



## Review Article

# The association of serum leptin levels with metabolic diseases

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### ABSTRACT

Leptin is a 167-amino-acid protein released by white adipose tissue and encoded by the obese gene. It has a role as a negative regulator of appetite control through sending a satiety signal to act on receptors within the hypothalamus. At normal levels, leptin can exert its effects on weight regulation according to white fat mass, induce sodium excretion, maintain vascular tone, and repair the myocardium. Beyond these effects, elevated serum leptin levels have been implicated in the pathogenesis of metabolic syndrome, diabetes mellitus, hypertension, and multiple cardiovascular diseases. In addition, hyperleptinemia had been reported to contribute to renal diseases through multiple mechanisms resulting in glomerulopathy presenting with a decreased glomerular filtration rate, increased albuminuria, and related clinical symptoms, which are pathophysiological features of chronic kidney disease. Because these cardiovascular and metabolic disorders are great challenges for physicians, understanding the related pathophysiological association with leptin might become a valuable aid in handling patients in daily clinical practice. This review will discuss the roles of leptin in the regulation of biological functions of multiple organs beyond the maintenance of feeding and metabolism.

**KEYWORDS:** *Cardiovascular diseases, Chronic kidney disease, Diabetes mellitus, Hypertension, Leptin*

### INTRODUCTION

Adipose tissue has several functions. It is associated with lipid metabolism including storage of triglycerides and release of fatty acid. Then, it catabolizes triglycerides to release glycerol and fatty acids that participate in glucose metabolism in the liver and other tissues. Moreover, adipocytes secrete adipokines, such as leptin, to regulate feeding behavior and cause satiety [1]. It is essential for healthy people to maintain a normal amount and distribution of adipose tissue. However, an imbalance might result in aberrant release of adipokines or an abnormal percentage of free form circulating in the blood which can cause diseases [2]. Leptin was discovered in 1994. It is a 16-kDa product of the obese gene mainly produced by white adipose tissue and functions as a major secretory and endocrine organ involved in a wide range of functions beyond fat storage. It reaches the hypothalamus through the blood-brain barrier and acts to reduce food intake and increase metabolism [3]. The classic effects of leptin include decreasing appetite, increasing energy expenditure, and regulating glucose homeostasis independent of insulin involvement. The serum concentration correlates with body fat content, and there are markedly elevated serum leptin concentrations and obese mRNA expression in the adipocytes of obese patients [4,5]. In humans, congenital leptin deficiency has been associated with severe obesity, glucose intolerance, and insulin resistance, and these disturbances can be reversed by leptin administration,

which indicates an association between leptin and insulin [5]. Elevated concentrations of serum leptin can be induced by increased secretion of leptin including free fatty acids, insulin stimulation, estrogen, tumor necrosis factor- $\alpha$ , or impaired renal clearance [6,7]. High leptin levels have been implicated in association with metabolic, inflammatory, and homeostatic factors involved in the pathophysiological processes of metabolic syndrome (MetS), hypertension (HTN), and other cardiovascular diseases (CVD), and a relationship between leptin and kidney diseases has been found [8-10]. This present review will highlight the pleiotropic actions of leptin that are potentially relevant not only to the control of satiety but also metabolic, CV, and renal disorders. Figure 1 shows the multiple physiological and pathophysiological roles of leptin in humans.

### ACTIONS OF LEPTIN IN METABOLIC AND CARDIOVASCULAR DISEASES

#### Leptin and metabolic syndrome

MetS is defined as a clustering of abdominal obesity,


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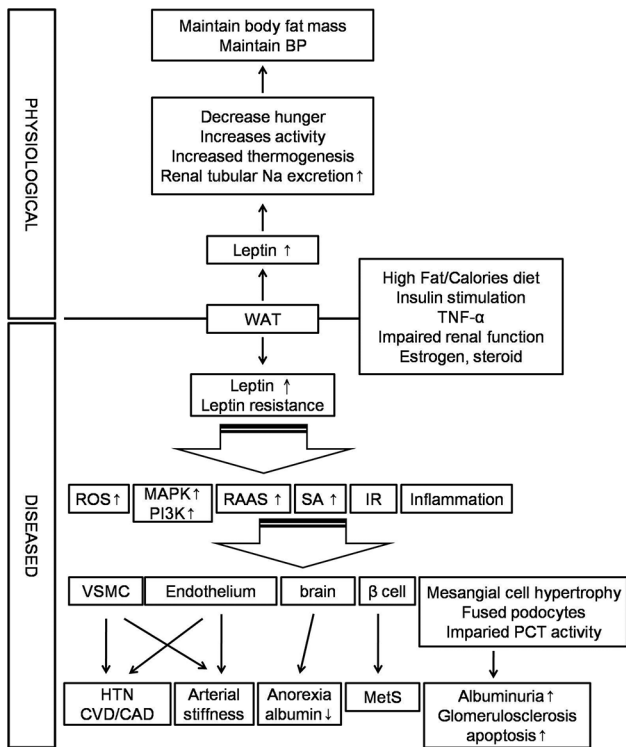
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**Figure 1:** Schematic presentation of the multiple roles of leptin in physiological regulation (upper half) and pathophysiological (lower half) conditions in humans. Abbreviations: BP: Blood pressure, CAD: Coronary artery disease, CVD: Cardiovascular disease, HTN: Hypertension, IR: Insulin resistance, MAPK: Mitogen-activated protein kinase, MetS: Metabolic syndrome, PCT: Proximal convoluted tubule, PI3K: Phosphatidylinositol-3 kinase, RAAS: Renin-angiotensin-aldosterone system, ROS: Reactive oxygen species, SA: Sympathetic activity, TNF- $\alpha$ : Tumor necrosis factor-alpha, VSMC: Vascular smooth muscle cell, WAT: White adipose tissue

increased blood pressure (BP), atherogenic dyslipidemia, insulin resistance, and pro-inflammatory and prothrombotic states and is considered a significant risk factor for the development and progression of diabetes mellitus, HTN, CVD, chronic kidney disease (CKD), and mortality. It is a major public health problem affecting all demographic groups [11,12]. Abdominal adiposity is mainly associated with these disorders. It has been reported that insulin resistance, an early step in the subsequent development of MetS, is present in the earliest stage of renal dysfunction and it is associated with CV morbidity in CKD patients [13]. Moreover, a rise in the incidence of CKD has paralleled the increasing prevalence of MetS with annual mortality rates attributed to accelerated atherosclerosis up to 250 times higher than those in the general population [14]. Visceral fat adipocytes, which are insulin-resistant cells within a network of blood capillaries and infiltrating inflammatory cells, represent a source of hormones and adipokines and have been strongly related to insulin sensitivity and CVD [2,15]. These adipokines with unbalanced secretion might lead to impaired insulin signaling and a state of inflammation leading to these metabolic disturbances [16]. Among these adipokines, the serum leptin concentration corresponds to body fat content and signals hypothalamic receptors about the body's stored energy to regulate feeding behavior. Leptin might play a critical role in the regulation of energy balance to maintain health and avoiding developing MetS

mainly through limiting the intake of high energy density foods. Considine *et al.* found that serum leptin levels and the mRNA content of adipocytes are elevated in obese patients compared with controls and strongly positively correlated with the amount of body fat [4]. Treating leptin deficiency with recombinant leptin resulted in reduced food intake and body weight, again demonstrating the role of leptin in mediating basal energy expenditure [5]. However, studies have shown that high levels of leptin are usually observed in obese patients. The possible mechanisms include decreased sensitivity to elevated leptin levels, which is called leptin resistance, caused by defects at or downstream of the leptin receptor, induction of inhibitors of leptin signaling, and alterations in the transport of leptin across the blood-brain barrier [2,4,17]. Leptin, insulin concentrations, and body weight are inter-related, and since leptin was reported to have a modulating role on insulin secretion by the pancreas, leptin resistance might occur in  $\beta$ -cells as well, thus inducing hyperinsulinemia observed in obese patients [18]. The concentration of serum leptin is indeed correlated with adiposity. Our previous studies showed that when patients receiving dialysis or renal transplantation were diagnosed with MetS or had several components of MetS, heavier prehemodialysis body weight, larger body fat mass, or mid-arm fat, they demonstrated significantly higher serum leptin levels [19-21]. This might imply the existence of vicious circles of leptin resistance and insulin resistance which both lead to less energy expenditure, thereby contributing to the occurrence of MetS and progression from obesity to overt MetS.

### Leptin and arterial stiffness

Arterial stiffness, as the gold standard surrogate marker of arterial wall function and structure, could be indicative of vascular damage and is an independent risk factor of coronary events and CVD [22]. Arterial stiffness can be measured by pulse wave velocity (PWV), a noninvasive method of assessing vascular function [23]. One meta-analysis showed that the pooled relative risks for total CV events, CV mortality, and all-cause mortality were 2.95, 5.36, and 2.45, respectively, for participants with a high versus low brachial-ankle PWV [22]. There are several risk factors for the development of arterial stiffness, and there is an association between arterial stiffness and leptin beyond the physiological role of regulating hunger and satiety [24,25]. Hyperleptinemia is believed to be associated with lower arterial distensibility, an index of circulatory function relevant to the atherosclerotic process through mechanisms other than vascular relaxation. Studies have shown an association between leptin and PWV, indicating that leptin could be a modulator between abdominal adiposity and arterial stiffness and have an impact on the pathophysiology of macrovascular diseases [25,26]. Leptin levels are higher in patients with uncontrolled HTN than in those with controlled BP and are associated positively with carotid-femoral PWV [27]. Apart from the influences of gender and body mass index (BMI), hyperleptinemia was found to be inversely associated with endothelial-dependent and endothelial-independent vasodilatation in the elderly population, indicating that leptin could play a mediating role in the regulation of endothelial function [24]. In another study, serum leptin and high-sensitivity C-reactive protein were shown to be significant determinants of arterial stiffness independent of age, sex, and other traditional CV

risk factors, indicating an association between inflammatory status and arterial stiffness [25]. There are several possible mechanisms for leptin contributing to the development of aortic mechanical dysfunction and arterial stiffness, including enhanced neointimal and medial thickening in injured arterial vascular walls, abnormal modulation of the renin–angiotensin–aldosterone system, abnormal proliferation and migration of vascular smooth muscle cells, and abnormal formation of reactive oxygen species from increasing fatty acid oxidation in endothelial cells [9,28-30]. Our previous research showed that hyperleptinemia was positively associated with PWV, and hyperleptinemia itself could be an independent risk factor in the development of arterial stiffness [31-33]. Because arterial stiffness represents vascular damage and is an independent predictor of coronary and CV events and leptin has a possible role in mediating vascular dysfunction, further longitudinal studies are needed to demonstrate the long-term influences of leptin on CV events, CV mortality, and all-cause mortality.

### **Leptin, chronic kidney disease, dialysis, and renal transplantation**

Studies show that serum leptin levels are higher in nondiabetic obese patients with impaired renal function (estimated glomerular filtration rate between 30 and 60 ml/min/1.73 m<sup>2</sup> or microalbuminuria >20 mg/L) than healthy patients and in patients with end-stage renal disease receiving dialysis who do not have an increase in body fat mass [34-36]. Serum leptin can be removed by hemodiafiltration in hemodialysis patients, and levels of serum leptin decrease early after kidney transplantation [37,38] but gradually increase consistent with serum insulin levels and insulin resistance, probably because of increased fat mass and steroid use in transplant recipients [37]. These studies indicate that the kidneys have a substantial role in removing leptin from plasma and also show that inflammation and hyperinsulinemia might affect serum leptin levels. Leptin, a large molecular weight protein and a uremic toxin, is independently associated with the risk and severity of CKD. Hyperleptinemia has been associated with glomerular mesangial cell hypertrophy, basement membrane thickening, fusion of podocytes, and reduced proximal tubule metabolic activity, resulting in albuminuria, glomerular sclerosis, and activation of apoptosis [6,7]. The altered balance of leptin in CKD patients might not only contribute to metabolic disturbances in the regulation of glucose and lipid metabolism but also might be involved in the evolution of insulin resistance, inflammation, and atherosclerosis [20,21,31,32,34-36,39]. In uremic patients, it was suggested that hyperleptinemia might induce anorexia with an ongoing inflammatory process and stimulatory effects on the sympathetic nervous system, inducing a negative energy balance [34-36,39]. In addition to its association with MetS and arterial stiffness, hyperleptinemia has been associated with pathophysiological changes typical of CKD and uremic anorexia and could be a predictor of the risk of CKD, represented as increased urinary albumin excretion, and decreased glomerular filtration rate.

### **Leptin, hypertension, and cardiovascular disease**

HTN has been associated with multiple causes, including absolute weight gain and distribution of adipose tissue, high sodium intake, hyperinsulinemia, increased sympathetic activity, and activation of the renin–angiotensin–aldosterone system.

In turn, these factors increase vascular sensitivity to catecholamines [8-10]. White adipose tissue has been identified as a metabolically active endocrine organ and a rich source of metabolically active substances including free fatty acids, angiotensinogen, and leptin, which affect a plethora of body functions including energy and feeding regulation, glucose function, lipid metabolism, and most relevantly, CV function [1,8,10,27]. Like other metabolic hormones such as insulin, leptin has potent vascular effects and participates in the regulation of sympathetic tone and arterial BP. There is crosstalk between leptin and the development of HTN and CVD [8,10,27]. Possible mechanisms of leptin with respect to the dysregulation of vessels include stimulating phosphorylation and activation of mitogen-activated protein kinases and phosphatidylinositol-3 kinase to increase the proliferation and migration of vascular smooth muscle cells, enhancing the effects of angiotensin II through modulating the sympathetic nervous system, initiating leukocyte and macrophage recruitment to the endothelial wall by induction of mitochondrial superoxide production, and inducing formation of reactive oxygen species in endothelial cells [28,29,40,41]. Increased leptin levels could serve as an adipose tissue-derived mediator for the development of HTN as hyperleptinemia was found to be associated with elevation of systolic and diastolic BP independent of BMI, plasma insulin, and abdominal adiposity in a cross-sectional study [42]. It was positively associated with prevalent HTN as well as prediction of new-onset HTN after adjustment for BMI, risk factors, and metabolic biomarkers in a 5-year observation study [43]. Another *in vivo* study showed that treatment with leptin could contribute to endothelial dysfunction and enhance the effects of angiotensin II in modulating BP through the activation of the sympathetic nervous system [41]. In addition, the relationship between leptin levels and abnormal vascular relaxation has been investigated in several cross-sectional studies which included elderly populations, those with resistant HTN, and healthy individuals and showed that hyperleptinemia was inversely associated with vasodilatation in resistance arteries [24-26]. Interestingly, leptin could normally act as a signaling mechanism to activate a compensatory mechanism for the potentially deleterious effects of an increased body fat mass as it could have facilitative effects on sodium excretion through a direct tubular action [44]. However, when there is resistance to the effects of leptin peripherally but not to the stimulatory effects of leptin on sympathetic and/or renin–angiotensin activity, it could cause abnormal regulation of vascular tone [44]. This would explain why hyperleptinemia occurs in these diseases as HTN often occurs in those with obesity. Taken together, these studies indicate that leptin could have an impact on the pathophysiology of macrovascular diseases and play a role in abdominal adiposity and the development of HTN.

In addition to be associated with HTN, serum leptin could strongly predict a first-ever acute myocardial infarction (MI), and increased serum leptin levels were in accordance with the number of diseased vessels in patients with acute MI [45,46]. Hyperleptinemia was positively associated with the degree of vessel narrowing, the proportion of abnormal coronary artery segments, and the complexity of atherosclerotic lesions in patients with angiographically diagnosed coronary

atherosclerosis [47]. Moreover, hyperleptinemia was found to be a risk factor for the development of coronary artery disease (CAD) in diabetic patients regardless of gender [48]. Recently, in addition to finding that hyperleptinemia was an independent risk factor for the development of arterial stiffness in patients with angiographically documented CAD, we also found that the serum levels of leptin correlated positively with the number of stenotic coronary arteries [33]. This finding is similar to previous studies showing that serum leptin plays an important role in the occurrence, severity, and extent of CAD [33,45,47,48]. Based on these studies, we believe that leptin may serve as an adipose tissue-derived intermediate for the development of arterial dysfunction and a mediator of the risk for the development and severity of CAD independent of obesity status and other traditional CV risk factors.

## CONCLUSIONS

Recent studies suggest that leptin has several functions beyond regulation of feeding and metabolism to include multiple biological functions influencing autonomic, CV, and kidney functions. However, there is no conclusion on the definite role of leptin as a cause or a result of the metabolic effects of altered adipokine patterns in patients with impaired renal function or in the pathogenesis of metabolic or CV diseases. Recently, this rapidly growing research field has contributed to a better understanding of the complex interaction between fat tissue (or leptin) and inflammation, dyslipidemia, and insulin resistance, on the one hand, and the role of leptin in the evolution of CKD and major CVD, on the other hand, and hopefully can contribute to better care of these diseases in the future.

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## Conflicts of interest

There are no conflicts of interest.

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