Editorial

Obesity: between "metabolically healthy" and "metabolically abnormal" phenotypes

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The vascular risk associated with obesity is correlated with insulin resistance and a state of inflammation predominantly in visceral adipose tissue.

A number of experimental studies had suggested that adipose tissue inflammation is linked to cardiovascular and metabolic complications of obesity by increased local production of proinflammatory adipocytokines that may lead to insulin resistance and endothelial dysfunction.

At least two mechanisms have been proposed for the insulin resistance development:

1. Enlargement of adipocyte size can lead to activation of adipocytes that begin to secrete cytokines and chemokines which attract macrophages into adipose tissue (1). This is a stimulus for preadipocytes and resident endothelial cells to produce MCP-1/CCr2 (Monocyte chemoattractant protein-1/ CC motif chemokine receptor-2) that stimulate bone marrow-derived macrophage recruitement and infiltration into adipose tissue.(2).

2. During weight gain local hypoxia may lead to adipocyte death. Macrophages infiltrate adipose tissue, as scavenger cells of lipid debris resulting from dead adipocytes.

Macrophages localize around dead adipocytes to scavenge the exposed "free lipid" in the interstitium forming crown-like structures – the hallmark of inflammation in adipose tissue.(3,5).

An important chemoattractant to dead adipocytes is osteopontin (4), a proinflammatory cytokine that is essential for monocyte chemotaxis, migration and expression of proinflammatory genes.

In obese patients the macrophage infiltration was paralleled by elevated expression of osteopontin in adipose tissue independent from insulin resistance and hepatic steatosis.

Recently it was shown, in a group of 77 obese subjects, that histology of subcutaneous adipose tissue disclosed in 50 of them the crown-like pattern of aggregated macrophages as the hallmark of adipose tissue inflammation. However, in the remaining 27 obese subjects no inflammatory adipose tissue activity (absence of any macrophage crowning) was observed. The subjects with proinflammatory changes of adipose subcutaneous tissue had significantly increased TNF-α mRNA expression in adipose tissue, increased insulin resistance (HOMA-IR) and decreased brachial artery flow-mediated dilatation as compared with obese subjects without adipose tissue inflammation. (6)

On the other hand, the relationship between visceral fat accumulation and metabolic complications of obesity is well recognized. Several epidemiological studies have documented the association of abdominal- visceral obesity with insulin resistance and increased risk of diabetes and

cardiovascular diseases (7). Macrophage infiltration take place preferentially in visceral (omental) versus subcutaneous fat and this preferential drive is exaggerated by obesity. This increased inflammatory response in visceral obesity could be a link between central obesity and metabolic complications of obesity: diabetes and cardiovascular disease. (8)Visceral fat could cause systemic inflammation by releasing NEFA and adipokines (such IL-6) into portal circulation (the so called "portal hypothesis"). In one study, portal vein IL-6 concentration was correlated with systemic CRP concentrations (9).

However, not all obese people are metabolically abnormal: approximately 20%-30% of obese people have a "metabolically healthy" obesity being insulin sensitive and apparently metabolically normal.

A few studies have addressed this issue. In a group of 43 obese postmenopausal women, 17 of them were classified as "metabolically normal" (MNO) and 26 as "metabolically abnormal"(MAO) based on insulin sensitivity. Compared to MAO, the MNO women had obesity onset at an earlier age and lower amounts of visceral obesity, higher levels of HDL-cholesterol and lower levels of fasting insulin, glucose and triglycerides (10).

Another study (11) compared 22 women with "metabolically healthy but obese " (MHO) phenotype to 22 insulin resistant women with similar body fatness.

MHO women had significantly lower levels of visceral fat, high-sensitivity C-reactive protein, fasting plasma triglycerides and insulin and higher HDL-cholesterol levels.

The prevalence and correlates of the two phenotypes (metabolic normal obese and normal-weight metabolically abnormal) were assessed (12) in a large populational study:

In a crossectional sample of 5440 adults 20 years and older, participants to the National Health and Nutrition Examination Surveys (NHANES), a high prevalence (23.5%) of metabolic abnormalities clustering among normal-weight individuals was observed. On the other hand, the prevalence of metabolically healthy phenotype among obese (MHO) individuals was 47.7% among those aged 20-34 years and decreased, along increasing age groups, to 14.3% among those aged 65-79 and 22.1% among those 80 years and older.

We have evaluated the differences of body composition and fat distribution in 65 type1 as compared to 108 type 2 diabetic people with similar body weight. Our data suggest that, at similar levels of body fatness, T2DM (as compared to T1DM) patients have a different body composition with significantly more ectopic fat accumulation in visceral area and liver steatosis (13).

A recent study (14) aimed to identify obese insulin-sensitive subjects with metabolically normal phenotype and to compare them with equally obese subjects but insulin-resistant. The group of obese subjects with metabolically normal phenotype had significantly lower ectopic fat in skeletal muscle and liver and intima-media thickness of the common carotid artery compared to obese insulin-resistant group with the metabolically unhealthy phenotype, but no significant differences in insulin sensitivity or intima-media thickness compared to a group of normal weight subjects.

Another recent study (15) investigated, using subcutaneous adipose tissue biopsies,

preadipocyte differentiation in 51 obese and non-obese subjects.

In the subcutaneous adipose tissue from obese subjects, the number of progenitor cells (CD 133) was not reduced and correlated positively with BMI. In contrast, the number of preadipocytes which can differentiate into adipose cells was reduced and negatively correlated with adipocyte cell size.

The preadipocytes exposed to TNFα in culture medium assumed a proinflammatory phenotype (with increased expression of cytokines and chemokines) including up-regulation of CD68 expression, a marker of macrophages. TNFα inhibits differentiation of preadipocytes into adipose cells and concomitantly promotes the differentiation of preadipocytes toward a macrophage-like "activated" phenotype that could be the predominant source of MCP-1 secretion. It is possible that TNFα induce a kinase (MAP4K4) that inhibits PPARγ activation and adipogenesis.

Because of TNFα –induced blockage of preadipocyte differentiation into normal adipocytes, a reduced lipid storage in enlarged adipocyte cells could ensue, associated to a proinflammatory state and lipid accumulation in ectopic sites.

According to data of this study, the development of insulin resistance may be associated with abdominal obesity and increased fat cells size (hypertrofic obesity) possibly due to a limited differentiation of preadipocytes into adipose cells.

At the opposite pole, in "metabolically healthy"obesity, the differentiation of preadipocytes into small insulin-sensitive adipose cells is keeping pace with increased alimentary lipid afflux and could store increased amounts of lipids. In this way, the peripheral tissues that are not prepared for fat storage (especially liver and muscle cells) are protected from increased lipid delivery.

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