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Review Article

Research Progress on Leptin in Metabolic Dysfunction-associated Fatty Liver Disease

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) poses a significant challenge in modern medicine due to its high prevalence. The pathogenesis of MAFLD involves a complex dysmetabolic process consistent with the "multiple-hit" hypothesis. This process includes excessive triglyceride (TC) accumulation within hepatocytes, lipotoxicity, insulin resistance (IR), chronic low-grade inflammation, and increased oxidative stress. The role of leptin in the liver has been extensively studied, demonstrating both direct effects on hepatic cells and indirect actions mediated through the central nervous system (CNS). In MAFLD, leptin modulates several physiological processes: it improves glucose metabolism by enhancing insulin sensitivity and lowering glucose levels; regulates lipid metabolism by promoting β-oxidation and TC export while inhibiting lipogenesis; and contributes to fibrogenesis by upregulating transforming growth factor-β (TGF-β) expression and activating hepatic stellate cells (HSCs) and the immune response. This review explores the structure of leptin, its primary physiological functions, its potential role in MAFLD pathogenesis, and its promise as a novel therapeutic target.

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Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD), the recently proposed term replacing nonalcoholic fatty liver disease according to a multi-society Delphi consensus statement, has emerged as the most common chronic liver disease,[1,2] affecting over 25% of the general adult population and more than 50% of individuals with type 2 diabetes mellitus (T2DM).[3,4] MAFLD is diagnosed when fatty liver is detected through histology, imaging, or blood biomarkers in individuals with one of the following: overweight/obesity (ethnic-specific), T2DM, or metabolic dysregulation with two or more risk factors.[5] Approximately 10–30% of individuals with MAFLD progress to metabolic dysfunction-associated steatohepatitis (MASH), a more advanced stage characterized by hepatic inflammation and hepatocellular injury (ballooning).[6] MAFLD and MASH can lead to severe outcomes such as cirrhosis and hepatocellular carcinoma (HCC), and are also associated with extrahepatic complications, particularly atherosclerotic cardiovascular disease and ischemic stroke, which represent the leading causes of death in this population.[7–9] Moreover, the global syndemic framework, highlighted in The Lancet Commission Report, emphasizes the interconnectedness of metabolic disease, cardiovascular disease, disability, cancer, and premature death, all of which share common biological mechanisms and societal determinants.[10] Beyond genetic predisposition, major risk factors for MAFLD include obesity and/or sarcopenia, insulin resistance (IR), and metabolic comorbidities such as dyslipidemia and T2DM.[11–14] MAFLD is recognized as an independent condition, meaning that its diagnosis does not exclude the contribution of other factors to liver dysfunction.[15] Both extrahepatic factors—such as adipokine production, caloric and nutrient imbalance, and IR—and intrahepatic mechanisms—including impaired fatty acid oxidation, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, and activation of resident macrophages—drive the onset of MAFLD and its progression to MASH.[16] Understanding the pathophysiology of MAFLD and identifying molecular targets for diagnosis and treatment remain crucial research priorities.

Leptin, a prominent adipokine primarily secreted by adipocytes, plays a central role in appetite regulation and energy homeostasis.[17] It acts by stimulating anorexigenic pathways and suppressing orexigenic pathways within the central nervous system (CNS).[18] Beyond appetite control, leptin regulates multiple physiological processes, including lipid and glucose metabolism and immune responses.[18] Insights into leptin's role in hepatic metabolism largely stem from studies using ob/ob (leptin-deficient) and db/db (leptin receptor-deficient) mice. These models exhibit hepatic IR, TC and lipid accumulation, steatosis, and inflammation—phenotypes that are partially reversed by leptin administration.[19,20] Although leptin facilitates hepatic lipid clearance and mobilization, leptin resistance, commonly seen in obesity, may limit its effectiveness in reducing steatosis.[19,20] Furthermore, elevated circulating leptin levels, frequently observed in obese individ-

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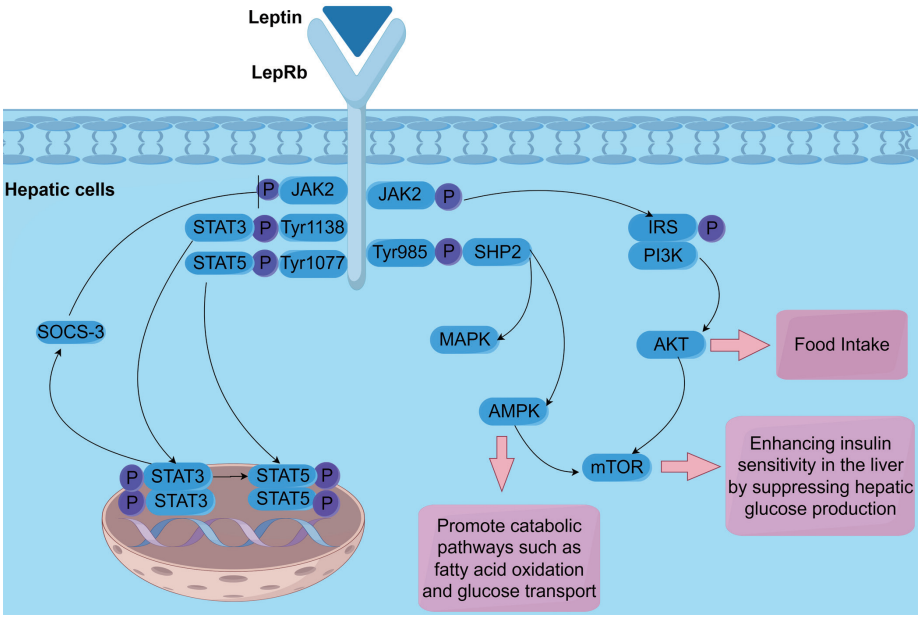

Fig. 1. Signal transduction of the leptin receptor in hepatic cells. Akt, protein kinase B; AMPK, 5′-adenosine monophosphate-activated protein kinase; ERK, extracellular signal-regulated kinase; Grb2, growth factor receptor-bound protein 2; IRS, insulin receptor substrate; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PTP, tyrosine-protein phosphatase; SHP2, tyrosine-protein phosphatase 2 containing SH2; STAT, signal transducer and activator of transcription; SOCS3, suppressor of cytokine signaling 3.

uals, are linked to hepatic inflammation and fibrosis, further implicating leptin in MAFLD progression.

This review provides a comprehensive overview of the interplay between leptin and MAFLD. We summarize experimental and clinical evidence linking leptin to MAFLD pathogenesis and evaluate its therapeutic potential, with a focus on its regulatory roles in IR, lipid metabolism, inflammation, and oxidative stress.

Leptin: Structure and receptor

The discovery of leptin began in the early 1950s with the identification of the ob/ob mouse, a model characterized by severe obesity and hyperphagia.[21] In the 1960s, the db/db mouse, another hyperphagic and obese diabetic model, was described.[22] In 1994, Jeffrey Friedman's team successfully cloned the obese gene and named the protein it encoded leptin.[23] The following year, the leptin receptor (Ob-R) was cloned and found to be mutated in the db/db mouse.[24] Leptin is a polypeptide hormone composed of 167 amino acids, transcribed from the human OB gene located on chromosome 7, which contains three exons and two introns.[23] Structurally, leptin exhibits the three-dimensional features of a four-helix bundle cytokine. It includes a short signal peptide (21 amino acids) and a longer functional segment of 146 amino acids. Although predominantly synthesized and secreted by subcutaneous white adipose tissue, leptin is also produced in several peripheral tissues and in the CNS.[25] Leptin secretion is positively correlated with adipocyte size and is regulated by multiple factors, including body fat mass, metabolic state, circadian rhythm, and hormones such as insulin, glucocorticoids, and leptin itself.[26–28] While classically regarded as a marker of long-term energy stores, leptin has pleiotropic functions: it modulates immune and inflammatory responses, neuroendocrine axes, autonomic nervous activity, cardiovascular function, reproduction, angiogenesis, osteogenesis, and hematopoiesis.[29–34] In addition, leptin influences gluconeogenesis, insulin sensitivity, and lipid and carbohydrate metabolism in the liver; skeletal muscle regeneration; lipolysis in adipose tissue; and nutrient utilization in the small intestine by regulating mucus and hormone secretion, nutrient absorption, gastric emptying, and intestinal motility.[35]

Leptin exerts its effects by binding to its cell surface receptor, Ob-R, encoded by the Ob-R gene in rodents. Throughout this discussion, murine nomenclature and numbering are used.[24,36–38] Alternative splicing of the Ob-R transcript produces several isoforms. These include the signaling-competent Ob-Rb (LepRb), which has a long intracellular tail; shorter isoforms with truncated intracellular domains (Ob-Ra, Ob-Rc, Ob-Rd); and a secreted form consisting of only the extracellular domain (Ob-Re).[39,40] CNS-expressed Ob-R isoforms are critical for energy balance, metabolism, feedback regulation, and immune function.[41] Ob-Rb is also expressed in peripheral tissues such as skeletal muscle, adipose tissue, liver, and pancreatic β-cells, suggesting autocrine and paracrine roles in energy regulation.[42,43] Shorter isoforms, Ob-Ra and Ob-Rc, are involved in leptin transport across the blood-brain barrier.[44] Leptin levels are inversely associated with the binding and clearance functions of these soluble receptors.[45,46] However, only the long Ob-Rb isoform has a complete intracellular domain capable of transmitting signals upon ligand binding.[47]

Leptin receptor signaling and MAFLD

Upon leptin binding, Ob-Rb in hepatocytes activates intracellular signaling via JAK2 (Janus kinase 2) phosphorylation (Fig. 1). JAK2 then phosphorylates three tyrosine residues (Tyr1077, Tyr1138, and Tyr985) on the intracellular domain of Ob-Rb.[20] Tyr1077 activates STAT5 (Signal transducer and activator of transcription 5), while Tyr1138 activates both STAT5 and STAT3 (Signal transducer and activator of transcription 3). Tyr985 engages the SHP2/MAPK (Tyrosine-protein phosphatase 2 containing SH2/ Mitogen-activated protein kinase)

cascade.[48–50] Activated STAT3 upregulates SOCS-3 (Cytokine signaling 3 suppressor), a negative feedback regulator of leptin and insulin signaling.[32,51,52] Elevated SOCS-3 contributes to hormone resistance, suggesting that SOCS-3 inhibition could represent a therapeutic approach in liver disease. In addition, IRS1/IRS2 (Insulin receptor substrate) phosphorylation and PI3K (Phosphatidylinositol 3-kinase) activation modulate JAK2 activity, playing a central role in leptin's regulation of food intake. Leptin also stimulates AMPK (5'-adenosine monophosphate-activated protein kinase) activity in peripheral tissues, promoting glucose uptake and fatty acid oxidation, while suppressing AMPK activity in the brain to regulate appetite.[51] The PI3K/Akt (protein kinase B) pathway, which regulates mTOR signaling, is also activated and improves insulin sensitivity by reducing hepatic glucose output.[53]

Leptin resistance

For leptin to exert its physiological effects, circulating concentrations must remain within a functional range. Excessive leptin, however, can induce receptor desensitization—even in genetically leptin-deficient mice.[54] In obesity, leptin resistance is characterized by impaired central and/or peripheral responsiveness despite elevated leptin levels.[35] This may result from impaired receptor signaling or defective transport across the blood-brain barrier (BBB).[55] Proposed mechanisms include suppression of the JAK-STAT pathway, downregulation of receptor expression, impaired post-receptor signaling, decreased histone deacetylase 5 activity in the hypothalamus, elevated C-reactive protein, endoplasmic reticulum stress, and hypothalamic inflammation.[56] SOCS3 plays a central role in diet-induced obesity by inhibiting STAT3 and downstream Ob-Rb signaling.[57,58]

Leptin resistance increases the risk of diet-induced obesity and creates a feedback loop in which elevated leptin levels further exacerbate resistance. This resistance can manifest in the CNS and peripheral tissues and is referred to as central and peripheral leptin resistance, respectively.[59] Peripheral leptin resistance occurs in tissues such as skeletal muscle, adipose tissue, and the liver; it diminishes leptin's effectiveness in regulating lipid and carbohydrate metabolism and is closely associated with inflammation.[60,61] Both leptin deficiency and leptin resistance are associated with hepatic lipid droplet accumulation, lymphocyte infiltration, and disturbances in glucose homeostasis.[62] Disruptions in leptin signaling are also significantly associated with IR in MASH.[63] In humans, leptin resistance is influenced by obesity, lipodystrophy, and genetic variations, including Ob-R polymorphisms linked to MAFLD.[64,65] Typically, obesity induces hyperleptinemia, which promotes inflammation and leptin resistance, leading to sustained postprandial hyperinsulinemia and ultimately metabolic dysfunction.

Possible models of leptin function in MAFLD pathogenesis

Glucose levels and IR

Leptin regulates blood glucose levels both directly, through peripheral tissues, and indirectly, via the CNS (Fig. 2).[66] In the CNS, these effects are mediated by leptin receptors (Ob-Rs) expressed on neurons.[67] Leptin primarily modulates glucose homeostasis in the context of obesity and IR through pro-opiomelanocortin-expressing neurons in the hypothalamic arcuate nucleus.[68,69] Notably, intracerebroventricular leptin administration in animal models produces minimal changes in circulating leptin levels but improves IR and glycemic control, supporting the hypothesis that leptin primarily regulates glucose metabolism via central mechanisms, independently of food intake or body weight.[70] Peripherally, leptin regulates glucose levels by binding to receptors in multiple tissues and modulating pancreatic hormone secretion, lowering both insulin and glucagon.[71] Although several studies show that leptin enhances glucose uptake, glycogenesis, and glucose oxidation in skeletal muscle, results have not been consistent across all investigations.[72–74] Leptin reduces glucose uptake in adipocytes and decreases fatty acid and glycerol release, thereby limiting gluconeogenic substrate availability to the liver.[75] In the liver, leptin inhibits gluconeogenesis via IRS-2 and reduces hepatic TC content.[76,77] Leptin may also interfere with insulin action by altering adipocyte sensitivity to lipid accumulation, reducing insulin receptor binding in the liver, and suppressing insulin secretion from pancreatic islets.[45,78,79] However, human studies suggest leptin does not directly affect insulin secretion from pancreatic β-cells.[80] Serum leptin levels are not consistently associated with insulin or glucose concentrations, nor with the homeostasis model assessment of IR.[81] Instead, leptin may lower blood glucose by reducing gluconeogenesis through substrate limitation. Furthermore, leptin-induced weight loss and reduced fat mass may improve insulin sensitivity, decrease glucose levels, and limit carbohydrate and lipid flux to the liver,[80] thereby suppressing de novo lipogenesis and reducing hepatic fat accumulation.[82]

Hyperleptinemia, however, can damage pancreatic β-cells and impair JAK2/PI3K signaling in obese individuals with T2DM and MAFLD. Leptin resistance may further contribute to hyperinsulinemia and worsening IR, thereby increasing the risk of T2DM.[83] IR inhibits lipid oxidation while promoting triglyceride and fatty acid synthesis.[45,78,84] Consequently, the leptin–insulin signaling axis that normally regulates glucose metabolism becomes disrupted. Hyperleptinemia also upregulates hepatic sterol regulatory element-binding protein 1 (SREBP-1), promoting lipogenesis.[85] Along with other pro-inflammatory adipokines, leptin has been strongly implicated in the development of IR, particularly in MAFLD.[86,87]

Lipid metabolism

Leptin plays a dual role in fatty liver disease (Fig. 2). In early MAFLD, leptin reduces hepatic lipid accumulation and promotes lipid oxidation.[19,88] Rodent models with impaired leptin signaling—including leptin-deficient ob/ob and db/db mice—support these findings.[89,90] Hepatic steatosis arises from disruptions in both glucose and lipid metabolism, and leptin limits TC storage in adipose and non-adipose tissues, including the liver, to prevent lipotoxicity.[20] Leptin reduces hepatic lipid accumulation through vagal signaling by activating the JAK2–STAT3/AMPK pathway, independent of food intake.[91] At physiological levels, leptin exerts anti-steatotic effects by suppressing lipogenesis and hepatic glucose production, thereby improving insulin sensitivity.[52,92] These mechanisms explain the prevention or reversal of hepatic steatosis in ob/ob mice treated with leptin.[93] Leptin's anti-steatotic properties have also been demonstrated in non-obese mice with uncontrolled T1DM, in which leptin therapy reduced lipogenic and cholesterogenic transcription factors, lowering plasma and tissue lipid levels.[94] Leptin regulates hepatic lipid synthesis by modulating key transcription factors such as carbohydrate-responsive element-binding protein.[95] It may act synergistically with insulin and inhibit the production of very low-density lipoproteins (VLDL).[94,96,97] Additionally, leptin may enhance VLDL-TC export, further reducing steatosis.[98] Some studies even suggest that leptin improves steatosis and IR in lipodystrophic mice.[99] Hackl *et al*. also reported leptin's protective role against ectopic lipid accumulation in the brain, underscor-

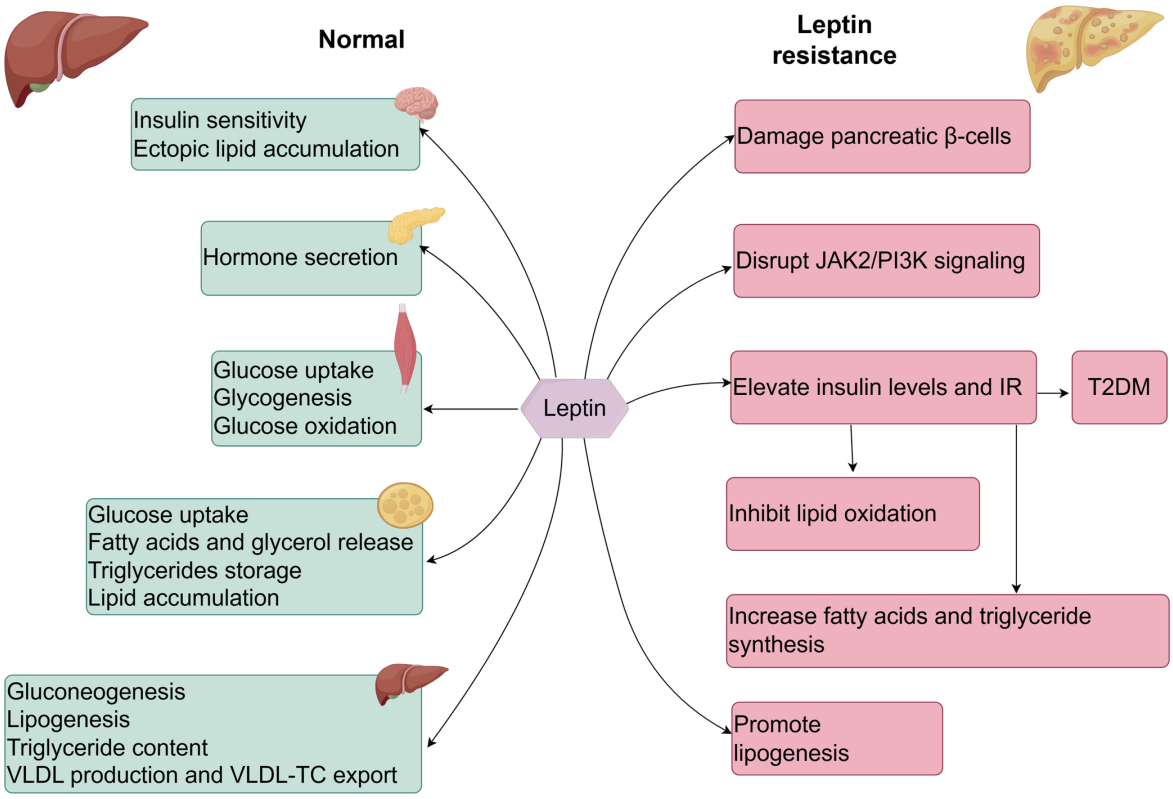

Fig. 2. Mechanisms of insulin resistance and lipid metabolism of leptin in MAFLD. In the early stages of MAFLD, leptin helps regulate glucose homeostasis, reduce hepatic lipid accumulation, and promote lipid oxidation. However, hyperleptinemia can damage pancreatic β-cells and disrupt JAK2/PI3K signaling, leading to elevated insulin levels and worsening IR. This IR inhibits lipid oxidation while promoting triglyceride and fatty acid synthesis. VLDL, very low-density lipoproteins; TC, Triglyceride; JAK, Janus kinase; PI3K, phosphatidylinositol 3-kinase; IR, insulin resistance; T2DM, diabetes mellitus, type2; MAFLD, metabolic dysfunction-associated fatty liver disease.

ing its therapeutic potential in obesity-related steatosis.[100]

Despite these beneficial effects, elevated leptin levels often fail to resolve hepatic steatosis because of leptin resistance, a central feature of MAFLD pathogenesis.[52,101,102] Mechanisms such as Tyr985 phosphorylation on Ob-Rb and increased SOCS-3 expression impair leptin signaling, particularly in the arcuate nucleus.[103] Leptin levels are positively correlated with steatosis severity, especially in individuals with high body mass index (BMI). In lean MAFLD patients, however, genetic and metabolic disorders (e.g., hypobetalipoproteinemia, celiac disease, cystic fibrosis) may play a greater role than leptin levels.[104] Leptin may also promote hepatic IR, attenuating its own anti-steatotic effects.[105] Cernea *et al*. reported increased MAFLD-related steatosis in T2DM patients,[45] while Pavlidis *et al*. found higher leptin levels associated with more severe steatosis in chronic hepatitis C.[106] Eshraghian *et al*. were the first to demonstrate that changes in leptin, adiponectin, and IR were associated with hepatic steatosis in liver transplant recipients.[107]

Inflammation

The severity of hepatic steatosis in MAFLD correlates with progressive liver damage, ranging from simple steatosis to MASH (Fig. 3). While most patients present with isolated steatosis, approximately one-third progress to MASH, increasing the risk of advanced stages of MAFLD.[1] This progression is driven by inflammation, which arises when hepatic TC levels exceed the liver's adaptive capacity, resulting in lipotoxicity. Lipotoxicity is characterized by the production of reactive oxygen species (ROS), endoplasmic reticulum stress, and hepatocellular injury.[16] These cellular insults activate immune and apoptotic pathways, ultimately leading to cell death and contributing to fibrosis and cirrhosis over time.[108] Although leptin possesses anti-steatotic properties, it also exhibits pro-inflammatory and fibrogenic effects.[109] In animal models fed a high-fat diet, elevated leptin levels have been associated with inflammation and MASH.[110] In the context of diet-induced obesity, leptin contributes to IR, T2DM, and chronic inflammation.[111–113] Studies have shown that myeloid cells lacking leptin signaling demonstrate improved glucose tolerance in obese mice, underscoring leptin's role in low-grade systemic inflammation.[114] Furthermore, leptin resistance has been linked to low-grade inflammation and steatosis in obese individuals, implicating leptin in the transition from simple steatosis to MASH.[115]

Early studies in ob/ob and db/db mice revealed immune deficiencies, including impaired antibody production, reduced cytotoxic activity, and increased susceptibility to autoimmune and allergic diseases.[116,117] Leptin enhances lipopolysaccharide-induced production of tumor necrosis factor-alpha (TNF-α) in monocytes and macrophages.[118,119] It can also independently stimulate inflammation by promoting the M1 macrophage phenotype.[120] Leptin deficiency exacerbates inflammatory cell infiltration and promotes MASH development.[121] In murine preadipocytes and adipose-derived stromal cells, leptin facilitates lipid droplet formation and upregulates adipogenic and lipogenic signaling pathways, particularly through PPARγ and SREBP-1c activation. Leptin

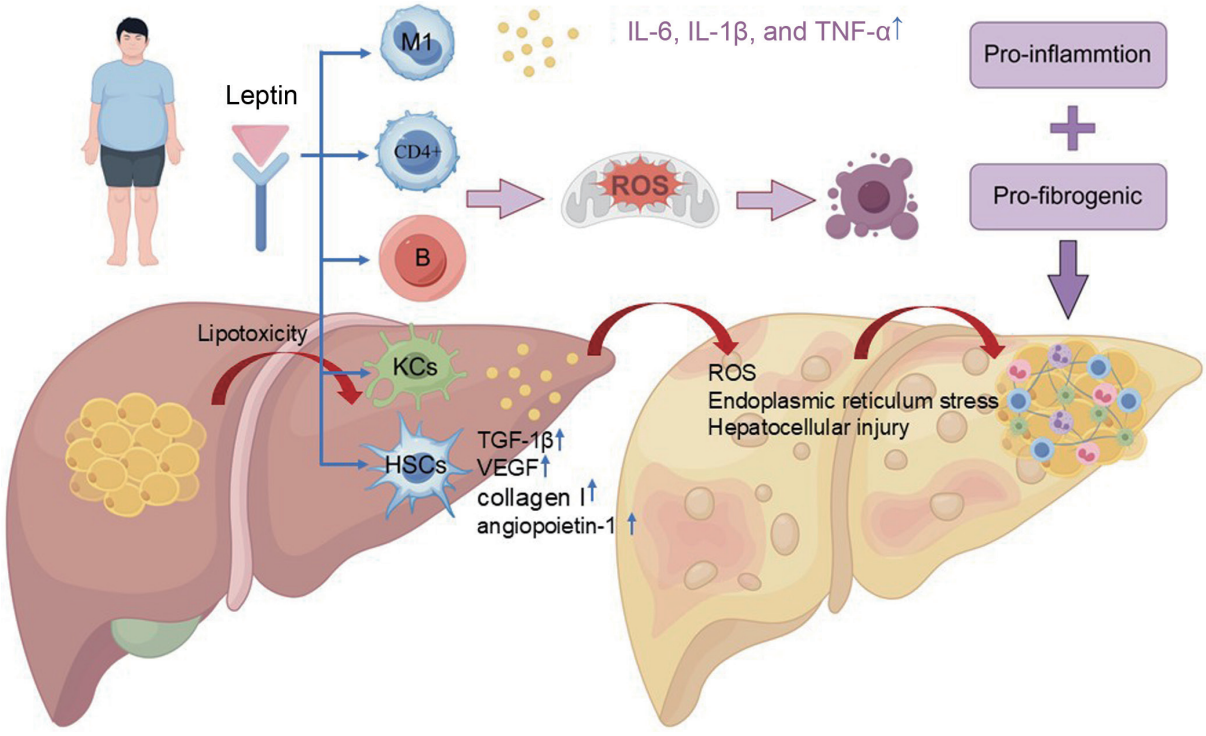

Fig. 3. Mechanisms of inflammation and oxidative stress of leptin in MAFLD. Leptin can independently stimulate inflammation by promoting the M1 macrophage phenotype while increasing pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. Leptin supports pro-inflammatory $CD4^+$ T-cell and B-cell proliferation while inhibiting regulatory T-cell (Treg) expansion. These lymphocytes can release granzymes that produce ROS in mitochondria and activate caspases, ultimately inducing pyroptosis. It can also induce ROS formation in both phagocytic and non-phagocytic cells, including endothelial cells, cardiomyocytes, and HSCs. IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha; ROS, reactive oxygen species; M1, macrophage phenotype 1; KCs, Kupffer cells; HSCs, hepatic stellate cells; TGF-1β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; MAFLD, metabolic dysfunction-associated fatty liver disease; ↑, increase.

also reduces interleukin (IL)-10 production while increasing pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[122] Conversely, TNF-α and IL-1 stimulate leptin secretion.[123,124] Leptin supports pro-inflammatory $CD4^+$ T-cell proliferation and inhibits regulatory T-cell expansion.[125,126] It also plays a role in TH17 cell differentiation in human $CD4^+$ T cells.[127] In B cells, leptin has been shown to promote the release of inflammatory mediators and accelerate immunosenescence. B cells from young, lean individuals treated with leptin displayed inflammatory and aging markers typically observed in B cells from individuals with obesity or advanced age.[128] In steatotic livers with active inflammation, OB-R expression is significantly increased in activated mouse $CD4^+CD8^+$ T cells and B cells. Leptin signaling promotes lymphocyte survival and function.[129] These lymphocytes can release granzymes that generate ROS in mitochondria and activate caspases, ultimately inducing pyroptosis.[130]

Tissue inflammation frequently leads to additional tissue injury. Leptin levels are elevated in patients with liver fibrosis, particularly among those with high BMI, whereas leaner individuals exhibit reduced inflammation and fibrosis.[104] Some studies suggest that leptin receptors on Kupffer cells (KCs) and sinusoidal endothelial cells contribute to the expression of matrix-remodeling enzymes, thereby initiating fibrosis through hepatic stellate cells (HSCs) activation.[89,104,131] Leptin also induces vascular endothelial growth factor expression in HSCs, which may drive irreversible cirrhosis and MASH progression.[132] In KCs, leptin upregulates transforming growth factor-β, likely activating HSCs through paracrine signaling.[89,104,131] Activated HSCs exacerbate hepatic inflammation and fibrosis by secreting angiopoietin-1, collagen I, transforming growth factor-β1 (TGF-β1), and vascular endothelial growth factor (VEGF). These cells also produce leptin and express ObRb, forming a feedback loop that sustains HSCs proliferation and inhibits apoptosis, thereby amplifying hepatic inflammation and fibrosis.[89] Moreover, leptin can activate KCs through oxidative stress mediated by peroxynitrite.[133] This activation promotes the presence of $CD8^+CD57^+$ T cells, which are implicated in MASH progression.[134] Prolonged hyperleptinemia may stimulate HSCs, KCs, and sinusoidal endothelial cells, triggering both pro-inflammatory and pro-fibrogenic signaling cascades.[52]

Oxidative stress

KCs are a major source of ROS in the liver, primarily through the activity of NADPH oxidase, the key enzyme responsible for ROS generation (Fig. 3).[135] Danger-associated molecular patterns, such as ATP (Adenosine Triphosphate), activate KCs and stimulate ROS production.[136] Additionally, lipid peroxidation products like 4-hydroxynonenal can activate HSCs,[137] which also produce ROS via phagocytic activity and NADPH oxidase expression.[138] The expression of cytochrome P450 2E1, an enzyme involved in fatty acid oxidation, is elevated in models of alcoholic steatohepatitis and MASH, contributing to oxidative liver damage.[139] Increased oxidative stress also promotes auto-oxidation of excess cholesterol, forming oxysterols. Elevated oxysterol levels have been observed in biopsy-proven MAFLD patients and are associated with pro-inflammatory, pro-apoptotic, and pro-fibrogenic effects.[140] A comparative study found that oxidative stress–related cel-

lular damage in MAFLD aligns with the multiple parallel hits hypothesis.[141] In this study, involving seven control subjects, 23 patients with MAFLD, and 17 with MASH, levels of 8-hydroxy-2′-deoxyguanosine and 4-hydroxynonenal were elevated in the MAFLD and MASH groups, indicating oxidative DNA damage and lipid peroxidation. Furthermore, compared with a non-hyperphagic rat model, obese hyperphagic rats showed increased hepatic oxidative stress.[16,142]

Watson *et al*. demonstrated that leptin treatment restored altered glutathione peroxidase levels in ob/ob mice, suggesting leptin's role in regulating antioxidant enzyme activity.[143] *In vitro* studies have shown that leptin decreases malondialdehyde and ROS levels while increasing glutathione content.[144] Additionally, leptin enhances natural antioxidant enzyme activity and suppresses inflammatory factor expression in 3T3-L1 preadipocytes, thereby reducing oxidative stress–induced cellular injury.[145] Leptin supplementation has also been effective in mitigating oxidative stress induced by a high-fat diet.[146] In one study, offspring of obese dams given oral leptin during the suckling period demonstrated greater antioxidant capacity and reduced inflammatory markers in the liver, retroperitoneal white adipose tissue, and plasma compared to those given vehicle control.[147] Leptin-treated male offspring also exhibited increased plasma adiponectin and a higher adiponectin/leptin ratio, which enhances the liver's anti-inflammatory and antioxidant functions.[148] The absence of leptin in pigs led to reduced JAK2-STAT3 and AMPK phosphorylation, resulting in increased fatty acid β-oxidation and mitochondrial autophagy—both contributing to oxidative stress in liver cells.[149] In human hepatoma cell lines, leptin treatment of ethanol-exposed cells reduced ROS generation.[150] Furthermore, leptin was shown to suppress oxidative stress responses in blood and reduce endotoxemia-induced rises in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α.[151]

However, leptin can also induce ROS formation in both phagocytic and non-phagocytic cells, including endothelial cells, cardiomyocytes, and HSCs.[152–154] Elevated leptin levels have been linked to increased ROS production, primarily through NADPH oxidase activation.[155] Hyperinsulinemia and hyperleptinemia are considered key contributors to oxidative stress in individuals with obesity or T2DM.[156,157] Systemically elevated leptin levels exacerbate oxidative stress and weaken antioxidant defenses, thereby intensifying hepatic inflammation, especially in alcoholic liver disease.[158] In mouse models with steatohepatitic lesions, high circulating leptin levels aggravated liver damage via NADPH oxidase activation, inducible nitric oxide synthase induction, and increased TNF-α and monocyte chemoattractant protein-1 release from KCs, all mediated through peroxynitrite-dependent pathways.[133] Leptin promotes oxidative and inflammatory effects through three primary mechanisms: leptin-induced protein radical formation, tyrosine nitration, and KCs activation.[133] It also upregulates CD14 expression on KCs, a receptor for the bacterial endotoxin lipopolysaccharide.[159] This upregulation heightens cellular sensitivity to harmful stimuli and enhances oxidative stress. Notably, CD14 overexpression has been implicated in the progression of steatohepatitis and liver fibrosis, even in the absence of prior steatosis.[160]

Leptin in MAFLD: Evidence from clinical studies

Basal leptin levels correlate with BMI and reflect the body's nutritional status. In severe obesity, the physiological set point for weight regulation may shift to a higher leptin threshold.[115] When BMI decreases to below 25 kg/m^2, fasting leptin levels fall by approximately 15 ng/dL, likely due to improved leptin delivery to the CNS and enhanced access to specific neuronal populations.[130,161] Low circulating leptin levels and increased leptin sensitivity, both of which exert anti-steatotic effects, are associated with several interventions, including physical activity,[162] bariatric surgery,[163] dietary polyphenol intake,[164,165] caloric restriction, and sustained weight loss.[166,167] Leptin thresholds vary among individuals due to genetic factors,[161] sex-related differences,[115,168] and, more recently, the use of GLP-1 receptor agonists.[169] Individuals with a history of obesity may retain elevated leptin levels even after returning to normal weight.[170]

Importantly, elevated leptin levels have been linked to MAFLD even in lean individuals and in the absence of IR.[171] Multiple studies demonstrate that high leptin levels are associated with both the presence and severity of MAFLD in children and adults, suggesting that early-onset leptin resistance may contribute to disease pathogenesis.[172–177] For instance, Marques *et al*. reported elevated leptin levels in MAFLD patients compared to healthy controls, with no significant difference between obese and non-obese groups—indicating that obesity is not a confounding factor.[178] Moreover, reducing leptin levels with antibodies has been shown to restore leptin sensitivity, suggesting a potential therapeutic strategy for obesity and diabetes.[179] These findings imply that early intervention to lower leptin levels in children could help prevent MAFLD.[172] Previous studies also reported associations between elevated leptin and hepatic fibrosis in MAFLD. In one study, high serum leptin was identified as a significant risk factor for hepatic steatosis, and receiver operating characteristic analysis confirmed leptin as an independent predictor of liver fat accumulation.[180]

However, not all findings are consistent. Canbakan *et al*. found that leptin was not an independent predictor of MAFLD or fibrosis severity; their study reported higher leptin levels in patients with moderate fibrosis compared to those with advanced fibrosis.[81] Similarly, in a pediatric cohort, children with prepubertal obesity and fatty liver disease had significantly lower leptin z-scores (adjusted for BMI) than peers with normal liver ultrasound findings,[181] with these z-scores inversely correlated with fatty liver severity. In adults, normal-weight Caucasians with MAFLD, commonly referred to as lean MAFLD, showed significantly lower circulating leptin levels than obese MAFLD patients, though no difference was observed between lean MAFLD patients and lean healthy controls.[182] A meta-analysis reported higher leptin levels in MAFLD patients with fibrosis compared to non-MAFLD controls; however, this association weakened after excluding one study involving morbidly obese individuals.[183] No significant differences in leptin levels were found between MAFLD patients without fibrosis and healthy controls, or between MAFLD patients with and without fibrosis. Interestingly, a two-sample Mendelian randomization study provided strong evidence suggesting that elevated leptin levels may be causally linked to a reduced risk of MAFLD, indicating a potential protective effect.[88]

Taken together, these findings emphasize the importance of considering weight, sex, age, and other individual factors when interpreting leptin levels in MAFLD. A key unresolved question is whether fluctuations in circulating leptin accurately reflect changes in hepatic leptin levels. Subtle differences in liver leptin content could influence hepatic inflammation and fibrosis, even if such changes are not mirrored in systemic circulation. However, this relationship has yet to be clearly established.

Leptin as a potential therapeutic target for patients with MAFLD

The ob/ob mouse model carries a mutation in the leptin

gene, resulting in leptin deficiency.[23] This deficiency causes severe obesity, primarily due to hyperphagia (overeating) and, to a lesser extent, reduced energy expenditure and physical activity. These mice also develop metabolic abnormalities, including elevated lipid, glucose, insulin, and hepatic fat levels.[184,185] Their metabolic and endocrine profiles closely resemble those of humans with congenital leptin deficiency. Notably, leptin administration corrects all metabolic and endocrine abnormalities in these animals. In contrast, the aP2-nSREBP-1c mouse model, which exhibits impaired adipocyte differentiation and reduced white adipose tissue mass, is commonly used to study lipodystrophy.[186] These mice develop hyperglycemia, hyperinsulinemia, mild hyperphagia, and hepatic steatosis. Leptin treatment reduces appetite, body weight, and liver steatosis while improving glucose levels and insulin sensitivity—benefits that occur independently of caloric restriction.[186] Conversely, diet-induced obesity models—characterized by high body fat and elevated circulating leptin—exhibit minimal or no weight loss even when administered high doses of leptin.[187,188] Collectively, these findings suggest that leptin therapy is more effective in conditions of leptin deficiency—such as congenital leptin deficiency, lipodystrophies, or fasting-induced hypoleptinemia—than in conditions associated with hyperleptinemia.[185]

In clinical studies, an open-label trial of patients with relative leptin deficiency and MASH, one year of metreleptin treatment improved liver fat content and MASH scores in five of seven patients with available liver biopsies, with additional improvements in inflammation, ballooning, and fibrosis in some cases.[189] Similarly, Akinci *et al*. reported that metreleptin significantly reduced overall MASH scores in obese adults with relative leptin deficiency.[190] In a placebo-controlled crossover study, a single leptin dose administered to lean individuals post-fasting enhanced VLDL-TC export and may have prevented the hepatic fat accumulation typically associated with fasting.[98] Improved insulin sensitivity and appetite suppression could reduce the flux of free fatty acids and carbohydrates to the liver, thereby decreasing de novo lipogenesis and hepatic fat accumulation.[82] However, despite these promising findings, existing studies are limited by small sample sizes. To date, no clinical trial has demonstrated fibrosis improvement without worsening MASH or MASH resolution without increasing fibrosis. Even in insulin-resistant patients, insulin therapy can effectively reduce blood glucose, suggesting that pharmacological doses of leptin might promote weight loss and improve liver fat content. Yet randomized controlled trials using pegylated recombinant human leptin or metreleptin at various doses have not shown significant benefits in energy expenditure, body composition, weight loss, adrenal hormones, sympathetic nervous system activity, lipid metabolism, or macronutrient utilization.[191–195] Strategies to overcome leptin resistance—such as leptin sensitization or co-treatment with amylin analogs—have been proposed, but to date, they have not produced significant advances in common obesity patients with relatively low leptin levels.

Future perspectives

Numerous studies and clinical cases have demonstrated that MAFLD imposes substantial long-term health, social, and economic burdens, largely due to its high global prevalence.[5] Without effective policy interventions, these consequences will continue to escalate. Given the increased cardiovascular and mortality risks associated with MAFLD, a multidisciplinary strategy is essential.[2] There remains an urgent need for non-invasive diagnostic tools to replace liver biopsy, enabling earlier detection and monitoring in broader populations. Both extrahepatic factors and intrahepatic mechanisms contribute to MAFLD onset and its progression to MASH.[16] Elucidating the underlying pathophysiology and identifying precise molecular targets for diagnosis and treatment remain crucial research priorities.

Leptin, a hormone closely associated with adiposity and IR, has been identified as an independent predictor of MAFLD onset and progression.[177,180,183] Although leptin exhibits anti-steatotic properties, it is also implicated in hepatic steatosis and the progression of MAFLD to more advanced stages, including MASH and fibrosis.[16] In the early stages of MAFLD, leptin helps regulate glucose homeostasis, reduce hepatic lipid accumulation, and promote lipid oxidation. However, hyperleptinemia can damage pancreatic β-cells and disrupt JAK2/PI3K signaling, contributing to elevated insulin levels and worsening IR.[83] This IR, in turn, inhibits lipid oxidation while promoting TC and fatty acid synthesis.[45,78,84] Leptin can also directly stimulate inflammation by promoting the M1 macrophage phenotype[120] and increasing pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[122] It supports the proliferation of pro-inflammatory $CD4^+$ T cells and B cells while inhibiting regulatory T-cell expansion.[125,126] These lymphocytes release granzymes that generate mitochondrial ROS and activate caspases, ultimately inducing pyroptosis.[130] Leptin can further promote ROS formation in both phagocytic and non-phagocytic cells, including endothelial cells, cardiomyocytes, and HSCs.[152–154] The effects of leptin on cirrhosis and HCC in MAFLD remain poorly defined, and its role in other cirrhosis etiologies is still debated.[20] Nonetheless, substantial evidence suggests a pro-tumorigenic role for leptin in HCC associated with liver diseases unrelated to MAFLD.

Leptin therapy has proven effective in individuals with congenital leptin deficiency; however, its broader therapeutic potential remains controversial.[185] This underscores the need for further research into the development of leptin analogs that preserve anti-steatotic properties while avoiding pro-inflammatory and fibrogenic effects. Investigating leptin sensitizers and their use in combination with other therapeutic agents should also be prioritized.[56]

Conclusions

Large-scale observational studies and long-term clinical trials are necessary to establish leptin's efficacy across diverse MAFLD phenotypes. Finally, leptin shows promise as a biomarker for MAFLD diagnosis and monitoring, particularly when combined with glucose, lipid, and metabolic profiling. Future research should explore not only leptin's therapeutic potential but also preventive strategies targeting leptin signaling to mitigate MAFLD development.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Manuscript preparation and drafting (JLW, YX, MLL), study conception and design (JLW, JLL), and drafting of the manuscript (JLW). All authors contributed to the manuscript by revising and editing it for important intellectual content. They gave final approval of the version and agreed to be accountable for all aspects of the work presented here.

References

[1] Huang DQ, Wong VWS, Rinella ME, Boursier J, Lazarus JV, Yki-Järvinen H, *et al*. Metabolic dysfunction-associated steatotic liver disease in adults. Nat Rev Dis Primers 2025;11(1):14. doi:10.1038/s41572-025-00599-1, PMID:40050362.

[2] Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, *et al*. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542–1556. doi:10.1016/j.jhep.2023.06.003, PMID:37364790.

[3] Polyzos SA, Mantzoros CS. Making progress in nonalcoholic fatty liver disease (NAFLD) as we are transitioning from the era of NAFLD to dys-metabolism associated fatty liver disease (DAFLD). Metabolism 2020;111S:154318. doi:10.1016/j.metabol.2020.154318, PMID:32707055.

[4] Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, *et al*. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71(4):793–801. doi:10.1016/j.jhep.2019.06.021, PMID:31279902.

[5] Zhang H, Targher G, Byrne CD, Kim SU, Wong VW, Valenti L, *et al*. A global survey on the use of the international classification of diseases codes for metabolic dysfunction-associated fatty liver disease. Hepatol Int 2024;18(4):1178–1201. doi:10.1007/s12072-024-10702-5, PMID:38878111.

[6] Diehl AM, Day C. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. N Engl J Med 2017;377(21):2063–2072. doi:10.1056/NEJMra1503519, PMID:29166236.

[7] Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, *et al*. Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol 2022;42(6):e168–e185. doi:10.1161/ATV.0000000000000153, PMID:35418240.

[8] Fan JG, Xu XY, Yang RX, Nan YM, Wei L, Jia JD, *et al*. Guideline for the Prevention and Treatment of Metabolic Dysfunction-associated Fatty Liver Disease (Version 2024). J Clin Transl Hepatol 2024;12(11):955–974. doi:10.14218/JCTH.2024.00311, PMID:39544247.

[9] Abdeldyem SM, Goda T, Khodeir SA, Abou Saif S, Abd-Elsalam S. Non-alcoholic fatty liver disease in patients with acute ischemic stroke is associated with more severe stroke and worse outcome. J Clin Lipidol 2017;11(4):915–919. doi:10.1016/j.jacl.2017.04.115, PMID:28579247.

[10] Malekpour MR, Abbasi-Kangevari M, Ghamari SH, Khanali J, Heidari-Foroozan M, Moghaddam SS, *et al*. The burden of metabolic risk factors in North Africa and the Middle East, 1990-2019: findings from the Global Burden of Disease Study. EClinicalMedicine 2023;60:102022. doi:10.1016/j.eclinm.2023.102022, PMID:37287869.

[11] Muzurović E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. Metabolism 2021;119:154770. doi:10.1016/j.metabol.2021.154770, PMID:33864798.

[12] Valenzuela-Vallejo L, Mantzoros CS. Time to transition from a negative nomenclature describing what NAFLD is not, to a novel, pathophysiology-based, umbrella classification of fatty liver disease (FLD). Metabolism 2022;134:155246. doi:10.1016/j.metabol.2022.155246, PMID:35780909.

[13] Polyzos SA, Vachliotis ID, Mantzoros CS. Sarcopenia, sarcopenic obesity and nonalcoholic fatty liver disease. Metabolism 2023;147:155676. doi:10.1016/j.metabol.2023.155676, PMID:37544590.

[14] Golabi P, Paik JM, Kumar A, Al Shabeeb R, Eberly KE, Cusi K, *et al*. Nonalcoholic fatty liver disease (NAFLD) and associated mortality in individuals with type 2 diabetes, pre-diabetes, metabolically unhealthy, and metabolically healthy individuals in the United States. Metabolism 2023;146:155642. doi:10.1016/j.metabol.2023.155642, PMID:37380016.

[15] Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, *et al*. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6(10):864–873. doi:10.1016/S2468-1253(21)00183-7, PMID:34364544.

[16] Petrescu M, Vlaicu SI, Ciumărnean L, Milaciu MV, Mărginean C, Florea M, *et al*. Chronic Inflammation-A Link between Nonalcoholic Fatty Liver Disease (NAFLD) and Dysfunctional Adipose Tissue. Medicina (Kaunas) 2022;58(5):641. doi:10.3390/medicina58050641, PMID:35630058.

[17] Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, *et al*. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;1(11):1155–1161. doi:10.1038/nm1195-1155, PMID:7584987.

[18] Francisco V, Pino J, Campos-Cabaleiro V, Ruiz-Fernández C, Mera A, Gonzalez-Gay MA, *et al*. Obesity, Fat Mass and Immune System: Role for Leptin. Front Physiol 2018;9:640. doi:10.3389/fphys.2018.00640, PMID:29910742.

[19] Martínez-Uña M, López-Mancheño Y, Diéguez C, Fernández-Rojo MA, Novelle MG. Unraveling the Role of Leptin in Liver Function and Its Relationship with Liver Diseases. Int J Mol Sci 2020;21(24):9368. doi:10.3390/ijms21249368, PMID:33316927.

[20] Jiménez-Cortegana C, García-Galey A, Tami M, Del Pino P, Carmona I, López S, *et al*. Role of Leptin in Non-Alcoholic Fatty Liver Disease. Biomedicines 2021;9(7):762. doi:10.3390/biomedicines9070762, PMID:34209386.

[21] INGALLS AM, DICKIE MM, SNELL GD. Obese, a new mutation in the house mouse. J Hered 1950;41(12):317–318. doi:10.1093/oxfordjournals.jhered.a106073, PMID:14824537.

[22] Hummel KP, Dickie MM, Coleman DL. Diabetes, a new mutation in the mouse. Science 1966;153(3740):1127–1128. doi:10.1126/science.153.3740.1127, PMID:5918576.

[23] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372(6505):425–432. doi:10.1038/372425a0, PMID:7984236.

[24] Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, *et al*. Identification and expression cloning of a leptin receptor, OB-R. Cell 1995;83(7):1263–1271. doi:10.1016/0092-8674(95)90151-5, PMID:8548812.

[25] Ur E, Wilkinson DA, Morash BA, Wilkinson M. Leptin immunoreactivity is localized to neurons in rat brain. Neuroendocrinology 2002;75(4):264–272. doi:10.1159/000054718, PMID:11979057.

[26] Saad MF, Damani S, Gingerich RL, Riad-Gabriel MG, Khan A, Boyadjian R, *et al*. Sexual dimorphism in plasma leptin concentration. J Clin Endocrinol Metab 1997;82(2):579–584. doi:10.1210/jcem.82.2.3739, PMID:9024258.

[27] Licinio J, Mantzoros C, Negrão AB, Cizza G, Wong ML, Bongiorno PB, *et al*. Human leptin levels are pulsatile and inversely related to pituitary-adrenal function. Nat Med 1997;3(5):575–579. doi:10.1038/nm0597-575, PMID:9142131.

[28] Trayhurn P, Thomas ME, Duncan JS, Rayner DV. Effects of fasting and refeeding on ob gene expression in white adipose tissue of lean and obese (oblob) mice. FEBS Lett 1995;368(3):488–490. doi:10.1016/0014-5793(95)00719-p, PMID:7635205.

[29] Flier JS, Maratos-Flier E. Lasker lauds leptin. Cell Metab 2010;12(4):317–320. doi:10.1016/j.cmet.2010.09.008, PMID:20889124.

[30] Hudkins KL, Pichaiwong W, Wietecha T, Kowalewska J, Banas MC, Spencer MW, *et al*. BTBR Ob/Ob mutant mice model progressive diabetic nephropathy. J Am Soc Nephrol 2010;21(9):1533–1542. doi:10.1681/ASN.2009121290, PMID:20634301.

[31] Zhou Y, Rui L. Leptin signaling and leptin resistance. Front Med 2013;7(2):207–222. doi:10.1007/s11684-013-0263-5, PMID:23580174.

[32] Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015;64(1):24–34. doi:10.1016/j.metabol.2014.08.004, PMID:25199978.

[33] Ahima RS, Flier JS. Leptin. Annu Rev Physiol 2000;62:413–437. doi:10.1146/annurev.physiol.62.1.413, PMID:10845097.

[34] 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.

[35] 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. doi:10.1016/j.neuropharm.2021.108877, PMID:34762922.

[36] Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ, *et al*. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell 1996;84(3):491–495. doi:10.1016/s0092-8674(00)81294-5, PMID:8608603.

[37] Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, *et al*. The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci U S A 1996;93(16):8374–8378. doi:10.1073/pnas.93.16.8374, PMID:8710878.

[38] Chua SC Jr, Chung WK, Wu-Peng XS, Zhang Y, Liu SM, Tartaglia L, *et al*. Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science 1996;271(5251):994–996. doi:10.1126/science.271.5251.994, PMID:8584938.

[39] Chung WK, Power-Kehoe L, Chua M, Lee R, Leibel RL. Genomic structure of the human OB receptor and identification of two novel intronic microsatellites. Genome Res 1996;6(12):1192–1199. doi:10.1101/gr.6.12.1192, PMID:8973914.

[40] Chua SC Jr, Koutras IK, Han L, Liu SM, Kay J, Young SJ, *et al*. Fine structure of the murine leptin receptor gene: splice site suppression is required to form two alternatively spliced transcripts. Genomics 1997;45(2):264–270. doi:10.1006/geno.1997.4962, PMID:9344648.

[41] Elmquist JK, Maratos-Flier E, Saper CB, Flier JS. Unraveling the central nervous system pathways underlying responses to leptin. Nat Neurosci 1998;1(6):445–450. doi:10.1038/2164, PMID:10196541.

[42] Pardo M, Roca-Rivada A, Al-Massadi O, Seoane LM, Camiña JP, Casanueva FF. Peripheral leptin and ghrelin receptors are regulated in a tissue-specific manner in activity-based anorexia. Peptides 2010;31(10):1912–1919. doi:10.1016/j.peptides.2010.06.022, PMID:20600421.

[43] Frühbeck G, Gómez-Ambrosi J, Martínez JA. Pre- and postprandial expression of the leptin receptor splice variants OB-Ra and OB-Rb in murine peripheral tissues. Physiol Res 1999;48(3):189–195. PMID:10523054.

[44] Guo DF, Cui H, Zhang Q, Morgan DA, Thedens DR, Nishimura D, *et al*. The BBSome Controls Energy Homeostasis by Mediating the Transport of the Leptin Receptor to the Plasma Membrane. PLoS Genet 2016;12(2):e1005890. doi:10.1371/journal.pgen.1005890, PMID:26926121.

[45] Cernea S, Roiban AL, Both E, Huţanu A. Serum leptin and leptin resistance correlations with NAFLD in patients with type 2 diabetes. Diabetes Metab Res Rev 2018;34(8):e3050. doi:10.1002/dmrr.3050, PMID:30052309.

[46] Ogier V, Ziegler O, Méjean L, Nicolas JP, Stricker-Krongrad A. Obesity

is associated with decreasing levels of the circulating soluble leptin receptor in humans. Int J Obes Relat Metab Disord 2002;26(4):496–503. doi:10.1038/sj.ijo.0801951, PMID:12075576.
[47] Wei L, Chen Y, Zhang C, Liu M, Xiong H. Leptin induces IL-6 and IL-8 expression through leptin receptor Ob-Rb in human dental pulp fibroblasts. Acta Odontol Scand 2019;77(3):205–212. doi:10.1080/00016357.2018.1536280, PMID:30600742.
[48] Robertson SA, Leinninger GM, Myers MG Jr. Molecular and neural mediators of leptin action. Physiol Behav 2008;94(5):637–642. doi:10.1016/j.physbeh.2008.04.005, PMID:18501391.
[49] Wauman J, Zabeau L, Tavernier J. The Leptin Receptor Complex: Heavier Than Expected? Front Endocrinol (Lausanne) 2017;8:30. doi:10.3389/fendo.2017.00030, PMID:28270795.
[50] Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol 2008;70:537–556. doi:10.1146/annurev.physiol.70.113006.100707, PMID:17937601.
[51] Münzberg H, Morrison CD. Structure, production and signaling of leptin. Metabolism 2015;64(1):13–23. doi:10.1016/j.metabol.2014.09.010, PMID:25305050.
[52] Polyzos SA, Kountouras J, Zavos C, Deretzi G. The potential adverse role of leptin resistance in nonalcoholic fatty liver disease: a hypothesis based on critical review of the literature. J Clin Gastroenterol 2011;45(1):50–54. doi:10.1097/MCG.0b013e3181ec5c66, PMID:20717042.
[53] German J, Kim F, Schwartz GJ, Havel PJ, Rhodes CJ, Schwartz MW, *et al*. Hypothalamic leptin signaling regulates hepatic insulin sensitivity via a neurocircuit involving the vagus nerve. Endocrinology 2009;150(10):4502–4511. doi:10.1210/en.2009-0445, PMID:19574396.
[54] Koch CE, Lowe C, Pretz D, Steger J, Williams LM, Tups A. High-fat diet induces leptin resistance in leptin-deficient mice. J Neuroendocrinol 2014;26(2):58–67. doi:10.1111/jne.12131, PMID:24382295.
[55] Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Leptin resistance: underlying mechanisms and diagnosis. Diabetes Metab Syndr Obes 2019;12:191–198. doi:10.2147/DMSO.S182406, PMID:30774404.
[56] Pena-Leon V, Perez-Lois R, Villalon M, Prida E, Muñoz-Moreno D, Fernø J, *et al*. Novel mechanisms involved in leptin sensitization in obesity. Biochem Pharmacol 2024;223:116129. doi:10.1016/j.bcp.2024.116129, PMID:38490517.
[57] Howard JK, Flier JS. Attenuation of leptin and insulin signaling by SOCS proteins. Trends Endocrinol Metab 2006;17(9):365–371. doi:10.1016/j.tem.2006.09.007, PMID:17010638.
[58] Mori H, Hanada R, Hanada T, Aki D, Mashima R, Nishinakamura H, *et al*. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. Nat Med 2004;10(7):739–743. doi:10.1038/nm1071, PMID:15208705.
[59] Shinjyo N, Kita K. Infection and Immunometabolism in the Central Nervous System: A Possible Mechanistic Link Between Metabolic Imbalance and Dementia. Front Cell Neurosci 2021;15:765217. doi:10.3389/fncel.2021.765217, PMID:34795562.
[60] Dyck DJ, Heigenhauser GJ, Bruce CR. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. Acta Physiol (Oxf) 2006;186(1):5–16. doi:10.1111/j.1748-1716.2005.01502.x, PMID:16497175.
[61] Balland E, Chen W, Tiganis T, Cowley MA. Persistent Leptin Signaling in the Arcuate Nucleus Impairs Hypothalamic Insulin Signaling and Glucose Homeostasis in Obese Mice. Neuroendocrinology 2019;109(4):374–390. doi:10.1159/000500201, PMID:30995667.
[62] Guan LJ, Xu KX, Xu SY, Li NN, Wang XR, Xia YK, *et al*. Profiles of metabolic gene expression in the white adipose tissue, liver and hypothalamus in leptin knockout (Lep(ΔI14/ΔI14)) rats. J Biomed Res 2017;31(6):528–540. doi:10.7555/JBR.31.20170021, PMID:28866659.
[63] De la Cruz-Color L, Dominguez-Rosales JA, Maldonado-González M, Ruíz-Madrigal B, Sánchez Muñoz MP, Zaragoza-Guerra VA, *et al*. Evidence That Peripheral Leptin Resistance in Omental Adipose Tissue and Liver Correlates with MASLD in Humans. Int J Mol Sci 2024;25(12):6420. doi:10.3390/ijms25126420, PMID:38928125.
[64] Casado ME, Collado-Pérez R, Frago LM, Barrios V. Recent Advances in the Knowledge of the Mechanisms of Leptin Physiology and Actions in Neurological and Metabolic Pathologies. Int J Mol Sci 2023;24(2):1422. doi:10.3390/ijms24021422, PMID:36674935.
[65] Petersen KF, Oral EA, Dufour S, Befroy D, Ariyan C, Yu C, *et al*. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J Clin Invest 2002;109(10):1345–1350. doi:10.1172/JCI15001, PMID:12021250.
[66] Pereira S, Cline DL, Glavas MM, Covey SD, Kieffer TJ. Tissue-Specific Effects of Leptin on Glucose and Lipid Metabolism. Endocr Rev 2021;42(1):1–28. doi:10.1210/endrev/bnaa027, PMID:33150398.
[67] Flier JS, Maratos-Flier E. Lasker lauds leptin. Cell 2010;143(1):9–12. doi:10.1016/j.cell.2010.09.021, PMID:20887884.
[68] Berglund ED, Vianna CR, Donato J Jr, Kim MH, Chuang JC, Lee CE, *et al*. Direct leptin action on POMC neurons regulates glucose homeostasis and hepatic insulin sensitivity in mice. J Clin Invest 2012;122(3):1000–1009. doi:10.1172/JCI59816, PMID:22326958.
[69] Huo L, Gamber K, Greeley S, Silva J, Huntoon N, Leng XH, *et al*. Leptin-dependent control of glucose balance and locomotor activity by POMC neurons. Cell Metab 2009;9(6):537–547. doi:10.1016/j.cmet.2009.05.003, PMID:19490908.
[70] Coppari R, Bjørbæk C. Leptin revisited: its mechanism of action and potential for treating diabetes. Nat Rev Drug Discov 2012;11(9):692–708. doi:10.1038/nrd3757, PMID:22935803.
[71] 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 beta-cells. Diabetes 1997;46(6):1087–1093. doi:10.2337/diab.46.6.1087, PMID:9166685.
[72] Sweeney G, Keen J, Somwar R, Konrad D, Garg R, Klip A. High leptin levels acutely inhibit insulin-stimulated glucose uptake without affecting glucose transporter 4 translocation in l6 rat skeletal muscle cells. Endocrinology 2001;142(11):4806–4812. doi:10.1210/endo.142.11.8496, PMID:11606447.
[73] Ceddia RB, William WN Jr, Curi R. Comparing effects of leptin and insulin on glucose metabolism in skeletal muscle: evidence for an effect of leptin on glucose uptake and decarboxylation. Int J Obes Relat Metab Disord 1999;23(1):75–82. doi:10.1038/sj.ijo.0800762, PMID:10094581.
[74] Berti L, Kellerer M, Capp E, Häring HU. Leptin stimulates glucose transport and glycogen synthesis in C2C12 myotubes: evidence for a P13-kinase mediated effect. Diabetologia 1997;40(5):606–609. doi:10.1007/s001250050722, PMID:9165231.
[75] Elimam A, Kamel A, Marcus C. In vitro effects of leptin on human adipocyte metabolism. Horm Res 2002;58(2):88–93. doi:10.1159/000064659, PMID:12207168.
[76] Anderwald C, Müller G, Koca G, Fürnsinn C, Waldhäusl W, Roden M. Short-term leptin-dependent inhibition of hepatic gluconeogenesis is mediated by insulin receptor substrate-2. Mol Endocrinol 2002;16(7):1612–1628. doi:10.1210/mend.16.7.0867, PMID:12089355.
[77] 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. J Biol Chem 2004;279(21):21695–21700. doi:10.1074/jbc.M401546200, PMID:14993225.
[78] Hossain IA, Akter S, Rahman MK, Ali L. Gender Specific Association of Serum Leptin and Insulinemic Indices with Nonalcoholic Fatty Liver Disease in Prediabetic Subjects. PLoS One 2015;10(11):e0142165. doi:10.1371/journal.pone.0142165, PMID:26569494.
[79] Angulo P, Alba LM, Petrovic LM, Adams LA, Lindor KD, Jensen MD. Leptin, insulin resistance, and liver fibrosis in human nonalcoholic fatty liver disease. J Hepatol 2004;41(6):943–949. doi:10.1016/j.jhep.2004.08.020, PMID:15582127.
[80] Quaye E, Chacko S, Startzell M, Brown RJ. Leptin Decreases Gluconeogenesis and Gluconeogenic Substrate Availability in Patients With Lipodystrophy. J Clin Endocrinol Metab 2023;109(1):e209–e215. doi:10.1210/clinem/dgad445, PMID:37515588.
[81] Canbakan M, Bakkaloglu OK, Atay K, Koroglu E, Tuncer MM, Canbakan B, *et al*. The liver-kidney axis: Is serum leptin a potential link in non-alcoholic fatty liver disease-associated chronic kidney disease? Arab J Gastroenterol 2023;24(1):52–57. doi:10.1016/j.ajg.2023.01.001, PMID:36764893.
[82] Baykal AP, Parks EJ, Shamburek R, Syed-Abdul MM, Chacko S, Cochran E, *et al*. Leptin decreases de novo lipogenesis in patients with lipodystrophy. JCI Insight 2020;5(14):137180. doi:10.1172/jci.insight.137180, PMID:32573497.
[83] Mantzoros CS, Liolios AD, Tritos NA, Kaklamani VG, Doulgerakis DE, Griveas I, *et al*. Circulating insulin concentrations, smoking, and alcohol intake are important independent predictors of leptin in young healthy men. Obes Res 1998;6(3):179–186. doi:10.1002/j.1550-8528.1998.tb00335.x, PMID:9618121.
[84] Arab JP, Arrese M, Trauner M. Recent Insights into the Pathogenesis of Nonalcoholic Fatty Liver Disease. Annu Rev Pathol 2018;13:321–350. doi:10.1146/annurev-pathol-020117-043617, PMID:29414249.
[85] Wu L, Chen G, Liu W, Yang X, Gao J, Huang L, *et al*. Intramuscular injection of exogenous leptin induces adiposity, glucose intolerance and fatty liver by repressing the JAK2-STAT3/PI3K pathway in a rat model. Gen Comp Endocrinol 2017;252:88–96. doi:10.1016/j.ygcen.2017.02.012, PMID:28242305.
[86] Utzschneider KM, Kahn SE. Review: The role of insulin resistance in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2006;91(12):4753–4761. doi:10.1210/jc.2006-0587, PMID:16968800.
[87] Khan RS, Bril F, Cusi K, Newsome PN. Modulation of Insulin Resistance in Nonalcoholic Fatty Liver Disease. Hepatology 2019;70(2):711–724. doi:10.1002/hep.30429, PMID:30556145.
[88] Guo Z, Du H, Guo Y, Jin Q, Liu R, Yun Z, *et al*. Association between leptin and NAFLD: a two-sample Mendelian randomization study. Eur J Med Res 2023;28(1):215. doi:10.1186/s40001-023-01147-x, PMID:37400922.
[89] Polyzos SA, Kountouras J, Mantzoros CS. Leptin in nonalcoholic fatty liver disease: a narrative review. Metabolism 2015;64(1):60–78. doi:10.1016/j.metabol.2014.10.012, PMID:25456097.
[90] Rodríguez A, Moreno NR, Balaguer I, Méndez-Giménez L, Becerril S, Catalán V, *et al*. Leptin administration restores the altered adipose and hepatic expression of aquaglyceroporins improving the non-alcoholic fatty liver of ob/ob mice. Sci Rep 2015;5:12067. doi:10.1038/srep12067, PMID:26159457.
[91] Xiong S, Wang Q, Chen Y, Du H, Zhao Y. Leptin limits hepatic lipid accumulation and inflammation via vagal activation of the JAK2-STAT3/AMPK pathway. J Nutr Biochem 2024;134:109748. doi:10.1016/j.jnutbio.2024.109748, PMID:39186956.
[92] Moon HS, Dalamaga M, Kim SY, Polyzos SA, Hamnvik OP, Magkos F, *et al*. Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant and diabetic individuals. Endocr Rev 2013;34(3):377–412. doi:10.1210/er.2012-1053, PMID:23475416.
[93] Asilmaz E, Cohen P, Miyazaki M, Dobrzyn P, Ueki K, Fayzikhodjaeva G, *et al*. Site and mechanism of leptin action in a rodent form of congenital lipodystrophy. J Clin Invest 2004;113(3):414–424. doi:10.1172/JCI19511, PMID:14755338.
[94] Wang MY, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, *et al*. Leptin therapy in insulin-deficient type I diabetes. Proc Natl Acad Sci U S A 2010;107(11):4813–4819. doi:10.1073/pnas.0909422107, PMID:201

94735.
[95] Denechaud PD, Dentin R, Girard J, Postic C. Role of ChREBP in hepatic steatosis and insulin resistance. FEBS Lett 2008;582(1):68–73. doi:10.1016/j.febslet.2007.07.084, PMID:17716660.
[96] Park HK, Ahima RS. Leptin signaling. F1000Prime Rep 2014;6:73. doi:10.12703/P6-73, PMID:25343030.
[97] Huang W, Metlakunta A, Dedousis N, Ortmeyer HK, Stefanovic-Racic M, O'Doherty RM. Leptin augments the acute suppressive effects of insulin on hepatic very low-density lipoprotein production in rats. Endocrinology 2009;150(5):2169–2174. doi:10.1210/en.2008-1271, PMID:19147673.
[98] Metz M, Beghini M, Wolf P, Pfleger L, Hackl M, Bastian M, *et al*. Leptin increases hepatic triglyceride export via a vagal mechanism in humans. Cell Metab 2022;34(11):1719–1731.e5. doi:10.1016/j.cmet.2022.09.020, PMID:36220067.
[99] Cortés VA, Cautivo KM, Rong S, Garg A, Horton JD, Agarwal AK. Leptin ameliorates insulin resistance and hepatic steatosis in Agpat2-/- lipodystrophic mice independent of hepatocyte leptin receptors. J Lipid Res 2014;55(2):276–288. doi:10.1194/jlr.M045799, PMID:24293639.
[100] Hackl MT, Fürnsinn C, Schuh CM, Krssak M, Carli F, Guerra S, *et al*. Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis. Nat Commun 2019;10(1):2717. doi:10.1038/s41467-019-10684-1, PMID:31222048.
[101] Adolph TE, Grander C, Grabherr F, Tilg H. Adipokines and Non-Alcoholic Fatty Liver Disease: Multiple Interactions. Int J Mol Sci 2017;18(8):1649. doi:10.3390/ijms18081649, PMID:28758929.
[102] Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011;34(3):274–285. doi:10.1111/j.1365-2036.2011.04724.x, PMID:21623852.
[103] Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148(5):852–871. doi:10.1016/j.cell.2012.02.017, PMID:22385956.
[104] Rotundo L, Persaud A, Feurdean M, Ahlawat S, Kim HS. The Association of leptin with severity of non-alcoholic fatty liver disease: A population-based study. Clin Mol Hepatol 2018;24(4):392–401. doi:10.3350/cmh.2018.0011, PMID:30068065.
[105] Chitturi S, Farrell G, Frost L, Kriketos A, Lin R, Fung C, *et al*. Serum leptin in NASH correlates with hepatic steatosis but not fibrosis: a manifestation of lipotoxicity? Hepatology 2002;36(2):403–409. doi:10.1053/jhep.2002.34738, PMID:12143049.
[106] Pavlidis C, Panoutsopoulos GI, Tiniakos D, Koutsounas S, Vlachogiannakos J, Zouboulis-Vafiadis I. Serum leptin and ghrelin in chronic hepatitis C patients with steatosis. World J Gastroenterol 2011;17(46):5097–5104. doi:10.3748/wjg.v17.i46.5097, PMID:22171144.
[107] Eshraghian A, Nikeghbalian S, Shamsaeefar A, Kazemi K, Fattahi MR, Malek-Hosseini SA. Hepatic steatosis and liver fat contents in liver transplant recipients are associated with serum adipokines and insulin resistance. Sci Rep 2020;10(1):12701. doi:10.1038/s41598-020-69571-1, PMID:32728230.
[108] Hirsova P, Gores GJ. Death Receptor-Mediated Cell Death and Proinflammatory Signaling in Nonalcoholic Steatohepatitis. Cell Mol Gastroenterol Hepatol 2015;1(1):17–27. doi:10.1016/j.jcmgh.2014.11.005, PMID:25729762.
[109] Becerril S, Rodríguez A, Catalán V, Ramírez B, Unamuno X, Gómez-Ambrosi J, *et al*. iNOS Gene Ablation Prevents Liver Fibrosis in Leptin-Deficient ob/ob Mice. Genes (Basel) 2019;10(3):184. doi:10.3390/genes10030184, PMID:30818874.
[110] Zhao S, Li N, Zhu Y, Straub L, Zhang Z, Wang MY, *et al*. Partial leptin deficiency confers resistance to diet-induced obesity in mice. Mol Metab 2020;37:100995. doi:10.1016/j.molmet.2020.100995, PMID:32289482.
[111] Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, *et al*. Leptin and Obesity: Role and Clinical Implication. Front Endocrinol (Lausanne) 2021;12:585887. doi:10.3389/fendo.2021.585887, PMID:34084149.
[112] Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 1999;194(1):6–11. doi:10.1006/cimm.1999.1490, PMID:10357875.
[113] Kiernan K, MacIver NJ. The Role of the Adipokine Leptin in Immune Cell Function in Health and Disease. Front Immunol 2020;11:622468. doi:10.3389/fimmu.2020.622468, PMID:33584724.
[114] Pereira S, Cline DL, Chan M, Chai K, Yoon JS, O'Dwyer SM, *et al*. Role of myeloid cell leptin signaling in the regulation of glucose metabolism. Sci Rep 2021;11(1):18394. doi:10.1038/s41598-021-97549-0, PMID:34526546.
[115] Martelli D, Brooks VL. Leptin Increases: Physiological Roles in the Control of Sympathetic Nerve Activity, Energy Balance, and the Hypothalamic-Pituitary-Thyroid Axis. Int J Mol Sci 2023;24(3):2684. doi:10.3390/ijms24032684, PMID:36769012.
[116] de Candia P, Prattichizzo F, Garavelli S, Alviggi C, La Cava A, Matarese G. The pleiotropic roles of leptin in metabolism, immunity, and cancer. J Exp Med 2021;218(5):e20191593. doi:10.1084/jem.20191593, PMID:33857282.
[117] Fernandes G, Handwerger BS, Yunis EJ, Brown DM. Immune response in the mutant diabetic C57BL/Ks-dt+ mouse. Discrepancies between in vitro and in vivo immunological assays. J Clin Invest 1978;61(2):243–250. doi:10.1172/JCI108933, PMID:340468.
[118] Flores Gomez D, Bekkering S, Ter Horst R, Cossins B, van den Munckhof ICL, Rutten JHW, *et al*. The effect of leptin on trained innate immunity and on systemic inflammation in subjects with obesity. J Leukoc Biol 2024;115(2):374–384. doi:10.1093/jleuko/qiad118, PMID:37776323.
[119] Monteiro LB, Prodonoff JS, Favero de Aguiar C, Correa-da-Silva F, Castoldi A, Bakker NVT, *et al*. Leptin Signaling Suppression in Macrophages Improves Immunometabolic Outcomes in Obesity. Diabetes 2022;71(7):1546–1561. doi:10.2337/db21-0842, PMID:35377454.
[120] Wang Y, Wan R, Hu C. Leptin/obR signaling exacerbates obesity-related neutrophilic airway inflammation through inflammatory M1 macrophages. Mol Med 2023;29(1):100. doi:10.1186/s10020-023-00702-w, PMID:37488474.
[121] Lu P, Yang G, Jiang L, He W, Wu W, Qi L, *et al*. Characterizing disease progression of nonalcoholic steatohepatitis in Leptin-deficient rats by integrated transcriptome analysis. Exp Biol Med (Maywood) 2021;246(6):678–687. doi:10.1177/1535370220976530, PMID:33302736.
[122] Palhinha L, Liechocki S, Hottz ED, Pereira JADS, de Almeida CJ, Moraes-Vieira PMM, *et al*. Leptin Induces Proadipogenic and Proinflammatory Signaling in Adipocytes. Front Endocrinol (Lausanne) 2019;10:841. doi:10.3389/fendo.2019.00841, PMID:31920961.
[123] Wabitsch M, Jensen PB, Blum WF, Christoffersen CT, Englaro P, Heinze E, *et al*. Insulin and cortisol promote leptin production in cultured human fat cells. Diabetes 1996;45(10):1435–1438. doi:10.2337/diab.45.10.1435, PMID:8826983.
[124] Faggioni R, Fantuzzi G, Fuller J, Dinarello CA, Feingold KR, Grunfeld C. IL-1 beta mediates leptin induction during inflammation. Am J Physiol 1998;274(1):R204–R208. doi:10.1152/ajpregu.1998.274.1.R204, PMID:9458919.
[125] Lord GM, Matarese G, Howard JK, Bloom SR, Lechler RI. Leptin inhibits the anti-CD3-driven proliferation of peripheral blood T cells but enhances the production of proinflammatory cytokines. J Leukoc Biol 2002;72(2):330–338. PMID:12149424.
[126] Tilg H, Ianiro G, Gasbarrini A, Adolph TE. Adipokines: masterminds of metabolic inflammation. Nat Rev Immunol 2025;25(4):250–265. doi:10.1038/s41577-024-01103-8, PMID:39511425.
[127] Reis BS, Lee K, Fanok MH, Mascaraque C, Amoury M, Cohn LB, *et al*. Leptin receptor signaling in T cells is required for Th17 differentiation. J Immunol 2015;194(11):5253–5260. doi:10.4049/jimmunol.1402996, PMID:25917102.
[128] Frasca D, Diaz A, Romero M, Blomberg BB. Leptin induces immunosenescence in human B cells. Cell Immunol 2020;348:103994. doi:10.1016/j.cellimm.2019.103994, PMID:31831137.
[129] Papathanassoglou E, El-Haschimi K, Li XC, Matarese G, Strom T, Mantzoros C. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. J Immunol 2006;176(12):7745–7752. doi:10.4049/jimmunol.176.12.7745, PMID:16751422.
[130] Zhang Q, Wang J, Huang F, Yao Y, Xu L. Leptin induces NAFLD progression through infiltrated CD8+ T lymphocytes mediating pyroptotic-like cell death of hepatocytes and macrophages. Dig Liver Dis 2021;53(5):598–605. doi:10.1016/j.dld.2020.10.025, PMID:33172809.
[131] Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest 2017;127(1):55–64. doi:10.1172/jci88881, PMID:28045404.
[132] Procaccini C, Galgani M, De Rosa V, Carbone F, La Rocca C, Ranucci G, *et al*. Leptin: the prototypic adipocytokine and its role in NAFLD. Curr Pharm Des 2010;16(17):1902–1912. doi:10.2174/138161210791208884, PMID:20370676.
[133] Chatterjee S, Ganini D, Tokar EJ, Kumar A, Das S, Corbett J, *et al*. Leptin is key to peroxynitrite-mediated oxidative stress and Kupffer cell activation in experimental non-alcoholic steatohepatitis. J Hepatol 2013;58(4):778–784. doi:10.1016/j.jhep.2012.11.035, PMID:23207144.
[134] Seth RK, Das S, Kumar A, Chanda A, Kadiiska MB, Michelotti G, *et al*. CYP2E1-dependent and leptin-mediated hepatic CD57 expression on CD8+ T cells aid progression of environment-linked nonalcoholic steatohepatitis. Toxicol Appl Pharmacol 2014;274(1):42–54. doi:10.1016/j.taap.2013.10.029, PMID:24211274.
[135] Krenkel O, Tacke F. Liver macrophages in tissue homeostasis and disease. Nat Rev Immunol 2017;17(5):306–321. doi:10.1038/nri.2017.11, PMID:28317925.
[136] Chatterjee S, Rana R, Corbett J, Kadiiska MB, Goldstein J, Mason RP. P2X7 receptor-NADPH oxidase axis mediates protein radical formation and Kupffer cell activation in carbon tetrachloride-mediated steatohepatitis in obese mice. Free Radic Biol Med 2012;52(9):1666–1679. doi:10.1016/j.freeradbiomed.2012.02.010, PMID:22343416.
[137] Dunning S, Hannivoort RA, de Boer JF, Buist-Homan M, Faber KN, Moshage H. Superoxide anions and hydrogen peroxide inhibit proliferation of activated rat stellate cells and induce different modes of cell death. Liver Int 2009;29(6):922–932. doi:10.1111/j.1478-3231.2009.02004.x, PMID:19386027.
[138] Zhan SS, Jiang JX, Wu J, Halsted C, Friedman SL, Zern MA, *et al*. Phagocytosis of apoptotic bodies by hepatic stellate cells induces NADPH oxidase and is associated with liver fibrosis in vivo. Hepatology 2006;43(3):435–443. doi:10.1002/hep.21093, PMID:16496318.
[139] Leung TM, Nieto N. CYP2E1 and oxidant stress in alcoholic and non-alcoholic fatty liver disease. J Hepatol 2013;58(2):395–398. doi:10.1016/j.jhep.2012.08.018, PMID:22940046.
[140] Chung HK, Kim YK, Park JH, Ryu MJ, Chang JY, Hwang JH, *et al*. The indole derivative NecroX-7 improves nonalcoholic steatohepatitis in ob/ob mice through suppression of mitochondrial ROS/RNS and inflammation. Liver Int 2015;35(4):1341–1353. doi:10.1111/liv.12741, PMID:25443620.
[141] Seki S, Kitada T, Sakaguchi H. Clinicopathological significance of oxidative cellular damage in non-alcoholic fatty liver diseases. Hepatol Res 2005;33(2):132–134. doi:10.1016/j.hepres.2005.09.020, PMID:16198621.
[142] Schuster S, Cabrera D, Arrese M, Feldstein AE. Triggering and resolution of inflammation in NASH. Nat Rev Gastroenterol Hepatol 2018;15(6):349–

364. doi:10.1038/s41575-018-0009-6, PMID:29740166.
[143] Watson AM, Poloyac SM, Howard G, Blouin RA. Effect of leptin on cytochrome P-450, conjugation, and antioxidant enzymes in the ob/ob mouse. Drug Metab Dispos 1999;27(6):695–700. PMID:10348799.
[144] Kaeidi A, Hajializadeh Z, Jahandari F, Fatemi I. Leptin attenuates oxidative stress and neuronal apoptosis in hyperglycemic condition. Fundam Clin Pharmacol 2019;33(1):75–83. doi:10.1111/fcp.12411, PMID:30203422.
[145] Zwirska-Korczala K, Adamczyk-Sowa M, Sowa P, Pilc K, Suchanek R, Pierzchala K, *et al*. Role of leptin, ghrelin, angiotensin II and orexins in 3T3 L1 preadipocyte cells proliferation and oxidative metabolism. J Physiol Pharmacol 2007;58(Suppl 1):53–64. PMID:17443027.
[146] Sailaja JB, Balasubramaniyan V, Nalini N. Effect of exogenous leptin administration on high fat diet induced oxidative stress. Pharmazie 2004;59(6):475–479. PMID:15248464.
[147] Pomar CA, Trepiana J, Besné-Eseverri I, Castillo P, Palou A, Palou M, *et al*. Maternal Dietary Improvement or Leptin Supplementation During Suckling Mitigates the Long-Term Impact of Maternal Obesogenic Conditions on Inflammatory and Oxidative Stress Biomarkers in the Offspring of Diet-Induced Obese Rats. Int J Mol Sci 2024;25(22):11876. doi:10.3390/ijms252211876, PMID:39595945.
[148] Santoleri D, Titchenell PM. Resolving the Paradox of Hepatic Insulin Resistance. Cell Mol Gastroenterol Hepatol 2019;7(2):447–456. doi:10.1016/j.jcmgh.2018.10.016, PMID:30739869.
[149] Tan T, Song Z, Li W, Wang R, Zhu M, Liang Z, *et al*. Modelling porcine NAFLD by deletion of leptin and defining the role of AMPK in hepatic fibrosis. Cell Biosci 2023;13(1):169. doi:10.1186/s13578-023-01124-1, PMID:37705071.
[150] Balasubramaniyan V, Shukla R, Murugaiyan G, Bhonde RR, Nalini N. Mouse recombinant leptin protects human hepatoma HepG2 against apoptosis, TNF-alpha response and oxidative stress induced by the hepatotoxin-ethanol. Biochim Biophys Acta 2007;1770(8):1136–1144. doi:10.1016/j.bbagen.2007.04.009, PMID:17543459.
[151] Vallejos A, Olivares P, Varela D, Echeverria C, Cabello-Verrugio C, Pérez-Leighton C, *et al*. Preventive Leptin Administration Protects Against Sepsis Through Improving Hypotension, Tachycardia, Oxidative Stress Burst, Multiple Organ Dysfunction, and Increasing Survival. Front Physiol 2018;9:1800. doi:10.3389/fphys.2018.01800, PMID:30618812.
[152] Caldefie-Chezet F, Poulin A, Tridon A, Sion B, Vasson MP. Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? J Leukoc Biol 2001;69(3):414–418. PMID:11261788.
[153] Yamagishi S, Amano S, Inagaki Y, Okamoto T, Takeuchi M, Inoue H. Pigment epithelium-derived factor inhibits leptin-induced angiogenesis by suppressing vascular endothelial growth factor gene expression through anti-oxidative properties. Microvasc Res 2003;65(3):186–190. doi:10.1016/s0026-2862(03)00005-0, PMID:12711260.
[154] Schroeter MR, Leifheit-Nestler M, Hubert A, Schumann B, Glückermann R, Eschholz N, *et al*. Leptin promotes neointima formation and smooth muscle cell proliferation via NADPH oxidase activation and signalling in caveolin-rich microdomains. Cardiovasc Res 2013;99(3):555–565. doi:10.1093/cvr/cvt126, PMID:23723060.
[155] Dong F, Zhang X, Ren J. Leptin regulates cardiomyocyte contractile function through endothelin-1 receptor-NADPH oxidase pathway. Hypertension 2006;47(2):222–229. doi:10.1161/01.HYP.0000198555.51645.f1, PMID:16380530.
[156] Hamed EA, Zakary MM, Ahmed NS, Gamal RM. Circulating leptin and insulin in obese patients with and without type 2 diabetes mellitus: relation to ghrelin and oxidative stress. Diabetes Res Clin Pract 2011;94(3):434–441. doi:10.1016/j.diabres.2011.08.023, PMID:21924513.
[157] 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):156–163. doi:10.1016/j.diabres.2007.07.019, PMID:17850913.
[158] Balasubramaniyan V, Kalaivani Sailaja J, Nalini N. Role of leptin on alcohol-induced oxidative stress in Swiss mice. Pharmacol Res 2003;47(3):211–216. doi:10.1016/s1043-6618(02)00317-1, PMID:12591016.
[159] Imajo K, Fujita K, Yoneda M, Nozaki Y, Ogawa Y, Shinohara Y, *et al*. Hyperresponsivity to low-dose endotoxin during progression to nonalcoholic steatohepatitis is regulated by leptin-mediated signaling. Cell Metab 2012;16(1):44–54. doi:10.1016/j.cmet.2012.05.012, PMID:22768838.
[160] Pal SC, Eslam M, Mendez-Sanchez N. Detangling the interrelations between MAFLD, insulin resistance, and key hormones. Hormones (Athens) 2022;21(4):573–589. doi:10.1007/s42000-022-00391-w, PMID:35921046.
[161] Diéguez-Campa CE, Angel-Chávez LI, Reyes-Ruvalcaba D, Talavera-Zermeño MJ, Armendáriz-Cabral DA, Torres-Muro D, *et al*. Leptin Levels and Q223R Leptin Receptor Gene Polymorphism in Obese Mexican Young Adults. EJIFCC 2020;31(3):197–207. PMID:33061875.
[162] Peng J, Yin L, Wang X. Central and peripheral leptin resistance in obesity and improvements of exercise. Horm Behav 2021;133:105006. doi:10.1016/j.yhbeh.2021.105006, PMID:34087669.
[163] Ceccarini G, Pelosini C, Ferrari F, Magno S, Vitti J, Salvetti G, *et al*. Serum IGF-binding protein 2 (IGFBP-2) concentrations change early after gastric bypass bariatric surgery revealing a possible marker of leptin sensitivity in obese subjects. Endocrine 2019;65(1):86–93. doi:10.1007/s12020-019-01915-y, PMID:30945111.
[164] Montserrat-de la Paz S, Pérez-Pérez A, Vilariño-García T, Jiménez-Cortegana C, Muriana FJG, Millán-Linares MC, *et al*. Nutritional modulation of leptin expression and leptin action in obesity and obesity-associated complications. J Nutr Biochem 2021;89:108561. doi:10.1016/j.jnutbio.2020.108561, PMID:33249183.
[165] 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. doi:10.3389/fendo.2021.749050, PMID:34899599.
[166] Fishman S, Muzumdar RH, Atzmon G, Ma X, Yang X, Einstein FH, *et al*. Resistance to leptin action is the major determinant of hepatic triglyceride accumulation in vivo. FASEB J 2007;21(1):53–60. doi:10.1096/fj.06-6557com, PMID:17099068.
[167] López V, Bonzón-Kulichenko E, Moltó E, Fernández-Agulló T, Arribas C, Andrés A, *et al*. Food Restriction is Required to Preserve the Antisteatotic Effects of Central Leptin in the Liver of Middle-Aged Rats. Obesity (Silver Spring) 2018;26(5):877–884. doi:10.1002/oby.22152, PMID:29575696.
[168] Licinio J, Negrão AB, Mantzoros C, Kaklamani V, Wong ML, Bongiorno PB, *et al*. Sex differences in circulating human leptin pulse amplitude: clinical implications. J Clin Endocrinol Metab 1998;83(11):4140–4147. doi:10.1210/jcem.83.11.5291, PMID:9814504.
[169] Pontes-da-Silva RM, de Souza Marinho T, de Macedo Cardoso LE, Mandarim-de-Lacerda CA, Aguila MB. Obese mice weight loss role on nonalcoholic fatty liver disease and endoplasmic reticulum stress treated by a GLP-1 receptor agonist. Int J Obes (Lond) 2022;46(1):21–29. doi:10.1038/s41366-021-00955-7, PMID:34465857.
[170] LeDuc CA, Skowronski AA, Rosenbaum M. The Role of Leptin in the Development of Energy Homeostatic Systems and the Maintenance of Body Weight. Front Physiol 2021;12:789519. doi:10.3389/fphys.2021.789519, PMID:34955895.
[171] Lu CW, Yang KC, Chi YC, Wu TY, Chiang CH, Chang HH, *et al*. Adiponectin-leptin ratio for the early detection of lean non-alcoholic fatty liver disease independent of insulin resistance. Ann Med 2023;55(1):634–642. doi:10.1080/07853890.2023.2179106, PMID:36790383.
[172] Yi X, Han L, Li L, Zhu H, Li M, Gao S. Adipokine/hepatokines profiling of fatty liver in adolescents and young adults: cross-sectional and prospective analyses of the BCAMS study. Hepatol Int 2025;19(1):143–155. doi:10.1007/s12072-024-10736-9, PMID:39400684.
[173] Wang H, Wu S, Weng Y, Yang X, Hou L, Liang Y, *et al*. Increased serum carboxylesterase-1 levels are associated with metabolic dysfunction associated steatotic liver disease and metabolic syndrome in children with obesity. Ital J Pediatr 2024;50(1):162. doi:10.1186/s13052-024-01733-7, PMID:39227971.
[174] Valenzuela-Vallejo L, Chrysafi P, Kouvari M, Guatibonza-Garcia V, Mylonakis SC, Katsarou A, *et al*. Circulating hormones in biopsy-proven steatotic liver disease and steatohepatitis: A Multicenter Observational Study. Metabolism 2023;148:155694. doi:10.1016/j.metabol.2023.155694, PMID:37757973.
[175] Lazo-de-la-Vega-Monroy ML, Preciado-Puga MD, Ruiz-Noa Y, Salum-Zertuche M, Ibarra-Reynoso LD. Correlation of the pediatric metabolic index with NAFLD or MAFLD diagnosis, and serum adipokine levels in children. Clin Res Hepatol Gastroenterol 2023;47(6):102137. doi:10.1016/j.clinre.2023.102137, PMID:37149032.
[176] Özkan EA, Sadigov A, Öztürk O. Evaluation of Serum Omentin-1, Vaspin, Leptin, Adiponectin Levels in Obese/Overweight Children and Their Relationship With Non-Alcoholic Fatty Liver Disease. Clin Nutr Res 2022;11(3):194–203. doi:10.7762/cnr.2022.11.3.194, PMID:35949560.
[177] Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, Mantzoros CS. Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 2016;59(1):30–43. doi:10.1007/s00125-015-3769-3, PMID:26407715.
[178] Marques V, Afonso MB, Bierig N, Duarte-Ramos F, Santos-Laso Á, Jimenez-Agüero R, *et al*. Adiponectin, Leptin, and IGF-1 Are Useful Diagnostic and Stratification Biomarkers of NAFLD. Front Med (Lausanne) 2021;8:683250. doi:10.3389/fmed.2021.683250, PMID:34249975.
[179] Zhao S, Zhu Y, Schultz RD, Li N, He Z, Zhang Z, *et al*. Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy. Cell Metab 2019;30(4):706–719.e6. doi:10.1016/j.cmet.2019.08.005, PMID:31495688.
[180] Qamar M, Fatima A, Tauseef A, Yousufzai MI, Liaqat I, Naqvi Q. Comparative and Predictive Significance of Serum Leptin Levels in Non-alcoholic Fatty Liver Disease. Cureus 2024;16(4):e57943. doi:10.7759/cureus.57943, PMID:38738048.
[181] Brandt S, von Schnurbein J, Denzer C, Kratzer W, Wabitsch M. Lower Circulating Leptin Levels Are Related to Non-Alcoholic Fatty Liver Disease in Children With Obesity. Front Endocrinol (Lausanne) 2022;13:881982. doi:10.3389/fendo.2022.881982, PMID:35677722.
[182] Feldman A, Eder SK, Felder TK, Kedenko L, Paulweber B, Stadlmayr A, *et al*. Clinical and Metabolic Characterization of Lean Caucasian Subjects With Non-alcoholic Fatty Liver. Am J Gastroenterol 2017;112(1):102–110. doi:10.1038/ajg.2016.318, PMID:27527746.
[183] Makri ES, Evripidou K, Polyzos SA. Circulating leptin in patients with nonalcoholic fatty liver disease-related liver fibrosis: a systematic review and a meta-analysis. J Gastroenterol Hepatol 2024;39(5):806–817. doi:10.1111/jgh.16480, PMID:38238084.
[184] Perakakis N, Farr OM, Mantzoros CS. Leptin in Leanness and Obesity: JACC State-of-the-Art Review. J Am Coll Cardiol 2021;77(6):745–760. doi:10.1016/j.jacc.2020.11.069, PMID:33573745.
[185] 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.
[186] Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 1999;401(6748):73–76. doi:10.1038/43448, PMID:10485707.
[187] Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc Natl Acad Sci U S A 1997;94(16):8878–8883.

doi:10.1073/pnas.94.16.8878, PMID:9238071.
[188] Cusin I, Rohner-Jeanrenaud F, Stricker-Krongrad A, Jeanrenaud B. The weight-reducing effect of an intracerebroventricular bolus injection of leptin in genetically obese fa/fa rats. Reduced sensitivity compared with lean animals. Diabetes 1996;45(10):1446–1450. doi:10.2337/diab.45.10.1446, PMID:8826985.
[189] Akinci B, Subauste A, Ajluni N, Esfandiari NH, Meral R, Neidert AH, *et al*. Metreleptin therapy for nonalcoholic steatohepatitis: Open-label therapy interventions in two different clinical settings. Med 2021;2(7):814–835. doi:10.1016/j.medj.2021.04.001, PMID:35291351.
[190] Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, *et al*. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 1999;282(16):1568–1575. doi:10.1001/jama.282.16.1568, PMID:10546697.
[191] Hukshorn CJ, van Dielen FM, Buurman WA, Westerterp-Plantenga MS, Campfield LA, Saris WH. The effect of pegylated recombinant human leptin (PEG-OB) on weight loss and inflammatory status in obese subjects. Int J Obes Relat Metab Disord 2002;26(4):504–509. doi:10.1038/sj.ijo.0801952, PMID:12075577.
[192] Mittendorfer B, Horowitz JF, DePaoli AM, McCamish MA, Patterson BW, Klein S. Recombinant human leptin treatment does not improve insulin action in obese subjects with type 2 diabetes. Diabetes 2011;60(5):1474–1477. doi:10.2337/db10-1302, PMID:21411512.
[193] Moon HS, 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 2011;60(6):1647–1656. doi:10.2337/db10-1791, PMID:21617185.
[194] Westerterp-Plantenga MS, Saris WH, Hukshorn CJ, Campfield LA. Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. Am J Clin Nutr 2001;74(4):426–434. doi:10.1093/ajcn/74.4.426, PMID:11566639.
[195] Zelissen PM, Stenlof K, Lean ME, Fogteloo J, Keulen ET, Wilding J, *et al*. Effect of three treatment schedules of recombinant methionyl human leptin on body weight in obese adults: a randomized, placebo-controlled trial. Diabetes Obes Metab 2005;7(6):755–761. doi:10.1111/j.1463-1326.2005.00468.x, PMID:16219020.