The case of visceral fat: argument for the defense

Samuel Klein


Commentary

Increased plasma fatty acid concentrations may be responsible for many of the metabolic abnormalities associated with abdominal obesity. Excessive visceral fat is associated with insulin resistance and other metabolic risk factors for coronary heart disease. A study reported in this issue of the _JCI_ evaluates the relative contribution of fatty acids released during lipolysis of visceral adipose tissue triglycerides to portal and systemic fatty acid flux in human subjects.

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Increased plasma fatty acid concentrations may be responsible for many of the metabolic abnormalities associated with abdominal obesity. Excessive visceral fat is associated with insulin resistance and other metabolic risk factors for coronary heart disease. A study reported in this issue of the JCI evaluates the relative contribution of fatty acids released during lipolysis of visceral adipose tissue triglycerides to portal and systemic fatty acid flux in human subjects (see the related article beginning on page 1582).

The relationship between excess abdominal fat mass and insulin resistance was recognized a half century ago, when Jean Vague, a French physician, reported an association between a “masculine” or “android” obesity phenotype and diabetes (1). Subsequently, many large epidemiological and smaller physiological studies have confirmed the relationship between abdominal obesity and insulin resistance, diabetes, and other metabolic risk factors for coronary heart disease (2–5). In fact, excess abdominal fat is even associated with impaired insulin-mediated glucose uptake in lean adults (6).

Abdominal fat is composed of several distinct anatomic depots: subcutaneous fat, which can be divided into anterior and posterior or superficial and deep layers, and intraabdominal fat, which can be divided into intraperitoneal and retroperitoneal sites. Intrapertoneal fat, also known as visceral fat, is composed of mesenteric and omental fat masses. Although the absolute amount of each of these depots is much larger in upper-body obese than in lean persons, the relative amount of abdominal fat with respect to total body fat mass is often similar in both groups. For example, visceral fat constitutes about 10% of total body fat mass in a clinical setting. Based on data from epidemiological studies, the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, convened by the NIH, proposed that men with a waist circumference greater than 102 cm (40 in.) and women with a waist circumference greater than 88 cm (35 in.) are at increased risk for metabolic diseases (9).

Fatty acid metabolism and insulin resistance
The association between abdominal fat and insulin resistance does not prove causality, and it is possible that environmental, biological, or inherited factors that induce insulin resistance also cause abdominal fat accumulation (10). Nonetheless, it has been proposed that alterations in fatty acid metabolism associated with abdominal obesity are responsible for impaired insulin action because excessive circulating FFAs inhibit the ability of insulin to stimulate muscle glucose uptake and to suppress hepatic glucose production (11). The notion of a link between abdominal fat, FFA metabolism, and insulin resistance is supported by the observation that basal whole-body FFA flux rates are greater in upper-body obese than in lower-body obese and lean subjects (12, 13) and that diet-induced weight loss decreases whole-body FFA flux and improves insulin sensitivity (14). It has been hypothesized that excess visceral fat is more harmful than excess subcutaneous fat, because lipolysis of visceral adipose tis-

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1530
Figure 1
Approximate relative contributions of FFAs released from lower- and upper-body subcutaneous fat depots and from splanchnic tissues to the systemic venous circulation, and FFAs from visceral fat and the systemic arterial circulation to the portal circulation in lean and obese subjects. Values are based on data from ref. 20.

Table

<table>
<thead>
<tr>
<th>Fat Depots</th>
<th>Portal Circulation</th>
<th>Systemic Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral Fat</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Subcutaneous Fat</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Splanchnic Tissues</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

The results of this study demonstrate that the release of FFAs into the portal vein from lipolysis in visceral fat depots increases with increasing amounts of fat. However, the relative contribution at any individual visceral fat mass was quite variable. For example, in subjects with approximately 150 cm² of visceral fat, the percentage of total FFAs delivered to the liver that were derived from visceral fat ranged from 0% to 45%, and the relative contribution of FFAs from visceral fat was lower in some subjects with a larger amount of visceral fat (about 300 cm²) than it was in others with a small amount (about 10 cm²). Therefore, although there is a direct relationship between visceral fat mass and its contribution to hepatic FFA metabolism, it is impossible to determine which individuals have a high rate of visceral FFA flux based on analysis of body composition and fat distribution alone.
distribution in liver and muscle cells, which can also influence insulin action.

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Getting stents to go with the flow

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Implantation of expandable stents into stenotic arteries after percutaneous coronary intervention to relieve arterial narrowing has become a standard therapeutic tool. The improvement in vascular interventional technology, and especially stent technology, has, arguably, outstripped understanding of the biologic consequences of opening an obstructed artery. In the case of bifurcation stenoses, new evidence suggests that opening a stenotic sub- side branch may create unfavorable hemodynamics in the stented main branch that can lead to in-stent restenosis (see the related article beginning on page 1607).

The branching arterial system has com- plex hemodynamics. Flow is laminar in straight segments away from the ostia of side branches or the flow dividers that form the origin of subsidiary vessels of a main branch. The inherently disturbed flow at branch points creates an environment that predisposes to the development of atherosclerosis (1, 2). This permissive environment is characterized by low, oscillating, or reversed flow created opposite flow divid- ers or branch points and is caused by flow separation in which streamlines of flowing blood curve away from the artery wall proximally and back toward the wall dis- tally (3). The impact of local hemodynamic in- fluences on the pathogenesis of atherosclerosis has been studied extensively, both in vitro and in vivo (4). In vitro flow models have defined the effects of a given geometry on flow dynamics, and biologic responses have been associated with predicted flow patterns (5, 6). Generally, these models have not incorporated consideration of the evolving effects of the dynamic outward or inward remodeling of arteries that is asso- ciated with atherosclerosis (7). In partic- ular, such approaches have not been applied extensively to exploration of the conse- qences of the acute hemodynamic chang- es inherent in the practice of interventional cardiology for clinical outcomes, specifically restenosis. The optimum approach to the clinical situation of, for example, the pres- ence of proximal stenoses in both the main branch and a relatively large side branch of a coronary artery has not been agreed upon generally (8). With the advent of the use of vascular stents, a common approach has been to stent both arteries, although long- term outcomes are less than optimal (9). A guiding clinical principle has been the drive for complete revascularization. The under- lying vascular biology and, in particular, the interdependence of the hemodynamic environment in the main and side branch- es in the presence of stenoses in each has been poorly understood. Thus, beyond the imperative of relieving ischemia, there has been no firm biologic basis guiding clinical decision-making with regard to interven- tion to open a severely stenotic side branch when percutaneous coronary interven- tion is being performed to open the main branch stenosis.

In vitro simulation of flow patterns of branching arteries

In this issue of the JCI, Richter and col- leagues describe experimental approaches that represent a major advance in under- standing the interrelatedness of stenoses

commentsary

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