"From Metabolic Signalling to Systemic Dysfunction: A Comprehensive Review of the Adiponectin-Leptin-Resistin Axis"

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Abstract
Obesity and Type 2 Diabetes Mellitus (T2DM) have evolved from individual lifestyle concerns into an overwhelming global public health crisis. Far from being a simple, passive energy dump, adipose tissue is now recognized as a highly active endocrine organ that dictates systemic metabolism. This review maps out the complex biochemical network governing the adiponectin-leptin-resistin axis and examines how its breakdown drives cellular and structural dysfunction. Under normal conditions, adiponectin coordinates insulin sensitivity and provides anti-inflammatory protection through the AdipoR1/2-AMPK pathway. However, as excess weight expands fat stores, this protective mechanism is compromised, leading to hypoadiponectinemia. Concurrently, a state of leptin resistance develops, turning what should be a vital satiety signal into a catalyst for chronic sympathetic overactivity and vascular stress. In humans, this metabolic breakdown is further aggravated by resistin, which is secreted by mononuclear cells and fuels persistent inflammatory responses by binding to TLR4 and CAP1 receptors. This shift in the adipokine balance sparks low-grade systemic inflammation, which directly triggers insulin resistance, metabolic syndrome, and cardiovascular decline. By exploring these molecular interactions, this paper emphasizes the clinical value of the Adiponectin-Leptin Ratio (ALR) as a predictive biomarker and highlights the therapeutic potential of restoring adipokine equilibrium to curb the rising global burden of metabolic diseases.

Keywords
Adipokines, Adipose tissue endocrine function, Insulin resistance pathways, Adiponectin-leptin ratio (ALR), Resistin inflammation, Metabolic syndrome mechanisms, Obesity-induced diabetes
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Introduction:
Obesity is no longer viewed as a simple lifestyle choice but as a chronic, relapsing condition fuelled by a complex mix of genetics, neurobiology, and socioeconomic factors.[1] These drivers have created "obesogenic environments" that have pushed the global number of people living with obesity past one billion. While once considered a burden of wealthy nations, obesity rates are now surging in low- and middle-income regions. [1] The physiological impact is severe: in 2021 alone, elevated BMI was linked to roughly 3.7 million deaths across the globe, primarily due to chronic illnesses like heart disease, diabetes, and cancer.[2]
The global burden of excess weight has reached critical proportions. By 2022, approximately 2.5 billion adults aged 18 and older were classified as overweight, with over 890 million of these individuals living with obesity.[1] This represents 43% of the global adult population, a striking increase from the 25% prevalence recorded in 1990. While regional disparities exist, with the South-East Asia and African Regions reporting a 31% prevalence compared to 67% in the America, the upward trend is nearly universal. Notably, the global prevalence of obesity alone has more than doubled since 1990, now affecting 16% of adults worldwide.[3] The paediatric landscape of the obesity epidemic is equally alarming, with an estimated 35 million children under the age of five classified as overweight in 2024.[2] This crisis is particularly acute in developing regions; for instance, Africa has seen a 12.1% increase in the number of overweight children in this age bracket since 2000. Geographically, the burden is heavily concentrated, with nearly half of the world's overweight or obese children under five residing in Asia. [3]
India is experiencing a rapid escalation of overweight and obesity across all demographic segments, signalling a burgeoning nationwide health crisis. Data from the National Family Health Survey (NFHS-5), 2019-21 reveals a staggering surge in prevalence over the last 15 years. Among children under five, rates rose by 127% (from 1.5% to 3.4%), while adolescents experienced even more dramatic increases: 125% for girls (2.4% to 5.4%) and a remarkable 288% for boys (1.7% to 6.6%). [4]
The adult population mirrors this trend, with prevalence nearly doubling among women (12.6%

to 24.0%) and increasing by 146% among men (9.3% to 22.9%). Projections suggest that by 2030, India will be home to over 27 million obese children and adolescents aged 5–19, representing approximately 11% of the total global burden. [5]

Overweight and obesity are characterized by the excessive accumulation of adipose tissue, which is clinically assessed using the **Body Mass Index (BMI)**—a surrogate marker for body fatness calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). [6] According to the World Health Organization (WHO), adults are classified as overweight if their BMI is greater than or equal to 25, while a BMI of 30 or higher signifies obesity. In paediatric populations under the age of five, these conditions are determined using weight-for-height measurements relative to the WHO Child Growth Standards median. For these children, overweight is defined as being more than 2 standard deviations above the median, whereas obesity is diagnosed when the measurement exceeds 3 standard deviations. [3,7]

Obesity primarily stems from a chronic imbalance between energy intake and expenditure, typically driven by overnutrition and a sedentary lifestyle. Excess energy is stored as triglycerides within adipose tissue (AT), which serves as a metabolic reservoir to be mobilized via lipolysis during nutrient deficits. [8] Beyond these behavioural drivers, obesity is a multifactorial condition influenced by family history, genetic predisposition, and the gut microbiome. Emerging research also highlights the critical role of epigenetics in obesity prevalence. These epigenetic marks can significantly alter a child's metabolic risk profile and may even be transmitted trans-generationally, suggesting that the "obesogenic" impact extends far beyond the individual to future generations. [9]

Excess adiposity is a powerful predictor of morbidity and mortality across major chronic conditions, including type 2 diabetes mellitus, hypertension, and hypercholesterolemia.[10] Diabetes mellitus arises from a complex interplay of biological and environmental influences and remains largely modifiable, with obesity acting as a dominant driver of its development. Recent epidemiological data highlight the rapidly increasing global burden of diabetes. [11] According to the International Diabetes Federation Diabetes Atlas 2025, 11.1% of adults aged 20–79 years (approximately one in nine) are living with diabetes, with over 40% remaining undiagnosed. [11] Additionally, about 374 million individuals have impaired glucose tolerance, and the number of adults with diabetes is projected to rise to around 853 million by 2045, representing a substantial global increase. [11,12]

The surging global prevalence of obesity and its robust association with Type 2 Diabetes have placed adipose tissue metabolism at the centre of modern clinical research.[13] Fundamentally, obesity is characterized as a state of chronic, low-grade systemic inflammation originating within the adipose tissue itself. [14, 15] As obesity progresses, adipose tissue expands through two distinct mechanisms: hypertrophy (the enlargement of existing adipocytes) and hyperplasia (the proliferation of new adipocytes). In advanced obesity, excessive hypertrophy can exceed the lipid storage capacity of these cells, triggering ectopic fat deposition in vital organs like the liver and fuelling the onset of metabolic syndrome. Conversely, while visceral adipose tissue can expand via hyperplasia, it is notoriously prone to inflammation. This inflammatory environment acts as a primary driver for metabolic disturbances and significantly elevates the risk of cardiovascular disease [16, 17].

Although lifestyle modification continues to be fundamental in preventing obesity, deeper insights into adipose tissue biology offer a crucial pathway to address the growing obesity burden and its associated metabolic complications.[18]

Adipose Tissue: Structure, Types, and Obesity

For decades, adipose tissue was largely overlooked, regarded merely as a passive energy reservoir. Recent discoveries, however, have revealed its critical roles in cellular and systemic signalling, sparking renewed scientific interest. [18] Adipose tissue is traditionally classified into two main types—white adipose tissue (WAT) and brown adipose tissue (BAT)—distinguishable by their characteristic colour. [19] The adipocytes within these depots differ physiologically, giving rise to specialized functions such as energy storage, thermogenesis, and metabolic regulation. Importantly, in conditions of obesity, these tissues undergo significant remodelling through adipocyte (hypertrophy and hyperplasia) along with inflammation, contribute to metabolic disturbances and increased disease risk. [18,20]

Adipose tissue is primarily composed of adipocytes, but a diverse array of other cells—including preadipocytes, lymphocytes, macrophages, fibroblasts, and vascular cells (Figure1)—also contribute to its growth, remodelling, and metabolic function. [21] In obesity, both the cellular composition and the phenotypes of individual adipose tissue cells undergo significant changes. Metabolically dysfunctional adipose tissue has been shown to produce excess extracellular matrix components, which can constrain tissue expansion and promote systemic metabolic dysregulation. These observations underscore the importance of intercellular communication for maintaining normal metabolic function. Macrophages, in particular, are more abundant in visceral adipose depots compared with subcutaneous fat, reflecting the critical role of visceral tissue in the development of insulin resistance. Interestingly, macrophage accumulation is also observed during the early phase of weight loss, likely as a response to increased adipose tissue lipolysis (Figure 2), highlighting the dynamic and adaptive nature of adipose tissue in both energy surplus and deficit. [21,24]

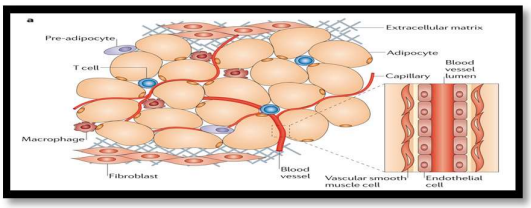

Figure1: Adipose tissue consists of preadipocytes, lymphocytes, macrophages, fibroblasts, and vascular cells

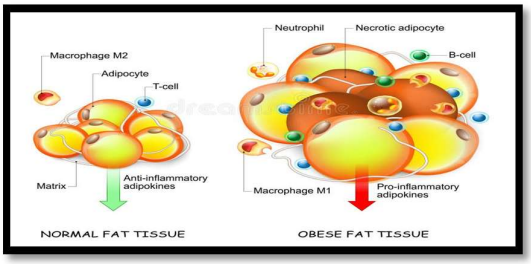

Figure 2: Normal Adipose tissue and Obese Adipose tissue with macrophages infiltration

Types of Adipose Tissue

In mammals, adipose tissue exists in two main forms: white and brown (Figure 3). White adipose tissue (WAT) constitutes the largest proportion of total body fat and is distributed around major organs, blood vessels in the abdominal cavity, and subcutaneously. WAT serves primarily as an energy reservoir, storing excess calories as triglycerides, and excessive accumulation—especially in visceral depots—is strongly associated with increased risk of cardiometabolic disorders, hypertension, and cardiovascular disease. In contrast, brown adipose tissue (BAT) comprises only about 4.3% of total adipose tissue in adult humans and is located in regions such as the cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal depots (Figure 4). In newborns, interscapular BAT is prominent but diminishes over time, becoming largely undetectable in adults. BAT is specialized for thermogenesis. Beyond developmentally established brown adipocytes, both humans and mice possess inducible brown-like adipocytes, known as beige or brite cells. These multilocular cells arise from a distinct developmental lineage, are interspersed within WAT, and express uncoupling protein 1 (UCP1) (Figure 3). Under baseline conditions or thermoneutrality, beige adipocytes resemble white adipocytes, with large lipid droplets and minimal thermogenic gene expression. However, exposure to cold, β-adrenergic stimulation, or exercise triggers a pronounced thermogenic program, a process referred to as "browning." [17,25,]

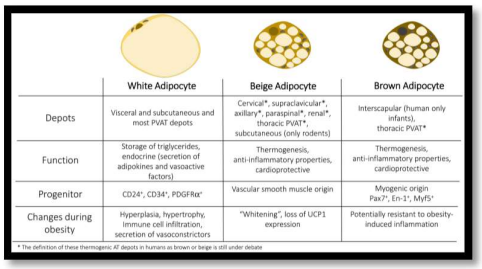

Figure 3: Types and functions of Adipocytes

Adipose Tissue as an Endocrine Organ

Adipose tissue is now understood to be a primary regulator of systemic metabolic balance, a role it fulfils largely through the release of various bioactive proteins known as adipokines. [27,28] The onset of obesity causes a significant shift in the secretory activity of these fat depots, driven by structural remodelling and changes in cellular makeup, including the quantity, phenotype, and arrangement of immune, vascular, and stromal cells. Furthermore, adipokine production is dependent on the anatomical location of the tissue. [21] Specifically, visceral and subcutaneous fat—the two most prominent depots—demonstrate unique secretion profiles that reflect their distinct contributions to metabolic health. [29] Beyond these primary sites, adipose depots are situated within various organs, including the heart, kidneys, lungs, bone marrow, and the adventitia of major blood vessels. Exposure to high-calorie diets has been shown to trigger a pro-inflammatory environment in these areas, mirroring the pathological changes observed in larger visceral and subcutaneous stores. [30] While the precise physiological roles of many of these localized depots are still being determined, evidence suggests that diet-induced changes in their adipokine output can directly influence the function of adjacent tissues. It should be noted that brown adipose tissue, which is functionally separate from white adipose tissue and found mostly in infants and hibernating animals, [21] is not addressed in this review.

White adipose tissue (WAT) serves as a prolific secretory organ, releasing a diverse array of proteins such as adipsin, angiotensin, retinol-binding protein, and acylation-stimulating protein. Its secretome also includes tissue factor, resistin, metallothionein, and plasminogen activator inhibitor-1, alongside inflammatory markers like interleukin-6 and tumour necrosis factor-alpha, and regulatory proteins such as adiponectin. [31] The dysfunction of WAT is considered a hallmark of obesity and is a primary driver of its associated metabolic disorders, most notably type 2 diabetes. In its hypertrophic state, WAT is distinguished by elevated rates of spontaneous lipolysis and an increased release of pro-inflammatory adipokines, both of which work in tandem to disrupt systemic metabolic stability. [32]

The impairment of white adipose tissue significantly fuels immune system imbalances, as the condition of obesity is defined by a persistent state of low-grade inflammation resulting from a

disproportionate release of adipokines and cytokines. [32] Because a functional immune response relies on a finely tuned cytokine environment, the metabolic health of the individual is compromised when adipocytes dysregulate the secretion of key factors like tumor necrosis factor-alpha, interleukin-6 (IL-6), and C-reactive protein. [33] In the context of obesity, there is a marked increase in the production of various adipokines, many of which possess pro-inflammatory properties that facilitate the development of metabolic complications. In addition to well-known factors such as leptin, TNF-α, and IL-6, the catalogue of inflammation-promoting adipokines continues to expand, now including resistin, retinol-binding protein 4 (RBP4), lipocalin-2, and interleukin-18. Other contributors to this pathological state include angiopoietin-like protein 2 (ANGPTL2), CC-chemokine ligand 2 (CCL2), CXC-chemokine ligand 5 (CXCL5), and nicotinamide phosphoribosyltransferase (NAMPT). Conversely, while pro-inflammatory signals dominate in obese states, adipose tissue is also responsible for a smaller subset of anti-inflammatory mediators. The most prominent among these is adiponectin, which has been widely researched for its role in providing metabolic protection and counteracting systemic inflammation. [21]

Adiponectin, leptin, and resistin (Figure 4) are among the most important adipokines regulating metabolic homeostasis. Owing to their distinct structural characteristics and diverse physiological roles, they play a crucial part in maintaining energy balance, modulating insulin sensitivity, and influencing inflammatory pathways. In conditions such as obesity and diabetes, altered secretion and impaired signalling of these adipokines significantly contribute to the development of insulin resistance and associated metabolic complications.[21,34] This review highlights their structural biology, physiological relevance, and pathological alterations, emphasizing their pivotal role in the pathogenesis of metabolic disorders.

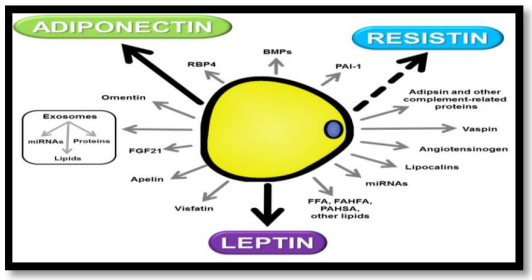

Figure 4: Adipokines secreted by Adipocytes

Materials and Methods

A literature review was conducted to evaluate the role of adiponectin, leptin, and resistin in obesity, insulin resistance, type 2 diabetes mellitus, and related metabolic disorders. Relevant articles were identified through a search of the PubMed/MEDLINE database using a combination of Medical Subject Headings (MeSH) terms and free-text keywords-

The search strategy included terms such as "adiponectin", "leptin", "resistin", "adipokines", "obesity", "overweight", "body mass index", "type 2 diabetes mellitus", and "insulin resistance". Articles published in English up to March 2026 were considered.

Inclusion Criteria: Human studies involving adults, observational studies, clinical trials, cohort studies, case-control studies, systematic reviews, meta-analyses, and review articles reporting the physiological functions, molecular mechanisms, or clinical significance of adiponectin, leptin, and resistin in obesity, diabetes, and related metabolic disorders were included.

Exclusion Criteria: Animal studies, paediatric studies, editorials, conference abstracts, letters to the editor, case reports, duplicate publications, and studies lacking relevant outcome data were excluded.

Titles and abstracts of retrieved articles were screened for relevance, followed by full-text evaluation of selected studies. Additional articles were identified through cross-referencing of relevant publications. Data relating to the structure, signalling pathways, physiological functions, and disease associations of adiponectin, leptin, and resistin were extracted and synthesized narratively to provide a comprehensive overview of the adiponectin–leptin–resistin axis in metabolic health and disease.

Adiponectin: The Protective Adipokine in Metabolic Disease

Adiponectin serves as a major peptide hormone and circulating adipokine, primarily released by white adipose tissue. It functions as a critical endocrine regulator, offering significant anti-inflammatory protection. By improving insulin sensitivity in both human subjects and obese animal models, it plays a vital role in maintaining metabolic equilibrium. [35] Structurally, this 244-amino acid monomeric protein has a molecular mass of roughly 26 kDa and stands as the most prevalent hormone secreted by white adipocytes. It is encoded by the *ADIPOQ* gene, which is mapped to chromosome 3q27. [36] Within the plasma, this hormone circulates at substantial concentrations ranging from 3 to 30 µg/mL, representing nearly 0.05% of the total serum protein. Despite its high availability, it is characterized by a rapid turnover rate, with a circulating half-life restricted to approximately 45–75 minutes. To facilitate its diverse physiological roles, it assembles into various oligomeric structures, specifically low-molecular-weight (LMW) trimers, medium-molecular-weight (MMW) hexamers, and high-molecular-weight (HMW) multimers (Figure 5). Among these, the HMW isoform is identified as the most potent and biologically significant configuration. The architectural framework of the protein consists of two primary domains: an N-terminal collagen-like region and a C-terminal globular domain. This C-terminal structure is particularly noteworthy due to its homology with the globular complement factor C1q. Furthermore, it displays a striking structural

resemblance to tumor necrosis factor-α (TNF-α), highlighting the complex evolutionary and functional links between metabolic regulators and inflammatory mediators.[36,37] Typically, women maintain higher plasma levels of both total and HMW adiponectin compared to men. This distinct sexual dimorphism suggests that sex-specific hormonal profiles significantly influence the circulating concentration of these adipokines.[38]

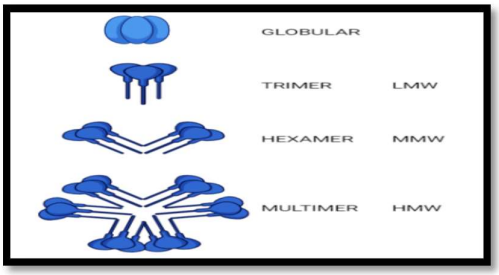

Figure 5: Structural Organisation of Adiponectin

Adiponectin- Mechanism of action

Biological effects are mediated through the cell surface receptors AdipoR1 and AdipoR2, (Figure 6) which show distinct tissue distribution; AdipoR1 is primarily found in skeletal muscle, whereas AdipoR2 is most prevalent in the liver (Figure 7). Interestingly, recent evidence indicates that skeletal muscle cells also produce adiponectin, which then acts locally via autocrine and paracrine mechanisms by binding to these same receptors. The signalling cascade involves the interaction between AdipoR1 and the adaptor protein APPL, which is characterized by its pleckstrin homology, phosphotyrosine-binding, and leucine zipper domains. When APPL binds to the intracellular portion of AdipoR1, it triggers the small GTPase Rab5. This activation is a critical step in facilitating the translocation of glucose transporter-4 (GLUT4) to the cell membrane, thereby boosting glucose uptake within the muscle tissue. Furthermore, the association of APPL with phosphatidylinositol 3-kinase (PI3K) and Akt suggests a significant convergence between adiponectin signalling and traditional insulin-dependent pathways to refine insulin sensitivity. [39,40] This process is augmented by the activation of AMP-activated protein kinase (AMPK), which not only increases muscular glucose consumption and lactate production but also serves to suppress gluconeogenesis.[41]

In addition to its role in glucose regulation, the synergy between APPL and AdipoR1 triggers the activation of AMP-activated protein kinase (AMPK). Once activated, AMPK phosphorylates and shuts down acetyl-CoA carboxylase (ACC), which effectively accelerates fatty acid oxidation. This AdipoR1-driven AMPK signalling pathway allows adiponectin to boost lipid metabolism, ultimately assisting in the reduction of overall adiposity. [41]

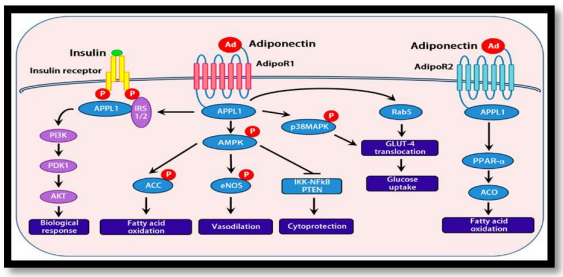

Figure 6: Receptors of Adiponectin: Mechanism of action

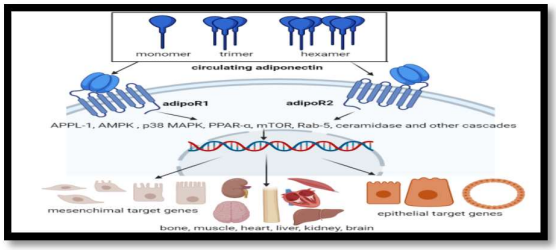

Figure 7: Adiponectin receptors on different organs like bone, muscle heart, liver, brain

Physiological functions of Adiponectin:

Acting as a central regulator of energy metabolism, adiponectin exerts broad pleiotropic effects across various tissues. [36] While it is best known for improving insulin sensitivity, it also triggers apoptosis in malignant cells and provides robust anti-inflammatory and antioxidant protection. These diverse properties allow it to produce specialized, tissue-specific responses throughout different organ systems.[35]

Role in Central Nervous System-

Adiponectin enters the Central Nervous System (CNS) by crossing the blood-brain barrier from the peripheral circulation, where it modulates essential neural functions such as satiety, energy balance, synaptic plasticity, and hippocampal neurogenesis. Once inside the brain, it regulates body weight and exerts anti-inflammatory effects by suppressing the activation of glial cells. [42] Furthermore, diminished levels of adiponectin in the dentate gyrus (DG) are linked to impaired neurogenesis, a factor critical to mood regulation; while stress typically inhibits the production of new neurons in the hippocampus, antidepressant therapies are known to promote this regenerative process.[43]

Role in Skeletal Muscle and Cardiac Muscle-

Adiponectin enhances insulin sensitivity and drives fatty acid oxidation through the coordinated activation of AMPK, p38 mitogen-activated protein kinase (p38-MAPK), and peroxisome proliferator-activated receptor-α (PPAR-α). [44] In skeletal muscle, it specifically facilitates metabolic efficiency by increasing glucose uptake and utilization. [45] Beyond these metabolic functions, the hormone provides significant cardio protection by boosting fatty acid uptake, amplifying insulin-stimulated glucose consumption, and promoting oxidative phosphorylation within cardiomyocytes. [35]

Role in Liver-

Adiponectin bolsters hepatic insulin sensitivity by simultaneously suppressing gluconeogenesis and accelerating both glycolysis and fatty acid oxidation. It achieves this by downregulating the transcription of critical gluconeogenic enzymes like phosphoenolpyruvate carboxy kinase (PEPCK) and glucose-6-phosphatase, which effectively curbs hepatic glucose output. [46] Furthermore, it limits lipid synthesis by inhibiting acetyl-CoA carboxylase (ACC) activity, thereby reducing malonyl-CoA levels. Since malonyl-CoA naturally blocks carnitine palmitoyl transferase-I (CPT-I), its reduction allows for more efficient mitochondrial transport and oxidation of long-chain fatty acids. Ultimately, through the activation of AMPK signalling, adiponectin shifts the liver's metabolic profile toward lipid utilization and away from triglyceride storage. [47]

The liver serves as the primary hub for metabolic control, with insulin functioning as the chief anabolic hormone. While both are essential, insulin and adiponectin drive distinct and frequently opposing metabolic responses within hepatic tissue, the details of which are outlined in below table no 1:

Metabolic Pathways	Effect of Insulin	Effect of Adiponectin
Glycogenesis	↑	-
Glycogenolysis	↓	↓
Gluconeogenesis	↓	↓
Lipid Synthesis	↑	↓
Fatty acid Oxidation	↓	↑
Glycolysis	↑	↑

Role in Kidney -

Adiponectin provides significant renoprotection, particularly in its ability to limit the progression of albuminuria. Research by Tsioufis et al. (2005) demonstrated that non-diabetic hypertensive men with microalbuminuria exhibit notably lower circulating levels of the hormone compared to those without the condition. These protective benefits stem largely from its anti-inflammatory and antioxidant properties. [48]

Role in Bone-

Higher levels of adiposity are generally linked with increased bone mass, while lower body fat is associated with reduced bone mineral density and a heightened risk of fractures. Beyond the effects of mechanical loading, the interaction between adipose tissue and bone is mediated through endocrine pathways involving adipokines. Among these, adiponectin plays a significant role in regulating the fat–bone axis. Importantly, circulating adiponectin levels are inversely correlated with bone mineral density, suggesting its involvement in the regulation of bone metabolism and skeletal integrity.[49]

Adiponectin exerts potent anti-inflammatory effects across various. It further mitigates vascular and cellular damage by suppressing ROS production and blocking pro-inflammatory mediators like CRP, NF-κB, and TNF-α. These combined mechanisms fundamentally stabilize the internal environment, offering a critical defence against inflammatory diseases such as atherosclerosis. [50]

Adiponectin and Disease: Lessons from Fat Biology

Adiponectin in Obesity-

Dysregulation of adiponectin production plays an important role in the development of metabolic diseases. Adiponectin acts as an insulin-sensitizing adipokine, improving insulin resistance and providing protection against metabolic syndrome. Its inverse association with obesity, diabetes, and other metabolic disorders highlights its potential as a non-invasive biomarker of metabolic health. Therefore, strategies aimed at increasing adiponectin levels may offer a promising approach for the prevention and management of hypoadiponectinemia-associated conditions. [51]

Beyond its well-established insulin-sensitizing role, adiponectin exerts important immunomodulatory and anti-inflammatory effects by regulating the activity of various immune cells and suppressing inflammatory signalling pathways in metabolic tissues. These actions contribute to reduced inflammation in adipose tissue, skeletal muscle, and liver, highlighting adiponectin as a potential therapeutic target in metabolic and inflammatory disorders. [52,53]

However, the role of adiponectin in inflammation remains complex and context-dependent. While numerous studies demonstrate its anti-inflammatory properties, others have reported pro-inflammatory effects in specific cell types and disease states. Emerging evidence suggests that adiponectin may exert either anti-inflammatory or pro-inflammatory actions depending on the cellular environment, metabolic status, and tissue involved. This dual nature underscores the need for further research to better understand its role in immune regulation, energy metabolism, and obesity-related disorders. [52,53]

Several studies have demonstrated an inverse relationship between adiposity and adiponectin levels. Hotta et al. (2000) [54] and Yang et al. (2001) [55]reported significantly reduced adiponectin concentrations in obese individuals, with levels increasing following weight-loss interventions. These findings suggest that adiponectin is negatively associated with body fat mass and positively associated with metabolic health. Supporting this observation, Delporte et al. (2003) found markedly elevated adiponectin levels in malnourished patients with anorexia nervosa who had extremely low body fat content compared with age- and sex-matched healthy controls. [56] Collectively, these studies indicate that adiponectin levels tend to increase with leanness and decrease with obesity.

Adiponectin and Diabetes-

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels and

is associated with complications affecting the kidneys, eyes, blood vessels, and nerves. Obesity is a major risk factor for the development of insulin resistance, which subsequently predisposes individuals to type 2 diabetes mellitus. Adipose tissue plays an important endocrine role by secreting adipokines such as adiponectin, which enhances insulin sensitivity, regulates glucose metabolism, promotes lipid oxidation, and helps maintain metabolic homeostasis. [35,57] Several studies have demonstrated an inverse relationship between circulating adiponectin levels and insulin resistance, suggesting that reduced adiponectin concentrations may contribute to the development and progression of type 2 diabetes mellitus. [35,58]

Genetic variations in the ADIPOQ gene have been associated with an increased risk of type 2 diabetes mellitus. [35] Adiponectin improves insulin sensitivity through several direct and indirect mechanisms:

1. **Reduction of triglyceride accumulation:** Adiponectin promotes fatty acid transport and oxidation by increasing the expression of molecules such as CD36 and acyl-CoA oxidase, thereby reducing triglyceride content in skeletal muscle and improving insulin signalling. [35,59]
2. **Enhancement of glucose uptake:** By facilitating GLUT-4 translocation, adiponectin increases glucose uptake into peripheral tissues and helps counteract insulin resistance. [35,59]
3. **Activation of PPAR-α pathway:** Adiponectin activates PPAR-α, leading to enhanced fatty acid oxidation, increased energy expenditure, and reduced lipid accumulation in liver and muscle tissues. [35]
4. **Activation of AMPK signalling:** Adiponectin stimulates AMP-activated protein kinase (AMPK), which promotes β-oxidation of fatty acids, improves glucose metabolism, and enhances insulin sensitivity. [35,60]

Enhancing adiponectin production has emerged as a potential therapeutic strategy for the prevention and management of cardiovascular and metabolic disorders, particularly because direct adiponectin supplementation remains challenging. Thiazolidinediones (TZDs), a class of oral antidiabetic agents, have been shown to increase adiponectin secretion through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) in adipocytes, thereby contributing to improved insulin sensitivity and metabolic regulation.[61]The clinical significance of adiponectin in metabolic health is further supported by numerous human studies and meta-analyses conducted over the past two decades, which consistently demonstrate altered adiponectin levels in the development and progression of diabetes mellitus (Table 2).

Study / Meta-Analysis	Year	Population / Design	Major Findings
Adiponectin, insulin resistance & metabolic syndrome in Type 2 Diabetes [62]	2006/2007	Type 2 Diabetes patients (clinical study)	Lower adiponectin in T2D associated with insulin resistance and metabolic syndrome features.
Adiponectin Levels and Risk of Type 2 Diabetes A Systematic Review and Meta-analysis [63]	2009	13 prospective studies (n ~14,598)	Higher adiponectin associated with lower risk of T2D; RR 0.72 per 1-log increase.
Serum adiponectin and type 2 diabetes: a 6-year follow-up cohort study. [64]	2013	Initially normoglycemic (n ~42,845)	Lowest adiponectin tertile had significantly higher future T2D risk.
Association between the level of circulating adiponectin and prediabetes: a meta-analysis. [65]	2015	Case-control & cohort (18 studies, ~41,841)	Circulating adiponectin significantly lower in prediabetes vs controls (WMD −1.694 µg/mL).
Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis [66]	2015	11–13 studies, n~2865 women	Circulating adiponectin predicted gestational diabetes with moderate accuracy (AUC ~0.78).
Serum Adiponectin Levels Are Positively Associated with Diabetic Peripheral Neuropathy	2020	Chinese Type 2 Diabetes patients (n -219)	Higher adiponectin associated with increased odds of diabetic neuropath

in Chinese Patients with Type 2 Diabetes [67]			y.
Adiponectin gene polymorphisms and risk of type 2 diabetes: updated evidence for meta-analysis. [68]	2021	Metanalysis of 21 studies evaluating ADIPOQ polymorphisms.	ADIPOQ (+276 G>T) genotype associated with higher Type 2 Diabetes risk in Europeans.
Linking adiponectin expression and kidney dysfunction among Indian patients with and without diabetic nephropathy. [69]	2022	Meta-analysis of 34 studies (n ~5254)	Adiponectin correlated positively with diabetic kidney disease severity.
Association of serum adiponectin level with glycaemic control and atherogenic lipid profile in Sudanese patients with type 2 diabetes mellitus. [70]	2025	Cross-sectional study (n – 302)	Lower adiponectin correlated with worse glycaemic control and adverse lipid profile.
The Cardioprotective Effects of Adiponectin in Diabetes [71]	2025	Narrative review	In T2D, adiponectin levels are typically reduced; lower HMW adiponectin and receptor dysfunction contribute to metabolic dysregulation.

Adiponectin and Cardiovascular Disease-

Clinical studies consistently demonstrate an inverse association between adiponectin and cardiovascular risk. Lower adiponectin concentrations have been reported in acute coronary syndrome, whereas higher circulating levels are associated with a reduced risk of myocardial infarction.[72] Furthermore, persistently low adiponectin levels following acute myocardial infarction have been linked to an increased risk of subsequent adverse cardiac events, highlighting its potential cardioprotective and prognostic significance.[72] Mechanistically, adiponectin exerts vasculo-protective effects by enhancing nitric oxide production and reducing endothelial activation, thereby preserving vascular function.[35] However, paradoxically elevated adiponectin levels have been observed in patients with heart failure, leading to ongoing debate regarding its utility as a reliable biomarker of cardiovascular disease.[35]

Adiponectin and Liver diseases-

Adiponectin is an important regulator of hepatic glucose and lipid metabolism, promoting glycolysis and fatty acid oxidation while suppressing gluconeogenesis through AdipoR1- and AdipoR2-mediated signalling pathways. Emerging evidence implicates hypoadiponectinemia in the pathogenesis of NAFLD, NASH, and hepatocellular carcinoma, with disease progression associated with reduced adiponectin levels, receptor expression, and downstream signalling. Conversely, higher adiponectin concentrations are linked to improved liver outcomes, highlighting its hepatoprotective role. These findings support the potential of adiponectin as both a biomarker and a therapeutic target in liver diseases, warranting further investigation into adiponectin-based therapies and the roles of its various isoforms. [73]

Adiponectin and Kidney Disease-

Accumulating evidence over the last two decades has established adiponectin as an important mediator in renal disease. Unlike its reduced levels in most metabolic disorders, circulating adiponectin concentrations are significantly elevated in patients with ESRD, reaching nearly twice those observed in individuals with normal renal function. Patients receiving haemodialysis or peritoneal dialysis exhibit even higher levels, suggesting that renal dysfunction markedly influences adiponectin homeostasis, while dialysis itself has limited impact on circulating concentrations. [74]

Elevated adiponectin levels have also been reported in diabetic nephropathy, particularly in advanced stages and in patients with severe albuminuria. This increase is largely driven by the high-molecular-weight (HMW) isoform, which is inversely associated with eGFR. Furthermore, higher baseline adiponectin concentrations have been linked to CKD progression in men and in individuals with type 1 diabetes, indicating its potential value as a prognostic biomarker in renal disease. [75]

Adiponectin and Rheumatoid arthritis-

Elevated serum adiponectin levels have been linked to a greater risk of rheumatoid arthritis, especially among obese individuals, indicating a potential role for adiponectin in disease susceptibility. [76]

Adiponectin and cancer-

The relationship between adiponectin signalling and cancer is multifaceted and involves the regulation of several intracellular pathways. [77] Through interaction with AdipoR1 and AdipoR2 receptors, signalling cascades such as AMPK, Fas ligand-mediated pathways, and JNK are activated, whereas Wnt, STAT3, PI3K/Akt, USP-2, and ERK1/2 pathways are suppressed. Furthermore, enhanced ceramidase activity promotes the conversion of ceramide to sphingosine-1-phosphate (S1P), contributing to its diverse biological effects. [78]

Alterations in adiponectin signalling have been implicated in the development and progression of various malignancies. Evidence suggests that dysregulated adiponectin activity may represent an important mechanistic link between obesity and colon cancer. [35] In breast cancer, reduced adiponectin expression accompanied by increased receptor expression has been reported, particularly in invasive disease. [35] Lower circulating adiponectin concentrations have also been associated with a higher risk of uterine cancer in women younger than 65 years, independent of BMI, ethnicity, IGF levels, and other recognized risk factors. [79] In contrast, higher adiponectin activity appears to confer protection against gastric and hepatic malignancies. [35]

Adiponectin and Alzheimer's Disease-

Neurodegenerative changes in Alzheimer's disease (AD) are characterized by the accumulation of β-amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein. Growing evidence suggests that impaired insulin signaling and cerebral insulin resistance play important roles in the pathogenesis of AD.[80] Since circulating adiponectin levels are inversely related to body weight, the weight loss commonly observed in patients with AD may influence serum adiponectin concentrations. Moreover, several therapeutic agents, including acetylcholinesterase inhibitors, PPAR-γ agonists such as thiazolidinediones, and certain lipid-lowering drugs including niacin and statins, have been shown to increase circulating adiponectin levels.[81]

Emerging studies indicate that reduced adiponectin concentrations or defective adiponectin signaling may contribute to cognitive decline and disease progression through disruption of insulin signaling pathways and diminished insulin sensitivity within the brain.[82] Conversely, increased adiponectin levels have been proposed to exert neuroprotective effects, suggesting a potential role for adiponectin in mitigating the progression of Alzheimer's disease.[81]

Leptin: The Satiety Signal Turned Pathological

Leptin is a 167-amino-acid peptide hormone encoded by the *ob* gene and is predominantly produced by white adipose tissue in proportion to body fat stores. Initially identified through studies in leptin-deficient (*ob/ob*) mice, it is now recognized as a key regulator of appetite, energy expenditure, and overall energy homeostasis through its actions on hypothalamic centres. [83] The biological functions of leptin are highly conserved across species owing to the preservation of critical structural features, including disulfide bond formation. Structurally, leptin belongs to the long-chain helical cytokine family, which also includes leukemia inhibitory factor, ciliary neurotrophic factor (CNTF), and human growth hormone. [83, 84]

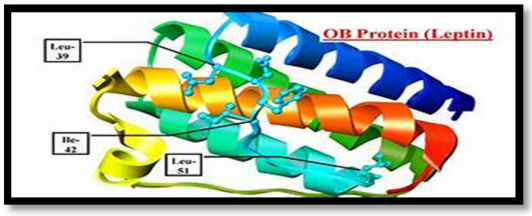

Figure 8: Structure of Leptin (OB protein)

Leptin- Mechanism of action

The leptin receptor (LepR) belongs to the type I cytokine receptor family and exists in multiple isoforms generated through alternative splicing, including short, soluble, and long forms. Among these, the long isoform (LepRb) contains an extended intracellular domain that is essential for signal transduction. Binding of leptin to LepRb promotes receptor oligomerization and initiates intracellular signaling through activation of Janus kinase 2 (JAK2). This subsequently triggers phosphorylation of STAT3, which translocates to the nucleus and regulates the expression of genes involved in appetite and energy homeostasis, including *POMC*. In addition to the JAK2–STAT3 pathway, leptin signaling also activates several downstream pathways such as PI3K–AKT, MAPK/ERK, AMPK, and mTOR, thereby mediating its diverse metabolic and physiological effects. [85] (Leptin-30-Years-Later-1)

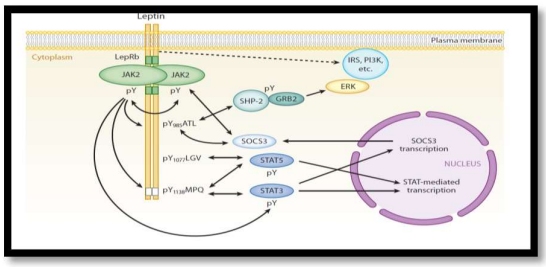

Figure 9: Mechanism of action of Leptin through JAK2–STAT3 pathway.

Physiological Functions of Leptin

Leptin serves as a key integrator of energy status and physiological function, linking adipose tissue stores with central mechanisms that regulate appetite and metabolism. Acting primarily through the hypothalamic arcuate nucleus, leptin stimulates anorexigenic POMC/CART neurons while inhibiting orexigenic NPY/AgRP neurons, thereby reducing food intake and promoting satiety. Beyond appetite regulation, leptin enhances energy expenditure through sympathetic activation and

thermogenesis and modulates reward-related feeding via the mesolimbic dopaminergic pathway. During periods of fasting or energy deficiency, a rapid decline in circulating leptin levels triggers adaptive responses aimed at conserving energy, including increased hunger and reduced metabolic expenditure. These actions establish leptin as a critical mediator of energy homeostasis and metabolic adaptation. [86,87]

Being a critical link between nutritional status and neuroendocrine function, Leptin ensure that energy-intensive physiological processes occur only when adequate energy reserves are available. [86] It is essential for normal reproductive function. Conditions associated with low leptin levels, such as hypothalamic amenorrhea, result in suppression of gonadotropin secretion and infertility. [88] Leptin also influences the thyroid axis by regulating thyrotropin-releasing hormone (TRH) expression, thereby maintaining basal metabolic rate. Furthermore, it modulates the hypothalamic–pituitary–adrenal axis and growth hormone secretion, although these effects may vary depending on physiological and pathological states. [89]

Beyond its central effects on appetite and endocrine regulation, leptin exerts significant metabolic actions independent of changes in body weight. It plays a crucial role in glucose homeostasis by improving insulin sensitivity and suppressing hepatic glucose production. [87,90] Additionally, leptin enhances lipid metabolism by promoting lipolysis and increasing fatty acid oxidation in peripheral tissues such as skeletal muscle and liver. An important protective function of leptin is its ability to prevent lipotoxicity by limiting ectopic lipid accumulation in non-adipose tissues, including the pancreas and skeletal muscle, thereby preserving organ function and metabolic integrity. [90]

Leptin also acts as an immunomodulatory molecule, linking energy availability with immune competence. It enhances innate immune responses by stimulating the activity of neutrophils and macrophages and promoting the production of pro-inflammatory cytokines. In the adaptive immune system, leptin favors T-helper 1 (Th1) responses while inhibiting regulatory T-cell proliferation, thereby promoting a pro-inflammatory state. While this is beneficial during acute infections, chronically elevated leptin levels, as observed in obesity, contribute to persistent low-grade inflammation and have been implicated in the pathogenesis of autoimmune disorders. [91]

Leptin also influences bone metabolism through both peripheral and central mechanisms. Peripherally, it promotes osteoblast differentiation and inhibits adipogenesis within bone marrow, thereby supporting bone formation. However, centrally mediated effects via hypothalamic pathways and sympathetic activation can inhibit bone formation, indicating a complex dual regulatory role. The net effect of leptin on bone metabolism is therefore dependent on the balance between its peripheral anabolic and central inhibitory actions. [92]

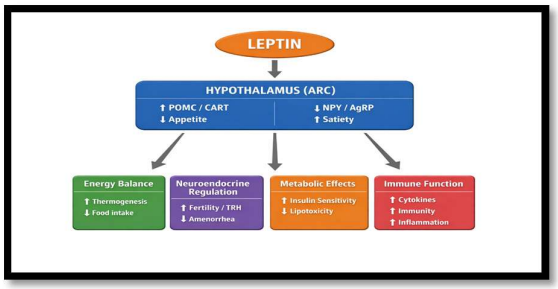

Figure 10: Summary of physiological role of leptins

Leptin and Diseases: Lessons from Energy Homeostasis

Leptin in Obesity

Leptin is the prototypical and most extensively studied adipokine, with substantial evidence supporting its role in the development and progression of obesity, insulin resistance, and diabetes across both paediatric and adult populations. Its discovery transformed the understanding of adipose tissue from a passive energy reservoir to an active endocrine organ involved in metabolic regulation. [93]

In obesity, circulating leptin levels are markedly elevated due to increased adipose tissue mass; however, this state is paradoxically associated with leptin resistance, wherein central responsiveness to leptin, particularly at the hypothalamic level, is impaired.[87,90] As a result, the expected anorexigenic and energy-expenditure–enhancing effects of leptin are blunted, leading to persistent hyperphagia and reduced metabolic efficiency. [94] The development of leptin resistance has been linked to impaired transport of leptin into the brain, hypothalamic inflammation, and defects in intracellular signaling pathways, all of which reduce the body's ability to respond to leptin despite elevated circulating levels. [87] This explains why exogenous leptin administration in obese individuals produces minimal or no significant weight loss, indicating that the underlying defect lies in signaling rather than hormone deficiency. [90,95]

Leptin in Diabetes

In type 2 diabetes mellitus (T2DM), leptin levels are typically elevated and correlate positively with adiposity and insulin resistance. [96] Despite this, clinical studies have demonstrated only modest reductions in glycated haemoglobin (HbA1c) and no significant improvement in insulin sensitivity or body weight following leptin therapy. [97] This limited therapeutic response is consistent with the presence of leptin resistance in T2DM, similar to that observed in obesity. [90] In contrast, in type 1 diabetes mellitus (T1DM), where insulin deficiency predominates and leptin levels may be relatively low, leptin exerts pronounced metabolic effects in experimental models. [98,99] Leptin administration has been shown to normalize hyperglycaemia, reduce HbA1c levels, suppress hyperglucagonemia, and improve lipid metabolism. [99] These effects are

largely mediated through central nervous system pathways, highlighting leptin's ability to regulate glucose homeostasis independently of insulin in insulin-deficient states. [98]

Leptin and Cardiovascular diseases:

Leptin also contributes to cardiovascular regulation through its action on the autonomic nervous system. Elevated leptin levels stimulate sympathetic nervous system activity, which in turn increases blood pressure and contributes to the development of obesity-associated hypertension. Experimental evidence indicates that leptin or leptin receptor deficiency confers protection against hypertension despite the presence of obesity, underscoring the role of leptin signaling as a key mediator linking excess adiposity to cardiovascular dysfunction. [100,101]

Leptin and Immunity:

In the immune system, leptin functions as a cytokine-like mediator that links nutritional status to immune competence. Circulating leptin levels increase during infection and inflammatory states, enhancing immune cell activation and cytokine production. While this response is beneficial in acute conditions, chronic elevation of leptin, as seen in obesity, contributes to a state of low-grade systemic inflammation that plays a central role in the pathogenesis of metabolic syndrome and insulin resistance. [91,102]

Leptin and Reproduction:

Leptin plays a crucial role in reproductive physiology. Low leptin levels, as observed in conditions of energy deficiency such as starvation or excessive physical stress, result in hypothalamic amenorrhea and infertility. [88, 103] Clinical studies have shown that leptin replacement in such hyperleptinemic states restores gonadotropin secretion, improves ovulatory function, and enhances fertility, emphasizing its essential role in linking energy availability with reproductive capability. [104]

Leptin and Central Nervous System:

Leptin also influences central nervous system functions, including cognition, mood, and behavior. Leptin receptors in the hippocampus and mesolimbic pathways regulate processes such as learning, memory, and reward-related behavior. Leptin deficiency has been associated with impaired neurocognitive development and altered mood states. [105]

Therapeutic role of Leptin:

A clear therapeutic application of leptin is observed in lipodystrophy, a condition characterized by reduced or absent adipose tissue and consequently low circulating leptin levels. These patients develop severe metabolic abnormalities, including insulin resistance, hyperglycemia, dyslipidemia, and hepatic steatosis. Leptin replacement therapy in such cases leads to significant improvement in metabolic parameters, and recombinant leptin (metreleptin) has been approved for the treatment of generalized lipodystrophy, demonstrating the effectiveness of leptin therapy in states of true deficiency. [106]

Overall, leptin acts as a key integrator of metabolic, neuroendocrine, immune, and reproductive functions. Its deficiency leads to profound yet reversible metabolic disturbances.

Resistin: A Molecular Link Between Inflammation and Insulin Resistance

Resistin, a member of the cysteine-rich secretory protein family, has emerged as a critical mediator in the complex interplay between metabolism, inflammation, and immunity. Originally identified in 2001 as an adipocyte-secreted peptide that induced insulin resistance in rodents, its discovery sparked significant interest in the scientific community regarding its potential role as a link between obesity and type 2 diabetes [107, 108] In humans, resistin is predominantly synthesized and secreted by mononuclear cells, including macrophages and peripheral blood mononuclear cells (PBMCs), rather than adipocytes. [107,109] This shift in cellular origin suggests that in the human context, resistin functions more prominently as a pro-inflammatory cytokine and a host defense peptide rather than a simple metabolic regulator. Its pleiotropic nature allows it to influence a wide array of biological processes, ranging from the modulation of vascular inflammation to the regulation of innate immune responses against microbial pathogens. [110]

The clinical significance of resistin is underscored by its association with numerous pathological conditions. Elevated serum levels of resistin have been consistently observed in patients suffering from metabolic disorders, cardiovascular diseases, chronic inflammatory conditions, and various malignancies. [108] As a pro-inflammatory molecule, resistin triggers intracellular signaling pathways that lead to the production of other cytokines and chemokines, thereby perpetuating a state of subclinical inflammation.[111] Furthermore, recent evidence has highlighted its role in the central nervous system, where it can affect energy homeostasis and insulin sensitivity through hypothalamic signaling. [107] Beyond its metabolic and inflammatory roles, resistin is increasingly recognized for its involvement in cancer progression, where it promotes cell proliferation, migration, and angiogenesis. [108]

Mechanisms of Resistin Action and Signal Transduction

The biological effects of resistin are mediated through its interaction with specific cell surface receptors, primarily Toll-like receptor 4 (TLR4) and adenylyl cyclase-associated protein 1 (CAP1). TLR4, a receptor classically involved in innate immune responses, has been recognized as a functional receptor for resistin in both central and peripheral tissues. Binding of resistin to TLR4 activates pro-inflammatory signaling pathways, contributing to chronic low-grade inflammation, impaired insulin sensitivity, and metabolic dysfunction. This interaction is particularly relevant in obesity, where resistin may amplify inflammatory responses and promote cardiometabolic complications. [112]

CAP1 has also been identified as an important receptor for human resistin, particularly in monocytes and fibroblast-like synoviocytes (FLSs). Upon binding to CAP1, resistin activates the cAMP–protein kinase A (PKA) signaling pathway, resulting in increased production of pro-inflammatory cytokines and chemokines. This mechanism contributes to sustained inflammation and immune cell recruitment, particularly in conditions such as rheumatoid arthritis. Together, the TLR4 and CAP1 pathways mediate the broad metabolic and inflammatory effects of resistin across multiple tissues. [113]

Physiological Functions of Resistin

Regulation of Metabolic Homeostasis and Insulin Sensitivity

The role of resistin in metabolic homeostasis is complex and varies significantly between species and physiological contexts. In rodents, resistin is a clear-cut adipokine that impairs glucose tolerance and insulin sensitivity, with its levels rising in models of obesity and diabetes. [111] In humans, while the link is less direct, resistin still plays a significant role in modulating insulin action. It interferes with the insulin signaling pathway at multiple levels, from the insulin receptor itself to downstream molecules like Akt and IRS-1. [112] By promoting the expression of SOCS-3 and PTP1B, resistin reduces the efficiency of insulin-mediated glucose uptake in skeletal muscle and adipose tissue, while simultaneously increasing hepatic glucose production, [107,112] These actions contribute to the development of hyperglycemia and hyperinsulinemia, the hallmarks of type 2 diabetes. [111]

Furthermore, resistin's influence extends to the regulation of energy balance and food intake through its actions in the central nervous system. It has been shown to interact with the hypothalamus, a key region for the control of metabolism, where it can induce local insulin resistance and alter the expression of neuropeptides involved in appetite regulation. [107] Resistin also affects the function of the pituitary gland, specifically somatotrope cells, where it stimulates the release of growth hormone (GH) and modulates the expression of the ghrelin receptor. [114] Since GH and ghrelin are integral to the regulation of growth, metabolism, and energy expenditure, resistin's impact on the pituitary-somatotropic axis represents another layer of its metabolic influence. Despite the controversy surrounding its exact contribution to human obesity, the cumulative evidence suggests that resistin acts as a significant modulator of metabolic homeostasis, primarily by fostering an environment of insulin resistance and altered endocrine signaling. [114,115]

Resistin and Disease: Lessons from Inflammation and Metabolic Dysfunction

Involvement in Cardiovascular Inflammation and Atherosclerotic Plaque Development

Resistin has emerged as an important contributor to cardiovascular disease, particularly atherosclerosis, through its pro-inflammatory effects on endothelial cells, vascular smooth muscle cells (VSMCs), and macrophages. It promotes endothelial dysfunction by increasing the expression of adhesion molecules, oxidative stress, and reducing nitric oxide bioavailability, thereby facilitating monocyte recruitment and vascular inflammation.[110]

As atherosclerosis progresses, resistin enhances foam cell formation by promoting oxidized LDL uptake and impairing cholesterol efflux. It also stimulates VSMC proliferation and migration while increasing matrix metalloproteinase (MMP) expression, contributing to plaque instability and rupture. [110] Elevated circulating resistin levels have been associated with coronary artery disease, myocardial infarction, and heart failure, highlighting its potential role as both a biomarker and therapeutic target in cardiovascular disease. [108,110]

Resistin in Chronic Inflammatory Disorders, Malignancies, and Innate Immunity

The pro-inflammatory properties of resistin make it a key player in a wide range of chronic inflammatory disorders. In rheumatoid arthritis (RA), resistin levels are elevated in both the serum and synovial fluid, where it correlates with markers of joint inflammation and destruction. [116] It stimulates fibroblast-like synoviocytes to produce chemokines and cytokines, which in turn recruit and activate more immune cells, leading to a self-perpetuating cycle of inflammation and bone erosion. [116] Similarly, resistin has been implicated in the pathogenesis of other inflammatory conditions, such as non-alcoholic fatty liver disease (NAFLD), inflammatory bowel disease (IBD), asthma, and chronic kidney disease. [111] In each of these cases, resistin acts as a mediator that links systemic or local inflammation to tissue damage and disease progression.

Resistin is increasingly recognized for its role in cancer progression, with elevated levels reported in several malignancies, including breast, colorectal, lung, and prostate cancers. It promotes tumor growth, survival, metastasis, and angiogenesis through the activation of multiple signaling pathways and modulation of the tumor microenvironment. [108] Beyond its pathological role, resistin also functions as a component of the innate immune system, exhibiting antimicrobial activity and contributing to host defense against infections. [108] This dual role highlights the complex nature of resistin, where its protective effects in acute immune responses may become detrimental when chronically elevated, contributing to metabolic, cardiovascular, and neoplastic diseases

Conclusion

Moving away from the old idea that body fat is just passive storage has fundamentally changed how we approach metabolic health. Today, we recognize adipose tissue as a sophisticated endocrine command centre. When pathological weight gain disrupts this system, it triggers a metabolic domino effect driven by a profound adipokine imbalance. The protective shield normally provided by adiponectin drops away, disrupting the critical

AdipoR1/2-APPL1 signaling pathway. Simultaneously, a state of leptin resistance develops, turning what should be a helpful satiety signal into a chronic driver of nervous system stress and vascular strain. Compounding this damage, resistin acts as a dangerous bridge between the immune and metabolic systems, binding to TLR4 and CAP1 receptors on mononuclear cells to actively fuel blood vessel inflammation.

From a practical medical standpoint, these molecular shifts give us invaluable clinical tools. Monitoring the Adiponectin-Leptin Ratio (ALR) along with circulating resistin levels provides a precise, non-invasive way to flag cardiovascular and kidney risks long before standard symptoms surface. Ultimately, addressing this "adipokine gap"—whether through targeted therapies like PPAR-γ agonists or lifestyle changes that promote tissue browning—stands as the next critical frontier. Underscoring these cellular interactions is no longer just an academic exercise; it is essential for shaping precision medicine to halt the rising global crisis of metabolic disease.

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