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Role of Adipokines In Insulin Resistance: Potential Implications In Translational Medicine- A Review Article

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Abstract

There is a clinical need for improved pharmacological therapies to help type II diabetic patients handle glucose better, as they are insulin insensitive. To do this, research on medication discovery has focused on figuring out how adipokines affect insulin resistance. This review compiles data on the functional significance of adipokines in insulin signalling, emphasizes numerous understudied new adipokines, and offers suggestions for further research.

Despite having anorexigenic effects, obese persons have high leptin levels and leptin resistance due to the hormone's poor blood-brain barrier transit. Higher leptin levels were linked to a higher incidence of type 2 diabetes mellitus in a five-year prospective analysis of white men without diabetes. Resistin stimulates the expression of TNF and IL-6 by human mononuclear cells, demonstrating its pro-inflammatory characteristics.

It may be possible to create new therapies for people with type 2 diabetes by comprehending the role and function of adipokines in mediating insulin resistance. However, there have only been a few investigations into the tissues and cells of human skeletal muscle to date. Prioritizing these human-in-vitro investigations may lessen the chance that potential therapeutics will fail in human clinical trials because it was assumed that results from animal validation studies would apply to humans.

Keywords: adipokine, insulin resistance, Leptin, adiponectin, diabetes

Introduction

Insulin-dependent tissues such as skeletal muscle, the liver, and adipose tissue exhibit diminished cellular responsiveness to insulin signalling, which is described as insulin resistance[1]. This concept of metabolic disturbance was first advanced as the underlying cause of diabetes in 1931 and confirmed by Sir Harold in 1936[2]. Most patients required substantially high doses of insulin to control their hyperglycemia in old years and further developed antibodies to therapeutic insulin, leading to resistance because early forms of insulin were impure and originated from nonhuman species[1]. However, in the current era of recombinant human insulin, anti-insulin antibodies do not rise to enough levels to interfere with insulin activity.

It has now been demonstrated that insulin insensitivity is a critical factor in type 2 diabetes (DM2) and malfunctioning of pancreatic cells. The International Diabetes Federation projects that there will be 700 million diabetics worldwide by 2045, up from the current 463 million, with 83.9% of cases occurring in low- and middle-income nations[3]. More than 60% of the world's burden of diabetes mellitus is borne by Asia, which is the hub of the epidemics of diabetes. The term "Asia Paradox" describes the quick socioeconomic and demographic transitions of the Asian people to a developed economy, apparent in the country's economic growth, urbanization, and nutritional change. India is the nation with the second-highest population with diabetes mellitus

globally, after China, with 69.2 million individuals having T2DM[4]. With worrying future forecasts and a 21.9% crude incidence of type 2 diabetes among the Indian adult population[5], this illness is one of the leading global causes of adult death.

Increased adiposity, which is associated with the dysregulated production of adipokines, causes inflammation, peripheral and systemic insulin resistance, and adipocyte dysfunction. Pro-inflammatory adipokines and anti-inflammatory adipokines are two types of adipokines; the former increases inflammation and insulin resistance, whilst the latter has a protective and advantageous effect[6]. Pathogenic alterations arise from an imbalance of the pro- and anti-inflammatory adipokines in the body. Patients with type 2 diabetes and obesity frequently have changed adipokine profiles, which increases metabolic risk and alters insulin sensitivity[7].

Additionally, insulin insensitivity plays a crucial role in the pathology of several other endocrine-metabolic conditions, including hypertension, dyslipidaemias, polycystic ovarian syndrome, metabolic syndrome, and cardiovascular disease[8]. There is a clinical need for improved pharmacological therapies to help type II diabetic patients handle glucose better, as they are insulin insensitive. Insulin resistance can be intellectualized and reframed as a distinct medical condition that can be treated with various pricey diabetes drugs, invasive peripheral and cardiovascular revascularization surgeries, and increased morbidity and death[9]. In order to do this, research on medication discovery has focused on figuring out how adipokines affect insulin resistance. This review combines information on the role that adipokines play in insulin signalling, highlights several recently discovered understudied adipokines, and makes recommendations for further studies.

More than 200 adipokines have been discovered through secretome analysis of human adipocyte culture media[10]. Thus, identifying new targets for therapeutic intervention may be made possible by comprehending the effect of these adipokines on insulin signalling, both functionally and molecularly. Here, we highlight many novel adipokines that have received little attention so far, summarise the significant studies that have been done so far on the functional impact of adipokines on insulin signalling, and offer some guidance for future research.

Aims and objectives:

1. To describe the role of several adipokines in insulin resistance
2. To establish the potential implications of adipokines favouring in translational medicine

Methodology:

The goal of this review article was to present the role of adipokines in insulin resistance and the potential implications of several adipokines in translational medicine from the past twenty years, its present scenario, and its future applications. Thus, high-quality data that met the study objectives were included. In addition, comprehensive investigations on articles available in renowned databases like Google Scholar, PubMed, Research Gate, and PMC articles were considered for literature review. The critical index words or phrases used during the literature search were adipokines, insulin resistance, adiponectin, diabetes, metabolism, inflammation in adipose tissues, pro-inflammatory adipokines, secretion, anti-inflammatory adipokines, Leptin, chemerin, resistin, insulin insensitivity, adipogenesis.

Inclusion criteria: Scientific articles addressing the study objectives and written in the English language were included in the literature review.

Exclusion Criteria: Studies published in languages other than English, literature that did not address the role of adipokines in insulin resistance, and literature dated before 2000 were excluded.

Pathophysiology of adipokine involvement in insulin resistance:

Adipose tissue serves as an energy reservoir that can supply energy in times of external nutritional constraint and has many complementary activities. However, during the past 20 years, adipocytes have solidified their place as actual professional endocrine cells that integrate eating habits, energy expenditure, and insulin sensitivity into the body's overall energy state. Additionally, adipose tissue has developed into a focal point for promoting regional and systemic sterile inflammation, a crucial component of obesity-related insulin resistance[11].

Additionally, it would seem that adipokines have distinct purposes in those with average weight compared to those who are obese. Adipokines influence physiological processes in lean people;

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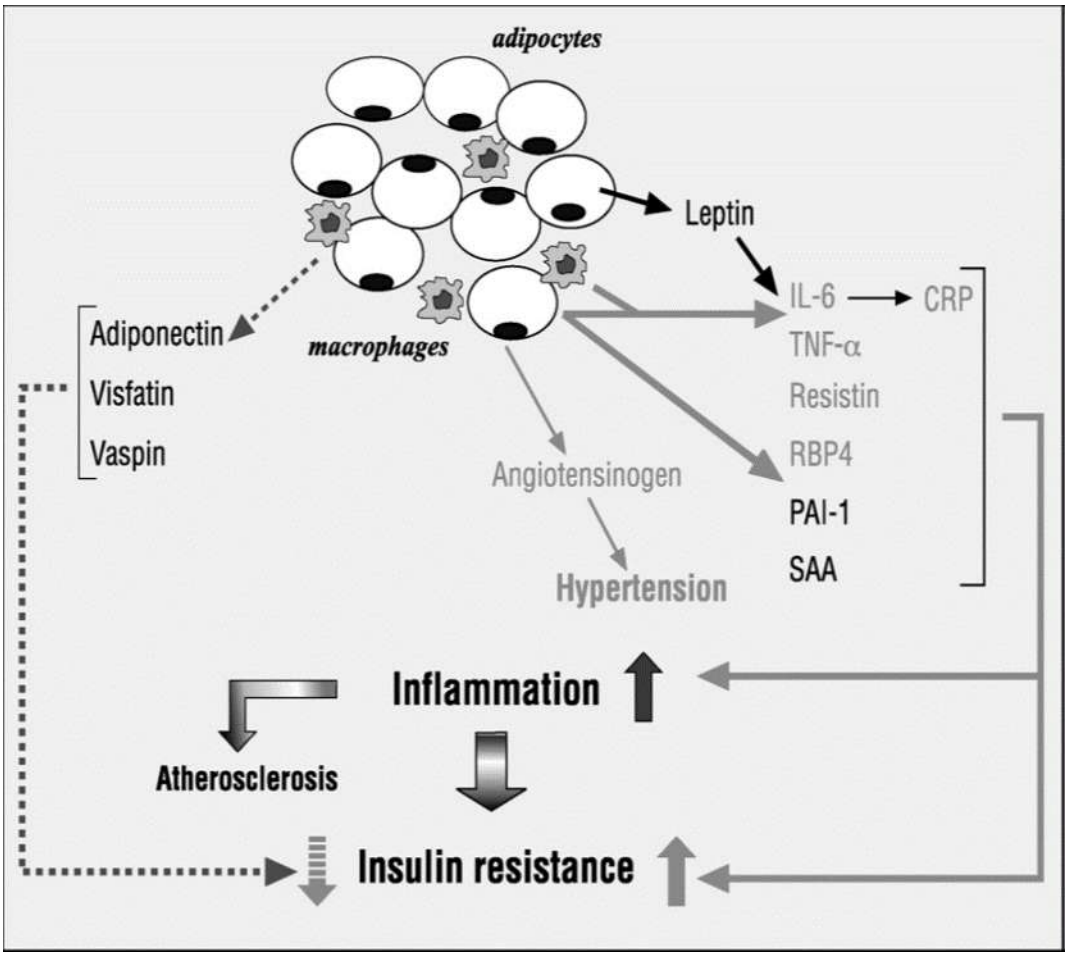
however, under conditions of metabolic illness, they have different effects, modifying insulin resistance by interfering with the insulin signalling system directly or indirectly by triggering inflammatory pathways. Insulin signalling pathways are disrupted, which may result in insulin resistance, by serine phosphorylating insulin receptor substrate (IRS) 1 by various adipocytokines, either directly or through the inflammatory pathway.

Figure 1 Adipokines' suppression of insulin signalling.[12]



Leptin: Despite having anorexigenic effects, obese persons have been shown to have high leptin levels and leptin resistance due to the hormone's poor blood-brain barrier transit. In both a trial of individuals with schizophrenia and a 14-year follow-up period, higher leptin levels were linked to an increased prevalence of metabolic syndrome. Higher leptin levels were linked to a higher incidence of type 2 diabetes mellitus in a five-year prospective analysis of white men without diabetes[13]. Systemic levels of Leptin are associated with the emergence of insulin resistance and have a favourable correlation with BMI and waist circumference. According to several studies, Leptin has been shown to affect insulin signalling in skeletal muscle.

Resistin: Human mononuclear cells are stimulated to produce TNF and IL-6, confirming this substance's pro-inflammatory properties in these cells. Additionally, this directly opposes the pro-inflammatory adhesion molecules in these cells, enhancing the anti-inflammatory effects of adiponectin on vascular endothelial cells. Leukocyte adhesion is boosted by this. The relationship suggests a function for resistin in developing insulin resistance in humans. There is an association between plasma resistin and both fat and insulin resistance. Recombinant resistin activation of C2C12 and L6

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myotubes reduces AKT phosphorylation and glucose absorption, according to in vitro studies. However, only lately have a few studies examined the functional significance of resistin in human skeletal muscle cells' development of insulin resistance[14,15].

Retinol Binding Protein-4: People with type II diabetes have greater plasma levels of RBP4 and transthyretin, which stabilizes RBP4 and lengthens its half-life. Numerous studies have emphasized the intriguing connections between RBP4 levels and plasma markers in the setting of metabolic syndrome. In those with early, untreated rheumatoid arthritis, higher RBP4 serum levels were linked to an increased risk of insulin sensitivity. It may play an essential part in the growth of atherosclerosis in obese individuals; however, more thorough research is required to ascertain how RBP4 impacts lipid profiles. It is still challenging to determine if this might be a novel valuable biomarker in cardiovascular diseases[16].

Adiponectin: It is thought to be a beneficial adipokine in terms of metabolism. The association between its plasma concentrations with respect to central obesity and insulin resistance is inverse. Maintaining a low-calorie diet also increases adiponectin circulatory concentrations and adipocyte expression. In animal models, adiponectin treatment increases insulin sensitivity, while adiponectin levels are low in obese persons. Subjects with obesity and insulin resistance showed lower adiponectin expression levels in their adipose tissue compared to lean individuals, which is associated with higher insulin sensitivity levels and reduced TNF expression levels. When overexpressed, adiponectin improves glucose tolerance and insulin sensitivity in mice, while adiponectin deficiency results in insulin resistance. The adiponectin receptors AdipoR1 and AdipoR2 are thought to have a role in mediating adiponectin's anti-metabolic actions and are reduced in obesity-related insulin resistance.

Visfatin: Regarding its role in modulating insulin insensitivity, it is overexpressed in male Wistar rats, further boosting insulin sensitivity and accelerating insulin-mediated IRS-1 phosphorylation in adipose tissue and the liver. Studies on mice are the only source of information on visfatin's role in skeletal muscle insulin sensitivity. In the fibres of rat skeletal muscle, visfatin enhances glucose transport. Additionally, visfatin increases GLUT4 expression and translocation, stimulates glucose uptake, and activates AMPK/p38 MAPK in C2C12 myotubes. These findings suggest that human skeletal muscle could have comparable insulin-sensitizing effects.

Vaspin: At this time, it is unknown how vaspin affects insulin signalling and metabolism in human skeletal muscle. Similar to vaspin, the receptor and mode of action have yet to be fully understood. According to a recent discovery, a 7KDa voltage-dependent anion channel known as glucose-regulated protein (GRP78) binds to vaspin in HepG2 cells. Additionally, recombinant vaspin activation of the rat hepatoma cell line stimulated the cell proliferation and survival signal pathways, which was stopped by GRP78 inhibition. Vaspin may interact with GRP78 to affect insulin signalling. However, at this time, neither functional investigations in human skeletal cells nor a profile of GRP78 expression in human adipose or skeletal muscle tissue have been done to confirm GRP78 as the vaspin receptor.

TNF-α: TNF levels in people with obesity are greater in their plasma and adipose tissue, and their circulating levels drop when they lose weight. This was also observed to correlate positively with other insulin resistance indicators, although acute TNF inhibitor therapy in obese diabetic patients lowered various other inflammatory markers without improving insulin resistance. Recent studies have confirmed that TNF plays a part in insulin resistance associated with obesity in humans by improving fasting blood sugar and raising adiponectin levels when anti-TNF inhibitor therapy is administered long-term to people with metabolic syndrome.

Plasminogen Activator Inhibitor-1(PAI-1): Through its function, plasminogen activator inhibitor-1 (PAI-1) operates as a significant negative regulator of fibrinolysis (tPA). It has been shown that adipose tissue, particularly tissue from the omentum, produces PAI-1, and this may play a significant role in the higher plasma PAI-1 levels seen in insulin-resistant individuals. When fed a high-fat/high-carbohydrate diet, experimental investigations in mice demonstrated protective benefits against obesity and insulin resistance. Similarly, early cross-sectional human investigations have shown links between higher PAI-1 concentrations and indicators of insulin resistance, impaired glucose tolerance (IGT), and

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type 2 diabetes (T2D). The importance of genetic control has been stressed in addition to the impact of the metabolic state on plasma PAI-1 levels, although new findings from family segregation research indicate that its involvement may be limited.

IL-6: The amount of circulating IL-6 declines after weight loss, and it is positively correlated with rising body weight and plasma-free fatty acids. It has been shown that it is increased in T2DM patients and increases the risk of T2DM in the future. Because of this, IL-6 appears to have a range of effects that may be brought on by acute or chronic effects such as exercise, tissue-specific actions in the liver/muscle or the source of IL-6 from adipose tissue/ muscle, all of which appear to affect the degree of inflammation and insulin resistance.

IL-18: Plasma IL-18 is lowered following weight reduction and is connected to changes in insulin resistance. Weight reduction has little impact on the AT expression of IL-18, showing that changes in plasma IL-18 are caused by insulin resistance rather than by changes in obesity per se. Cross-sectional studies have repeatedly found higher levels of circulating IL-18 in people with type 2 diabetes mellitus. It has also been proposed that this may be a factor in microangiopathy, including nephropathy, in this population.

Table: 1 Summary of the impact of each adipokine on insulin resistance

Adipokines	Source	Mechanism of action on insulin resistance
Adiponectin	Adipocytes	serving as a biomarker for metabolic syndrome, particularly in elderly or perimenopausal women. Low levels of adiponectin were discovered in obese diabetic children, and a polymorphism in the adiponectin gene that causes low adiponectin levels has been linked to diabetes[17].
Resistin	Peripheral blood mononuclear cells (human), adipocytes (rodent)	activation of SOCS-3 reduces insulin-arbitrate signalling in adipocytes and inhibits cytokine signalling. [18]
Visfatin	Skeletal muscle, liver, lymphocytes, and adipose tissue	regulates JAK2/STAT3 and IKK/NF-kB signalling to cause insulin resistance. Furthermore, visfatin treatment raises inflammatory cytokines such as interleukin (IL)-6, tumour necrosis factor-alpha (TNF-), and IL-1[19].
Vaspin	Subcutaneous adipose tissue, skin, stomach, skeletal muscle	In HepG2 cells, GRP78 suppression reduced the AKT and AMPK signalling pathways after recombinant vaspin activation of H-4-II-E-C3 cells.[20]
TNF-α	Monocytes, Macrophages	reduces the insulin receptor's tyrosine kinase activity. Due to this, signalling pathways are changed, which can lead to insulin resistance and other disorder.[21]

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Leptin	Adipocytes	Leptin may facilitate insulin resistance, as seen by decreased IRS-1 phosphorylation and poor glucose uptake[22]
PAI -1	Adipose tissue	Higher LDL cholesterol levels, blood pressure, skin fold thickness, body mass index, and HOMA-IR are all positively correlated with metabolic syndrome components.[23]
IL-6	Adipocytes, stromal vascular fraction cells, liver, muscle	PPAR gamma, GLUT-4, and IRS-1 gene transcription inhibitory effects. As a result, IRS-1, or insulin-stimulated tyrosine phosphorylation, is reduced. [24].
IL-18	Stromal vascular fraction cells, dendritic cells, kupffer cells	It belongs to the IL-1 cytokine superfamily, controls both innate and acquired immune responses, and is a solid pro-inflammatory cytokine raised in metabolic syndrome linked to plaque destabilization [25].
RBP-4	Liver, adipocytes, macrophages	decreasing GLUT-4 in adipocytes encourages increased RBP-4 expression, which prevents insulin-mediated phosphorylation of insulin receptor substrate-1 (IRS-1), which can lead to insulin resistance.[26]

Novel adipokines:

Omentin is a secretory glycoprotein, also known as Intelectin-1, that is far more prevalent and preferentially located in visceral adipose tissue. The homologous genes omentin-1 and omentin-2 are located in the region of chromosome 1q22-q23 that has previously been associated with type 2 diabetes and share 83% of their amino acid sequences.[27,28].

Chemerin: A recently identified chemokine, chemerin is significantly expressed in the liver and white adipose tissue. In a cysteine protease-dependent way, when applied to active macrophages that express the chemerin receptor CMKLR1, it exerts potent anti-inflammatory effects (chemokine-like receptor-1). Chemerin's role as an insulin resistance trigger is supported by in vitro research. Chemerin pre-treatment decreased insulin-mediated glucose absorption by favouring the release of pro-inflammatory cytokines like IL-6 and TNF-α C2C12 myotubes[29].

Apelin: The endogenous ligand of the orphan G protein-coupled receptor known as APJ is discovered as apelin, which is expressed in various tissues, including the lung, mammary gland, and testis[30]. Apelin regulates fluid balance, heart rate, and metabolic processes in a variety of physiological ways.

Potential implications in translational medicine:

Adipokine activities are associated with obesity, metabolic dysfunction, rheumatic, and cardiovascular illnesses, according to experimental and clinical studies. The investigation of these molecules' role in the aetiology of various disorders is highly challenging due to their pleiotropic activities, which have both local and systemic metabolic, immunomodulatory, and other impacts. The pro- and

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anti-inflammatory effects that have been shown for the same molecule in several adipokines suggest that the presence of inflammation and disease may only influence their biological activities.

Although the cause-and-effect relationship has not been shown beyond a reasonable doubt, the evidence that is now available has thrown considerable light on the crucial function that is played by adipose tissue in metabolic syndrome. Therefore, future research on bioactive compounds released from adipose tissue will help us better understand how metabolic syndrome associated with obesity develops. It may also lead to the development of new treatment approaches to address the metabolic side effects of obesity and its prevention. It will also be beneficial to concentrate on the interactions between each adipokine signalling pathway and the many intracellular signalling cascades that are triggered by other stimuli in adipose tissue and other tissues.

With the discovery of adipokines, the idea of adipose tissue as a passive lipid storage depot was transformed into one of an active endocrine organ. Adipocytes, through a feedback loop involving substances secreted from them, were thought to be able to perceive the relative quantity of fat storage, according to theories that date back many years. Many adipokines from adipose tissue have now been discovered, and they may serve as biomarkers and biosensors. On the other hand, the creation and release of adipokines itself may contribute to the adipocyte's ability to sense nutrients, regulate cellular activity, and modify physiological processes.

Numerous adipokines have been shown to co-ordinately control a number of bodily energy homeostasis processes, including hunger, thermogenesis, and energy expenditure, in order to maintain a constant level of activity and adiposity. However, knowledge of the release of these adipokines and their relationship to the remodelling of adipose tissue during obesity is still, at best, elementary. The next significant obstacle on the road to a more thorough comprehension of the function of adipose tissue physiology in overall body energy balance will be the clarification of the molecular processes by which adipokines are generated and released from adipocytes.

The increased adipokine production associated with obesity and insulin resistance increases the risk of cardiovascular disease and creates new opportunities for therapeutic therapies. New approaches to lessen the load of pro-inflammatory adipokines will need to be incorporated into treating the metabolic syndrome. A novel family of anti-diabetic medications known as thiazolindiaones TZDs are involved in insulin sensitization. In addition to that, it is also been shown to decrease inflammatory proteins and their pro-inflammatory properties. As a result, they may be valuable supplements to lower the risk of cardiovascular disease in diabetes and insulin resistance linked to obesity. For instance, TZDs reduce the expression of TNF- α in adipose cells and the expression of VCAM-1 and ICAM-1 in endothelial cells that TNF produces- α.

Conclusion:

It may be possible to create new therapies for people with type 2 diabetes by comprehending the role and function of adipokines in mediating insulin resistance. However, there have only been a few investigations into the tissues and cells of human skeletal muscle to date. Prioritizing these human- in-vitro investigations may lessen the chance that potential therapeutics will fail in human clinical trials because it was assumed that results from animal validation studies would apply to humans.

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