

Leptin as a Key between Obesity and Cardiovascular Disease

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Obesity increases the risk of cardiovascular disease through various influencing factors. Leptin, which is predominantly secreted by adipose tissue, regulates satiety homeostasis and energy balance, and influences cardiovascular functions directly and indirectly. Leptin appears to play a role in heart protection in leptin-deficient and leptin-receptor-deficient rodent model experiments. Hyperleptinemia or leptin resistance in human obesity influences the vascular endothelium, cardiovascular structure and functions, inflammation, and sympathetic activity, which may lead to cardiovascular disease. Leptin is involved in many processes, including signal transduction, vascular endothelial function, and cardiac structural remodeling. However, the dual (positive and negative) regulator effect of leptin and its receptor on cardiovascular disease has not been completely understood. The protective role of leptin signaling in cardiovascular disease could be a promising target for cardiovascular disease prevention in obese patients.

Key words: Obesity, Leptin, Cardiovascular disease

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INTRODUCTION

Obesity increases the risk of cardiovascular disease through various influencing factors,¹ such as hemodynamic changes, cardiac structure and cardiac function, inflammation, neurohumoral changes, and cellular remodeling (Fig. 1).² The presence of large emerging adipocytes may be directly associated with production of leptin, angiotensin, proinflammatory cytokines, and reactive oxygen species.³ Moreover, progressive inflammation processes, oxidative stress, and hyperleptinemia in obesity is significantly correlated with developing cardiovascular diseases⁴ and hypertension (Fig. 1).⁵⁻⁷ Adipocyte-derived leptin exhibits pleiotropic effects. In obese people, hyperleptinemia is not sufficient to prevent energy balance dysreg-

ulation, indicating that obese individuals are leptin resistant. Although most obese cases are associated with hypothalamic leptin resistance, the peripheral effects of leptin signaling or leptin resistance in obesity are not fully elucidated. Moreover, the net effects of hyperleptinemia or leptin resistance on cardiovascular disease in obese people are complex and not completely understood. In this review, we discuss leptin as a key between obesity and cardiovascular disease (Fig. 1).

RELATIONSHIP BETWEEN OBESITY AND CARDIOVASCULAR DISEASE

Obesity can lead to cardiac structural remodeling, causing left

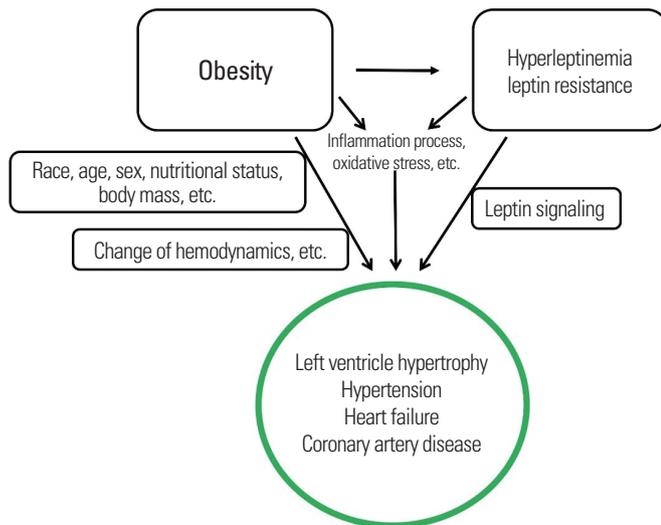


Figure 1. Overview of leptin as a key between obesity and cardiovascular disease. Obesity increases the risk of cardiovascular disease through the various factors: obesity-induced changes in hemodynamics, cardiac structure and cardiac function, inflammation, neurohumoral changes, and cellular remodeling, as well as hyperleptinemia and leptin resistance.

ventricular (LV) hypertrophy.^{8,9} When body mass index (BMI) increases by 1 kg/m², the risk of LV hypertrophy increases by 5.1%, and when waist circumference increases by 1 cm, the risk of LV hypertrophy increases by 2.6%.¹⁰ Furthermore, obesity is associated with vascular injuries, such as increased arterial stiffness,¹¹ coronary artery calcification,¹² increased carotid intima-media thickness, and higher incidence of carotid stenosis,¹³ all of which contributes to early vascular aging.¹⁴ Obesity has been recognized as an independent predictor of coronary artery disease^{15,16} and carries an approximately two-fold higher risk of developing heart failure than a healthy weight.^{17,18} Studies have also shown correlations between stroke and BMI and waist-hip ratio,^{19,20} and population-based cohort studies have reported a 49% higher risk of arteriosclerosis in obese patients compared with non-obese patients.²¹

In contrast, among patients with heart failure, those who were overweight or obese (BMI > 27.8 kg/m²) were clinically shown to have a higher survival rate.²² A follow-up analysis of 7,767 patients with chronic heart failure reported lower hazard ratios (HRs) in overweight or obese subjects (HR, 0.81; 95% confidence interval [CI], 0.72–0.92) than in normal-weight subjects (HR, 0.88; 95% CI, 0.80–0.96).²³ Similar results were observed in patients who experienced sudden cardiac arrest, wherein a higher BMI was associated with reduced mortality.²⁴ Higher BMI was also associated with

lower mortality in cases of coronary artery disease, heart failure, and diabetes.²⁵ In general, obese patients have higher mortality; however, paradoxically, higher mortality is often observed in normal-weight patients compared with obese patients.²⁶ This phenomenon, in which survival rates are higher among obese patients, in contrast to conventional expectations, is known as the “obesity paradox,” and is most commonly observed in patients with coronary artery disease or heart failure.²⁷

THE ROLE OF LEPTIN

Leptin is an important hormone involved in weight regulation and energy homeostasis.^{28–31} It is a 16-kDa protein with 167 amino acids.³² Leptin is predominantly secreted by adipose tissue and is also secreted from other tissues, including the heart, via autocrine or paracrine effects.^{33,34} Leptin regulates appetite by controlling satiety signals to the central nervous system (CNS)³⁵ and it influences cardiovascular functions either directly or indirectly via secondary responses mediated by the vasculature (such as hypertension, endothelial function, atherosclerosis, and thrombopoiesis) or the CNS.³⁶

The *ob* (obesity) gene mutation and leptin receptor (*LepR*) mutants—*ob/ob* and *db/db* mouse models, respectively—and *fa/fa* Zucker rat models were developed as obesity animal models.³⁷ Heart failure is common to these animals,³⁸ suggesting that leptin is linked to cardiovascular disease. In research using leptin- or *LepR*-deficient rodent models, leptin appears to play a role in heart protection.

Despite varying interpretations of the results of a meta-analysis of the effects of leptin on coronary artery disease,³⁹ in the Multi-ethnic Study of Atherosclerosis study that included 1,910 patients with atherosclerosis only, leptin was not significantly correlated with cardiovascular disease.⁴⁰ However, contradictory results have been reported in other studies that found a correlation between leptin and cardiovascular disease. In contrast, hyperleptinemia was found to be correlated with a positive prognosis for cardiovascular disease through coronary artery vasodilation, endothelial nitric oxide synthase (eNOS) activation, endothelial precursor cell activation, and reduced lipid accumulation.⁴¹

LEPTIN RECEPTOR AND SIGNAL TRANSDUCTION

LepR is simultaneously expressed in adipose, heart, muscle, lung, small intestine, and liver tissue, as well as the CNS, particularly the hypothalamus. LepR is a type-I cytokine receptor, from which six subtypes (LepRa to LepRf) are generated by selective splicing.⁴² Leptin signaling relies on LepR autophosphorylation, which triggers the pathways for Janus kinase (JAK), signal transducer and activator of transcription (STAT), insulin receptor substrate (IRS)/phosphatidylinositol 3 kinase (PI3K), mitogen-activated protein kinase (MAPK), extracellular signal-regulated protein kinase (ERK), and 5'-adenosine monophosphate-activated protein kinase (AMPK) (Fig. 2). Leptin may activate JAK2, IRS1, and ERK via LepRa; however, LepRb, with its long intracellular tail, appears to be the only subtype capable of mediating JAK/STAT signaling (Fig. 2).^{43,44}

JAK/STAT signaling is triggered by JAK2 phosphorylation, followed by STAT3 phosphorylation and a conformational change due to binding. STAT3 forms a dimer that enters the nucleus to

regulate the expression of genes governing food ingestion.⁴⁴ Such signaling pathways include negative feedback—suppressor of cytokine signaling 3 (SOCS3) negatively regulates the JAK/STAT pathway by interfering with the phosphorylation of the tyrosine residue of LepR (Fig. 2). Moreover, STAT3 repressor hinders STAT3 binding to DNA, and protein tyrosine phosphatase-1B interrupts phosphorylation of JAK2 and STAT3 and negatively regulates leptin signaling (Fig. 2).⁴⁴

Leptin also mediates MAPK and ERK signaling (Fig. 2). Binding of leptin results in SH2-containing protein tyrosine phosphatase 2 (SHP2) phosphorylation, and growth factor receptor-bound protein 2 (Grb2) activates ERK. Moreover, irrespective of LepRb phosphorylation, JAK2 activates downstream signaling via Grb2 and SHP2.⁴⁵ PI3K is a dimer and has a component that regulates signaling by acting as a catalyst. LepR activation facilitates the interaction and complex formation of JAK2/IRS1 to downregulate targets such as protein kinase B (Akt).⁴⁴

Elevated leptin levels are generally observed in obese people, which led to a hypothesis that elevated leptin levels may be linked

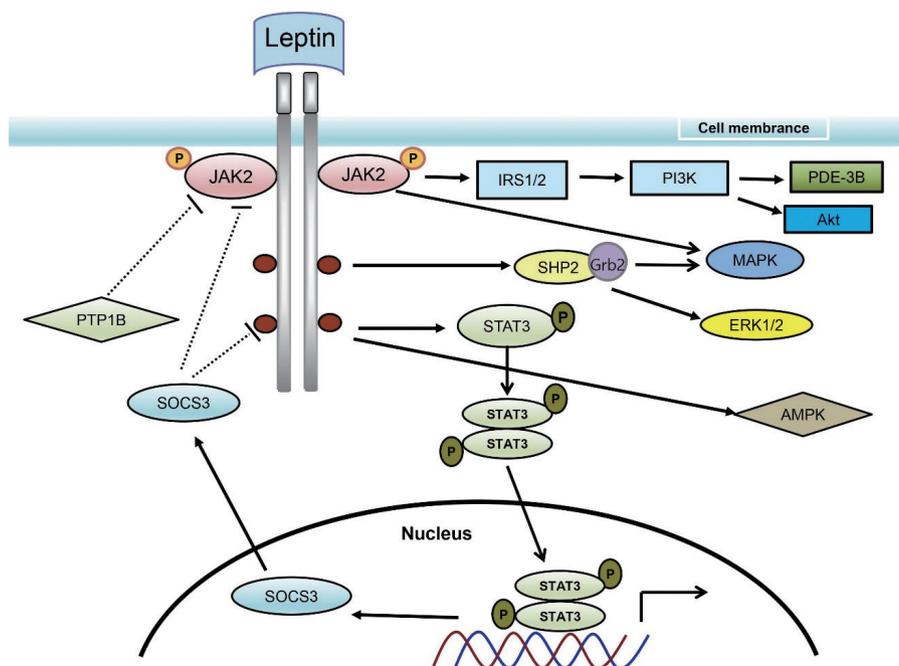


Figure 2. Signal transduction process of leptin. Leptin signaling relies on leptin receptor autophosphorylation, which triggers the JAK2, STAT3, IRS/PI3K, MAPK, ERK, and AMPK pathways. JAK, Janus kinase; IRS, insulin receptor substrate; PI3K, phosphatidylinositol 3 kinase; PDE, phosphodiesterase; Akt, protein kinase B; SHP2, SH2-containing protein tyrosine phosphatase 2; Grb2, growth factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; PTP, protein tyrosine phosphatase; STAT, signal transducer and activator of transcription; ERK, extracellular signal-regulated protein kinase; SOCS3, suppressor of cytokine signaling 3; AMPK, 5'-adenosine monophosphate-activated protein kinase.

to leptin resistance.^{35,46} If leptin resistance causes changes in leptin signaling (such as changes in LepR tyrosine residues or the leptin-binding site), additional studies are required to understand this phenomena. Whether leptin resistance is just inhibition of leptin signaling that affects the heart or whether other adipokines also affect the heart needs to be investigated.

RELATIONSHIP BETWEEN LEPTIN AND CARDIAC HYPERTROPHY

The increased blood volume in obese patients increases cardiac output and stimulates biomechanical stress and structural remodeling that may result in cardiac hypertrophy.^{8,9,47} A correlation between plasma leptin levels and cardiac hypertrophy has been clinically demonstrated.⁴⁸ Numerous studies observed that leptin directly induces cardiac hypertrophy in humans and mice.^{33,49-55} Leptin induces cardiac hypertrophy through diverse pathways such as the mammalian target of rapamycin signaling,⁵⁶ calcineurin activation and nuclear factor of activated T cells transportation into the nucleus,⁵⁷ peroxisome proliferator-activated receptor- α activation,⁵⁸ MAPK 14 (p38) activation and transportation into the nucleus,^{50,52} activation of Rho and actin dynamics,⁴⁹ and increases in intracellular reactive oxygen species.^{51,59}

LV hypertrophy is often observed in ob/ob and db/db mice morbidly predisposed to obesity.⁶⁰⁻⁶³ However, when adequate leptin levels are provided, the LV returns to its normal thickness, regardless of the mouse's weight.⁶² Hyperleptinemia is observed in the heart in a diet-induced obese mouse model, and LepR constantly responds to elevated plasma or cardiac leptin levels. This appears to provide protection against cardiac hypertrophy via STAT3 activation and its downstream pathways and by affecting p38 and p42/44 MAPK as well as Akt, in comparison to LepR mutants or db/db mouse models.⁶⁰

Despite the studies that conclude that leptin causes cardiac hypertrophy, research by Leifheit-Nestler et al.⁶⁰ showed protective effects of leptin on cardiac hypertrophy. They investigated LepR in relation to STAT3, but other effects of leptin also require investigation. Influential factors that require consideration are the mouse model species, leptin resistance in obesity, age, sex, and patient nutritional status. Without this knowledge, it is unclear whether obe-

sity-induced cardiac hypertrophy is the result of leptin-driven cardiac hypertrophy or resistance to the cardio-protective effects of leptin.⁶⁰

RELATIONSHIP BETWEEN LEPTIN AND CARDIAC FUNCTION

Ca²⁺ influx into the heart acts as a multifunctional signal that causes the heart muscles to contract, controls the period of action potential maintenance, and regulates gene expression.⁶⁴ During the period of excitation-contraction coupling in the heart, β -adrenergic signals activate the Na⁺/Ca²⁺ exchange channels via protein kinase A (PKA) signaling while causing depolarization of the sarcolemma.⁶⁵ Depolarization of the sarcolemma leads to the opening of high-voltage-activated L-type calcium channels and allows Ca²⁺ entry into the cytoplasm, which, in turn, causes Ca²⁺ release through ryanodine receptor channels into the sarcoplasmic reticulum (SR) for muscle contraction initiation.⁶⁵ Sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (SERCA2) and phospholamban (PLN) play crucial roles in transporting Ca²⁺ from myocytes and the cytoplasm.⁶⁶ Abnormal Ca²⁺ circulation in the SR characterizes cardiac diseases such as heart failure and arteriosclerosis and contributes to the pathophysiology of disease progression.^{66,67}

Decreased activation of SERCA2 and Na⁺/Ca²⁺ exchange channels is observed in leptin-deficient mice,⁶⁸ whereas leptin treatment to the myocytes of ob/ob mice improved β -adrenergic signaling and increased G α expression, PKA activation, and PLN phosphorylation.⁶⁹ These results suggest a definite correlation between leptin and cardiac function.^{70,71} Moreover, leptin treatment to cardiomyocytes of adult mice also resulted in suppressed contraction via different pathways (e.g., endothelin-1 receptor- nicotinamide adenine dinucleotide phosphate H oxidase pathway,^{70,71} nitric oxide,⁷² JAK/STAT pathway,⁷³ interleukin-1 β signaling,⁷⁴ autophagy induction⁷⁵).

RELATIONSHIP BETWEEN LEPTIN AND CARDIOMYOCYTE APOPTOSIS

Apoptosis, through strict regulation of specific signaling steps, is the main cause of cell loss in the heart.⁷⁶ Cardiomyocyte apoptosis

plays a key role in the progression of heart failure and is especially important for compensatory remodeling in heart failure.⁷⁷ Cells undergoing apoptosis experience structural changes including shrinking, plasma membrane blebbing, nuclear condensation, and DNA and nuclear fragmentation.⁷⁸ Once cells become apoptotic bodies, they are removed by macrophages.⁷⁶ Apoptosis is mediated via two different pathways: the first is the extrinsic or death receptor pathway activated by death-domain-containing receptors in the plasma membrane, and the second is the intrinsic or mitochondrial pathway activated by intracellular stress from growth factors, low oxygen concentration, oxidative stress, and DNA damage.⁷⁶ Apoptotic signals instantly activate caspases and disable the mitochondria, leading to cell death.

Zucker rats showed increased apoptosis via both the extrinsic and intrinsic pathways.^{79,80} In *ob/ob* and *db/db* mice and *fa/fa* rats, impaired leptin signaling caused a rise in triglyceride levels, which led to lipid accumulation and induction of cardiomyocyte apoptosis. However, when normal leptin levels were reached, excessive lipid accumulation was prevented and cardiac function was restored,^{61,81} indicating that increased apoptosis in obese mouse models was not due to aging or cellular damage but directly associated with impaired leptin signaling. Moreover, in knock-out mice models with cardiomyocyte-specific deletions of *LepR*, impaired leptin signaling directly led to increased cardiac hypertrophy, apoptosis, deterioration of cardiac structure and function, and impairment of energy, glucose, and fatty acid metabolism, which further accelerated heart damage due to myocardial infarction.⁸²

Apoptosis can be induced by a mechanism where the opening of the mitochondrial permeability transition pore (mPTP) releases cytochrome C into the cytoplasm.⁸³ Leptin prevents the opening of mPTP in mouse cardiomyocytes⁸⁴⁻⁸⁶ and can also protect cardiomyocytes from apoptosis induced by H₂O₂ or hypoxia-reoxygenation conditions.^{87,88}

Tumor necrosis factor (TNF)- α at high concentrations binds to TNFR-1 to cause cardiomyocyte apoptosis, leading to various cardiovascular diseases.⁸⁹⁻⁹¹ Leptin treatment in mouse cardiomyocytes interfered with the caspase-3 fragmentation and the intrinsic mitochondrial pathway, thereby preventing TNF- α -induced apoptosis.⁸⁷ Despite reports that leptin treatment causes apoptosis,^{92,93} it seems clear that leptin plays a protective role against apoptosis pro-

gression under stressful physiological conditions. Furthermore, it should be noted that leptin treatment could prevent apoptosis by blocking TNF- α -induced pathways (e.g., caspase-3 fragmentation, poly adenosine diphosphate ribose polymerase segmentation, p38 MAPK/nuclear factor kappa B phosphorylation, Bax transport).⁹⁴ If these downstream pathways could be regulated by leptin, cardiomyocyte apoptosis could be controlled and cardiovascular disease progression could be halted.

RELATIONSHIP BETWEEN LEPTIN AND ENDOTHELIAL VASCULAR FUNCTION

Leptin was initially thought to stimulate the sympathetic nerve,⁹⁵ raising blood pressure. However, leptin was not found to exert significant effects on blood pressure on its own.⁹⁶⁻⁹⁸ A number of experiments demonstrated that leptin is involved in endothelium-dependent vasodilation via nitric oxide,⁹⁹⁻¹⁰¹ which was further observed in leptin-deficient *ob/ob* mice, where arterial vessel contraction mediated by noradrenaline or phenylephrine increased while vasodilation by acetylcholine weakened. These anomalies disappeared when leptin levels were restored.¹⁰²

Leptin induces Akt phosphorylation¹⁰³ and phosphorylated Akt then induces phosphorylation of the eNOS serine residue, which heightens its activity. eNOS produces nitric oxide, which activates soluble guanylyl cyclase. This stimulates cyclic guanosine monophosphate synthesis in smooth muscle cells, leading to vasodilation. Although eNOS can also be activated by insulin, leptin is capable of activating the PI3K-independent Akt/eNOS pathway.¹⁰⁴ Leptin also seems to mediate vasodilation via endothelium-derived hyperpolarizing factor (EDHF).¹⁰⁵

Leptin resistance is observed in obesity and metabolic syndrome,^{35,46} where the effect of leptin on nitric-oxide-induced vasodilation becomes less significant. During the early stages, a compensatory response may originate from EDHF, but even this becomes inadequate as leptin resistance duration increases. Consequently, lack of dilation and continued stimulation of the sympathetic nerve causes hypertension and atherosclerosis.¹⁰⁶ Nonetheless, it is anticipated that elucidating the signaling pathway between leptin and endothelial cells and uncovering the mechanism of the role of leptin resistance in blood vessels would lead to a reliable

treatment strategy for obesity-associated vascular diseases.

Leptin causes atherosclerosis through diverse mechanisms including the entry of monocytes into blood vessels, transformation of macrophages into foam cells, proliferation of vascular smooth muscle cells, and secretion of atherosclerotic cytokines, which suggests that leptin indirectly causes atherosclerosis.¹⁰⁷ A recent study reported a protective role for leptin against atherosclerosis in a concentration-dependent manner in low-density lipoprotein receptor^{-/-} ob/ob mice.¹⁰⁸ Leptin exerts protective effects by reducing liver cholesterol or lowering its synthase mRNA expression.¹⁰⁹⁻¹¹¹ Furthermore, adiposity and related inflammation are independent prognostic factors alongside fibrosis in the progression and detection of atherosclerosis, and leptin relieves local inflammation in the liver by down-regulating inflammatory cytokines such as monocyte chemoattractant protein-1, TNF- α , and fibrosis marker transforming growth factor- β .^{112,113} Based on these findings, it seems important to elucidate the mode of liver cholesterol metabolism under physiological conditions and in leptin deficiency for ameliorating atherosclerosis progression. Moreover, the facilitated release of nitric oxide by leptin and the association of nitric oxide and sympathetic nerve activation may be another mechanism that prevents atherosclerosis.¹¹⁴ Such results, however, do not contradict the role of leptin in causing atherosclerosis when its levels are higher than normal. As previously mentioned, leptin causes atherosclerosis indirectly. Leptin and its receptors are expressed in atherosclerotic plaques in mice as well as humans,^{115,116} and high levels of leptin are known to elevate cardiovascular risk factors such as plasma fibrinogens, which suggest that high levels of leptin may contribute to atherosclerosis.¹¹⁷

RELATIONSHIP BETWEEN LEPTIN AND SYMPATHETIC STIMULATION

Sympathetic nerve activation is observed in obese patients¹¹⁸ as well as in animal models of obesity.¹¹⁹ In several tissue types, leptin seems to promote sympathetic nerve activation involved in cardiovascular regulation, which raises arterial pressure.¹²⁰ Furthermore, although leptin, when administered, was ineffective in regulating energy homeostasis in obesity, its influence on cardiovascular sympathetic nerve hyperactivity and blood pressure was maintained.¹²¹

This indicates a selective influence of leptin resistance. This is supported by the finding that blood pressure decreased when sympathetic nerve activity was inhibited and central leptin signaling was blocked in obese rabbits.¹²²

It is broadly agreed that hypertension is caused by sympathetic nerve activation that affects peripheral resistance or blood flow in the kidneys, and that leptin levels are elevated in obese individuals.¹²³ However, because leptin treatment in healthy individuals does not affect hypertension, it is worth considering whether hypertension is caused by elevated leptin levels or leptin signaling deficiency due to leptin resistance or by the burden of cardiac hypertrophy due to obesity. Additionally, demographic factors besides leptin (e.g., race, age, sex) should be considered. If it is the elevated leptin or leptin signaling deficiency due to leptin resistance in obesity that causes hypertension, then the condition might be controlled by regulating the downstream pathways (STATs, PI3K, ERK1/2, SOCS, etc.) (Fig. 2).¹²⁴

CONCLUSION

Leptin exerts its influence on the cardiovascular system in a number of ways. Obesity and leptin cannot be simply said to have either a negative or a protective role in cardiovascular disease. Nevertheless, a number of studies have shown that leptin has protective effects on cardiovascular disease. Future investigations should confirm whether elevated leptin levels themselves are responsible for cardiovascular disease or whether leptin resistance is responsible for cardiovascular disease in human obesity. If leptin plays different roles under different conditions, other factors including race, age, sex, nutritional status, BMI, and leptin resistance should be considered. The protective role of leptin signaling in cardiovascular disease could be a promising target to prevent cardiovascular disease in obese patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: KWK and SKL; analysis and interpre-

tation of data: KWK and MO; drafting of the manuscript: KWK and MO; critical revision of the manuscript: SKL; and study supervision: SKL.

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