

META-INFLAMMATION AND ADIPOSE TISSUE DYSFUNCTION: IMMUNOMETABOLIC MECHANISMS OF OBESITY AS A SYSTEMIC INFLAMMATORY DISEASE

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RESUMO

ABSTRACT Obesity is a chronic and multifactorial disease characterized by a state of persistent low-grade systemic inflammation, known as meta-inflammation. Unlike acute inflammation, meta-inflammation is triggered by nutrient excess and metabolic dysfunction, compromising endocrine homeostasis and insulin signaling. To analyze the role of chronic low-grade inflammation in the pathophysiology of obesity and its repercussions on the cardiometabolic axis. A narrative literature review was conducted in PubMed and the CAPES Periodicals Portal (2021-2026). The PICO strategy was applied using MeSH descriptors: "Obesity", "Adipose Tissue", "Cytokines", and "Insulin Resistance". Selection prioritized studies detailing inflammatory molecular signaling and leukocyte polarization in visceral adipose tissue. Adipose tissue expansion promotes cellular hypoxia, endoplasmic reticulum stress, and adipocyte death, triggering the release of damage-associated molecular patterns (DAMPs). These signals activate pattern recognition receptors (such as TLR-4), leading to macrophage polarization from the anti-inflammatory M2 phenotype to the pro-inflammatory M1. It was observed that excessive secretion of TNF- α and IL-6 activates stress kinases (JNK and IKK β), which promote serine phosphorylation of the insulin receptor substrate (IRS-1), blocking the PI3K/Akt pathway. Visceral fat demonstrates higher expression of chemotactic proteins (such as MCP-1), sustaining the infiltration of CD8 $^{+}$ T cells and dendritic cells, which directly correlates the inflammatory burden with increased C-Reactive Protein (CRP) levels and cardiovascular event risk. Meta-inflammation constitutes a central pathophysiological link between adipose tissue expansion and the onset of cardiometabolic comorbidities. In obesity, adipose tissue ceases to function merely as an energy reservoir and begins to act as a dysfunctional endocrine and immunological organ. The accumulation of fat, especially visceral fat, activates receptors such as TLR-4, which recognize lipid excess and trigger the inflammatory response. This process favors macrophage polarization from the anti-inflammatory (M2) to the pro-inflammatory (M1) profile, with increased release of cytokines such as TNF- α and IL-6, perpetuating a chronic state of low-grade inflammation. At the molecular level, these cytokines activate stress kinases such as JNK and IKK β -mediated pathways, promoting serine phosphorylation of IRS-1. As a consequence, insulin signaling is impaired, particularly through attenuation of the PI3K/Akt pathway a key mechanism in obesity-associated insulin resistance. This scenario supports the understanding of obesity as a chronic immunometabolic condition, in which persistent inflammation contributes to both metabolic dysfunction and endothelial damage. Therefore, therapeutic management must go beyond isolated weight loss, incorporating strategies aimed at modulating cell communication and resolving inflammation, with the goal of reducing the risk of type 2 diabetes and cardiovascular disease.

Palavras-chave: Obesity; Adipose Tissue; Cytokines; Insulin Resistance; Chronic Disease.