International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 18, Issue 4, 2026

Review Article

ROLE OF LEPTIN IN OBESITY AND TYPE 2 DIABETES: MECHANISMS, CLINICAL EVIDENCE, AND THERAPEUTIC POTENTIAL

RAJYALAKSHMI DEVI P.[1*], M. VINYAS[2], MOTE SRINATH[3], VASANTHI A. V.[4]

[1,4]Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, India. [2]Department of Pharmacology, GITAM School of Pharmacy, GITAM Deemed to be University, Hyderabad, India. [3]Viral Research and Diagnostic Laboratory, Department of Microbiology, Osmania Medical College, Hyderabad, India

*Corresponding author: Rajyalakshmi Devi P.; *Email: rpothula@gitam.in

Received: 24 Dec 2025, Revised and Accepted: 11 Feb 2026

ABSTRACT

Adipocytes are responsible for synthesizing predominantly leptin, a hormone that regulates appetite, energy expenditure, and glucose metabolism. The discovery of leptin in 1994 revolutionized the understanding of systemic energy homeostasis is providing an understanding of obesity and type 2 diabetes mellitus (T2DM) as two connected global health issues. In physiological environments, leptin functions as a satiety signal and metabolic regulator. In obesity and T2DM, however, hyperleptinemia occurs (i. e., elevated levels of leptin) with leptin resistance (i. e., diminished leptin signaling) in which central leptin signaling is impaired regardless of elevated leptin levels. Leptin resistance or malfunction occurring in persons may lose its effects of appetite suppression and metabolic regulation to increase weight gain, insulin resistance, and disruption of glucose homeostasis.

The review deals with the molecular structure of leptin, functions, and its mechanism in the pathogenesis of obesity and type II diabetes mellitus (T2DM). It further covers the key pathways such as hypothalamic regulation, hepatic glucose production, muscle metabolism, and function in pancreatic β cells. Moreover, clinical observations are reviewed to highlight the therapeutic potential of leptin-targeted therapies, including leptin sensitizers and combination therapeutics. Although effective in treating rare leptin-deficient disorders, leptin replacement therapy has limited usefulness in treatment of common obesity and type II diabetes mellitus because of widespread resistance. To unlock the potential of leptin therapy, future research needs to be steered toward restoring leptin-sensitivity, leveraging interactions with the microbiome, and the application of precision medicine approaches.

Keywords: Obesity, Type 2 diabetes mellitus, Leptin resistance, Insulin sensitivity, Energy homeostasis, Leptin therapy

DOI: https://dx.doi.org/10.22159/ijpps.2026v18i4.57256 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) are closely linked metabolic disorders with a rapidly increasing global prevalence and substantial public health consequences. According to recent World Health Organization (WHO) reports (2022–2024), the worldwide burden of obesity has risen sharply across all age groups, paralleling the growing incidence of insulin resistance, metabolic syndrome, and T2DM. Excess adiposity disrupts metabolic homeostasis through altered secretion of adipokines, chronic low-grade inflammation, and impaired hormonal signaling, among which leptin plays a central regulatory role [1].

Leptin is a peptide hormone predominantly secreted by white adipose tissue and functions as a key signal linking peripheral energy stores to central and peripheral metabolic regulation. Since the discovery of the ob gene, leptin has been recognized as a major regulator of appetite, energy expenditure, glucose metabolism, and neuroendocrine function through its actions on leptin receptors in the hypothalamus and peripheral tissues. In rare conditions such as congenital leptin deficiency, absence of leptin results in severe hyperphagia, early-onset obesity, and profound metabolic disturbances, all of which can be dramatically reversed by leptin replacement therapy [2].

In contrast, the vast majority of individuals with common obesity and T2DM exhibit elevated circulating leptin levels, reflecting a state of leptin resistance rather than leptin deficiency. In these individuals, the anorexigenic and metabolic actions of leptin are markedly blunted despite hyperleptinemia, leading to persistent overeating, reduced energy expenditure, insulin resistance, and impaired glucose homeostasis. Experimental and clinical evidence indicates that leptin resistance contributes not only to obesity but also to hepatic glucose overproduction, skeletal muscle insulin resistance, pancreatic β-cell dysfunction, and chronic inflammation and key pathophysiological features of T2DM.

Despite extensive investigation, the precise mechanisms underlying leptin resistance and its clinical implications remain incompletely understood. Importantly, while leptin replacement therapy is highly effective in true leptin-deficient states, it has consistently shown minimal efficacy in common obesity and T2DM, highlighting a clear distinction between leptin deficiency and leptin resistance. Therefore, a critical synthesis of current evidence is required to clarify leptin's biological role, distinguish its utility as a biomarker from its therapeutic limitations, and evaluate emerging strategies aimed at restoring leptin sensitivity [3].

The objective of this review is to integrate mechanistic, experimental, and clinical evidence on leptin signaling and resistance in obesity and T2DM, critically evaluate therapeutic interventions targeting leptin pathways, and identify future directions for translational and precision-based approaches to metabolic disease management.

Rationale for linking leptin to metabolic diseases

In its roles central to energy balance and metabolic control, leptin has also emerged as a central molecular link between obesity and T2DM. Paradoxically, elevated levels of leptin in obese individuals, so-called leptin resistance, are commonly observed, indicative of impaired signalling in the setting of hyperleptinemia. Leptin resistance is contrary to the anorexigenic action of leptin and metabolic effect and leads to hyperphagia, obesity, insulin resistance, and glucose intolerance. These actions highlight the functions of leptin not just as an adiposity biomarker but also as a therapeutic target in metabolic disease.

Higher levels of leptin can be used as a marker of leptin resistance. The pathogenesis of leptin resistance includes genetic mutations, autoregulation of leptin, reduced tissue access, and molecular/cellular circulatory regulation. Evidence supports that

the central leptin resistance is the central mechanism behind the etiology of obesity. The consequent leptin resistance of obesity, however, can have adverse effects on other peripheral tissues, i. e., the liver, pancreas, platelets, vasculature, and myocardium. The metabolic and inflammatory derangement can be through either resistance to the action of leptin in target tissues or an overproduction of leptin action due to hyperleptinemia of obesity. Different reports suggest that leptin deficiency is an important risk factor for obesity and CVD. Leptin resistance is a complex and not completely understood pathophysiologic process, and its clinical significance requires further investigation [3].

Scope and objectives of the review

This review is based on a systematic literature search conducted across PubMed, Scopus, Web of Science, and Google Scholar for studies published between 1994 and 2024. Search terms included "leptin," "leptin resistance," "leptin signalling," "obesity," "T2DM," "energy homeostasis," and "adipokines." Priority was given to peer-reviewed original research, clinical trials, meta-analyses, and high-quality review articles.

Regulation of leptin secretion

Leptin secretion is tightly regulated by nutritional, hormonal, and inflammatory signals. Circulating leptin concentrations increase with overnutrition and expansion of adipose tissue, acting as a feedback signal to suppress appetite and enhance energy expenditure. Conversely, caloric restriction and fasting rapidly reduce leptin levels, promoting hunger and energy conservation.

Insulin is an important positive regulator of leptin synthesis and secretion, linking postprandial nutrient availability to adipose tissue signaling. In addition, pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6 can upregulate leptin expression, particularly in states of chronic inflammation. Sex steroids and glucocorticoids also modulate leptin production, reflecting complex endocrine control over leptin dynamics [4].

Leptin receptors and signalling pathways

Leptin receptor (LEPR, Ob-Rb)

The leptin receptor (LEPR) belongs to the class I cytokine receptor family. Among its multiple isoforms, the long isoform (Ob-Rb) is the principal signaling-competent receptor and is abundantly expressed in the hypothalamus. Binding of leptin to Ob-Rb activates Janus kinase 2 (JAK2), leading to phosphorylation of signal transducer and activator of transcription 3 (STAT3). Activated STAT3 translocates to the nucleus and regulates transcription of genes involved in appetite suppression, energy expenditure, and glucose homeostasis.

In addition to the JAK2/STAT3 pathway, leptin activates phosphatidylinositol 3-kinase (PI3K)/Akt and AMP-activated protein kinase (AMPK) pathways, which mediate metabolic effects in both central and peripheral tissues, including enhanced glucose uptake and fatty acid oxidation. Negative regulators such as suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B) attenuate leptin receptor signaling and play a central role in the development of leptin resistance. These regulatory mechanisms are specific to leptin signaling and should not be conflated with insulin, IGF-1, or adiponectin receptor pathways [5].

Leptin receptor (Short isoforms)

Shorter LEPR isoforms possess truncated intracellular domains and limited signaling capacity. These isoforms are expressed primarily in peripheral tissues such as the kidney, lung, and vasculature and are involved in leptin transport, clearance, and selected peripheral actions. While they may activate MAPK-related pathways, they do not mediate the full metabolic signaling attributed to Ob-Rb.

Table 1: Central vs peripheral actions of leptin Role in appetite regulation, energy expenditure, and glucose metabolism

Aspect	Central actions of leptin	Peripheral actions of leptin	Ref
Primary site	Hypothalamus (mainly arcuate nucleus).	Peripheral tissues: liver, skeletal muscle, pancreas, adipose tissue, immune cells.	[6]
Appetite regulation	Inhibits appetite by acting on hypothalamic neurons (POMC activation, NPY/AgRP inhibition) → reduces food intake.	Minimal direct effect on appetite, peripheral leptin mainly modulates metabolic functions.	[6]
Energy expenditure	Increases energy expenditure via sympathetic nervous system activation, thermogenesis (brown adipose tissue activation).	Enhances fatty acid oxidation in muscle and liver via AMPK activation, promoting energy utilization.	[6]
Glucose metabolism	Improves insulin sensitivity indirectly through CNS pathways, suppresses hepatic glucose production via autonomic outputs.	Directly increases glucose uptake in muscle and adipose tissue, modulates insulin secretion by pancreatic β-cells, decreases gluconeogenesis in liver.	[6]
Mechanisms	Leptin binds LEPR in hypothalamus → activates JAK2/STAT3 → alters neuropeptide expression (↓ NPY/AgRP, ↑ POMC/CART) → suppresses hunger and stimulates energy use.	Leptin binds LEPR isoforms in peripheral tissues → activates PI3K, AMPK pathways → enhances glucose uptake, fatty acid oxidation, reduces inflammation.	[6]
Role in disease	Central leptin resistance → obesity due to failure to suppress appetite.	Peripheral leptin resistance → impaired glucose metabolism, fatty liver, inflammation.	[6]
Therapeutic potential	Target CNS leptin signalling to reduce food intake and increase metabolism.	Target peripheral leptin pathways to improve insulin sensitivity and lipid metabolism.	[6]

Leptin in obesity

Leptin functions as a key satiety hormone by conveying information about energy stores to the hypothalamus. It suppresses orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) while activating anorexigenic pro-opiomelanocortin (POMC) and cocaine-and amphetamine-regulated transcript (CART) neurons. These actions reduce food intake and promote energy expenditure [7].

Hyperleptinemia and the leptin paradox

Individuals with obesity typically exhibit elevated circulating leptin levels proportional to fat mass, a condition known as hyperleptinemia. Despite this increase, appetite suppression and metabolic responses to leptin are diminished, a phenomenon termed the "leptin paradox" or leptin resistance. Mechanisms underlying leptin resistance include impaired leptin transport across the blood–brain barrier, defective leptin receptor signaling, hypothalamic inflammation, and endoplasmic reticulum stress. This impaired feedback loop perpetuates weight gain and metabolic dysfunction [8].

Leptin in type 2 diabetes mellitus (T2DM)

Altered leptin dynamics in T2DM

In T2DM, leptin dynamics are altered beyond the effects of adiposity alone. Circulating leptin levels are frequently elevated even after adjustment for body mass index, reflecting complex interactions between leptin resistance, chronic inflammation, and oxidative stress. Under physiological conditions, leptin suppresses hepatic gluconeogenesis via hypothalamic-autonomic pathways, enhances skeletal muscle glucose uptake through AMPK and PI3K signaling,

and modulates pancreatic β-cell function and survival. In leptin-resistant states, these regulatory effects are blunted, contributing to fasting hyperglycemia, peripheral insulin resistance, β-cell dysfunction, and impaired glucagon suppression [9].

Table 2: Mechanisms linking leptin to obesity

Aspect	Description	Molecular details	Ref
Central leptin resistance	Impaired leptin receptor signalling in hypothalamus leads to failure in appetite regulation and energy balance.	Causes include reduced LEPRb expression, impaired JAK2/STAT3 phosphorylation, increased expression of negative regulators (SOCS3, PTP1B), inflammation, ER stress, reduced leptin transport across BBB.	[8]
Peripheral leptin resistance	Resistance in peripheral tissues (muscle, liver, adipose) blunts leptin's metabolic effects (glucose uptake, fatty acid oxidation).	Inflammatory cytokines (TNF-α, IL-6) induce ER stress → upregulate SOCS3/PTP1B → inhibit LEPR signalling → impaired PI3K/Akt, AMPK activation → metabolic dysfunction.	[8]
Dysregulation of lipid and glucose metabolism	Leptin resistance reduces activation of pathways that promote lipid oxidation and glucose utilization, contributing to ectopic fat accumulation and insulin resistance.	Impaired AMPK activation → ↓ fatty acid oxidation, reduced PI3K signalling → ↓ glucose uptake in muscle and liver → hyperglycemia, dyslipidemia.	[8]
Leptin and adipose tissue dysfunction	Leptin dysregulation promotes chronic low-grade inflammation and macrophage infiltration in adipose tissue, worsening insulin resistance and metabolic dysfunction.	Increased secretion of pro-inflammatory adipokines (TNF-α, MCP-1) → recruitment of M1 macrophages → further ER stress and leptin resistance in adipocytes.	[8]

Key mechanisms of leptin in T2DM

Circulating leptin levels correlate strongly with total body fat mass and are therefore a reliable biomarker of adiposity. Hyperleptinemia is commonly observed in obesity, metabolic syndrome, and T2DM and reflects leptin resistance rather than enhanced biological activity. Although leptin levels are consistently associated with insulin resistance and cardiometabolic risk, their utility as independent predictors of T2DM progression or therapeutic response is limited.

Importantly, elevated leptin levels do not predict responsiveness to leptin-based therapies in common obesity or T2DM. Thus, leptin's primary clinical value lies in its role as a biomarker of adiposity and metabolic dysregulation rather than as a direct therapeutic agent in hyperleptinemic states.

Leptin plays a crucial role in regulating glucose and lipid metabolism, and its dysregulation contributes significantly to the pathophysiology of type 2 diabetes mellitus (T2DM). One of the key metabolic actions of leptin is its influence on hepatic glucose production. Under normal physiological conditions, leptin suppresses hepatic gluconeogenesis through hypothalamic signalling. Leptin binds to its receptor (LEPR) in the hypothalamus, activating neural pathways that modulate autonomic output to the liver, thereby reducing hepatic glucose output. In states of leptin resistance, this inhibitory effect is lost, leading to excessive hepatic glucose production and fasting hyperglycemia.

Leptin also exerts a significant influence on skeletal muscle metabolism. It promotes glucose uptake and enhances fatty acid oxidation by activating the AMPK and PI3K pathways in muscle cells. These signalling cascades increase insulin sensitivity and energy utilization. However, in leptin-resistant states, these pathways are impaired, resulting in reduced glucose uptake, diminished fatty acid oxidation, and insulin resistance in peripheral tissues. In the pancreas, leptin regulates both insulin secretion and β-cell survival. Through leptin receptor signalling in pancreatic β-cells, leptin modulates insulin release and prevents β-cell apoptosis. When leptin signalling is defective, β-cell function deteriorates, contributing to impaired insulin secretion and progression of T2DM.

Leptin also interacts with other metabolic hormones such as adiponectin, resistin, and insulin, creating a complex hormonal network that influences glucose homeostasis. Adiponectin enhances insulin sensitivity, while resistin promotes insulin resistance; leptin regulates their expression and activity. Disruption in this cross-talk leads to metabolic imbalance and worsened insulin resistance. Furthermore, leptin directly enhances peripheral insulin sensitivity by stimulating the PI3K/Akt and AMPK pathways, which facilitate glucose uptake in muscle and adipose tissues. In leptin resistance, this signalling is blunted, further impairing insulin-mediated glucose disposal and aggravating hyperglycemia. Leptin and insulin share a reciprocal relationship, often termed leptin–insulin crosstalk. Their coordinated signalling through PI3K/Akt pathways ensures proper regulation of glucose homeostasis. Disruption of this crosstalk in obesity and T2DM contributes to the development of systemic insulin resistance. Lastly, leptin influences glucagon regulation by suppressing glucagon secretion and its hepatic action. Central leptin signalling inhibits α-cell activity in the pancreas, thereby lowering glucagon levels. In leptin-resistant states, this inhibitory control is diminished, resulting in elevated glucagon secretion, which further exacerbates hyperglycaemia in T2DM [9].

Table 3: Physiological functions of leptin

S. No.	Function	Description	Mechanism/site of action	Physiological outcome	Ref
1	Regulation of Appetite and Energy Homeostasis	Leptin suppresses hunger and promotes satiety.	Acts on LEPRb in the hypothalamic arcuate nucleus → activates POMC/CART neurons and inhibits NPY/AgRP.	Decreased food intake, prevention of weight gain.	[10]
2	Role in Metabolism and Thermogenesis	Enhances energy expenditure and thermogenic activity.	Stimulates sympathetic nervous system → ↑ brown adipose tissue (BAT) activity, ↑ UCP1 expression.	Increased heat production and fat burning	[10]
3	Interaction with the Hypothalamus	Central role in neuroendocrine regulation of energy and reproduction.	Leptin signals via JAK2/STAT3 in hypothalamic nuclei (ARC, VMH, PVN).	Integration of metabolic and neuroendocrine signals.	[10]
4	Role in Glucose and Lipid Metabolism	Improves insulin sensitivity and lipid handling.	Activates PI3K/Akt and AMPK pathways in muscle, liver, adipose tissues.	Enhanced glucose uptake, fatty acid oxidation, ↓ lipogenesis.	[10]
5	Leptin in Reproductive Physiology	Regulates onset of puberty and fertility.	Modulates GnRH, LH, and FSH secretion via hypothalamic-pituitary-gonadal axis.	Normal reproductive function and fertility.	[10]
6	Leptin and Bone Metabolism	Influences bone formation and resorption.	Central leptin action via SNS → inhibits osteoblasts, also peripheral effects.	Modulates bone mass; controversial dual role.	[10]
7	Role in Immune Modulation	Modulates innate and adaptive immune responses	Enhances macrophage, neutrophil, and T-cell activity via cytokine-like signalling.	Supports immune surveillance; may promote inflammation.	[10]

Clinical evidence of leptin's role in obesity and T2DM

Human studies on leptin levels and BMI, fat mass, and insulin resistance

Serum leptin can be considered a biological marker for total body fat. Circulating leptin levels are directly proportional to total body fat. A number of studies have a close positive correlation between serum or plasma leptin levels and body fat percentage. Leptin is mainly secreted by adipocytes. In obesity, high circulating leptin levels (hyperleptinemia) are commonly observed in these patients, which are directly proportional to their excess fat mass [11].

Leptin resistance is linked to reduced satiety, overconsumption of nutrients, and increased total body weight, often leading to obesity. Hyperleptinemia has been identified as a marker of leptin resistance, and the resistance is directly proportional to the amount of adipose tissue an individual possesses. Obese children have also been reported to present with elevated levels of leptin compared to healthy controls, indicating potential impairment of metabolic processes [12].

Insulin is believed to play a crucial role in regulation of the release of leptin. Most obese mammals have elevated plasma levels of leptin and insulin, and they are resistant to leptin's anorectic effect. Insulin resistance is underlying the pathogenesis of metabolic syndrome (MetS), and dysregulation of adipokines, including elevated levels of leptin, is involved. Elevated circulating levels of leptin may be the etiology of disturbances of glucose and lipid metabolism in MetS patients. Serum level of leptin was highly and positively correlated with HOMA-IR (indicator of insulin resistance) and metabolic risk factors in MetS women.

These discrepancies likely arise from differences in study populations, baseline adiposity, ethnic backgrounds, and degrees of insulin resistance. Furthermore, leptin levels may reflect adiposity rather than directly predict future glycemic deterioration, which limits their utility as an independent prognostic marker. Thus, while leptin is consistently associated with metabolic dysfunction, its role in predicting T2DM onset remains uncertain [12].

Leptin levels in T2DM patients

Correlation of T2DM with plasma leptin reveals very high levels in T2DM patients when compared to controls. Research has consistently demonstrated elevated serum leptin in DM patients when compared to non-DM [12]. Observational research has demonstrated serum leptin to be highly elevated in non-obese diabetic patients when compared to normal healthy controls, and even highly elevated in obese diabetes patients when compared to normal controls. A population study also demonstrated elevated serum leptin in obese and non-obese patients of newly diagnosed T2DM [13].

Longitudinal observational research has also yielded conflicting findings for baseline leptin levels and later risk of T2DM. A Japanese-American study, for instance, observed that increased baseline leptin levels were associated with increased risk of developing T2DM in men but not women. Another study of Mexican-Americans did find that leptin levels were not significantly different in diabetic compared to non-diabetic patients, and the correlation between leptin and BMI was the same [14].

Despite the augmented leptin levels in T2DM, administration of leptin (metreleptin) to type 2 diabetic obese individuals in clinical trials has resulted in only minor changes in HbA1c. In another study that included studies done on obese insulin-resistant subjects, it was not possible to show any influence on markers of insulin sensitivity with leptin treatment. This suggests that in common T2DM with obesity, a condition of leptin excess and likely leptin resistance, therapeutic leptin infusion is ineffective for the improvement of glucose homeostasis [14].

Genetic leptin deficiency and monogenic obesity

Severe early obesity may arise from uncommon genetic mutations in leptin signalling. These mutations typically cause congenital leptin deficiency (CLD) or hyperleptinemia with ineffective leptin (leptin resistance). CLD is a condition characterized by a deficiency of leptin secondary to a mutation in the leptin gene. Ob/ob mice, a leptin-deficient model, become profoundly obese, have abnormalities in metabolism (hyperglycemia, hyperinsulinemia, hyperlipidemia, hepatic steatosis), and diminished fertility. Individuals with congenital leptin deficiency exhibit a metabolic and endocrine phenotype closely resembling that of these mice [14].

Leptin replacement therapy with metreleptin has been very successful for congenital leptin deficiency. In CLD, metreleptin decreases body weight profoundly, suppresses appetite, and in turn, improves metabolic derangements. Metreleptin has also received approval for generalized and partial lipodystrophy, disorders of partial or complete absence of fat tissue and extremely low leptin levels, which cause profound metabolic disturbances such as insulin resistance and T2DM. In such cases of lipodystrophy, metreleptin decreases hypertriglyceridemia, hyperglycemia, and hepatic steatosis [15].

Observational studies and metabolic outcomes

Multiple observational clinical trials have helped establish the role of leptin in physiology as well as in disease conditions. They have created an association between leptin, leptin resistance, and diseases such as DM and obesity, which are most commonly associated with serious complications like CVD [14].

One meta-analysis indicated drastically higher circulating levels of leptin among patients with MetS compared to normal controls [12]. Higher circulating levels of leptin were associated with higher MetS risk. Many studies have demonstrated the positive correlation between MetS scores or presence of MetS and leptin levels. Circulating leptin levels also present strong associations with indices of insulin resistance in humans [15].

Leptin resistance is a multifactorial pathophysiological state associated with obesity and metabolic conditions. It not only plays a role in weight gain but could potentially contribute to enhanced cardiac inflammation, enhanced fibrosis, hypertension, and defective cardiac metabolism. Elucidation of the correlation between leptin resistance and cardiovascular risk among obese patients with T2DM has been viewed as essential for better management and prevention.

Leptin as a biomarker: clinical utility and limitations

Serum leptin is a reliable biomarker of total body fat and is useful for identifying hyperleptinemia and potential leptin resistance. When serum leptin is elevated hyperleptinemia), it may indicate leptin resistance, the latter being implicated in obesity. As leptin is elevated in MetS, and is tied to increases in risk for MetS, it may represent a useful biomarker for MetS, with an opportunity to aid in the early detection of MetS, and contribute to the discovery of new biomarkers. The ratio of leptin/adiponectin has also been proposed as a useful biomarker for identifying people with hypertension that may be at risk for MetS.

However, despite its biomarker utility, leptin has limited value as a pharmacotherapy for common obesity and T2DM, because individuals already have high leptin levels and are resistant to its effects. While individuals with obesity and common T2DM have high circulating leptin levels, they don't respond effectively (or at all) to therapeutic leptin, this is defined as leptin resistance or leptin tolerance. Clinical trials of metreleptin or other formulations of leptin in patients with common obesity or T2DM have often lacked clinically significant effects on weight loss and/or metabolic abnormalities.

In rare conditions of true leptin deficiency such as CLD and lipodystrophies, leptin replacement therapy is very effective, however, the inability to apply this treatment in the context of common obesity and T2DM where leptin is typically in surplus, is a major limitation to wider clinical application of leptin replacement as a treatment. Alternative strategies to overcome leptin resistance are being studied, but need validation in human trials, therefore, while serum levels of leptin may be useful as markers of adiposity or potential resistance, they cannot reliably predict response to leptin therapy in the common forms of obesity and T2DM [16].

Recombinant leptin therapy: successes and limitations

Recombinant human leptin (metreleptin) is highly effective in rare conditions characterized by true leptin deficiency, such as congenital leptin deficiency and generalized or partial lipodystrophy. In these disorders, metreleptin therapy results in marked appetite suppression, weight reduction, and significant improvements in insulin resistance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis.

In contrast, clinical trials in individuals with common obesity and T2DM conditions characterized by leptin excess and leptin resistance have demonstrated minimal or no clinically meaningful benefit of metreleptin on body weight, glycemic control, or insulin sensitivity. These findings underscore that leptin replacement therapy is ineffective when leptin signaling pathways are already impaired or saturated, reinforcing the need to clearly distinguish leptin-deficient from leptin-resistant states [17].

Leptin sensitizers (e. g., metreleptin, amylin co-therapy)

Since common obesity and T2DM have leptin resistance rather than deficiency, it seems preferable to think about overcoming or improving leptin sensitivity rather than just increasing already high leptin levels. The development of leptin sensitizers is a current focus of pharmaceutical development. There is now a small body of research aiming to pharmacologically restore or sensitize the impaired function of the leptin receptor.

One proposed future approach is to integrate leptin therapy and the newly proposed leptin sensitizers as a way to overcome leptin resistance or produce weight loss. Some exciting approaches to ameliorate leptin resistance have been proposed. These leptin-sensitizing compounds may enhance the anorectic effect of exogenous leptin directly, or encourage weight loss and restore endogenous leptin signalling in hyperleptinemic obese animals [18].

Table 4: Emerging Strategies to Enhance Leptin Sensitivity or Mimic Leptin action

S. No.	Approach	Compound/Agent	Mechanism of action	Key outcome/Benefit	Status/Notes	Ref
1	Combination with Amylin	Pramlintide+Metreleptin	Amylin enhances leptin signalling via IL-6–mediated activation of pSTAT3 in LepR neurons.	Enhanced weight loss; restored leptin sensitivity.	Clinical studies show additive effects.	[20]
2	Incretin-Based Therapies	GLP-1 and GLP-1/GIP agonists (e. g., semaglutide, tirzepatide)	Induce weight loss, reduce leptin levels, improve leptin sensitivity.	Profound weight loss in obese, hyperleptinemic models.	Tirzepatide+leptin agonist (mibavademab) under investigation.	[20]
3	Inhibitors of Negative Regulators	SOCS3, PTP1B inhibitors	Block leptin signalling inhibitors (e. g., PTP1B dephosphorylates JAK2; SOCS3 blocks STAT3).	Enhanced leptin signalling; reduced food intake.	Preclinical models show efficacy.	[19]
4	Natural Compounds	Celastrol, Withaferin A	Increase hypothalamic IL1R1 expression; improve leptin sensitivity and signalling.	Reduced body weight and metabolic abnormalities in DIO mice.	Preclinical animal studies.	[19]
5	Leptin Receptor Agonists	Mibavademab (monoclonal antibody)	Directly activates leptin receptor (Ob-R) without inducing neutralizing antibodies.	Mimics leptin effect; under evaluation for synergy with tirzepatide.	Completed Phase I studies and ongoing phase II (based on updated ClinicalTrials. gov data).	[21]

Although there are many promising viewpoints of pharmacological approaches to diminish leptin resistance in pre-clinical studies, many in clinical studies have had limited benefit or serious adverse effects. Clearly, a single treatment for leptin resistance has not been determined. New viewpoints continue to remain to be explored in trials with humans.

Effects of weight loss, exercise, and bariatric surgery on leptin signalling

Weight loss achieved by caloric restriction and/or exercise can curtail hyperleptinemia, many lifestyle changes (e. g., restrictive diet, exercise) can cause weight reduction and potentially re-establish leptin sensitivity. Re-establishing the effect of leptin to curb weight can lead to the maintenance of body weight goals, and the prevention of obesity associated diseases.

Bariatric surgery also causes a significant weight loss and decrease in circulating leptin levels. Energy-restricted diets may exhibit decreases in leptin (or leptinemia), and potentially restore leptin sensitivity in humans [22].

Nutraceuticals and dietary compounds modulating leptin sensitivity

Dietary treatments are being investigated for the possibility of normalizing leptin levels and leptin resistance. Evidence from animal studies and from human studies increasingly points to dietary factors as cause of leptin resistance. Diets that are high in fat, carbohydrates, fructose, and sucrose, and low in protein are finding to be associated with leptin resistance.

Specific natural or dietary compounds that have been evaluated as potentially leptin sensitizing compounds:

- Celastrol potential leptin sensitizer and anti-obesity compound. In hyperleptinemic obese mice models, celastrol suppresses food intake and body weight.
- Withaferin A potential leptin sensitizer and anti-diabetic compound, which reverses leptin resistance and metabolic abnormalities in mice, associated with increased leptin receptor expression.
- Resveratrol regulates leptin expression in adipocytes and promotes the elevation of STAT3 phosphorylation within the hypothalamus. Resveratrol also reverses leptin resistance in offspring of rat mothers fed a high-fat diet, and attenuated obesity in offspring.

However, although the findings of these studies are encouraging, especially in animals, the current evidence regarding diet and leptin resistance is limited by some significant limitations, e. g. methodological heterogeneity and the need for additional high-quality studies in humans [23].

Novel pharmacological agents targeting leptin resistance

The intricate processes related to leptin resistance, including hyperleptinemia, impaired central leptin transport, ER stress, and impaired receptor signalling, provide several potential targets for new pharmacotherapies. Strategies under investigation for restoring leptin sensitivity in common obesity and obesity-related metabolic disease include:

- Kinetic strategies targeting impaired central leptin transport: Creating analogs or modifying leptin to facilitate transport across the BBB.
- Pharmacological approaches targeting leptin signal transduction: Examples include potentiating the activation of downstream

signalling pathways or inhibiting negative feedback regulators. The use of SOCS3 and PTP1B inhibitors.

- Creating new agonists targeting the leptin receptor: Evidence exists of bioactive molecules that can directly activate the leptin receptor.

- Combination therapies: A uniquely significant component of this area of research concerns combinations of leptin or leptin receptor agonists with other agents, including gut hormones, and their analogs (eg-GLP-1 or amylin).

- Leptin neutralizing antibodies: In experimental animal models, the partial prevention of bioactive leptin (via neutralization) resulted in pronounced benefits. Leptin neutralization enhanced CNS sensitivity to leptin while simultaneously improving the efficacy of leptin, inducing increased peripheral sensitivity that may capitalize on the improved leptin sensitivity in the CNS.

- Genetic Manipulation: The presence of genes involved with leptin signalling or leptin resistance pathways provide targets for genetic manipulation, though this is being investigated primarily in a preclinical setting [24].

Although these novel strategies are promising in preclinical studies, they do not readily translate to effective human treatments for common obesity and T2DM, and often suffer from obvious drawbacks, such as limited efficacy or enhanced adverse effects, resulting in termination during human clinical development. There is a clear need for new therapeutic modalities, as well as investigation into new effective treatments to improve leptin sensitivity [25].

Leptin and the gut-brain axis

Emerging studies are supporting the evolution of the gut-brain axis as a vital regulator of energy balance, with leptin as a central integrative signal. In addition to informing the brain of the nutritional state, leptin relays satiety to the brain via communication with gut-derived hormones (e. g. ghrelin, GLP-1, and PYY) at the level of the hindbrain to regulate appetite. Dysregulated communication in the gut-brain axis is increasingly implicated in leptin resistance, especially in obesity. Characterizing how leptin action interfaces with gut-derived hormones and their associated neural circuits establishes potentially novel therapeutic approaches for the treatment of obesity that affect both a central and peripheral system at the same time [26].

Microbiome-leptin interactions in metabolic regulation

The gut microbiome has been thought to modulate systemic inflammation, insulin sensitivity and energy extraction all these factors which influence leptin biology. Changes in composition can alter leptin expression and receptor sensitivity; therefore, the microbiome can be a potential contributor to metabolic disease. Microbiota-derived metabolites that are known to affect leptin production and functioning include short-chain fatty acids among others. Future studies on the microbiome-leptin interaction network can inform microbiota-directed therapy that targets leptin/functionality and improve outcomes in obesity and T2DM [26].

Leptin gene therapy and CRISPR possibilities

New gene-editing technologies (e. g., CRISPR-Cas9) offer remarkable possibilities to correct mutations in the leptin gene, causing congenital leptin deficiency or alter impaired leptin signalling. Preclinical studies have previously demonstrated that genetic editing of LEP or LEPR genes can replace leptin function and prevent obesity. Current human applications are still in the early stages of development; however, leptin gene therapy could change the treatment approach for rare genetic forms of obesity and help understand ways of modifying leptin signalling in the context of more general metabolic diseases [27].

Systems biology and multi-hormonal approaches to metabolic disease

Leptin is not acting alone, it is interacting with a more complex web of hormones, including insulin, adiponectin, resist in, cortisol, and the thyroid hormones as noted previously. A systems biology approach that can model these hormonal interactions could help unravel the complexity of the metabolic diseases we refer to as obesity and T2DM. Moreover, utilizing omics technologies, including genomics, proteomics, and metabolomics, in conjunction with computational modelling, may reveal novel regulatory nodes and identify areas for potentiation between hormonal targets to improve accuracy for both diagnosis and treatment of T2DM [28].

Personalized and precision medicine strategies involving leptin

Leptin research will increasingly focus on the concept of precision medicine that is, interventions that are tailored based on a person's unique genetic make-up, hormone profile, microbiome make-up, and environmental triggers. Biomarker-guided therapy that assesses leptin sensitivity (both together and individually), performs genetic screenings for LEP/lEPR polymorphisms (and variants), and performs metabolic phenotyping may allow clinicians to personalize therapy, stratify patients based on risk, ultimately lead to better-tailored treatments. Customized therapy holds the potential for further disentangling variability in leptin biology and leptin responses as it relates to improving outcomes in obesity, diabetes, and commonly associated metabolic disorders [29-31].

Emerging strategies to overcome leptin resistance

Given the limitations of leptin replacement therapy in common obesity and T2DM, current research focuses on strategies aimed at restoring leptin sensitivity. These include combination therapies with amylin or incretin-based agents, inhibition of negative regulators such as SOCS3 and PTP1B, development of leptin receptor agonists, and investigation of natural compounds with leptin-sensitizing properties. While several of these approaches have shown promise in preclinical models, their translation to effective human therapies remains limited.

CONCLUSION

Leptin serves as a critical link between adipose tissue and metabolic regulation, however leptin resistance fundamentally limits its physiological and therapeutic effectiveness in common obesity and T2DM. While leptin replacement therapy is transformative in rare leptin-deficient conditions, it offers little benefit in hyperleptinemic, leptin-resistant states. Current evidence supports leptin's role primarily as a biomarker of adiposity and metabolic dysfunction rather than as a standalone therapeutic agent in common metabolic disease. Future advances will depend on strategies that restore leptin sensitivity, integrate gut–brain and microbiome interactions, and apply precision medicine approaches to identify responsive patient subgroups.

ACKNOWLEDGMENT

GITAM School of Pharmacy and Sarojini Naidu Vanita Pharmacy Maha Vidyalaya are acknowledged by the authors for providing the guidance.

AUTHORS CONTRIBUTIONS

Rajyalakshmi Devi P, as the Lead Author, writing the original draft and was responsible for the conceptualization and methodological framework of the review, Dr. M. Vinyas contributed through supervision, critical reviewing, and editing of the manuscript. Mote Srinath contributed to data curation and investigation, supporting the compilation and verification of relevant scientific evidence. Vasanthi A V was involved in writing the original draft and participated in the review and formal analysis of the manuscript, ensuring accuracy, coherence, and clarity across sections.

CONFLICT OF INTERESTS

The author/editor has no conflicts of interest, financial or otherwise, to declare.

REFERENCES

1. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ. Leptin and obesity: role and clinical implication. Front Endocrinol. 2021;12:585887. doi: 10.3389/fendo.2021.585887, PMID 34084149.

2. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic, appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism. 2022;133:155217. doi: 10.1016/j.metabol.2022.155217. PMID 35584732.
3. Dornbush S, Aeddula NR. Physiology, leptin. In: Treasure Island, FL: StatPearls Publishing; Updated 2023 Apr. 10. StatPearls; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537038.
4. Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010;152(2):93-100. doi: 10.7326/0003-4819-152-2-201001190-00008, PMID 20083828.
5. Frühbeck G. Intracellular signalling pathways activated by leptin. Biochem J. 2006;393(1):7-20. doi: 10.1042/BJ20051578, PMID 16336196.
6. Myers MG Jr, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol. 2008;70:537-56. doi: 10.1146/annurev.physiol.70.113006.100707. PMID 17937601.
7. Suryapani A, Uniyal SM. Correlation of leptin and adiponectin levels with metabolic and hormonal profiles in PCOS patients: A comparative study with normal controls. Int J Curr Pharm Sci. 2024 nov. 15;16(6):62-5. doi: 10.22159/ijcpr.2024v16i6.6009.
8. Yeung AY, Tadi P. Physiology, obesity, neurohormonal appetite and satiety control. In: Treasure Island, FL: StatPearls Publishing; StatPearls; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555906.
9. Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol. 2008;70:537-56. doi: 10.1146/annurev.physiol.70.113006.100707. PMID 17937601.
10. Manglani K, Anika NN, Patel D, Jhaveri S, Avanthika C, Sudan S. Correlation of leptin in patients with type 2 diabetes mellitus. Cureus. 2024;16(4):e57667. doi: 10.7759/cureus.57667, PMID 38707092.
11. Stefanakis K, Upadhyay J, Ramirez-Cisneros A, Patel N, Sahai A, Mantzoros CS. Leptin physiology and pathophysiology in energy homeostasis, immune function, neuroendocrine regulation and bone health. Metabolism. 2024;161:156056. doi: 10.1016/j.metabol.2024.156056. PMID 39481533.
12. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ. Leptin and obesity: role and clinical implication. Front Endocrinol. 2021;12:585887. doi: 10.3389/fendo.2021.585887, PMID 34084149.
13. Sheth ND, Shaker IA, Bidwe S. Diagnostic potential of elevated leptin in metabolic syndrome: a comprehensive review and meta-analysis. IJCBR. 2025;11(4):214-22. doi: 10.18231/j.ijcbr.2024.032.
14. Gawali R, Bahulikar A, Phalgune DS, Tambolkar A. Association between serum leptin levels in obesity and type 2 diabetes mellitus. J Clin Diagn Res. 2019;13(10):OC17-20. doi: 10.7860/JCDR/2019/42410.13235.
15. Perakakis N, Mantzoros CS. Evidence from clinical studies of leptin: current and future clinical applications in humans. Metabolism. 2024;161:156053. doi: 10.1016/j.metabol.2024.156053, PMID 39490439.
16. Vilariño Garcia T, Polonio Gonzalez ML, Perez Perez A, Ribalta J, Arrieta F, Aguilar M. Role of leptin in obesity, cardiovascular disease, and type 2 diabetes. Int J Mol Sci. 2024;25(4):2338. doi: 10.3390/ijms25042338, PMID 38397015.
17. Gómez WA, Humeres G, Orozco Castano CA, Cannataro R, Munoz Contreras AM, Gomez Miranda LM. Leptin signaling and its relationship with obesity-induced insulin resistance: a bioinformatics-assisted review. Gene Expr. 2024;0(0):56-63. doi: 10.14218/GE.2024.00039.
18. Greco M, De Santo M, Comande A, Belsito EL, Ando S, Liguori A. Leptin-activity modulators and their potential pharmaceutical applications. Biomolecules. 2021;11(7):1045. doi: 10.3390/biom11071045, PMID 34356668.
19. Rajan S, Satish S, Shankar K, Pandeti S, Varshney S, Srivastava A. Aegeline-inspired synthesis of novel β3-AR agonist improves insulin sensitivity in vitro and in vivo models of insulin resistance. Metabolism. 2018;85:1-13. doi: 10.1016/j.metabol.2018.03.001, PMID 29524448.
20. Roth JD, Roland BL, Cole RL, Trevaskis JL, Weyer C, Koda JE. Leptin responsiveness restored by amylin agonism in diet-induced obesity: evidence from nonclinical and clinical studies. Proc Natl Acad Sci USA. 2008;105(20):7257-62. doi: 10.1073/pnas.0706473105, PMID 18458326.
21. Altarejos JY, Montrose-Rafizadeh C, Smith EP. Pharmacologic activation of the leptin receptor with a monoclonal antibody agonist and implications for combination therapy with incretin-based agents. Sci Transl Med. 2023;15(703):eabq1234. doi: 10.1126/scitranslmed.abq1234.
22. Ravussin E, Smith SR, Mitchell JA, Shringarpure R, Shan K, Maier H. Enhanced weight loss with pramlintide/Metreleptin: an integrated neurohormonal approach to obesity pharmacotherapy. Obesity (Silver Spring). 2009;17(9):1736-43. doi: 10.1038/oby.2009.184, PMID 19521351.
23. De Assis GG, Murawska Ciałowicz E. Exercise and weight management: the role of leptin-a systematic review and update of clinical data from 2000-2022. J Clin Med. 2023;12(13):4490. doi: 10.3390/jcm12134490, PMID 37445524.
24. Aragonès G, Ardid Ruiz A, Ibars M, Suarez M, Blade C. Modulation of leptin resistance by food compounds. Mol Nutr Food Res. 2016;60(8):1789-803. doi: 10.1002/mnfr.201500964, PMID 26842874.
25. Tam CS, Lecoultre V, Ravussin E. Novel strategy for the use of leptin for obesity therapy. Expert Opin Biol Ther. 2011;11(12):1677-85. doi: 10.1517/14712598.2011.619974, PMID 21910668.
26. van Son J, Koekkoek LL, La Fleur SE, Serlie MJ, Nieuwdorp M. The role of the gut microbiota in the gut-brain axis in obesity: mechanisms and future implications. Int J Mol Sci. 2021;22(6):2993. doi: 10.3390/ijms22062993, PMID 33804250.
27. Perakakis N, Mantzoros CS. Evidence from clinical studies of leptin: current and future clinical applications in humans. Metabolism. 2024;161:156053. doi: 10.1016/j.metabol.2024.156053. PMID 39490439.
28. Devi RP, Vinyas M, Vinod Kumar N, Srinath M. Comparative anti-obesity activity of probiotics with short-chain fatty acids (SCFAs) through GLP 1 and PYY activityin high-fat diet-induced obesity in rats. TexilaInt J Public Health. 2024;12(3):Art.007. doi: 10.21522/TIJPH.2013.12.03.2.
29. Devi PR, Srinath M, Venu T, Nelson VK, Vinyas M. Acute and sub-acute toxicological study of short-chain fatty acids (SCFAs) in rats. IJASE. 2025;11(4):4424-34. doi: 10.29294/IJASE.11.4.2025.4424-4434.
30. Mohammad M, Olabi A, Lahdo R. Investigating the relationship between serum leptin levels and C-reactive protein in polycystic ovary syndrome (PCOS) patients. Innovare J Med Sci. 2016;4(3):10-3.
31. Devi PR, Srinath M, Reddy BM, Chaitanya KR, Vinyas M. Investigating the role of probiotics and short-chain fatty acids (Scfas) in modulating leptin for improved anti-diabetic effects in streptozotocin-nicotinamide induced type Ii diabetes in rats. Int J App Pharm. 2025;17(6):560-7. doi: 10.22159/Ijap.2025v17i6.54383.