Obesity is a growing epidemic. Obesity is not just a cosmetic matter but a serious health problem. Obesity is part of the metabolic syndrome and an established risk factor for type 2 diabetes, cardiovascular disease, and, notably, for myocardial infarction. Mechanistically, the common denominator underlying the metabolic syndrome, the development and progression of systemic atherosclerosis, and ultimately even the acute initiation of myocardial infarction by the rupture of an atherosclerotic coronary plaque is inflammation. Apparently, not all obesity is created equal, in that abdominal/visceral adipose tissue is a particular risk factor and a particular source of inflammation. More specifically, visceral adipose tissue differs from subcutaneous adipose tissue in that visceral adipose tissue produces and secretes cytokines, as well as factors that promote vasoconstriction and thrombosis.

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Clearly, obesity results from an energetic imbalance of caloric intake and expenditure; clearly, also, there is a genetic predisposition to such energetic imbalance through a number of factors that affect energy metabolism, its neuroendocrine control, and energy expenditure and its efficiency. The most direct and causal treatment is, of course, a behavioral modification of food intake and of exercise regimens. Reduction in caloric intake even beyond the reduction of obesity promotes health and longevity. Likewise, exercise has a number of beneficial effects on cardiovascular and mental health that go beyond the reduction of obesity. Nevertheless, behavioral modification of lifestyle with reduced caloric intake and increased amounts of exercise is often difficult if not impossible to achieve for a number of psychosocial reasons. Pharmacological approaches to reduce weight by interference with energy metabolism and its neuroendocrine control have been attempted but failed, largely because serious side effects outweighed the observed modest weight reduction. Surgical approaches to remove the excessive adipose tissue and to limit food intake, ie, bariatric surgery, are then a last option. The removal of abdominal subcutaneous fat by liposuction alone is not sufficient to favorably alter the metabolic abnormalities and increased inflammatory biomarkers associated with obesity. More drastic procedures, such as gastric banding/obstruction and various techniques to exclude/bypass parts of the gastrointestinal system, are needed to achieve a substantial weight loss and reduction of metabolic and cardiovascular risk factors. The study by Zhang et al in the present issue now attempts to identify mechanisms underlying the benefits of bariatric surgery. Using a genetically type 2 diabetic model, mice were subjected to bariatric surgery, which not only reduced food intake, as intended, but also body weight, fat mass, and plasma glucose levels already after 5 days and progressively over 30 days. The visceral adipose tissue infiltration with macrophages and lymphocytes, along with the expression of several cytokines on the mRNA and protein level, was also reduced. Importantly, the impaired endothelium-dependent, NO-mediated vasodilation of small mesenteric arteries was restored by bariatric surgery. Interferon γ was increased in visceral adipose tissue and increased, in turn, the gene expression of tumor necrosis factor-α (TNF-α); exogenous TNF-α, ultimately, impaired endothelial vasodilator function. The inflammation in visceral adipose tissue was associated with increased superoxide levels, which were also increased in small mesenteric vascular tissue. All these alterations were reversed by bariatric surgery.

The present study attributed a causal role to a signaling chain from infiltration of visceral adipose tissue by CD3-positive T lymphocytes and their formation of interferon γ, which in turn stimulates the formation of TNF-α and ultimately reactive oxygen species. Obesity-induced endothelial dysfunction and a causal involvement of TNF-α in endothelial dysfunction are well established, notably also in the coronary circulation. Also, TNF-α-induced increased formation of reactive oxygen species with subsequent oxidative protein modification is established in cardiomyocytes. Whether myocardium and coronary circulation were also affected by obesity and whether such potential changes were also reserved by bariatric surgery remains unclear from the present study (Figure).

Apart from the mechanistic information in the present study, the time frame of observed changes in inflammatory parameters and endothelial function was quite remarkable, in that it was corrected by bariatric surgery within only 5 days, supporting the notion that inflammation is more important than weight per se. This brings up the issue whether or not bariatric surgery might have a downside over longer periods of time. An obesity paradox has been observed for some cardiovascular conditions, including coronary revascularization. Also, leptin is an adipose-tissue derived cytokine with favorable effects on the cardiovascular system, including protection from myocardial infarction; finally, TNF-α not
only has a detrimental function in the cardiovascular system but also is cardioprotective under certain circumstances.24

As with any solid and mechanistic study, many more novel questions arise from the present one. Apart from the issue of more chronic effects of bariatric surgery, what makes the visceral/adipose tissue different from peripheral subcutaneous adipose tissue? What exactly is the chemotactic stimulus for macrophages and T lymphocytes, and what makes them secrete interferon? Is the observed inflammatory vasculopathy a local paracrine response of the mesenteric circulation or does it extend into a systemic response with effects also on other perfusion territories? Are there more causally oriented and specific interventions than bariatric surgery, which after all, is a traumatic and unspecific ultima ratio?

References


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