REVIEW ARTICLE

The Multifaceted Benefits of Leptin: Beyond Weight Regulation

Kinjal P. Patel[1], Rahul Trivedi[1], Rajesh Hadia[1], Rajesh A. Maheshwari[1], Sunil Kardani[1], Snigdha Das Mandal[2]

[1]Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India, [2]Parul Institute of Pharmacy and Research, Parul University, Waghodia, Vadodara, Gujarat, India

Abstract

Leptin is a hormone that is produced by a variety of different cells, most notably adipocytes, but also by the stomach, lungs, and other organs, which mainly acts on the brain's hypothalamus. Since its discovery in 1994, leptin's pleiotropic activities have attracted increased interest from the scientific community. As a result, many pathological states have been related to leptin signaling disturbance. This includes the connection between one's nutritional state and one's immune competence, which is one of the functions listed. It shares structural similarities with other inflammatory cytokines such as IL-6 and IL-12. Leptin regulates immunological responses, which is consistent with its structure as a cytokine. Leptin's most crucial physiological function is probably as a signal for the transition between the fasted and fed states. Although leptin may play a role in preventing obesity in some people, the prevalence of obesity is strongly correlated with elevated leptin levels. There are no human studies specifically designed to investigate the role of leptin, despite numerous reports of connections between leptin levels and various physiological and pathological states. In this review, the effect of leptin on different organ systems is described along with biology, mechanism of action, and its resistance factor.

Key words: Anti-inflammatory effect, leptin, leptin resistance, leptin receptor, obesity

INTRODUCTION

Many people believed that the treatment for obesity had been discovered when leptin was discovered 15 years ago. The Greek term "leptos," which means thinness, inspired the name "leptin," which was given to this protein/cytokine released by adipocytes. This nomenclature established that adipose tissue is an active organ of the endocrine system in addition to being a passive energy reserve, which signified a paradigm shift. The identification of leptin, a protein hormone, occurred in 1994. Produced by fat cells, leptin sends a signal to the brain instructing it to cease eating when a sufficient amount of food has been consumed. It also tells the body to raise its metabolic rate.[1,2] "Leptin resistance" is a syndrome that can cause you to feel constantly hungry. Leptin levels in the blood are linked to fat storage and fluctuate in response to a shift in energy balance. In addition, leptin plays a crucial role in aiding the body's adaptation to fasting, and this function might be the primary driving force behind the evolutionary development of leptin. Leptin has been demonstrated to control neuroendocrine, immunological, and developmental processes in addition to its role in energy balance. Leptin in humans is 84% similar to that in mice and 83% similar to that in rats.[3] The amounts of leptin in the bloodstream are strongly positively correlated with the expression of leptin mRNA and protein in adipose tissue.[4-6] Analysis of leptin's molecular structure suggests that it is comparable to cytokines in structure.[7,8] The intrachain disulfide bond in leptin appears to be essential for the hormone's bioactivity, as well.[1] Adipose tissue produces leptin, a hormone that has been written as the ob-gene, and its serum concentrations show a positive correlation with the quantity of energy stored in fat mass.[4] Although adipose tissue is the main source, other tissues such as brown adipose tissue, reproductive organs such as the placenta, the ovaries, digestive organ stomach, bone marrow, cells such

Address for correspondence:
Kinjal P. Patel, Assistant Professor, Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara - 391760, Gujarat, India.
Phone: 9727776379.
E-mail id: kinjalpatel54@gmail.com

Received: 05-08-2024
Revised: 06-11-2024
Accepted: 19-11-2024

as mammary epithelial cells, and skeletal muscle, all exhibit lower expression of leptin.[9]

Through positional cloning of ob/ob mice-a type of obese mice that Jackson Labs accidentally found 167-amino acid product derived from the human leptin gene was discovered.[10] These mice exhibited a homozygous mutation in the leptin gene, leading to infertility, hyperphagia, severe obesity, diabetes, neuroendocrine abnormalities, and significant weight gain.[11]

A characteristic 4-helical cytokine structure with an intramolecular disulfide bridge and four antiparallel helices arranged in an up-up-down-down sequence was discovered by crystallographic study at 2.4 Å resolutions. The db gene encodes the single-membrane, heavily glycosylated Class I cytokine receptor known as the leptin receptor (LEPR). The existence of cytokine receptor homology domains identifies members of this receptor family. Both of these (CRH1 and CRH2) can be found in the LEPR, in addition to additional IGD and fibronectin type III domains. Because of alternate mRNA splicing and/or ectodomain shedding, which is only seen in humans, six different LEPR isoforms are expressed. The long, short, and soluble forms are all included here. The long version is the only one with functional signaling properties and it is in large quantities expressed in the hypothalamus, a brain region critical for regulating food intake and body weight.[12] Other, peripheral tissues also show expression, though short and soluble isoforms are expressed more widely, it is hypothesized that they modulate leptin transit, renal clearance, and/or bioavailability. Like many other hormones, leptin is secreted pulsatilely and its levels show significant diurnal variation, being highest in the evening and the morning.[13-21]

Mechanism of action

Like many other cytokine receptors, the LEPR forms premade, inactive receptor complexes on the surface of cells. The proposed 4:4 leptin: LEPR complex is formed when leptin binds to the receptor with low nanomolar affinity, inducing the higher-order clustering of pre-existing dimers of the leptin receptor.[22] Leptin binding specifically requires only the CRH2 domain, whereas receptor activation is dependent on the presence of the IGD and FNIII domains. Cross-phosphorylation of JAK2 induces rapid phosphorylation of three conserved tyrosine residues in the cytoplasmic domain of LEPR. This process creates docking sites for signaling molecules, initiating crucial downstream signaling pathways such as JAK/STAT, MAPK, and PI3K. Following phosphorylation, STATs assemble into homo- or heterodimers, reach the nucleus, and control target gene transcription. A widely accepted model of JAK/STAT signaling suggests that STAT molecules bind to the phosphorylated receptor tyrosine residues, serving as substrates for JAK activity. It is worth noting that STAT3 is indispensable for the regulation of energy metabolism mediated by leptin.[23] The initiation of the mitogen-activated protein kinase (MAPK) pathway by LEPR requires the involvement of SH2-containing protein tyrosine phosphatase 2 (SHP2). A number of the insulin-receptor substrate family members become phosphorylated when LEPR is activated, facilitating the enrollment and activation of PI3K and the accumulation of the PI3K byproduct, phosphatidylinositol 3,4,5-triphosphate. This then causes Akt,3-phosphoinositide-dependent protein kinase-1, and cyclic nucleotide phosphodiesterase 3B to become activated.[24] In response to cytokine stimulation, members of the SOCS family are expressed. These SOCS proteins suppress signaling by reducing the activation of JAK kinases and/or by interfering with the ability of other proteins to bind to activated receptors. The principal antagonist of leptin's metabolic-regulating activities is a protein called SOCS3.[25] In addition to SOCS2 and CIS (cytokine-inducible SH2-containing protein), other proteins also add to the attenuation of LEPR signaling. Surface LEPR signaling control and dephosphorylating of JAK2 by protein tyrosine phosphatase 1B are two additional negative regulatory mechanisms.[26,27]

EFFECT OF LEPTIN ON DIFFERENT ORGAN SYSTEM

Digestive system

In several tissues, leptin appears to have a complex function that can be advantageous or harmful depending on the physiological context. Because your body must follow every instruction these little "chemical messengers" give, it is crucial to keep in mind their purpose. While Ghrelin increases Appetite, Leptin decreases appetite. It is created by fat cells and alerts the brain when you have had enough food. In addition, the body is told to speed up its metabolism. You may experience "leptin resistance," a disease that causes persistent hunger. Leptin resistance can also be caused by dehydration, excessive carbohydrate consumption, emotional distress, stress, and even visual stimuli.[28] Numerous roles for leptin in the digestive system have been shown, including the control of immunological responses, regulating glucose and lipid metabolism, and promoting cell development and tissue healing.[29-31] Meal ingestion, food digestion, and exercise all trigger the release of gastric leptin along with hormones such as secretin, gastrin, or cholecystokinin (CCK).[32,33] Leptin exhibits proteolysis resistance in the gastric juice after secretion.[34] Inside the stomach, leptin and CCK work together to increase vagal afferent activity, which controls the rate at which food leaves the stomach and adds to the feeling of fullness. Rats given leptin at a dosage of 10 μg/kg body weight showed a reduction in gastrointestinal ulcers in models of ethanol-induced gastric ulceration.[35] Interestingly, leptin's protective effects were shown to be similar to those of CCK-8, a powerful gastric protector.[36] By examining biopsy samples from people with Helicobacter pylori infection, Nishi *et al*. found a favorable relationship between stomach leptin levels and pro-inflammatory cytokines such as IL-1

and IL-6. This discovery raises the possibility that leptin affects inflammatory reactions when an *H. pylori* infection occurs. Further research has revealed that leptin controls the gastrointestinal tract's absorption of macronutrients. GLUT-2, GLUT-5, and sodium-glucose cotransporter-1 (SGLT-1) are among the carbohydrate transporters whose expression is upregulated by leptin. Reduced absorption of carbohydrates during the pre-prandial phase and enhanced absorption during the postprandial phase are the results of this leptin overexpression.[37-39]

Reproduction system

Leptin levels rise in both boys and girls before pubertal transition, with an initial increase of LH, follicle-stimulating hormone, and subsequently sex steroids. Leptin concentrations in boys fall despite rising BMI because of the inhibitory effects of testosterone, whereas leptin concentrations in girls continue to rise, maybe as a result of the stimulatory actions of estrogen.[40-42] Particularly, pregnancy and its related hormonal alterations (particularly to insulin, glucocorticoids, estrogen, and prolactin) appear to represent a physiologic condition.[43] Progesterone, prolactin, and placental lactogen may also be involved in leptin resistance, in pregnant rats.[44-47] It has been suggested that the development of hyperleptinemia and leptin resistance during pregnancy is a compensatory mechanism that permits an increase in hunger and food intake to satisfy the growing fetus calorie requirements.[47] The increase in appetite after childbirth may be explained by the rapid drop in blood leptin levels that occurs after childbirth but not the suppression of reproductive activity during lactation.[48] Mammary epithelial cells make leptin locally, which diffuses from the mother's circulation and appears in breast milk and colostrum.[49] How soon leptin levels in nursing rats continue to decline depends on the extent of metabolic drain from milk production.[41] Therefore, a lack of leptin may stop the growth of the mammary glands, which might prevent lactation. Blood leptin levels in postmenopausal women, particularly obese women, most likely decrease as a result of altered sex steroid levels. Furthermore, it has been shown that compared to non-obese women, obese women have more atretic follicles,[50] and that rising obesity is linked to an increase in the frequency of an ovulatory cycle.[44] These outcomes are consistent with the direct inhibition of ovarian steroid genesis by high leptin levels, which results in inefficient follicular development. Therefore, it can be hypothesized that obese women's high serum leptin levels may affect various aspects of the HPG axis' function or dysfunction, including early menarche, resistance to the gonadotropes' response to GnRH, and anovulation. This is because increased leptin levels have a central effect on early menarche, as well as a peripheral inhibitory effect on ovarian function. Fertile women with PCOS have lower blood and follicular fluid leptin concentrations than infertile women with PCOS after controlling for age and BMI.[51,52] Despite no change in leptin receptor or SCOS3 expression, high levels of leptin in blood and follicular fluid were linked to downregulation of STAT3 phosphorylation in granuloma cells, which may lead to infertility in PCOS.[52]

CENTRAL NERVOUS SYSTEM

Immunoreactivity with leptin mRNA is detected in the rat brain, particularly in the hypothalamus and hippocampus regions. In addition, the cortex and the dentate gyrus (DG) are also involved.[53] Neuroendocrine dysfunction, such as neurodegenerative illness, stroke, and cognitive impairment develops in mice as well as humans due to lack of leptin. The hypothalamic regions where ObRb is highly expressed include the ventromedial hypothalamus and paraventricular nucleus as well, adding up the dorsomedial hypothalamus and lateral hypothalamic area too.[54,55] The short-form leptin receptors, ObRa, are thought to participate a well-built responsibility in endocytosis process and transportation of leptin in the blood–brain barrier than ObRb.[17] There is mounting evidence that the soluble isoform, ObRe, is responsible for binding circulating leptin and so influencing the hormone's stability and availability.[56] According to a previous research reports, the risk of progression of Alzheimer's disease is reduced as the levels of leptin increase in circulation.[17,57] Research has also shown that, in comparison, reduced levels of leptin and less body mass index are seen in patients of Parkinson's disease (PD).[58,59] Loss of appetite and a corresponding drop in circulating leptin levels are also known to occur in depressed people.[60] Parkinson induced by (MPP+) 1-methyl-4-pyridinium in the brain particularly at dopaminergic cells as well as neuroblastoma. Specific protection will be provided by leptin. Leptin achieves this protective effect by maintaining stable levels of ATP and mitochondrial membrane potential. In neuroblastoma cells, treatment with leptin results in an increased synthesis of uncoupling protein-4 (UCP4) and mitochondrial uncoupling protein-2 (UCP2), both of which play crucial roles in reducing oxidative stress at the mitochondrial level.[61] Antidepressant-like effects are triggered by leptin injection into the hippocampus' DG. Deleting ObRb in the hippocampus results in depressive-like behavior and reduces the antidepressant benefits of leptin.[62,63] According to current investigations, leptin reduces the level of lactate dehydrogenase enzyme in the tissues which in turn reduces the lactic acid/pyruvate ratio and helps to prevent acidosis caused by anaerobic metabolism in the brain. The fact that PI3K inhibitor LY294002 can counteract this effect suggests that the PI3K/Akt signaling pathway is too essential for leptin-mediated neuroprotection.[64,65]

Respiratory system

Leptin affects a variety of immune cells, such as effector and regulatory T-lymphocytes, neutrophils, eosinophils, and monocytes/macrophages.[66,67] In the case of COVID-19, leptin stimulation activates monocytes, which in turn triggers a cytokine storm linked to the emergence of multiple organ

Table 1: Functions of leptin on different organ system

System	Function	Mechanism of action	References
Immunity system	Control immunological response	Increase the production of Th1-type cytokines by activating macrophages, dendritic cells and monocytes.	[28,30,31]
Digestive system	Decrease appetite	Inside the stomach, leptin and CCK work together to increase vagal afferent activity, which controls the rate at which food leaves the stomach and adds to the feeling of fullness.	[42]
Reproduction system	Early menarche and inhibitory effect of ovarian function	Despite no change in leptin receptor or SCOS3 expression, high levels of leptin in blood and follicular fluid were linked to down regulation of STAT3 phosphorylation in granuloma cells.	[60,61]
Urinary system	Urinary tract infection	Colon issues, infections, severe sepsis, nephritic syndrome, CKD increased the leptin level which linked to UTI.	[64-66]
Respiratory system	Pulmonary illnesses, such as pulmonary arterial hypertension, lung cancer, COPD	Leptin has important development of lungs and embryonic lung maturation because it seems to be involved in the production of surfactant proteins by fetal type II cells.	[67-77]
CNS	Neurodegenerative illness, stroke and cognitive impairment, Parkinson	Protective effect by maintaining stable levels of ATP and mitochondrial membrane potential. In neuroblastoma cells, synthesis of uncoupling protein-4 (UCP4) and mitochondrial uncoupling protein-2 (UCP2), both of which play crucial roles in reducing oxidative stress at the mitochondrial level.	[84,85]
CVS	Heart failure	When the conversion of glucose metabolism shift toward the oxidation of free fatty acid, which increases the consumption of myocardial oxygen (MVO2) and decreases efficiency of heart because free fatty acids are not as efficient as glucose as an energy source for cardiomyocytes.	[74-76]

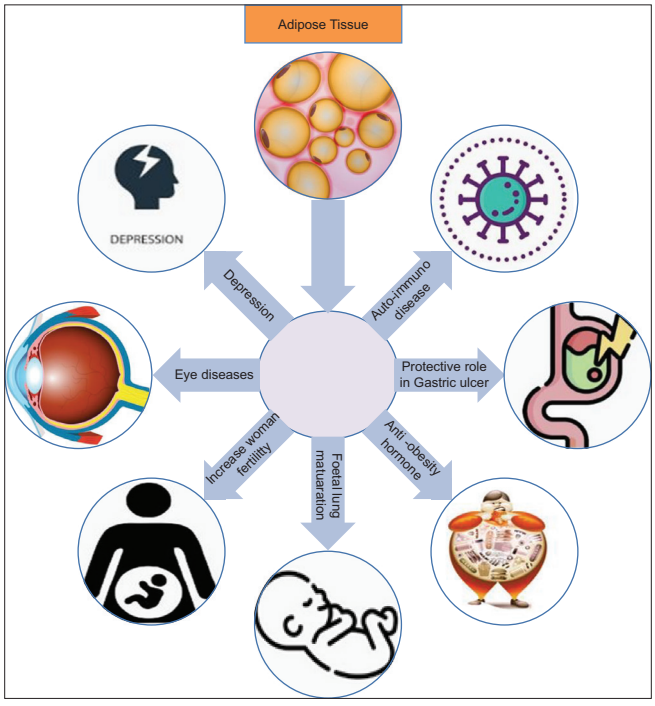

Figure 1: Effects of Leptin on different systems of body

failure and severe respiratory distress syndrome. Furthermore, leptin can change the width of the bronchi by opposing the parasympathetic effects on the airways.[68]

Finally, patients with congenital leptin deficiency have immune system impairments and face the risk of infection-related death.[69] Dysregulated leptin production and activity may have a role in the development of a number of pulmonary illnesses, such as pulmonary arterial hypertension, lung cancer, COPD, and idiopathic pulmonary fibrosis. It is interesting that in asthma sufferers, it seems to play a dual protective and detrimental effect through bronchodilating and increasing inflammation. Leptin also seems to be a defense against respiratory infections. Leptin levels and inflammatory indicators were adversely connected in pneumonia patients receiving hospital care.[70] The organs that express angiotensin-converting enzyme 2 (ACE-2) include the stomach, pancreas, kidneys, heart, blood vessels, and adipose tissue. The receptor is necessary for the entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells. The research indicates that ACE-2 expression is elevated in overweight and obese individuals.[71] In obese people with COVID-19, obesity-related chronic

inflammation worsens immunological function and raises ACE-2 expression, leading to an aggravation of disease severity and a poorer clinical prognosis.

Cardiovascular system

Leptin's function in the cardiovascular system is still debatable. Elevated leptin levels, independent of BMI or potential mediators, were associated with a higher risk of heart failure in men without a history of coronary heart disease.[72] The evolution of heart failure is monitored by leptin levels, which are independent of immunological responses.[73] Systemic metabolic disorders result from the conversion of glucose metabolism to free fatty acid oxidation, which increases myocardial oxygen consumption (MVO2) and decreases cardiac efficiency because free fatty acids are not as efficient as glucose as an energy source for cardiomyocytes.[74-76]

In animal models lacking leptin or LEPR, worse cardiac performance is linked to modified myocardial substrate uptake and metabolic stiffness. This is due to increased absorption and oxidation of vesicular fatty acids, along with decreased uptake and oxidation of carbohydrates and glucose. Appetite-induced endothelial dysfunction and cardiac fibrosis are thought to be specifically caused by leptin-mediated aldosterone production, which lowers myocardial relaxation and ultimately contributes to cardiovascular disease.[77] The hemodynamic effects of leptin, which include elevated blood pressure resting heart rate and sympathetic nervous system stimulation, frequently result in an increase in myocardial strain. Leptin influences the production of nitric oxide, a vasodilator, thus affecting vascular tone and blood pressure regulation.[78] Leptin can promote angiogenesis (formation of new blood vessels), which is a critical process in both physiological and pathological conditions, such as wound healing and tumor growth.[79] The balance of leptin's effects is crucial; while normal levels are essential for physiological functions, elevated levels, particularly in the context of obesity, can contribute to cardiovascular diseases.[80]

Urinary system

Leptin, an adipokine crucial for regulating appetite and body weight, also plays a role in various bodily functions, including kidney regulation.[81] As a large molecular weight protein, leptin can be problematic for renal filtration. Hyperleptinemia is associated with impaired kidney function, including increased excretion of urinary albumin and a reduced glomerular filtration rate in patients with chronic kidney diseases (CKD).[82-84] Renal tubules degrade leptin after it has been filtered by the glomeruli. Leptin levels in the blood were consequently elevated in people with renal failure, including those undergoing hemodialysis or who have CKD. Elevated leptin in CKD could stem from reduced clearance by malfunctioning kidneys and increased production by adipose tissue, possibly due to factors such as hyperinsulinemia, chronic inflammation, and significant lipid disturbances.[81,85,86] Heightened leptin levels in CKD patients may raise the risk of cardiovascular problems.[81,87-89] Leptin is considered a uremic toxin, as elevated levels are associated with glomerular mesangial cell hypertrophy, fusion of podocytes, reduced metabolic activity in the proximal convoluted tubule, and thickened basement membrane,[81-83] as observed in CKD patients. These consequences contribute to albuminuria, glomerular sclerosis, and apoptosis of nephrons. Moreover, studies have shown that in patients with advanced CKD, leptin levels are positively correlated with aortic stiffness.[90] We have summarized the functions of leptin hormone on various organ systems as presented in Table 1.

CONCLUSION

Since its discovery in 1994, leptin has garnered significant attention due to its diverse roles and physiological impacts. Acting on the hypothalamus, leptin plays a critical role in signaling satiety and regulating energy balance. Despite its potential in obesity prevention, elevated leptin levels are paradoxically associated with obesity, suggesting a complex relationship often involving leptin resistance. In the digestive system, leptin modulates appetite, glucose, and lipid metabolism, and contributes to tissue repair. Its influence on the reproductive system is evident in puberty, pregnancy, and lactation, where leptin levels are closely linked to hormonal changes and reproductive health. In the central nervous system, leptin's interactions are crucial for neuroendocrine function, with implications for neurodegenerative diseases and cognitive health. Respiratory health is also affected by leptin, with its involvement in immune responses and potential impacts on conditions like asthma and COVID-19. In the cardiovascular system, leptin influences heart function, vascular tone, and blood pressure regulation, highlighting its dual role in physiological processes and disease states. Finally, in the urinary system, leptin's role in kidney function and its implications in CKD emphasize the hormone's systemic importance. In Figure 1 we have represented the effects of leptin on different systems of the body.

Despite the extensive research on leptin's biological functions and mechanisms, human studies specifically designed to investigate leptin's role remain limited. The comprehensive understanding of leptin's influence across various organ systems underscores its significance and the need for further targeted research to explore its therapeutic potential and address the challenges posed by leptin resistance.

SOURCE OF SUPPORT

Nil.

CONFLICT OF INTEREST

The authors declare no conflicts of interest relevant to this article.

ACKNOWLEDGMENT

Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University provided the support for undertaking this work.

REFERENCES

1. Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. Cytokine 2019;121:154735.
2. Gelen V, Kükürt A, Şengül E, Deveci HA. Leptin and its role in oxidative stress and apoptosis: An overview. In: Role of Obesity in Human Health and Disease. London: IntechOpen; 2021. p. 143-63.
3. Picó C, Palou M, Pomar CA, Rodríguez AM, Palou A. Leptin as a key regulator of the adipose organ. Rev Endocr Metab Disord 2022;23:13-30.
4. Yoo S, Cha D, Kim S, Jiang L, Cooke P, Adebesin M, *et al*. Tanycyte ablation in the arcuate nucleus and median eminence increases obesity susceptibility by increasing body fat content in male mice. Glia 2020;68:1987-2000.
5. Bhat H, Bhat JA, Bhat MH, Rashid M, Jan R. Leptin in obesity and hypertension. Arterial Hypertens 2022;26:26-31.
6. Shi J, Fan J, Su Q, Yang Z. Cytokines and abnormal glucose and lipid metabolism. Front Endocrinol (Lausanne) 2019;10:703.
7. Yaghootkar H, Zhang Y, Spracklen CN, Karaderi T, Huang LO, Bradfield J, *et al*. Genetic studies of leptin concentrations implicate leptin in the regulation of early adiposity. Diabetes 2020;69:2806-18.
8. Song X, Zhong L, Lyu N, Liu F, Li B, Hao Y, *et al*. Inulin can alleviate metabolism disorders in ob/ob mice by partially restoring leptin-related pathways mediated by gut microbiota. Genomics Proteomics Bioinformatics 2019;17:64-75.
9. Allison MB, Myers MG Jr. 20 years of leptin: Connecting leptin signaling to biological function. J Endocrinol 2014;223:T25-35.
10. Yamada R, Odamaki S, Araki M, Watanabe T, Matsuo K, Uchida K, *et al*. Dietary protein restriction increases hepatic leptin receptor mRNA and plasma soluble leptin receptor in male rodents. PLoS One 2019;14:e0219603.
11. Evans MC, Campbell RE, Anderson GM. Physiological regulation of leptin as an integrative signal of reproductive readiness. Curr Opin Pharmacol 2022;67:102321.
12. Mosavat M, Mirsanjari M, Arabiat D, Smyth A, Whitehead L. The role of sleep curtailment on leptin levels in obesity and diabetes mellitus. Obes Facts 2021;14:214-21.
13. Amorim T, Khiyami A, Latif T, Fazeli PK. Neuroendocrine adaptations to starvation. Psychoneuroendocrinology 2023;157:106365.
14. Chrysafi P, Perakakis N, Farr OM, Stefanakis K, Peradze N, Sala-Vila A, *et al*. Leptin alters energy intake and fat mass but not energy expenditure in lean subjects. Nat Commun 2020;11:5145.
15. Perakakis N, Farr OM, Mantzoros CS. Leptin in leanness and obesity: JACC state-of-the-art review. J Am Coll Cardiol 2021;77:745-60.
16. Gogiraju R, Witzler C, Shahneh F, Hubert A, Renner L, Bochenek ML, *et al*. Deletion of endothelial leptin receptors in mice promotes diet-induced obesity. Sci Rep 2023;13:8276.
17. Fujita Y, Yamashita T. The effects of leptin on glial cells in neurological diseases. Front Neurosci 2019;13:828.
18. Butiaeva LI, Slutzki T, Swick HE, Bourguignon C, Robins SC, Liu X, *et al*. Leptin receptor-expressing pericytes mediate access of hypothalamic feeding centers to circulating leptin. Cell Metab 2021;33:1433-48.e5.
19. Rothzerg E, Ho XD, Xu J, Wood D, Märtson A, Maasalu K, *et al*. Alternative splicing of leptin receptor overlapping transcript in osteosarcoma. Exp Biol Med (Maywood) 2020;245:1437-43.
20. Zabeau L, Jensen CJ, Seeuws S, Venken K, Verhee A, Catteeuw D, *et al*. Leptin's metabolic and immune functions can be uncoupled at the ligand/receptor interaction level. Cell Mol Life Sci 2015;72:629-44.
21. Tan B, Hedbacker K, Kelly L, Zhang Z, Luo JD, Rabinowitz JD, *et al*. Cellular and Molecular Basis of Leptin Resistance. bioRxiv; 2023:1-52.
22. Park HK, Ahima RS. Physiology of leptin: Energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015;64:24-34.
23. Greco M, De Santo M, Comandè A, Belsito EL, Andò S, Liguori A, *et al*. Leptin-activity modulators and their potential pharmaceutical applications. Biomolecules 2021;11:1045.
24. Saxton RA, Caveney NA, Moya-Garzon MD, Householder KD, Rodriguez GE, Burdsall KA, *et al*. Structural insights into the mechanism of leptin receptor activation. Nat Commun 2023;14:1797.
25. Liu H, Du T, Li C, Yang G. STAT3 phosphorylation in central leptin resistance. Nutr Metab (Lond) 2021;18:39.
26. Abella V, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gómez-Reino JJ, *et al*. Leptin in the interplay of inflammation, metabolism and immune system disorders. Nat Rev Rheumatol 2017;13:100-9.
27. Amarilyo G, Iikuni N, Shi FD, Liu A, Matarese G, La Cava A. Leptin promotes lupus T-cell autoimmunity. Clin Immunol 2013;149:530-3.
28. Munoz MD, Irizarry S, Torres VC, Xu P, Liew CW. 155-OR: Brown Adipose tissue leptin feedback regulates feeding behavior. Diabetes 2022;71(Suppl 1):155.
29. Tazawa R, Uchida K, Fujimaki H, Miyagi M, Inoue G, Sekiguchi H, *et al*. Elevated leptin levels induce inflammation through IL-6 in skeletal muscle of aged female rats. BMC Musculoskelet Disord 2019;20:199.

30. Tsuchiya H, Fujio K. Emerging role of leptin in joint inflammation and destruction. Immunol Med 2022;45:27-34.
31. Mendoza-Herrera K, Florio AA, Moore M, Marrero A, Tamez M, Bhupathiraju SN, *et al*. The leptin system and diet: A mini review of the current evidence. Front Endocrinol (Lausanne) 2021;12:749050.
32. Goyal RK, Guo Y, Mashimo H. Advances in the physiology of gastric emptying. Neurogastroenterol Motil 2019;31:e13546.
33. Camilleri M. Gastrointestinal hormones and regulation of gastric emptying. Curr Opin Endocrinol Diabetes Obes 2019;26:3-10.
34. Rivero-Gutiérrez B, Aranda CJ, Ocón B, Arredondo M, Martínez-Augustin O, Sánchez de Medina F. Exogenous leptin reinforces intestinal barrier function and protects from colitis. Pharmacol Res 2019;147:104356.
35. Brzozowski T, Sikiric P, Chen D, Hahm KB, Seiwerth S. Editorial: Protection and healing in the digestive system and other tissues: Novel factors, mechanisms, and pharmaceutical targets. Front Pharmacol 2022;13:1116643.
36. Mirza KB, Alenda A, Eftekhar A, Grossman N, Nikolic K, Bloom SR, *et al*. Influence of cholecystokinin-8 on compound nerve action potentials from ventral gastric vagus in rats. Int J Neural Syst 2018;28:1850006.
37. Xu Y, Tan M, Tian X, Zhang J, Zhang J, Chen J, *et al*. Leptin receptor mediates the proliferation and glucose metabolism of pancreatic cancer cells via AKT pathway activation. Mol Med Rep 2020;21:945-52.
38. Jenks MZ, Fairfield HE, Johnson EC, Morrison RF, Muday GK. Sex steroid hormones regulate leptin transcript accumulation and protein secretion in 3T3-L1 Cells. Sci Rep 2017;7:8232.
39. Odle AK, Akhter N, Syed MM, Allensworth-James ML, Beneš H, Melgar Castillo AI, *et al*. Leptin regulation of gonadotrope gonadotropin-releasing hormone receptors as a metabolic checkpoint and gateway to reproductive competence. Front Endocrinol (Lausanne) 2017;8:367.
40. Odle AK, Beneš H, Melgar Castillo A, Akhter N, Syed M, Haney A, *et al*. Association of Gnrhr mRNA With the stem cell determinant Musashi: A mechanism for Leptin-mediated modulation of GnRHR expression. Endocrinology 2018;159:883-94.
41. Boyle CN, Le Foll C. Amylin and Leptin interaction: Role during pregnancy, lactation and neonatal development. Neuroscience 2020;447:136-47.
42. Rosenbaum M, Leibel RL. Clinical review 107: Role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. J Clin Endocrinol Metab 1999;84:1784-9.
43. Butterstein GM, Hirst C, Castracane VD. Maternal serum leptin in the pregnant rat: Fetal-placental implantation number and progesterone. Endocrine 2022;76:457-64.
44. Gustafson P, Ladyman SR, Brown RS. Suppression of Leptin transport into the brain contributes to leptin resistance during pregnancy in the mouse. Endocrinology 2019;160:880-90.
45. Grueso E, Rocha M, Puerta M. Plasma and cerebrospinal fluid leptin levels are maintained despite enhanced food intake in progesterone-treated rats. Eur J Endocrinol 2001;144:659-65.
46. Hadjieconomou D, King G, Gaspar P, Mineo A, Blackie L, Ameku T, *et al*. Enteric neurons increase maternal food intake during reproduction. Nature 2020;587:455-9.
47. Kominiarek MA, Gambala CT, Sutherland M, Varady K. Adipokinins in pregnancies at risk of preterm delivery. Gynecol Endocrinol 2016;32:78-81.
48. Perng W, Rifas-Shiman SL, McCulloch S, Chatzi L, Mantzoros C, Hivert MF, *et al*. Associations of cord blood metabolites with perinatal characteristics, newborn anthropometry, and cord blood hormones in project viva. Metabolism 2017;76:11-22.
49. Hajimirzaei SS, Samcan Z, Tehranian N. The effects of leptin on pregnancy and neonatal outcome, a review. Nursing Midwifery J 2015;13:699-717.
50. Sengupta P, Bhattacharya K, Dutta S. Leptin and male reproduction. Asian Pacific J Reproduct 2019;8:220-6.
51. Wołodko K, Castillo-Fernandez J, Kelsey G, Galvão A. Revisiting the impact of local leptin signaling in folliculogenesis and Oocyte maturation in obese mothers. Int J Mol Sci 2021;22:4270.
52. Mahutte N, Kamga-Ngande C, Sharma A, Sylvestre C. Obesity and reproduction. J Obstet Gynaecol Can 2018;40:950-66.
53. Li XM, Yan HJ, Guo YS, Wang D. The role of Leptin in central nervous system diseases. Neuroreport 2016;27:350-5.
54. Power DA, Noel J, Collins R, O'Neill D. Circulating leptin levels and weight loss in Alzheimer's disease patients. Dement Geriatr Cogn Disord 2001;12:167-70.
55. Zou X, Zhong L, Zhu C, Zhao H, Zhao F, Cui R, *et al*. Role of Leptin in mood disorder and neurodegenerative disease. Front Neurosci 2019;13:378.
56. Omrani A, De Vrind VA, Lodder B, Stoltenborg I, Kooij K, Wolterink-Donselaar IG, *et al*. Identification of novel neurocircuitry through which leptin targets multiple inputs to the dopamine system to reduce food reward seeking. Biol Psychiatry 2021;90:843-52.
57. Tunisi L, D'Angelo L, Fernández-Rilo AC, Forte N, Piscitelli F, Imperatore R, *et al*. Orexin-A/hypocretin-1 controls the VTA-NAc mesolimbic pathway via endocannabinoid-mediated disinhibition of dopaminergic neurons in obese mice. Front Synaptic Neurosci 2021;13:622405.
58. Erichsen JM, Fadel JR, Reagan LP. Peripheral versus central insulin and leptin resistance: Role in metabolic disorders, cognition, and neuropsychiatric diseases. Neuropharmacology 2022;203:108877.
59. Feinkohl I, Janke J, Slooter AJ, Winterer G, Spies C, Pischon T. The association of plasma Leptin, soluble Leptin receptor and total and high-molecular weight adiponectin with the risk of perioperative neurocognitive disorders. Am J Geriatr Psychiatry 2024;32:1119-29.
60. Mancini M, Patel JC, Affinati AH, Witkovsky P, Rice ME. Leptin promotes striatal dopamine release via cholinergic interneurons and regionally distinct signaling

pathways. J Neurosci 2022;42:6668-79.
61. Fiszer U, Michałowska M, Baranowska B, Wolińska-Witort E, Jeske W, Jethon M, *et al*. Leptin and ghrelin concentrations and weight loss in Parkinson's disease. Acta Neurol Scand 2010;121:230-6.
62. Akter S, Pham NM, Nanri A, Kurotani K, Kuwahara K, Jacka FN, *et al*. Association of 65. serum leptin and ghrelin with depressive symptoms in a Japanese working population: A cross-sectional study. BMC Psychiatry 2014;14:203.
63. Trinh T, Broxmeyer HE. Role for Leptin and Leptin receptors in stem cells during health and diseases. Stem Cell Rev Rep 2021;17:511-22.
64. Zhang J, Deng Z, Liao J, Song C, Liang C, Xue H, *et al*. Leptin attenuates cerebral ischemia injury through the promotion of energy metabolism via the PI3K/Akt pathway. J Cereb Blood Flow Metab 2013;33:567-74.
65. Savopoulos C, Michalakis K, Apostolopoulou M, Miras A, Hatzitolios A. Adipokines and stroke: A review of the literature. Maturitas 2011;70:322-7.
66. Vassiliou AG, Vitsas V, Kardara M, Keskinidou C, Michalopoulou P, Rovina N, *et al*. Study of inflammatory biomarkers in COPD and asthma exacerbations. Adv Respir Med 2020;88:558-66.
67. Lourenço EV, Liu A, Matarese G, La Cava A. Leptin promotes systemic lupus erythematosus by increasing autoantibody production and inhibiting immune regulation. Proc Natl Acad Sci U S A 2016;113:10637-42.
68. Ma C, Wang Y, Xue M. Correlations of severity of asthma in children with body mass index, adiponectin and leptin. J Clin Lab Anal 2019;33:e22915.
69. Abouhussein H, Mohamed S, Dougman T, ElHawary R. Serum Leptin in hospitalized community-acquired pneumonia children under the age of five years. Egypt Pediatr Assoc Gazette 2020;68:1-8.
70. Jutant EM, Tu L, Humbert M, Guignabert C, Huertas A. The thousand faces of Leptin in the lung. Chest 2021;159:239-48.
71. Mohammad S, Aziz R, Al Mahri S, Malik SS, Haji E, Khan AH, *et al.* Obesity and COVID-19: What makes obese host so vulnerable? Immun Ageing 2021;18:1.
72. Aryee EK, Ozkan B, Ndumele CE. Heart failure and obesity: The latest pandemic. Prog Cardiovasc Dis 2023;78:43-8.
73. Koutroumpakis E, Kaur R, Taegtmeyer H, Deswal A. Obesity and heart failure with preserved ejection fraction. Heart Fail Clin 2021;17:345-56.
74. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res 2021;128:1487-513.
75. Karwi QG, Biswas D, Pulinilkunnil T, Lopaschuk GD. Myocardial ketones metabolism in heart failure. J Card Fail 2020;26:998-1005.
76. Fillmore N, Mori J, Lopaschuk GD. Mitochondrial fatty acid oxidation alterations in heart failure, ischaemic heart disease and diabetic cardiomyopathy. Br J Pharmacol 2014;171:2080-90.
77. Xie D, Bollag WB. Obesity, hypertension and aldosterone: Is leptin the link? J Endocrinol 2016;230:F7-11.
78. Bruno RM, Ghiadoni L, Taddei S. Hypertension and endothelial dysfunction: Therapeutic approach. Curr Vasc Pharmacol 2012;10:262-9.
79. Cao Y, Zhao X. Leptin promotes proliferation and migration of colorectal carcinoma cells by activating endoplasmic reticulum stress. Biochem Biophys Res Commun 2013;430:372-7.
80. Schulze PC, Wu JM. Effects of leptin on cardiovascular function and hypertension. Curr Hypertens Rep 2010;12:206-13.
81. Korczynska J, Czumaj A, Chmielewski M, Swierczynski J, Sledzinski T. The causes and potential injurious effects of elevated serum leptin levels in chronic kidney disease patients. Int J Mol Sci 2021;22:4685.
82. Garonna E, Botham KM, Birdsey GM, Randi AM, Gonzalez-Perez RR, Wheeler-Jones CP. Vascular endothelial growth factor receptor-2 couples cyclo-oxygenase-2 with pro-angiogenic actions of leptin on human endothelial cells. PLoS One 2011;6:e18823.
83. Heida NM, Leifheit-Nestler M, Schroeter MR, Müller JP, Cheng IF, Henkel S, *et al.* Leptin enhances the potency of circulating angiogenic cells via src kinase and integrin (alpha)vbeta5: Implications for angiogenesis in human obesity. Arterioscler Thromb Vasc Biol 2010;30:200-6.
84. Park HY, Kwon HM, Lim HJ, Hong BK, Lee JY, Park BE, *et al*. Potential role of leptin in angiogenesis: Leptin induces endothelial cell proliferation and expression of matrix metalloproteinases *in vivo* and *in vitro*. Exp Mol Med 2001;33:95-102.
85. Korczyńska J, Czumaj A, Chmielewski M, Śledziński M, Mika A, Śledziński T. Increased expression of the Leptin Gene in adipose tissue of patients with chronic kidney disease-the possible role of an abnormal serum fatty acid profile. Metabolites 2020;10:98.
86. Mikolasevic I, Žutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: Etiology and management. Int J Nephrol Renovasc Dis 2017;10:35-45.
87. Kamel SM, Abdel Azeem Abd Elazeem ME, Mohamed RA, Kamel MM, Abdel Aleem Abdelaleem EA. High serum leptin and adiponectin levels as biomarkers of disease progression in Egyptian patients with active systemic lupus erythematosus. Int J Immunopathol Pharmacol 2023;37:3946320231154988.
88. Sharifian M, Shohadaee S, Esfandiar N, Mohkam M, Dalirani R, Akhavan Sepahi M. Serum and urine Leptin concentrations in children before and after treatment of urinary tract infection. Iran J Kidney Dis 2015;9:374-8.
89. Amin E, Eldesouky A, Abdel-Aziz H, Rageb O. Malnutrition markers and serum ghrelin levels in hemodialysis patients. GEGET 2019;14:32-40.
90. Lu JW, Chi PJ, Lin YL, Wang CH, Hsu BG. Serum leptin levels are positively associated with aortic stiffness in patients with chronic kidney disease stage 3-5. Adipocyte 2020;9:206-11.

Source of Support: Nil. **Conflicts of Interest:** None declared.