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Review Article

Adipokines as a link between adipose tissue with inflammation and insulin resistance in cardiometabolic diseases

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ABSTRACT

Obesity, a global health crisis, is associated with metabolic disorders and escalating healthcare burdens. This review explores the multifaceted dynamics of obesity, investigating the interplay of genetic, physiological, and environmental factors. Adipose tissue, traditionally regarded for energy storage, now emerges as a crucial contributor to systemic metabolism through the secretion of adipokines. Key adipokines, such as adiponectin, leptin, and the CTRPs superfamily (CTRP1, CTRP3, CTRP9, and CTRP12), are examined for their influence on inflammation, insulin resistance, and atherosclerosis. A critical understanding of the complex interplay between adipokines, inflammation, and insulin resistance is essential for comprehending the intricacies of metabolic dysfunction in obesity. Adipokines emerge as potential therapeutic targets to alleviate inflammation-related pathologies associated with obesity and related disorders. Ongoing research is pivotal to deepen the understanding of adipokine roles, paving the way for innovative therapeutic interventions. This review delves into the role of adipokines in cardiometabolic diseases, particularly emphasizing the intricate links between inflammation and insulin resistance in the context of obesity.

Keywords: Adipokine, Inflammation, Insulin Resistance, Cardiovascular Diseases, Diabetes, Fatty Liver.

Abbreviations: AMPK: AMP-activated protein kinase; APPL1: adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; BMI: body mass index; CAD: coronary artery disease; CVD: cardiovascular disease; CTRPs: C1q complement/tumor necrosis factor (TNF)–associated proteins; HMW: high-molecular weight; IRS: insulin receptor substrate; LEPR: leptin receptor; IL-6: interleukin 6; LMW: low-molecular weight; MAPK: mitogen-activated protein kinase; MMW: middle-molecular weight; NAFLD: non-alcoholic fatty liver disease; NF-kB: Nuclear factor kappa B; PAI-1: plasminogen activator inhibitor-1; PCOS: polycystic ovarian syndrome; PI3K: phosphoinositide 3-kinase; PBEF: pre-B cell colony enhancing factor; Ras: rat sarcoma viral oncogene; TLRs: toll-like receptors; TNF-α: tumor necrosis factor α; sFRP5: secreted frizzled related protein 5; wNT5a: Wnt family member 5A

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Introduction

Obesity constitutes a worldwide health crisis characterized by the excessive accumulation of lipids in adipose and peripheral tissues, precipitating a spectrum of metabolic maladies, notably encompassing insulin resistance, type 2 diabetes (T2D), hypertension, non-alcoholic fatty liver disease (NAFLD), polycystic ovarian diseases, and cardiovascular diseases (CVDs) (1, 2). Obesity, defined as a body mass index (BMI) equal to or exceeding 30 kg/m2, represents a multifaceted chronic ailment typified by the excessive accumulation of adipose tissue or body fat (3). According to data from the Non-Communicable Disease Risk Factor Collaboration, the worldwide prevalence of obesity exhibited a noteworthy upsurge from 1975 to 2016, varying from 3.7% in Japan to 38.2% in the United States (4). Despite this recognition, the global incidence of obesity continues to escalate, with the World Health Organization (WHO) projecting that one in every five adults worldwide will be afflicted by obesity by the year 2025 (4). Primarily, the etiology of obesity can be attributed to a scenario wherein the energy intake surpasses energy expenditure, a phenomenon influenced by genetic, physiological, and environmental factors (5). Indeed, genome-wide association studies have identified more than 300 single-nucleotide polymorphisms and 227 genetic variants related to obesity, though the functional repercussions of these genetic markers on the obese phenotype remain enigmatic (5-8). A growing body of evidence suggests that unhealthy lifestyles significantly contribute to obesity. Furthermore, the exposure to environmental endocrine disruptors, such as bisphenol A and perfluoroalkyl substances, amplifies the predisposition to obesity (9). Of particular concern, these acquired determinants not only disrupt the homeostasis of energy metabolism at the post-transcriptional level but also exert epigenetic modifications on individuals, thereby heightening the susceptibility of their offspring to obesity (9). In the context of burgeoning scientific and technological advancements, coupled with the burgeoning pharmaceutical sector, substantial progress has been achieved in the battle against obesity. Numerous strategies, encompassing calorie restriction, lifestyle management, pharmacotherapy, and bariatric surgery, have been suggested as interventions for combating obesity (10). Adipose tissue, traditionally seen as long-term energy storage, now plays a critical role in systemic metabolism through the secretion of proteins known as adipokines (11). Obesity can alter these secretions, driven by changes in the cellular composition of adipose tissue (12). Visceral and subcutaneous adipose tissues have unique adipokine profiles. Adipocytes are found in various body locations, and high-calorie diets can induce inflammation. Adipokines like adipsin, tumor necrosis factor α (TNF-α), leptin, plasminogen activator inhibitor-1 (PAI-1), and adiponectin have different roles, some contributing to metabolic disorders in obesity. The imbalance of pro- and anti-inflammatory adipokines production may lead to obesity-related complications. Adipokines are now recognized as key regulators of body homeostasis. This review primarily directs its attention towards the involvement of adipokines in mechanisms related to cardiometabolic diseases such as coronary artery disease (CAD), diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and polycystic ovarian syndrome (PCOS).

Inflammation and insulin resistance

Obesity and adipose tissue dysfunction contribute to a chronic low-grade inflammatory state, intricately linked to the genesis of obesity-related disorders, particularly metabolic dysfunction (13, 14). Dysregulated expression of adipokines, influenced by excessive adiposity and adipocyte dysfunction, plays a crucial role in the pathogenesis of various diseases through the modulation of immune responses (13, 15). A surge in research has been dedicated to unraveling the intricate immunoregulatory functions of adipose tissue. Within adipose tissue, macrophages play a pivotal role in orchestrating inflammation. In obesity, there is a significant influx of macrophages, particularly in visceral adipose tissue, emphasizing its crucial role in the development of insulin resistance (11). Intercellular communication within adipose tissue, involving adipocyte-derived anti-inflammatory factors like adiponectin and secreted frizzled related protein 5 (sFRP5), and macrophage-derived pro-inflammatory factors such as TNF-α and Wnt family member 5A (wNT5a), regulates metabolic functions (16). Under obesity conditions, TNF-α and wNT5a expression increases, while adiponectin and sFRP5 levels decline, perpetuating the pro-inflammatory milieu (17). The complexity of obesity-induced adipose tissue inflammation extends to macrophage subsets. In obese individuals, adipose tissue macrophages predominantly express genes associated with an M1 or ‘classically activated’ phenotype, promoting pro-inflammatory cytokines production. Conversely, lean adipose tissue macrophages exhibit an M2 or ‘alternatively activated’ phenotype, associated with anti-inflammatory responses and tissue repair (11, 18). Insulin resistance, a key component of the metabolic dysfunction, arises from disrupted insulin signaling (19). The pancreas, with its dual role in producing digestive enzymes and metabolic-regulating hormones, secretes insulin to control blood sugar levels, facilitates glucose uptake, glycogen storage, and regulate lipid production (20). Disruptions in the insulin signaling lead to systemic hyperglycemia, a hallmark of insulin resistance (19). At a molecular level, insulin binds to cell surface receptors, initiating a complex chain reaction involving various proteins and

pathways, particularly the phosphoinositide 3-kinase (PI3K)-AKT and rat sarcoma viral oncogene (Ras)-mitogen-activated protein kinase (MAPK) pathways (21). Insulin resistance can result from factors like mutations in the insulin receptor gene (INSR), changes in receptor expression, and downstream signaling abnormalities. Inflammatory cytokines such as TNF-α, interleukin 6 (IL-6), and IL-1β, exacerbate insulin resistance by degrading key proteins in the insulin signaling pathway (22, 23).

Adipokines as secretory factors from adipose tissue

Adipokines, bioactive molecules secreted by adipose tissue, play a pivotal role in the intricate relationship between inflammation and insulin resistance (24). These signaling molecules act as messengers, influencing both local and systemic responses within the adipose tissue microenvironment. Adipokines can either exacerbate or alleviate the inflammatory milieu, contributing to the development and perpetuation of insulin resistance (25). Notably, the dysregulated expression of adipokines, induced by the chronic low-grade inflammatory state associated with obesity, becomes a critical factor in shaping the metabolic landscape. Adiponectin, an adipokine with anti-inflammatory properties, tends to decline in obesity, while pro-inflammatory adipokines such as TNF-α and IL-6 become elevated. This imbalance in adipokine expression further amplifies the inflammatory cascade, fostering insulin resistance. Understanding the intricate interplay between adipokines, inflammation, and insulin resistance is essential for unraveling the complexities of metabolic dysfunction in obesity (26). This review aims to present evidence highlighting the correlation between adipokines and inflammation, as well as their association with insulin resistance in cardiometabolic diseases.

Adiponectin

Adiponectin, released from white adipose tissue, boasts a distinctive structure characterized by a collagen domain at its N-terminus and a globular domain at its C-terminus. Circulating in three molecular weight isoforms—low-molecular-weight (LMW) trimers, middle-molecular-weight (MMW) hexamers, and high-molecular-weight (HMW) multimers—adiponectin stands out for its association with enhanced insulin sensitivity and metabolic function (27). This multifunctional protein plays a pivotal role in various physiological processes, spanning inflammation, metabolic regulation, and cellular functions. Interacting with receptors like AdipoR1, AdipoR2, and T-Cadherin, adiponectin influences pathways linked to insulin sensitivity and glucose metabolism. Signaling proteins, such as adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) and APPL2, participate in multiple cascades, including AMP-activated protein kinase (AMPK), PI3K, insulin receptor substrate 2-1 (IRS1-2), shaping metabolic processes, inflammation, and vascular protection (27, 28). Adiponectin's involvement in inflammation is dual, acting both as an anti-inflammatory and pro-inflammatory agent depending on the context. Diminished adiponectin levels are correlated with obesity, insulin resistance, and inflammatory diseases (28-30). In inflammatory conditions like atherosclerosis, adiponectin showcases its anti-inflammatory prowess by diminishing the expression of pro-inflammatory factors and inhibiting nuclear factor kappa B (NF-κB) activation (31). In obesity and T2D, it curtails the secretion of pro-inflammatory cytokines, diminishes tissue damage, and modulates intricate signaling pathways. Adiponectin's collaboration with n-3 polyunsaturated fatty acids further reinforces its anti-inflammatory role in metabolic diseases (32). Circulating levels of adiponectin exhibit fluctuations in cardiometabolic diseases. Decreased levels have been observed in patients with conditions such as CAD (33), T2D (34), NAFLD (35), and PCOS (36). Numerous studies have demonstrated a correlation between adiponectin, insulin resistance, and inflammation in clinical settings (26, 35). In essence, adiponectin emerges as a versatile protein entwined in both metabolic and inflammatory processes. Its impact on various diseases, including atherosclerosis, obesity, and T2D, underscores its potential therapeutic significance in alleviating inflammation-related pathologies (28, 29).

Leptin

Leptin (LEP), a peptide hormone primarily originating from adipose tissue and encoded by the LEP gene, plays a crucial role in the regulation of body weight and energy expenditure (37). It typically presents in the bloodstream at levels around 16 ng/mL. Leptin reflects the energy stored in the adipose tissue and correlates with the degree of obesity (37). As a result, individuals with obesity generally exhibit higher leptin levels compared to those with leaner physiques (38, 39). While initially thought to primarily affect the brain, it has been discovered that leptin influences a broad range of physiological functions, both within the central nervous system and peripheral tissues. Over the past two decades, research on leptin has unveiled its intricate involvement in various aspects of nutrition, metabolism, reproduction, immune functions, and inflammation (38). Notably, leptin is produced not only by adipose tissue but also by other organs such as the stomach, skeletal muscles, pituitary cells, and the placenta, highlighting its multifaceted nature (40). The diverse role of leptin is underscored by the widespread distribution of its receptor, known as LEPR, which shares structural similarities with the class I cytokine receptor family. Researchers have identified at least six alternatively spliced forms of leptin receptor LEPR (LEPRa, LEPRb, LEPRc, LEPRd,

LEPRe, and LEPRf), each differing in the structure of their cytoplasmic regions (41, 42). The short isoform is found in nearly all peripheral tissues and is involved in transporting and degrading leptin, with distinct signaling capabilities such as activating the MAPK pathway. The long isoform, LEPRb, is concentrated in the hypothalamus, particularly in regions regulating appetite, body weight, and bone mass. Additionally, the soluble leptin receptor, a cleavage product, serves as the primary binding protein for circulating leptin, modulating its availability for biological functions (43). Leptin resistance, characterized by impaired signaling, is commonly observed in obesity, resulting in elevated leptin levels (hyperleptinemia). Since leptin acts as a pro-inflammatory adipokine, hyperleptinemia may contribute to the chronic inflammatory state associated with obesity (44). Conversely, chronic inflammation can impede leptin's actions, creating a feedback loop leading to leptin resistance by interfering with the leptin receptor signaling, particularly in the hypothalamus. This hypothalamic leptin resistance disrupts regulation of body weight, potentially contributing to the development of obesity (44). Leptin levels in circulation exhibit fluctuations in cardiometabolic diseases, providing clinical evidence of its functions. A systematic review and meta-analysis demonstrated an inverse relationship between leptin and the risk of CVD (45). Conversely, another study indicated that males with elevated leptin levels require more attention concerning the risk of CAD (46). The relationship between diabetes and leptin lacks consistency, possibly arising from obesity-related factors (47). Multiple studies have indicated a connection between hyperleptinemia and both the presence and severity of NAFLD (48). In summary, leptin, originating from adipose tissue, regulates body weight and energy expenditure, with levels reflecting adipose energy stores. Its influence extends beyond the brain, impacting diverse physiological functions. In cardiometabolic diseases, leptin's role is complex, showing both protective and concerning associations. Leptin resistance in obesity introduces further complications, emphasizing the need for ongoing research to understand its multifaceted roles and implications for therapeutic interventions.

CTRPs

The C1q complement/tumor necrosis factor (TNF)–associated proteins (CTRPs) superfamily, consisting of CTRP1-CTRP15, is a paralog of adiponectin. These proteins share a common structural domain with adiponectin, with a wide range of functions in the body (49, 50). There are several lines of evidence regarding the role of this family in insulin resistance and inflammation, and studies have shown changes in their levels in cardiometabolic diseases (51). CTRP1 plays a pivotal regulatory role in orchestrating low-grade chronic inflammation within coronary atherosclerosis (52). In response to inflammatory cues and pro-inflammatory cytokines, CTRP1 secretion increases, leading to upregulation of adhesion molecules and cytokines such as TNF-α, IL-6, and IL-1β. These effects are mediated through the activation of the p38 MAPK/ NF-kB pathway (53, 54). As a result, CTRP1 exerts a pro-inflammatory, pro-atherogenic influence, accelerating the deterioration of CAD (53). In addition, the level of CTRP1 is higher in patients with CAD compared to controls (55), similar results were found in patients with NAFLD and diabetes mellitus (56). CTRP3 has a robust anti-inflammatory adipokine effect, inhibiting pro-inflammatory pathways in monocytes. This impact leads to an anti-inflammatory, anti-apoptotic, and cardioprotective outcome (57). CTRP3's inhibitory effects on toll-like receptors (TLRs) and NF-κB signaling pathways result in reduced secretion of inflammatory adipo-cytokines, addressing insulin resistance and obesity-related chronic systemic anti-inflammatory responses (58, 59). Several studies have confirmed lower levels of CTRP3 in the context of T2D, NAFLD, and CAD (33, 34, 60, 61). CTRP9, as the closest paralog to adiponectin, indicates anti-inflammatory and anti-atherosclerotic effects, contributing a significant cardioprotective role (62). By stimulating the AMPK pathway, CTRP9 inhibits the expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 in endothelial cells (63). A study indicated elevated levels of CTRP9 in patients with diabetes mellitus and CAD, suggesting a potential compensatory response to insulin resistance and a pro-inflammatory milieu (64). CTRP12 is an anti-inflammatory adipokine which reduces pro-inflammatory cytokine expression and limits macrophage accumulation within the adipose tissue in mice. CTRP12 is associated with the secretion of inflammatory cytokines IL-6 and TNF-α, demonstrating its anti-inflammatory effect during the development and progression of CAD (65, 66).

Other adipokines

Visfatin, or pre-B cell colony enhancing factor (PBEF), stands out as a significant adipocytokine released by visceral fat adipocytes, contributing to a decrease in insulin resistance (67, 68). Originally identified as PBEF, visfatin has been associated with inflammatory conditions such as acute lung injury, and recent research has uncovered its upregulation in activated neutrophils, where it inhibits neutrophil apoptosis (69). Circulating levels of visfatin change during diabetes, obesity, and CVD, and a meta-analysis showed that visfatin can be a good predictor for these diseases (70). Resistin, initially identified for inducing insulin resistance in mice, is a member of the resistin-like molecules (RELMs) family, implicated in inflammatory regulation. It circulates in high-molecular-weight hexamers and

bioactive low-molecular-weight complexes (71). Its mRNA is present in various tissues in both mice and humans, with synthesis occurring in different cell types, including adipocytes, muscle, pancreatic cells, and mononuclear cells. The evolutionary non-conservation between human and mouse resistin suggests species-specific differences. Human resistin, upregulated by pro-inflammatory cytokines, plays a role in immunity by inducing TNF-α and IL-6 expression, contributing to arthritis in mice (72). Resistin levels were found to be higher in patients with diabetes mellitus (73). Similarly, patients with CAD and NAFLD indicated higher resistin levels compared to controls (74, 75).

Conclusion

Obesity poses a significant global health challenge, leading to various metabolic disorders. The interplay of genetic, physiological, and environmental factors contributes to its prevalence. Advances in science have provided diverse strategies for intervention, including lifestyle changes and pharmaceutical approaches. Adipose tissue, traditionally viewed for energy storage, now plays a critical role in systemic metabolism through the secretion of adipokines. This review has focused on the role of various adipokines in the pathogenesis of cardiometabolic diseases, emphasizing the link between inflammation and insulin resistance in obesity. Key players include adiponectin, leptin, and the CTRPs superfamily (CTRP1, CTRP3, CTRP9, and CTRP12), each influencing inflammation, insulin resistance, and atherosclerosis. Understanding the intricate relationship between adipokines, inflammation, and insulin resistance is crucial for unraveling the complexities of metabolic dysfunction in obesity. Adipokines emerge as potential therapeutic targets for mitigating inflammation-related pathologies in obesity and related disorders, warranting ongoing research to deepen the understanding of their roles and implications.

Conflict of Interest

Author has no conflict of interest.

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