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# Recent advances in the relationship between obesity, inflammation, and insulin resistance.

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## Abstract

It now appears that, in most obese patients, obesity is associated with a low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system and which can subsequently lead to insulin resistance, impaired glucose tolerance and even diabetes. WAT is the physiological site of energy storage as lipids. In addition, it has been more recently recognized as an active participant in numerous physiological and pathophysiological processes. In obesity, WAT is characterized by an increased production and secretion of a wide range of inflammatory molecules including TNF-alpha and interleukin-6 (IL-6), which may have local effects on WAT physiology but also systemic effects on other organs. Recent data indicate that obese WAT is infiltrated by macrophages, which may be a major source of locally-produced pro-inflammatory cytokines. Interestingly, weight loss is associated with a reduction in the macrophage infiltration of WAT and an improvement of the inflammatory profile of gene expression. Several factors derived not only from adipocytes but also from infiltrated macrophages probably contribute to the pathogenesis of insulin resistance. Most of them are overproduced during obesity, including leptin, TNF-alpha, IL-6 and resistin. Conversely, expression and plasma levels of adiponectin, an insulin-sensitising effector, are down-regulated during obesity. Leptin could modulate TNF-alpha production and macrophage activation. TNF-alpha is overproduced in adipose tissue of several rodent models of obesity and has an important role in the pathogenesis of insulin resistance in these species. However, its actual involvement in glucose metabolism disorders in humans remains controversial. IL-6 production by human adipose tissue increases during obesity. It may induce hepatic CRP synthesis and may promote the onset of cardiovascular complications. Both TNF-alpha and IL-6 can alter insulin sensitivity by triggering different key steps in the insulin signalling pathway. In rodents, resistin can induce insulin resistance, while its implication in the control of insulin sensitivity is still a matter of debate in humans. Adiponectin is highly expressed in WAT, and circulating adiponectin levels are decreased in subjects with obesity-related insulin resistance, type 2 diabetes and coronary heart disease. Adiponectin inhibits liver neoglucogenesis and promotes fatty acid oxidation in skeletal muscle. In addition, adiponectin counteracts the pro-inflammatory effects of TNF-alpha on the arterial wall and probably protects against the development of arteriosclerosis. In obesity, the pro-inflammatory effects of cytokines through intracellular signalling pathways involve the NF-kappaB and JNK systems. Genetic or pharmacological manipulations of these effectors of the inflammatory response have been shown to modulate insulin sensitivity in different animal models. In humans, it has been suggested that the improved glucose tolerance observed in the presence of thiazolidinediones or statins is likely related to their anti-inflammatory properties. Thus, it can be considered that obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory factors involved in the pathogenesis of insulin resistance.

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