OPINION

Obesity, cytokines and endothelial dysfunction: A link for the raised cardiovascular risk associated with visceral obesity

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Obesity (defined as a BMI >30 kg/m^2 has increased at an alarming rate over recent years and is now a worldwide public health problem. Obesity is a common condition in every continent. National surveys in the United States have shown a prevalence of obesity of 20% in men and 25% in women (1); the striking increase in prevalence in the last 2 decades of the past century also indicates that population-wide increase in obesity may occur over a short period of time. Data collected for the MONICA study indicate that more than half of the adult population between 36-65 yr of age in Europe are either overweight or obese (2).

Although physicians are familiar with the concept of obesity, few of them see it as a real disease. For reasons that are not fully known, obesity is associated with an increased risk of heart disease, Type 2 diabetes and certain forms of cancer (3). In the Framingham Study, the risk of death within 26 yr increased by 2% for each extra pound (0.45 kg) increase in weight between the ages of 50-62 yr. This evidence should convey the due attention to the morbidity and mortality associated with more modest degrees of overweight and the detrimental effect of intra-abdominal fat. The intra-abdominal visceral deposition of adipose tissue, which characterizes upper body obesity, is a major contributor to the development of hypertension, insulin resistance, Type 2 diabetes and dyslipidemia. As a corollary, the role of visceral fat may be more complex than suspected because even people who are not obviously overweight may still have disproportionately too much fat with the result of a predisposition toward atherosclerotic disease. We hypothesize that inappropriate cytokine secretion from adipose tissue plays a role in the increased cardiovascular risk associated with obesity and visceral fat distribution.

ENDOTHELIAL DYSFUNCTION AND BODY FAT

Endothelial dysfunction is implicated in the pathogenesis and clinical course of the majority of cardiovascular diseases, and is associated with future risks of adverse cardiovascular events (4). A critical balance between endothelium-derived relaxing and contracting factors maintains vascular homeostasis. Although studies often report endothelial dysfunction as a loss of vasodilatory capacity, the term encompasses a generalized defect in all the homeostatic mechanisms. In a more general sense, endothelial dysfunction implies diminished availability of the key factor nitric oxide (NO) that plays a pivotal role in the maintenance of vasomotion, smooth muscle proliferation, coagulation and fibrinolysis, thrombosis, inflammation and oxidation (5). Accordingly, the loss of one or more of these functions may characterize endothelial dysfunction which eventually may result in vascular decompensation.

Endothelial dysfunction has been reported in obese insulin-resistant subjects. In particular, an inverse relationship between obesity and endothelial function, as assessed by flow-mediated dilatation, or change in blood flow responses to methacoline, acetylcholine, or L-arginine, has been demonstrated (6-9). Since endothelial NO may mediate insulin-

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stimulated vasodilatation in skeletal muscle, it has been hypothesized that the physiological vasodilatory action of insulin is blunted in obese subjects. In fact, indexes of insulin sensitivity that are linearly related to indexes of body fat distribution (BMI, waist-to-hip ratio, waist girth) may explain nearly half of the endothelial dysfunction associated with obesity.

A number of soluble surrogate markers of endothelial dysfunction have been studied over the past few years (Table 1). Up-regulation of cell adhesion molecules (CAMs), also called endothelial activation, is thought to trigger and maintain atherogenesis. CAMs are expressed on the surface of endothelial cells and leukocytes, and orchestrate the complicate process of leukocyte rolling, adhesion, and transportation into the subintimal space. Increased circulating levels of ICAM-1, VCAM-1 and E-selectin have been found in obese men, irrespective of the presence of hypertension (10), while obese women present increased basal levels of ICAM-1, VCAM-1 and P-selectin, significantly related to BMI and waist-to-hip ratio (9). Even in diabetes mellitus, the level of adiposity is linked to endothelial activation: central fat deposition is the only significant predictor of plasma levels of ICAM-1, VCAM-1 and E-selectin (11, 12).

INAPPROPRIATE CYTOKINE SECRETION IN OBESITY

A growing body of evidence implicates adipose tissue in general, and visceral adiposity in particular, as key regulators of inflammation. As adipose tissue secretes proinflammatory cytokines, it becomes linked at the molecular level to the dysregulation of a variety of underlying systems all of which are causally implicated in the development of atherosclerosis and metabolic outcomes. Among the various cytokines released by the adipose tissue, TNF-α, and interleukin-6 (IL-6) seem to play a major role because they can influence endothelial function (13) and induce endothelial expression of chemokines and adhesion molecules (14) which are central to the early stage of the atherogenetic process. Plasma concentrations of IL-6 are predictive of future myocardial events among apparently healthy men (15); moreover, the contribution of adipose tissue in IL-6 secretion has been proposed to be the link between plasma C-reactive protein (CRP) and adiposity, as CRP synthesis in the liver is largely under the control of IL-6. Several large-scale studies have shown that plasma levels of CRP are a strong independent predictor of future myocardial events, stroke, peripheral vascular disease and vascular death among individuals without known cardiovascular disease (16). Moreover, circulating levels of CPR are elevated in human obesity and correlate with bw, visceral fat and insulin resistance (17).

Table 1 - *Markers of endothelial dysfunction in obesity.*

• Endothelium-dependent dilatation	↓	Ref.
Flow-dependent		6
Methacoline		7
Acetylcholine		8
L-arginine		9
• Adhesion molecules	↑	
ICAM-1		9,10
VCAM-1		9,10
E-selectin		10
P-selectin		9
• Cytokines	↑	
IL-6		9,19
TNF-α		9,19
• Inflammation marker	↑	
CRP		17

↓ reduced; ↑ increased (in plasma). CRP: plasma C-reactive protein; IL-6: interleukin 6, ICAM-1: intercellular adhesion molecule-1; VCAM-1: vascular adhesion molecule-1; TNF-α: tumor necrosis factor-α.

Both TNF-α and IL-6 plasma levels have been found to be elevated in obese people, as compared with levels of age- and disease-matched normal-weight people (9). TNF-α has been implicated as a potential mediator of obesity-associated insulin resistance (18). As TNF-α induces production of IL-6, which in turn promotes the synthesis of CRP in the liver, a low level of chronic inflammatory state may induce endothelial dysfunction and insulin resistance (19), which would link the latter phenomena with obesity, diabetes, and cardiovascular disease. The recent data of the Women's Health Study that enrolled apparently healthy individuals with no overt abnormalities of glucose metabolism, discovered that baseline levels of both CRP and IL-6 were significant predictor of Type 2 diabetes development (20). The association remained significant after adjustment for the degree of obesity.

CONCLUSIONS AND PERSPECTIVES

A likely mechanism for the association between intra-abdominal fat deposition and cardiovascular disease risk is through the plasma cytokine levels (TNF-α, IL-6), which may induce endothelial dysfunction, endothelial activation, and insulin resistance. In the long-term, the perturbation of glucose and lipid metabolism associated with insulin resistance may add to the vascular damage in-

duced by chronic endothelial dysfunction and facilitate the occurrence of cardiovascular events. This intriguing hypothesis linking adipose tissue, circulating markers of inflammation, diabetes, and cardiovascular disease is at present speculative and awaits definite answers. On the other hand, it is only in our modern times that obesity, diabetes and atherosclerosis have become epidemic. Whether this represented a natural selection among our ancestors for individuals with relatively enhanced inflammatory function (*e.g.* high cytokine responses to fight against infection) or mild to moderate insulin resistance (to protect from starvation), remains an interesting hypothesis. The real problem is that our modern environment is dominated by increasingly sedentary habits, an abundance of high carbohydrate foods, and a prolonged life expectancy, all which facilitate the occurrence of weight gain and its associated medical problems.

From a clinical perspective, however, it is reassuring that diet, exercise and lifestyle changes can so effectively reduce rates of both atherosclerosis and Type 2 diabetes in the population (15). Because treating obesity results in only a 10% weight loss, many patients are dissatisfied and doctors would prefer to treat hypertension, diabetes or dyslipidemia that are usually associated with obesity. Any delay in treatment increases the risk of future development of diabetes and its related complications, and of heart disease. However, because of the powerful association with obesity, weight loss may be a safe method for down-regulating an individual's inflammatory status.

The results of many recent reports indicate that this may be the case. Both short-term (12 weeks) circulating inflammatory markers, have found that weight reduction averaging from 5%-15% of initial bw, resulted in significant decrease of circulating CRP, IL-6, TNF-α and adhesion molecule levels (9, 17, 21, 22).

Weight loss, especially if associated with exercise, improves health and should be encouraged. In the light of recent evidence that visceral fat is a key regulator site for the general process of inflammation (23), such behaviors that affect fat deposits are presumed to have beneficial long-term implications for chronic outcomes such as cardiovascular diseases and Type 2 diabetes.

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