10^{-5} mol/l. Contractile responses to norepinephrine are presented as a percentage of high-potassium physiological saline solution constriction, consistent with published data (7,16–18).

Pharmacological assessment. Pharmacological protocols were applied to study the effect of PVAT on adjacent small arteries. In each case 2 segments of the same artery were prepared with and without PVAT attached as previously described (7).

The role of oxidative stress was evaluated by incubation of samples from pre-operative patients with superoxide dismutase and catalase (superoxide dismutase, Sigma-Aldrich,