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The Role of Adipokines and Myokines in the Crosstalk between Obesity and Type 2 Diabetes

Nambi Namusisi H.

School of Natural and Applied Sciences Kampala International University Uganda

ABSTRACT

Obesity and type 2 diabetes mellitus (T2DM) are intricately linked metabolic disorders with global health implications. The crosstalk between adipose and skeletal muscle tissues, primarily mediated through secreted signaling molecules like adipokines and myokines which plays a pivotal role in the development and progression of these diseases. Adipokines such as leptin, adiponectin, resistin, and visfatin influence systemic insulin sensitivity and inflammatory responses. Concurrently, myokines like irisin, interleukin-6 (IL-6), and myostatin regulate muscle metabolism, glucose homeostasis, and adipose tissue function. This manuscript explores the complex interplay between adipokines and myokines in obesity-induced insulin resistance and the pathogenesis of T2DM. Understanding this inter-organ communication network reveals novel therapeutic targets and strategies for the integrated management of obesity and T2DM.

Keywords: Adipokines, Myokines, Obesity, Type 2 Diabetes, Insulin Resistance, Crosstalk, Inflammation, Metabolic Syndrome

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are central components of the global epidemic of metabolic syndrome, a cluster of interrelated conditions that also includes hypertension, dyslipidemia, and insulin resistance[1–4]. These metabolic disorders are responsible for substantial morbidity and mortality worldwide and contribute significantly to escalating public health and economic burdens. Traditionally, the pathophysiology of obesity and T2DM has been attributed to a complex interplay of genetic predisposition, lifestyle choices such as poor diet and physical inactivity, and environmental exposures. However, emerging research has uncovered another critical layer of complexity which are inter-organ communication facilitated by bioactive molecules secreted by metabolically active tissues, particularly adipose tissue and skeletal muscle[5–8].

Adipose tissue, once considered merely a passive reservoir for excess energy storage, is now recognized as a dynamic endocrine organ[9–11]. It secretes a diverse range of signaling proteins known as adipokines, including leptin, adiponectin, resistin, visfatin, and tumor necrosis factor-alpha (TNF-α), among others[12–14]. These molecules regulate a wide array of physiological functions such as appetite control, glucose and lipid metabolism, immune responses, and insulin sensitivity. In healthy individuals, adipokines help maintain metabolic balance. However, in the context of obesity, adipose tissue undergoes structural and functional changes that alter its secretory profile marked by increased production of pro-inflammatory adipokines and decreased levels of protective ones like adiponectin[15–17]. This imbalance contributes to chronic low-grade inflammation, insulin resistance, and impaired glucose homeostasis, ultimately facilitating the onset and progression of T2DM.

Similarly, skeletal muscle, which accounts for approximately 40% of total body mass and serves as a major site for glucose disposal, is also a critical endocrine organ. It secretes a variety of cytokines and peptides termed myokines, including irisin, myostatin, interleukin-6 (IL-6), fibroblast growth factor-21 (FGF-21), and brain-derived neurotrophic factor (BDNF)[18, 19]. These molecules are produced in response to muscle contraction and play important roles in regulating metabolism, promoting lipid oxidation, enhancing insulin signaling, and modulating inflammatory pathways. Unlike adipokines, many myokines exert anti-inflammatory and insulin-sensitizing effects. Therefore, physical activity, which stimulates myokine release, has protective effects against obesity and T2DM by improving muscle-adipose tissue crosstalk and restoring metabolic balance[19].

The interplay between adipokines and myokines forms a sophisticated network of communication that governs whole-body energy homeostasis. In healthy states, this crosstalk promotes efficient glucose uptake, lipid

utilization, and inflammatory control. However, in obesity, this equilibrium is disrupted[20]. Excess adiposity leads to increased secretion of deleterious adipokines and reduced expression of beneficial ones, while physical inactivity diminishes myokine production. The resulting imbalance exacerbates insulin resistance, inflammation, and ectopic fat deposition in peripheral tissues, thereby accelerating metabolic dysfunction and the development of T2DM[20].

Understanding the molecular mechanisms underlying adipose-muscle communication is crucial for identifying new therapeutic targets. For instance, strategies aimed at increasing adiponectin levels or enhancing the expression of beneficial myokines like irisin and FGF-21 could offer promising interventions for mitigating insulin resistance and improving glycemic control[21]. Furthermore, exercise mimetics and pharmacological agents that modulate adipokine and myokine pathways are being actively explored for their potential to treat or prevent obesity-related metabolic diseases.

In sum, the intricate dialogue between adipokines and myokines plays a pivotal role in orchestrating metabolic health. Disruption of this communication in obesity leads to systemic metabolic derangements and facilitates the onset of T2DM. Targeting these bioactive mediators to restore inter-organ crosstalk represents a novel and promising avenue for therapeutic intervention. Continued research in this field will be essential to fully elucidate the complex regulatory networks involved and translate these insights into clinical practice for the effective management of metabolic syndrome.

Adipokines: Mediators of Adipose Tissue Function in Metabolic Regulation

Leptin

Leptin, a 16-kDa hormone encoded by the *ob* gene, is predominantly secreted by white adipose tissue and plays a central role in regulating energy homeostasis[22]. It functions primarily by acting on specific receptors in the hypothalamus, where it suppresses appetite and increases energy expenditure, promoting satiety and preventing excessive weight gain under normal physiological conditions[23, 24]. However, in obesity, leptin levels are paradoxically elevated due to increased fat mass, yet its effectiveness is markedly reduced a phenomenon termed leptin resistance. This resistance undermines the feedback mechanism that would typically reduce food intake and enhance energy utilization, thereby perpetuating weight gain and metabolic disturbances.

Beyond its central actions, leptin also exerts significant peripheral effects, particularly in modulating glucose metabolism, insulin sensitivity, and immune responses[25]. It has been implicated in the pathogenesis of insulin resistance through the promotion of a pro-inflammatory state. Leptin enhances the expression and secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), contributing to the chronic low-grade inflammation observed in obesity and type 2 diabetes mellitus (T2DM)[23]. Consequently, leptin serves as a critical link between adiposity, inflammation, and metabolic dysfunction, making it a potential target for therapeutic interventions in metabolic syndrome.

Adiponectin

Adiponectin is a 30-kDa protein secreted predominantly by adipocytes and stands out among adipokines due to its inverse relationship with body fat[21, 23]. Unlike leptin, circulating levels of adiponectin decrease with increasing adiposity. It plays a crucial role in enhancing insulin sensitivity, exerting anti-inflammatory effects,[23] and protecting against atherogenesis. Its metabolic actions are mediated through the activation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α) signaling pathways. These pathways stimulate glucose uptake in skeletal muscles and promote fatty acid oxidation in both liver and muscle, thereby improving systemic glucose and lipid metabolism[5].

In obesity and T2DM, reduced adiponectin levels referred to as hypoadiponectinemia are associated with impaired insulin action, increased hepatic glucose production, and ectopic lipid accumulation[26, 27]. Furthermore, low adiponectin levels contribute to endothelial dysfunction and increased risk of cardiovascular disease. Adiponectin also exerts anti-inflammatory effects by inhibiting nuclear factor-kappa B (NF-κB) signaling and reducing the expression of pro-inflammatory cytokines, thus counteracting the inflammatory milieu of obesity[26].

Therapeutic approaches aimed at increasing adiponectin levels—either through lifestyle interventions, pharmacological agents, or nutritional modulation—have shown promise in restoring insulin sensitivity and mitigating obesity-related metabolic and cardiovascular complications, underscoring its importance in metabolic homeostasis.

Resistin

Resistin, a cysteine-rich polypeptide initially identified in rodents, has garnered significant attention for its role in linking obesity to insulin resistance and inflammation. In mice, resistin is primarily secreted by adipocytes; however, in humans, its major source is mononuclear leukocytes, including macrophages[28]. Despite these species differences, resistin remains strongly associated with obesity and type 2 diabetes mellitus (T2DM). It disrupts insulin action by impairing insulin receptor substrate (IRS) signaling and reducing glucose uptake in peripheral tissues, thereby contributing to systemic insulin resistance[29].

Additionally, resistin acts as a pro-inflammatory cytokine, activating nuclear factor-kappa B (NF-κB) and promoting the expression of interleukins, TNF-α, and other inflammatory mediators[30]. These actions perpetuate a chronic inflammatory state, further exacerbating insulin resistance and increasing cardiovascular risk. Elevated plasma resistin levels have been linked to increased incidence of T2DM, atherosclerosis, and coronary artery disease. Its involvement in endothelial dysfunction, vascular inflammation, and plaque formation suggests a pivotal role in metabolic and cardiovascular pathology[30].
Given its dual role in metabolic dysfunction and inflammation, resistin is being explored as both a biomarker and potential therapeutic target. Understanding the precise mechanisms by which resistin influences metabolic and immune pathways may lead to novel strategies for managing obesity-related disorders[31].

Visfatin

Visfatin, also known as nicotinamide phosphoribosyltransferase (NAMPT) or pre-B-cell colony-enhancing factor (PBEF), is a multifaceted adipokine predominantly secreted by visceral adipose tissue. Initially identified for its insulin-mimetic effects, visfatin has been shown to bind to the insulin receptor at a site distinct from insulin and stimulate glucose uptake in adipocytes and myocytes[32]. These actions suggested its potential in improving glycemic control. However, subsequent studies have produced conflicting results regarding its metabolic functions, leading to ongoing debate about its physiological relevance in glucose homeostasis[32].
In obesity and T2DM, circulating visfatin levels are frequently elevated and correlate positively with markers of insulin resistance, inflammation, and visceral fat accumulation. Visfatin has been shown to promote the expression of pro-inflammatory cytokines, including TNF-α and IL-6, and to activate NF-κB signaling, thereby contributing to the chronic inflammatory state characteristic of metabolic syndrome[33]. It also participates in nicotinamide adenine dinucleotide (NAD^+) biosynthesis, influencing cellular energy metabolism, oxidative stress responses, and aging. While visfatin's precise physiological role remains controversial, its upregulation in obesity and its involvement in inflammation and metabolic dysregulation highlight its potential significance[33]. Further research is needed to clarify whether targeting visfatin may be beneficial in treating metabolic diseases.

Myokines: Skeletal Muscle as an Endocrine Organ in Metabolic Health

Irisin

Irisin is a myokine produced through the proteolytic cleavage of the membrane protein fibronectin type III domain-containing protein 5 (FNDC5), primarily in response to physical exercise[34]. It is regarded as a key molecular link between skeletal muscle and adipose tissue, mediating some of the metabolic benefits of exercise. One of its hallmark functions is to induce the browning of white adipose tissue, thereby promoting non-shivering thermogenesis via increased expression of uncoupling protein 1 (UCP1) in mitochondria[35]. This leads to enhanced energy expenditure and can help combat obesity and metabolic disorders. Additionally, irisin activates AMP-activated protein kinase (AMPK) signaling pathways, facilitating glucose uptake and fatty acid oxidation in skeletal muscle cells, improving insulin sensitivity[35]. Moreover, irisin exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines such as TNF-α and IL-6 when derived from adipose tissue[36]. Reduced levels of circulating irisin are often observed in sedentary individuals, obese patients, and those with type 2 diabetes mellitus (T2DM), indicating its essential role in metabolic homeostasis. These findings suggest that restoring or enhancing irisin levels through exercise or pharmacological agents could serve as a promising strategy for managing metabolic syndrome and improving insulin responsiveness in T2DM patients[36].

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a multifunctional cytokine with both pro-inflammatory and anti-inflammatory properties, depending on its source and context of action. In the setting of skeletal muscle, IL-6 is acutely released during exercise in response to muscle contractions[37]. Exercise-induced IL-6 plays a beneficial metabolic role by enhancing glucose uptake, promoting lipolysis, and activating AMPK signaling independently of insulin, thereby improving whole-body insulin sensitivity[37]. This muscle-derived IL-6 is considered a protective myokine that facilitates the crosstalk between muscle and other metabolic organs. However, in obesity and metabolic syndrome, chronically elevated IL-6 levels—particularly from adipose tissue contribute to a state of low-grade systemic inflammation[38]. This persistent elevation leads to insulin resistance by interfering with insulin receptor signaling and increasing hepatic glucose production. Therefore, IL-6 acts as a double-edged sword: transient elevations during physical activity support metabolic adaptation, while chronic overproduction, particularly in the absence of regular exercise, exacerbates metabolic dysfunction.[38] Understanding the dual roles of IL-6 is crucial in designing targeted therapies. Modulating IL-6 signaling may offer a therapeutic avenue enhancing its beneficial effects via exercise or mimetics while mitigating the harmful consequences of adipose-derived IL-6 in obese and diabetic individuals.

Myostatin

Myostatin, also known as growth differentiation factor 8 (GDF-8), is a member of the transforming growth factor-beta (TGF-β) superfamily and serves as a negative regulator of skeletal muscle growth[39]. It is predominantly expressed in skeletal muscle and inhibits myoblast proliferation and differentiation. Elevated

myostatin levels are linked to muscle atrophy, decreased lean body mass, increased fat deposition, and impaired metabolic health. In the context of metabolic diseases, myostatin negatively influences glucose metabolism by suppressing AMPK activity and reducing insulin-stimulated glucose uptake in muscle cells, thereby promoting insulin resistance[39].

Moreover, high levels of myostatin contribute to lipid accumulation and systemic inflammation, further exacerbating metabolic dysfunction in obesity and type 2 diabetes[40]. Conversely, experimental inhibition of myostatin—either through genetic deletion, antibodies, or pharmacological agents—has demonstrated profound metabolic benefits in animal models. These include increased muscle mass, enhanced insulin sensitivity, improved glucose tolerance, and reduced fat mass[40]. Such findings underscore the potential of myostatin antagonists as therapeutic strategies for sarcopenic obesity and insulin-resistant conditions[40]. Therefore, targeting myostatin may serve dual purposes: promoting muscle hypertrophy and combating the metabolic complications associated with obesity and T2DM, making it a valuable target in future metabolic disease management.

Adipokine–Myokine Crosstalk in Obesity and Type 2 Diabetes

Adipokines and myokines are bioactive molecules secreted by adipose tissue and skeletal muscle, respectively, which regulate energy balance, insulin sensitivity, inflammation, and metabolism[41]. In healthy, lean individuals, these mediators engage in a harmonious crosstalk that maintains metabolic homeostasis. For instance, adiponectin enhances insulin sensitivity, exerts anti-inflammatory effects, and facilitates lipid oxidation, while exercise-induced myokines like irisin and IL-6 promote glucose uptake and browning of white adipose tissue[42].

However, obesity disrupts this delicate balance, leading to a pathological shift in adipokine and myokine profiles. Pro-inflammatory adipokines such as leptin, resistin, and TNF-α become upregulated, while beneficial adipokines like adiponectin are suppressed[43]. Simultaneously, the lack of physical activity in obese individuals reduces the secretion of protective myokines such as irisin and IL-6 (from skeletal muscle), contributing to systemic inflammation and insulin resistance. This maladaptive state fosters the development and progression of type 2 diabetes.

Importantly, exercise can restore this balance by inducing myokine production, which in turn improves adipokine profiles and reduces inflammation[43]. For example, IL-6 released during exercise stimulates adiponectin release and inhibits pro-inflammatory cytokines[44]. Furthermore, these signaling molecules influence not only insulin sensitivity but also pancreatic β-cell function and survival. Therefore, restoring adipokine-myokine communication represents a promising strategy for preventing or treating obesity-linked metabolic diseases.

Molecular Mechanisms Underpinning the Crosstalk

The adipokine–myokine axis represents a complex network of signaling interactions between adipose and muscle tissues that play critical roles in regulating systemic energy metabolism, particularly insulin sensitivity and glucose homeostasis[45]. This axis integrates hormonal and cytokine signals through various intracellular pathways that converge on the insulin signaling cascade, directly influencing metabolic function[46]. Adipokines such as adiponectin and leptin are key regulators within this axis. Adiponectin enhances insulin sensitivity by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α) pathways[47]. These pathways promote fatty acid oxidation in muscle and liver tissues, inhibit hepatic gluconeogenesis, and improve lipid metabolism, contributing to enhanced glucose uptake and energy expenditure[47]. Leptin, another adipokine, exerts its metabolic effects primarily through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. This not only influences appetite and energy expenditure through central nervous system actions but also plays roles in immune modulation and peripheral glucose metabolism[48].

In parallel, myokines cytokines secreted by skeletal muscle during contraction also modulate metabolic health. Irisin, cleaved from fibronectin type III domain-containing protein 5 (FNDC5), activates AMPK and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), promoting mitochondrial biogenesis and increasing glucose utilization. Interleukin-6 (IL-6), transiently released during acute exercise, enhances insulin signaling through the phosphoinositide 3-kinase (PI3K)/Akt pathway[49]. However, chronic IL-6 elevation from inflamed adipose tissue induces suppressor of cytokine signaling 3 (SOCS-3), which impairs insulin receptor signaling and promotes insulin resistance. Furthermore, obesity-associated inflammation activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun N-terminal kinase (JNK) pathways[49]. These pro-inflammatory routes disrupt insulin receptor substrate (IRS) function via serine phosphorylation, contributing to insulin resistance. The intricate balance between these anabolic and catabolic signals across the adipokine–myokine axis is essential for maintaining metabolic homeostasis and preventing metabolic disorders such as type 2 diabetes.

Therapeutic Implications and Interventions

Understanding the crosstalk between adipokines and myokines offers promising avenues for therapeutic intervention in obesity and T2DM. Strategies to enhance beneficial adipokines (e.g., adiponectin) or reduce

deleterious ones (e.g., resistin) are being explored through pharmacological agents, dietary modulation, and lifestyle interventions. Exercise remains a cornerstone therapy, not only for reducing adiposity but also for stimulating myokine production. Regular physical activity increases irisin and IL-6 secretion, promotes anti-inflammatory adipokine profiles, and improves insulin sensitivity.

Pharmacological agents targeting adipokines and myokines, such as myostatin inhibitors, adiponectin receptor agonists, or irisin mimetics, are under development. Nutraceuticals like omega-3 fatty acids and polyphenols also modulate adipokine and myokine secretion and function. Bariatric surgery, in addition to weight loss, alters adipokine profiles and improves insulin sensitivity. Understanding the endocrine functions of adipose and muscle tissues post-surgery may help optimize patient outcomes.

CONCLUSION

The interplay between adipokines and myokines constitutes a central mechanism in the pathophysiology of obesity and T2DM. Dysregulation of these signaling molecules contributes to insulin resistance, systemic inflammation, and metabolic derangements. The bidirectional communication between adipose and muscle tissues highlights the importance of integrated approaches to treatment, including exercise, nutritional intervention, and potential pharmacological modulation of adipokine and myokine signaling. Future research should focus on identifying novel adipokines and myokines, elucidating their signaling mechanisms, and exploring their potential as biomarkers or therapeutic targets. A better understanding of the adipose-muscle endocrine axis will facilitate the development of more effective strategies for the prevention and management of obesity-related metabolic diseases.

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