Iraqi Journal of Pharmacy 22(4) (2025) 215-223

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage: https://iphr.uomosul.edu.iq/

Review Article:

Leptin: Biological Functions and Metabolic Regulation in Type 2 Diabetes Mellitus

Sura khalid Mohammed [1], Zainab Haitham Fathi [2], Jehan Abdulwahab Mohammad [2]

[1] Department of Pharmacy Techniques, Northen Technical University, Mosul, Iraq.
[2] Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Mosul, Mosul, Iraq.

Article Information

Article history:

Received on: 20 January 2025
Revised on: 09 March 2025
Accepted on: 15 April 2025
Published on: 01 December 2025

Keywords:

Type 2 diabetes,
Obesity,
Leptin,
Insulin resistance.

Abstract

Background: The exponential rise of Diabetes Mellitus (DM) presents significant health challenges. Leptin is an adipokine mostly produced by white adipose tissue and is involved in regulating appetite and energy balance. Leptin modulates blood glucose levels by either central effects or peripheral effects. **Objective:** This review explores the biological functions and role of leptin in the pathophysiology of T2DM.Also, it aims to improve disease prediction accuracy, offer new insights into the pathophysiology, and contribute to future prevention efforts. The primary objective is to highlight leptin's biological role in T2DM. **Method:** The authors collected data from PubMed, Google Scholar, Research Gate, Science Direct, Elsevier, and others. The objective was to collect as much information as possible from articles using the keywords leptin and T2DM. **Conclusion:** This review explores the role of leptin in T2DM, highlighting the need for multifaceted management due to its increasing prevalence and public health implications. Leptin is a potentially viable therapeutic target for T2DM

1. Introduction

DM is a chronic, multifactorial disorder characterized by high blood glucose levels resulting from the deficiency in insulin production, insulin action, or both (1). The common symptoms of DM are polyuria, polydipsia, and polyphagia. Other symptoms are tiredness, weight loss, blurred vision, impaired wound healing, and recurrent infection (2). It is a major risk factor for developing macrovascular and microvascular complications (3). Moreover, DM is classified according to etiology and pathophysiology into four groups. These are T1DM, T2DM, Gestational DM (GDM), and other specific types and causes of chronic hyperglycemia (4).

2. Type 2 diabetes mellitus

T2DM is one of the most common metabolic disorders, caused by a reduction in insulin secretion from the pancreatic β-cells, resistance to the actions of insulin in the tissues, and an insufficient compensatory response in insulin secretion. The progression of the condition impairs insulin secretion, resulting in an inability to maintain glucose homeostasis and elevated blood glucose levels (5). T2DM accounts for more than 90% of all diabetic patients (6). It is also known as non-insulin-dependent DM or adult-onset DM (7). Patients with T2DM are mainly identified by obesity or an elevated body fat percentage, usually distributed in the abdominal area.

The incidence of metabolic disorders, including obesity and T2DM, has increased as a result of sedentary lifestyle and high caloric intake characteristic of modern living (6). Obesity and T2DM are critical global health problems owing to their association with life-threatening disorders, including cardiovascular disorders and cancers (8,9). Obesity, considered an environmental factor, is characterized by abnormal or excess accumulation of adipose tissue (AT), which is associated with an elevated risk of development of T2DM. In this state, AT promotes IR via many mechanisms, which include elevated release of free fatty acids (FFAs) and adipokine dysregulation. The gradual impairment of serum glucose regulation leads to micro- and macrovascular disorders (10).

*Corresponding author: *Sura khalid Mohammed, Department of Pharmacy Techniques, Northen Technical University, Mosul, Iraq.*
Email: Sura.23php19@student.uomosul.edu.iq

How to cite:

Mohammed, S., Kh., Fathi, Z., H., Mohammad, J., A., (2025). Leptin: Biological Functions and Metabolic Regulation in Type 2 Diabetes Mellitus. Iraqi J. Pharm. 22(4), 215-223.

DOI: https://doi.org/10.33899/iraqij.p.2025.156767.1129

3. Pathogenesis of type 2 diabetes mellitus

The pathogenesis of T2DM often follows a certain sequence of events. In the beginning, IR causes impairment of glucose tolerance. The human body initiates reactive hyperplasia of the beta cells of the pancreas as compensation. Ultimately, there will be a gradual deterioration of the pancreatic cells and the onset of overt increased serum glucose levels (11). Obesity is tightly associated with IR and modifications in glucose metabolism via a process known as lipotoxicity (12). The progression of obesity correlates with elevated levels of FFAs. FFAs contribute to IR and lipotoxicity via two primary mechanisms. Randle et al. revealed that elevated levels of FFAs result in the accumulation of acetyl-CoA and citrate in muscle tissue, subsequently inhibiting two critical glycolytic enzymes, phosphofructokinase and pyruvate dehydrogenase, which further causes the accumulation of the glucose and glucose-6-phosphate. The accumulation of glucose and the glucose-6-phosphate diminishes insulin-mediated glucose uptake contributing to IR (13). Free fatty acids also induce stimulation of insulin receptors and subsequent downstream impacts (14). Two primary processes explain this: the dysfunction of insulin receptor-mediated downstream actions and the dysfunction of the glucose transporters. Dresner et al. 1999 showed that FFAs inhibit the downstream insulin receptor signaling by exerting a blocking influence on phosphoinositol-3-kinase, a crucial downstream enzyme via which insulin receptor mediates its actions (15). Karnieli and Armoni 1990 suggested that in diabetic patients, there is a decreased expression of glucose transporters due to the exhaustion of the intracellular receptor pool. Furthermore, the suppression of the whole activity of the receptors in these individuals has been shown (16).Due to such processes, there is a reduction in the metabolism of glucose and in the synthesis of glycogen by the liver, resulting in elevated serum glucose levels or hyperglycemia. Initially, the elevation in serum glucose is mitigated by a compensatory elevation in insulin production due to beta cell hyperplasia. IR at the tissue level initiates a detrimental loop of hyperglycemia mediated by IR, resulting in an increased demand on pancreatic beta cells, eventually failing beta cells (17,18).

4. Leptin

Leptin is the classical proinflammatory adipokine, primarily synthesized by adipocytes and, to a lesser extent, by the gastric fundic epithelium, placenta, intestine, skeletal muscle, mammary epithelium, and brain (19). It has been shown to have several biological functions, such as reproduction and immunological and inflammatory response, hematopoiesis, angiogenesis, bone formation, and wound healing. It is also known as a satiety hormone that regulates food consumption and energy expenditure; hence, it plays an essential role in metabolic and neuroendocrine functions in both animals and humans (20). Also, it is secreted in a pulsating pattern. However, the amplitude of release is greater in obese people (21). Leptin is significant in the pathogenesis and consequences of T2DM. In healthy people, it inhibits appetite and controls body weight. Its levels are abnormally elevated in obese persons, indicating resistance to its actions at elevated concentrations, resulting in elevated leptin (22). Additionally, research indicates that leptin induces IR, thereby contributing to obesity by modifying the metabolism of glucose (23). This establishes a feedback loop whereby leptin induces IR, resulting in obesity, which in turn stimulates leptin synthesis, resulting in beta-cell failure (24).Leptin concentration is proportional to the mass of AT, and excessive leptin, known as leptin resistance, indicates obesity (6). Studies show that blood leptin levels may serve as a marker for obesity. Recent research has shown leptin inhibits the release of insulin and has actions that are contrary to those of insulin in the liver and adipose tissue. It significantly contributes to IR in T2DM and obesity (25).

4.1. Chemistry of leptin

The leptin molecule is a 167-amino-acid structure with a three-dimensional arrangement. It consists of four antiparallel α-helices that are joined by two long crossover links and one short loop, as shown in **Figure 1**. The protein becomes biologically inactive if any of the cysteine residues undergo mutation (26). The structure of leptin, which impacts both its biological activities in living organisms and its receptor-binding activities in laboratory settings, may be classified into three types (27) :

- The N-terminal amino acid sequence (22–115) is important for biology binding activities.
- The C-terminal amino acid sequence (116–166) has a loop structure that plays a crucial role in increasing the functions of the N-terminal portion.
- The C-terminal disulfide bond is not necessary for the activity of leptin.

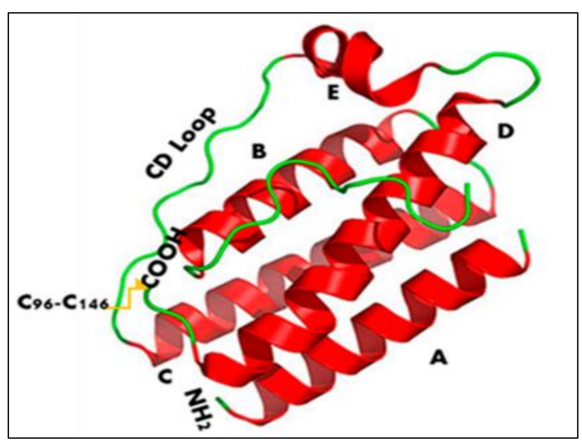

Figure 1. Structure of leptin (28)

4.2. Glucoregulatory actions of leptin

Adipocytes release adipocytokines, like leptin and adiponectin, that have an important effect on the body's energy, lipid, and glucose metabolism. An imbalance in adipocytokine levels has been associated with obesity, IR, and T2DM (29). Adiponectin is an anti-inflammatory adipokine that is produced by adipocytes and has shown a beneficial effect on lipid and glucose metabolism by increasing the sensitivity to insulin and has an essential role in maintaining the homeostasis of glucose and the metabolism of lipids (30).

On the other hand, Leptin modulates blood glucose levels by either central effects (indirectly influencing the CNS) or peripheral effects (directly affecting peripheral tissues) (31). Central impacts are mediated by the interaction with leptin receptors present on neurons in the CNS (32,33). However, the roles of leptin on regulating glucose levels in individuals with obesity and IR are controlled via pro-opiomelanocortin (POMC)-expressing neurons found in the hypothalamic (34). Regarding the peripheral effects, leptin controls blood glucose levels by directly interacting with its receptors, known as the leptin receptors, which are found in many peripheral organs (35) as shown in **Figure 2**.

Leptin directly regulates the release of hormones from the endocrine pancreas. It reduces the secretion of glucagon and insulin. The basic mechanisms involve the activation and movement of the ATP-sensitive K+ (KATP) channels across the membrane, which results in hyperpolarization of the pancreatic beta-cell membrane leading to decreased production of insulin (36). The liver immediately receives instructions from leptin in the circulation to control glucose and fat metabolism. Furthermore, leptin inhibits the process of gluconeogenesis by acting on insulin receptor substrate-2 and depleting the amount of TG in the liver (37, 38).

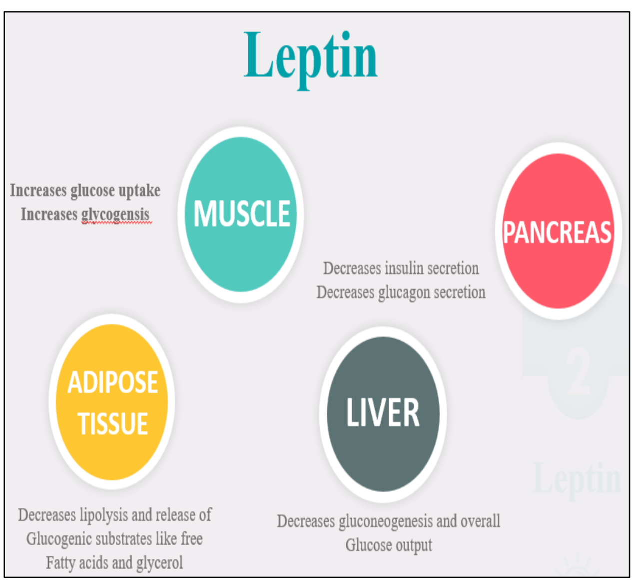

Figure 2. Metabolic actions of leptin

4.3. Role of leptin in energy balance

The majority of individuals maintain body weight in a stable state. To achieve a consistent weight, it is necessary to maintain an energy equilibrium; the total amount of energy received must be equal to the total amount of energy expended. However, when an equilibrium of energy intake and expenditure is disrupted, it may ultimately result in persistent weight issues, such as in those who are obese. Body weight regulation is controlled by a complex mechanism that includes both peripheral and central elements. Leptin and ghrelin are two hormones that appear to have a major effect on the control of food consumption and body weight. Both begin in the periphery and transmit signals via distinct routes to the brain, specifically to the hypothalamus. Activation of the leptin or ghrelin receptor in the brain triggers distinct signaling cascades that result in alterations in food consumption. Ghrelin (also known as hunger hormone) has an essential role in activating the neuropeptide Y (NPY) neurons (appetite-stimulating neuropeptides). In contrast, leptin has the opposite effect of suppressing NPY neurons in the arcuate nucleus of the hypothalamus. (39,40). Once released by the adipose tissue into the circulation, leptin passes the blood-brain barrier (BBB) and attaches to the leptin receptors in the hypothalamus. This interaction provides information about the body's energy stores. Leptin affects the function of different hypothalamus neurons as well as the production of Orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) neuropeptides by binding to its receptors (41,42).

Leptin is activated when it binds to its receptor and initiates the Janus kinase II (JAK2) route, which promotes the phosphorylation of two tyrosine residues on functional LEP-R's intracellular region, promoting the binding of STAT proteins. Subsequently, leptin is transported to the nucleus, where it functions as a transcription factor to control the synthesis of orexigenic NPY and anorexigenic POMC, as seen in **Figure 3** (43).

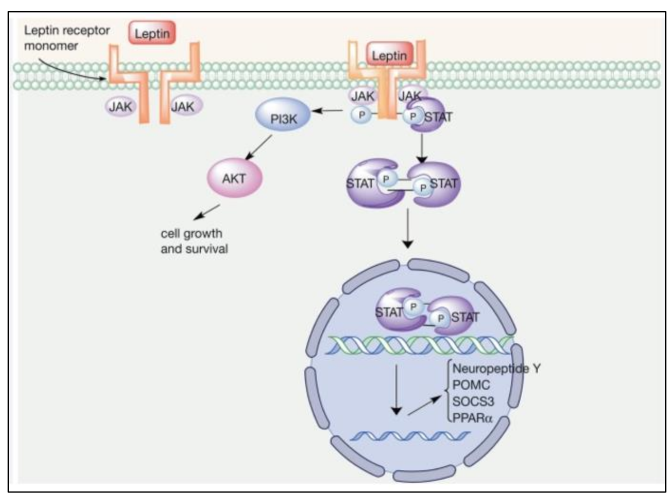

Figure 3. Mechanism of action of leptin (44)

Neuropeptide Y (NPY) is most abundantly present in the hypothalamus, brain stem, and anterior pituitary. NPY is also present in the hypothalamus's arcuate nucleus (ARC). ARC projects to the paraventricular nuclei (PVN) and the dorsomedial nuclei (45). ARC has a specific anatomical structure, it does not have the BBB. Therefore, the NPY in the ARC acts as the center for sensing and integrating peripheral energy signals including serum glucose levels, leptin, insulin, and ghrelin (46).

NPY produces its actions via NPY receptors which are G-protein-coupled receptors. Arcuate nucleus NPY neurons are stimulated when there is lack of energy and higher metabolic demands, such as during intensive physical activity, exposure to cold temperatures, and pregnancy. Energy deficits and decreased glucose levels stimulate forty percent of the NPY neurons (47).

Ghrelin has an essential role in activating NPY neurons in the arcuate nucleus. While insulin and leptin have the opposite effect of suppressing the NPY neuron. Many of the ARC neurons possess leptin and insulin receptors (48). Also, leptin and insulin reduce the activation of NPY neurons triggered by ghrelin by 30-40% (46).

Regarding POMC, leptin stimulates the production of POMC by interacting with LEP-R via the JAK2 signaling route, as seen in **Figure 4** (49). After being activated, POMC undergoes post-translational cleavage, leading to the production of an alpha-melanocyte-stimulating hormone (α-MSH). Likewise,α-MSH subsequently stimulates melanocortin receptors 3 (MC3R) and 4 (MC4R) located in the hypothalamus, resulting in a reduction in food consumption and an elevation in energy expenditure (50).

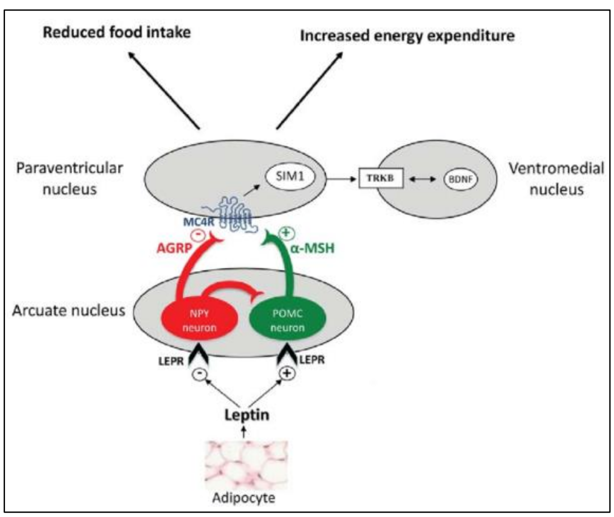

Figure 4. Leptin action via the POMC pathway (51)

4.4. Anti-obesity action of leptin

The anti-obesity action of leptin mainly acts on ObR-expressing neurons in the hypothalamus. Leptin inhibits hunger by binding to receptors in the lateral hypothalamus (52) and counteracting the effects of neuropeptide Y and anandamide, which are powerful hunger stimulants (53). While the medial hypothalamus leptin promotes satiety by improving the production of α-MSH, which suppresses appetite (54). Studies have shown that when mice have a genetic lack of leptin or a malfunctioning leptin receptor, it leads to changes in brain proteins and neuronal activities. This ultimately results in serious weight gain and T2DM. However, these effects may be repaired by leptin replacment therapy (55, 56). On the other hand, elevated leptin levels are associated with atherosclerosis, increasing your risk of cardiovascular disorders (57). However, in several instances, obese subjects have abnormally elevated levels of circulating leptin compared to those of normal weight. This is attributed to the development of leptin resistance, which refers to the decreased ability of leptin to suppress appetite and prevent weight gain. Several mechanisms have been suggested to explain leptin resistance; however, the most common cause is the reduced transportation of leptin across the BBB, which hinders its anti-obesity effects (58, 59).

4.5. Regulation of energy consumption by 5-hydroxytryptamine

Leptin in the circulation interacts with peripheral serotonin (5HT) and reduces the appetite (60). Serotonin, also known as 5-hydroxytryptamine, or 5HT is linked to various psychological and behavioral aspects and serves as a biochemical mood indicator (61). 5HT has a role in regulating energy consumption in the hypothalamus, and the levels of 5HT in the CNS are affected by the energy conditions (62). 5HT has a hypophagic effect by inhibiting the orexigenic system via interactions with hypocretins and NPY in the CNS. Additionally, 5HT probably has a stimulating impact on the anorexigenic POMC system (63). Regarding the interactions between leptin and 5HT, prior research using a mouse model found that 5HT decreased peripheral leptin levels. Additionally, 5HT directly affects adipocytes and controls the release of leptin from adipocytes (64).

4.6. Other biological functions of leptin

In addition to regulation of appetite and energy intake, leptin also has been shown to exert effects on several biological functions, such as reproduction, the immunological and inflammatory response, hematopoiesis, angiogenesis, bone formation, and wound healing.

It plays a key role in reproductive health. It sends signals to the brain about the body's nutritional status and fat reserves, which is crucial for the onset of puberty and maintenance of reproductive function. Adequate leptin levels are required for the release of the gonadotropin-releasing hormone (GnRH), which is critical for regulating reproductive hormones. Furthermore, leptin affects bone metabolism. It has been shown to control the activity of osteoblasts, which are cells that produce bones, and to alter the balance between bone formation and resorption. Additionally, leptin has an essential role in immunological function by acting as a cytokine. By affecting the activity of different immune cells, such as T-cells and macrophages, it aids in regulating immunological responses (65-67).

4.7. Leptin and insulin resistance

The relationship between leptin and insulin is very intricate (68). Exposure of adipocytes to insulin and glucose leads to an apparent increase in leptin production (69). Conversely, elevated levels of leptin in the bloodstream enhance the sensitivity of peripheral tissues to insulin while simultaneously decreasing the release of insulin from pancreatic beta cells (70).

In individuals with normal health, leptin inhibits appetite and controls body weight. Obese individuals have abnormally elevated levels of leptin, indicating a resistance to its effects at greater concentrations. This leads to a condition of elevated leptin (71, 72). In addition, studies indicate that leptin induces IR, hence contributing to obesity via altering glucose metabolism (71-74). Thus, a feedback loop is created in which the hormone leptin induces IR, which leads to obesity. In turn, obesity triggers the production of leptin, which ultimately leads to the failure of beta cells (72, 75).

4.8. Leptin as the potential target for several therapeutic approaches

Food and Drug Administration approved leptin replacement therapy for generalized lipodystrophy syndromes and congenital leptin deficiency. The approved pharmaceutical formulation, metreleptin, is given subcutaneously and is recognized for its ability to correct the metabolic abnormalities associated with these disorders (76). It results in considerable reductions in body weight, serum insulin, and glucose concentrations, markedly enhancing insulin sensitivity (77). A research study including 9 individuals with leptin deficiency and lipodystrophy demonstrated a 1.9% absolute reduction in HbA1c, a 60% decrease in triglyceride levels, and a 30% rise in high-density lipoprotein cholesterol (78).

In animals, leptin therapy has shown efficacy in improving serum glucose concentration by reducing glucose synthesis in the liver, suppressing glucagon release, and enhancing the uptake of glucose (79). Clinical studies in patients with T1DM indicate that administering of leptin as an adjunct to insulin treatment results in weight reductions of 3.7% at week 12 and 6.6% at week 20 (p-value of 0.003) (80). Furthermore, insulin needs in these individuals were markedly decreased by 12.6% at week 12 and 15.0% at week 20 (p-value = 0.006), attributable to enhanced insulin sensitivity. A further positive result of the study was the lack of any serious adverse responses associated with the subcutaneous leptin administration. Nonetheless, the medication failed to demonstrate efficacy in improving glycemic status, as there was no significant alteration in HbA1c levels after twenty weeks relative to the baseline level (p-value was 0.75) (80).

Non-obese people with T2DM exhibiting either normal or low leptin levels may potentially get advantages from leptin subcutaneous administration since they have greater leptin sensitivity compared to obese patients (81). Recent clinical studies involving obese individuals with T2DM have shown that leptin treatment is either unsuccessful or only slightly beneficial in improving metabolic disorders and IR. The research indicated that neither body weight nor inflammatory markers altered in hyperleptinemic obese and diabetic patients during metreleptin therapy (82). The findings were significant, showing no change in body mass index or fat mass after 2 weeks of therapy with a low dosage (30 mg/day) and a high dose (80 mg/day) of leptin. These findings demonstrate a strong correlation between obesity and resistance to the actions of leptin (83).

The processes behind leptin resistance are challenging to delineate; however, many hypotheses have been proposed. Mutations in leptin receptors or BBB transport proteins may disrupt leptin signaling intracellularly (83). Strategies that enhance leptin kinetics and facilitate its transport across the BBB, irrespective of the leptin transporter, represent a possible therapeutic target (84).

Numerous pharmaceutical interventions have been used to address leptin resistance historically, including the administration of leptin with glucagon-like peptide 1 (GLP-1) agonist, amylin, and fibroblast growth factor 21 (FGF-21). To get optimum leptin responsiveness, all interventions need substantial weight reduction via lifestyle adjustments (85). A viable strategy in such a situation is a combined treatment of GLP-1 agonists, FGF-21, or insulin with partial leptin reduction (e.g., monoclonal leptin-neutralizing antibodies). Given that substantial weight gain is a common side effect of insulin therapy, the addition of leptin-neutralizing antibodies might reestablish the sensitivity of leptin and be beneficial for obesity control in T2DM (86).

5. Conclusions

The present study aimed to clarify the role of leptin in T2DM and to summarize the relevant information. Leptin is a potentially viable therapeutic option for T2DM. For a condition as extraordinary as T2DM, both in its prevalence and its effect on quality of life, it is essential to investigate all possible strategies to alleviate the burden of the disease.

6. References

1. Arroyave F, Montaño D, Lizcano F. Diabetes mellitus is a chronic disease that can benefit from therapy with induced pluripotent stem cells. *International Journal of Molecular Sciences*. 2020;21(22):8685.
2. Roystonn K, AshaRani P, Siva Kumar FD, Wang P ‹Abdin E, Sum CF, et al. Factor structure of the diabetes knowledge questionnaire and the assessment of the knowledge of risk factors, causes, complications, and management of diabetes mellitus: A national population-

based study in Singapore. *Plos one*. 20:(8)17؛22e0272745.

3. Sun B, Luo Z, Zhou J. Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. *Cardiovascular Diabetology*. 2021;20:1-13.
4. Petersmann A, Nauck M, Müller-Wieland D, Kerner W, Müller UA, Landgraf R, et al. Definition, classification and diagnosis of diabetes mellitus. *Experimental and clinical endocrinology & diabetes*. 2018;126(07):406-10.
5. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiological reviews*. 2018.
6. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. *International journal of molecular sciences*. 2020;21(17):6275.
7. Leslie RD, Vartak T. Allostasis and the origins of adult-onset diabetes. *Diabetologia*. 2020;63(2):261-5.
8. Scherer PE, Hill JA. Obesity, Diabetes, and Cardiovascular Diseases: A Compendium. *Circ Res*. 2016;118(11):1703-5.
9. Choudhury AA, Rajeswari VD. Gestational diabetes mellitus-A metabolic and reproductive disorder. *Biomedicine & Pharmacotherapy*. 2021;143:112183.
10. Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. *Frontiers in endocrinology*. 2023;14:1161521.
11. Mahler RJ, Adler ML. Type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. *The Journal of Clinical Endocrinology & Metabolism*. 1999;84(4):1165-71.
12. Wende AR, Symons JD, Abel ED. Mechanisms of lipotoxicity in the cardiovascular system. *Current hypertension reports*. 2012;14:517-31.
13. Randle P, Garland P, Hales C, Newsholme E. The glucose fatty-acid cycle its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *The Lancet*. 196.9-785:(7285)281؛3
14. Kashyap SR, Belfort R, Berria R, Suraamornkul S, Pratipranawatr T, Finlayson J, et al. Discordant effects of a chronic physiological increase in plasma FFA on insulin signaling in healthy subjects with or without a family history of type 2 diabetes. *American Journal of Physiology-Endocrinology and Metabolism*. 2004;287(3):E537-E46.
15. Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, et al. Effects of free fatty acids on glucose transport and IRS-1–associated phosphatidylinositol 3-kinase activity. *The Journal of clinical investigation*. 1999;103(2):253-9.
16. Karnieli E, Armoni M. Regulation of glucose transporters in diabetes. *Hormone Research in Paediatrics*. 1990;33(2-4):99-104.
17. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo R. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study A. Gastaldelli et al.: Beta-cell dysfunction and glucose intolerance. *Diabetologia*. 2004;47.(1)
18. Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. *Frontiers in endocrinology*. 2023;14:1149239.
19. Mir MM, Mir R, Alghamdi MAA, Wani JI, Sabah ZU, Jeelani M, et al. Differential association of selected adipocytokines, adiponectin, leptin, resistin, visfatin and chemerin, with the pathogenesis and progression of type 2 diabetes mellitus (T2DM) in the asir region of Saudi Arabia: A case control study. *Journal of Personalized Medicine*. 2022;12(5):735.
20. Himms-Hagen J. Physiological roles of the leptin endocrine system: differences between mice and humans. *Critical reviews in clinical laboratory sciences*. 1999;36(6):575-655.
21. López-Jaramillo P, Gómez-Arbeláez D, López-López J, López-López C, Martínez-Ortega J ،Gómez-Rodríguez A, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Hormone molecular biology and clinical investigation*. 2014;18(1):37-45.
22. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Leptin resistance: underlying mechanisms and diagnosis. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2019:191-8.
23. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Signal transduction and targeted therapy*. 2022;7(1):216.
24. Thorand B, Zierer A, Baumert J, Meisinger C, Herder C, König W. Associations between leptin and the leptin/adiponectin ratio and incident Type 2 diabetes in middle- aged men and women: results from the MONICA/KORA Augsburg Study 1984–2002. *Diabetic medicine*. 2010;27(9):1004-11.
25. Paz-Filho G, Mastronardi C, Wong M-L, Licinio J. Leptin therapy, insulin sensitivity, and glucose homeostasis. *Indian journal of endocrinology and metabolism*. 2012;16(Suppl 3):S549-S55.
26. Staiger H, Kausch C, Guirguis A, Weisser M, Maerker E, Stumvoll M, et al. Induction of adiponectin gene expression in human myotubes by an adiponectin-containing HEK293 cell culture supernatant. *Diabetologia*. 2003;46:956-60.
27. Delaigle AlM, Jonas J-C, Bauche IB, Cornu O, Brichard SM. Induction of adiponectin in skeletal muscle by inflammatory cytokines: in vivo and in vitro studies. *Endocrinology*. 2004;145(12):5589-97.
28. 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(7):1045.

29. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *New England Journal of Medicine*. 1996;334(5):292-5.

30. Yanai H, Yoshida H. Beneficial Effects of Adiponectin on Glucose and Lipid Metabolism and Atherosclerotic Progression: Mechanisms and Perspectives. *Int J Mol Sci*. 2019;20.(5)

31. Pereira S, Cline DL, Glavas MM, Covey SD, Kieffer TJ. Tissue-specific effects of leptin on glucose and lipid metabolism. *Endocrine reviews*. 2021;42(1):1-28.

32. Friedman JM. Leptin at 14 y of age: an ongoing story. *The American journal of clinical nutrition* . 973:(3)89؛2009S-9S.

33. Flier JS, Maratos-Flier E. Lasker lauds leptin. *Cell Metabolism*. 2010;12(4):317-20.

34. Berglund ED, Vianna CR, Donato J, Kim MH, Chuang J-C, Lee CE, et al. Direct leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. *The Journal of clinical investigation*. 2012;122(3):1000-9.

35. Lee G-H, Proenca R, Montez J, Carroll K, Darvishzadeh J, Lee J, et al. Abnormal splicing of the leptin receptor in diabetic mice. *Nature*. 1996;379(6566):632.5-

36. Kieffer TJ, Heller RS, Leech CA, Holz GG, Habener JF. Leptin suppression of insulin secretion by the activation of ATP-sensitive K+ channels in pancreatic β-cells. *Diabetes*. 1997;46(6):1087-93.

37. Anderwald C, Müller Gn, Koca G, Fürnsinn C, Waldhäusl W, Roden M. Short-term leptin-dependent inhibition of hepatic gluconeogenesis is mediated by insulin receptor substrate-2. *Molecular Endocrinology*. 2002;16(7):1612-28.

38. Huang W, Dedousis N, Bhatt BA, O'Doherty RM. Impaired activation of phosphatidylinositol 3-kinase by leptin is a novel mechanism of hepatic leptin resistance in diet-induced obesity. *Journal of Biological Chemistry*. 2004;279(21):21695-700.

39. Sahu A. Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. *Frontiers in neuroendocrinology*. 2003;24(4):225-53.

40. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obesity reviews*. 2007;8(1):21-34.

41. Meister B. Control of food intake via leptin receptors in the hypothalamus. 2000.

42. Golden PL, Maccagnan TJ, Pardridge WM. Human blood-brain barrier leptin receptor. Binding and endocytosis in isolated human brain microvessels. *The journal of clinical investigation*.8-14:(1)99؛1997 .

43. Frühbeck G. Intracellular signalling pathways activated by leptin. *Biochemical Journal*. 2006;393(1):7-20.

44. Torres N, Vargas-Castillo AE, Tovar AR. Adipose Tissue: White Adipose Tissue Structure and Function. In: Caballero B, Finglas PM, Toldrá F, editors. Encyclopedia of Food and Health. Oxford: Academic Press; 2016. p. 35-42.

45. Broberger C, Johansen J, Johansson C, Schalling M, Hökfelt T. The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proceedings of the National Academy of Sciences*. 1998;95(25):15043-8.

46. Kohno D, Yada T. Arcuate NPY neurons sense and integrate peripheral metabolic signals to control feeding. *Neuropeptides*. 2012;46(6):315-9.

47. Leibowitz SF, Wortley KE. Hypothalamic control of energy balance: different peptides, different functions. *Peptides*. 2004;25(3):473-504.

48. Speakman JR. Obesity: the integrated roles of environment and genetics. *The Journal of nutrition*. 2004;1342090:(8)S-105S.

49. Laque A, Zhang Y, Gettys S, Nguyen T-A, Bui K, Morrison CD, et al. Leptin receptor neurons in the mouse hypothalamus are colocalized with the neuropeptide galanin and mediate anorexigenic leptin action. *American Journal of Physiology-Endocrinology and Metabolism*. 2013;304(9):E999-E1011.

50. KALLIO J, PESONEN U, KAIPIO K, KARVONEN MK, JAAKKOLA U, HEINONEN OJ, et al. Altered intracellular processing and release of neuropeptide Y due to leucine 7 to proline 7 polymorphism in the signal peptide of preproneuropeptide Y in humans1. *The FASEB Journal*. 2001;15(7):1242-4.

51. Huvenne H, Dubern B, Cl, ment K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. *Obesity facts*. 2016;9:158-73.

52. Elmquist JK, Elias CF, Saper CB. From lesions to leptin: hypothalamic control of food intake and body weight. *Neuron*. 1999;22(2):221-32.

53. Elias CF, Aschkenasi C, Lee C, Kelly J, Ahima RS, Bjorbæk C, et al. Leptin differentially regulates NPY and POMC neurons projecting to the lateral hypothalamic area. *Neuron*. 1999;23(4):775-86.

54. Fekete C, Légrádi G, Mihály E, Huang Q-H, Tatro JB, Rand WM, et al. α-Melanocyte-stimulating hormone is contained in nerve terminals innervating thyrotropin-releasing hormone-synthesizing neurons in the hypothalamic paraventricular nucleus and prevents fasting-induced suppression of prothyrotropin-releasing hormone gene expression. *Journal of Neuroscience*. 2000;20(4):1550-8.

55. Farr SA, Banks WA, Morley JE. Effects of leptin on memory processing. *Peptides*. 2006;27(6):1420-5.

56. Piattini F, Le Foll C, Kisielow J, Rosenwald E, Nielsen P, Lutz T, et al. A spontaneous leptin receptor point mutation causes obesity and differentially affects leptin signaling in hypothalamic nuclei resulting in metabolic

dysfunctions distinct from db/db mice. *Molecular metabolism*. 2019;25:131-41.

57. Zhao S, Kusminski CM, Scherer PE. Adiponectin, leptin and cardiovascular disorders. *Circulation research*. 2021;128(1):136-49.

58. Dardeno TA, Chou SH, Moon HS, Chamberland JP, Fiorenza CG, Mantzoros CS. Leptin in human physiology and therapeutics. *Front Neuroendocrinol*. 2010;31(3):377-93.

59. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, obesity, and leptin resistance: where are we 25 years later? *Nutrients*. 2019;11(11):2704.

60. Leibowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biological psychiatry*. 1998;44(9):851-64.

61. Duffy ME, Stewart-Knox BJ, McConville C, Bradbury I, O'Connor J, Helander A, et al. The relationship between whole-blood serotonin and subjective mood in apparently healthy postmenopausal women. *Biological Psychology*. 2006;73(2):165-8.

62. Stunes A, Reseland JE, Hauso Ø, Kidd M, Tømmerås K, Waldum H, et al. Adipocytes express a functional system for serotonin synthesis, reuptake and receptor activation. *Diabetes, Obesity and Metabolism*. 2011;13(6):551-8.

63. Aronne L, Thornton- Jones Z. New targets for obesity pharmacotherapy. *Clinical Pharmacology & Therapeutics*. 2007;81.52-748:(5)

64. Park H-J, Lee S-E, Oh J-H, Seo K-W, Song K-H. Leptin, adiponectin and serotonin levels in lean and obese dogs. *BMC veterinary research*. 2014;10:1-8.

65. Pérez-Pérez A, Vilariño-García T, Fernández-Riejos P, Martín-González J, Segura-Egea JJ, Sánchez-Margalet V. Role of leptin as a link between metabolism and the immune system. *Cytokine & growth factor reviews*. 2017;35:71-84.

66. Singh H, Almabhouh FA, Alshaikhli HSI, Hassan MJM, Daud S, Othman R, et al. Leptin in reproduction and hypertension in pregnancy. *Reproduction, Fertility and Development*. 2024;36.(12)

67. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al. Leptin regulates bone formation via the sympathetic nervous system. *Cell*. 2002;111(3):305-17.

68. Flier JS. Starvation in the midst of plenty: reflections on the history and biology of insulin and leptin. *Endocrine reviews*. 2019;40(1):1-16.

69. Martínez-Sánchez N. There and back again: leptin actions in white adipose tissue. *International journal of molecular sciences*. 2020;21(17):6039.

70. Zhao S, Kusminski CM, Elmquist JK, Scherer PE. Leptin: less is more. *Diabetes*. 2020;69(5):823-9.

71. Stefanović A, Kotur-Stevuljević J, Spasić S, Bogavac-Stanojević N, Bujisić N. The influence of obesity on the oxidative stress status and the concentration of leptin in type 2 diabetes mellitus patients. *Diabetes Res Clin Pract*. 2008;79(1):156-63.

72. Manglani K, Anika NN, Patel D, Jhaveri S, Avanthika C, Sudan S, et al. Correlation of Leptin in Patients With Type 2 Diabetes Mellitus. *Cureus*. 2024;16.(4)

73. Abdella NA, Mojiminiyi OA, Moussa MA, Zaki M, Al Mohammedi H, Al Ozairi ES, et al. Plasma leptin concentration in patients with Type 2 diabetes: relationship to cardiovascular disease risk factors and insulin resistance. *Diabet Med*. 2005;22(3):278-85.

74. Kumar R, Mal K, Razaq MK, Magsi M, Memon MK, Memon S, et al. Association of leptin with obesity and insulin resistance. *Cureus*. 2020;12.(12)

75. Thorand B, Zierer A, Baumert J, Meisinger C, Herder C, Koenig W. Associations between leptin and the leptin / adiponectin ratio and incident Type 2 diabetes in middle-aged men and women: results from the MONICA / KORA Augsburg study 1984-2002. *Diabet Med*. 2010;27(9):1004-11.

76. Simha V. Metreleptin for metabolic disorders associated with generalized or partial lipodystrophy. *Expert review of endocrinology & metabolism*. 2014;9(3):205-12.

77. Frank-Podlech S, von Schnurbein J, Veit R, Heni M, Machann J, Heinze JM, et al. Leptin replacement reestablishes brain insulin action in the hypothalamus in congenital leptin deficiency. *Diabetes Care*. 2018;41(4):907-10.

78. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, et al. Leptin-replacement therapy for lipodystrophy. *New England Journal of Medicine*. 2002;346(8):570-8.

79. Kruger AJ, Yang C, Lipson KL, Pino SC, Leif JH, Hogan CM, et al. Leptin treatment confers clinical benefit at multiple stages of virally induced type 1 diabetes in BB rats. *Autoimmunity*. 2011;44(2):137-48.

80. Vasandani C, Clark GO, Adams-Huet B, Quittner C, Garg A. Efficacy and safety of metreleptin therapy in patients with type 1 diabetes: a pilot study. *Diabetes care*. 2017;40(5):694-7.

81. Coppari R, Bjørbæk C. Leptin revisited: its mechanism of action and potential for treating diabetes. *Nature reviews Drug discovery*. 2012;11(9):692-708.

82. Moon H-S, Matarese G, Brennan AM, Chamberland JP, Liu X, Fiorenza CG, et al. Efficacy of metreleptin in obese patients with type 2 diabetes: cellular and molecular pathways underlying leptin tolerance. *Diabetes*. 20.56-1647:(6)60؛11

83. Liu J, Yang X, Yu S, Zheng R. The leptin resistance. *Neural Regulation of Metabolism*. 2018:145-63.

84. Crujeiras AB, Carreira MC, Cabia B, Andrade S, Amil M, Casanueva FF. Leptin resistance in obesity: an epigenetic landscape. *Life sciences*. 2015;140:57-63.

85. Müller TD, Sullivan LM, Habegger K, Yi CX, Kabra D, Grant E, et al. Restoration of leptin responsiveness in diet-induced obese mice using an optimized leptin analog in combination with exendin- 4 or FGF21. *Journal of Peptide Science*. 2012;18(6):383-93.
86. Starling S. New therapeutic promise for leptin. *Nature Reviews ndocrinology*. 2019;15(11):625.

اللبتين: الوظائف البيولوجية والتنظيم الأيضي في داء السكري من النوع الثاني

الملخص

المقدمة: يمثل الارتفاع الهائل في الإصابة بمرض السكري (DM) تحديات صحية كبيرة. اللبتين هو أحد الأديبوكينات التي ينتجها النسيج الدهني الأبيض في الغالب ويشارك في تنظيم الشهية وتوازن الطاقة. ينظم اللبتين مستويات الجلوكوز في الدم إما من خلال التأثيرات المركزية أو التأثيرات الطرفية. **الهدف:** يقيم هذا البحث الوظائف البيولوجية ودور اللبتين في الفسيولوجيا المرضية لمرض السكري من النوع 2. كما يهدف إلى تحسين دقة التنبؤ بالمرض، وتقديم رؤى جديدة في الفسيولوجيا المرضية، والمساهمة في جهود الوقاية المستقبلية.الهدف الأساسي هو تسليط الضوء على الدور البيولوجي للببتين في مرض السكري من النوع 2.**الطريقة:** جمع المؤلفون البيانات من PubMed وGoogle Scholar وResearch Gate وScience Direct وElsevier وغيرها. كان الهدف هو جمع أكبر قدر ممكن من المعلومات من المقالات التي تستخدم الكلمات الرئيسية اللبتين ومرض السكري من النوع 2. **الاستنتاج:** يستكشف هذا البحث دور اللبتين في مرض السكري من النوع 2، مسلطًا الضوء على الحاجة إلى إدارة متعددة الأوجه بسبب انتشاره المتزايد وتداعياته على الصحة العامة. اللبتين هو هدف علاجي قابل للتطبيق لمرض السكري من النوع 2.

الكلمات المفتاحية: داء السكري من النوع الثاني، السمنة، اللبتين، مقاومة الأنسولين.