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# Leptin and Metabolic Effects

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**Abstract**

*Leptin is a metabolic hormone secreted from adipose tissue, also called satiety hormone. This hormone plays an important role in the regulation of body weight and energy homeostasis. Studies have shown that deficiency or excess of this hormone causes many metabolic changes in our body (such as obesity, type 2 diabetes, cardiovascular diseases, cancer). In this review, the general properties of leptin and its effect on these metabolic diseases were examined.*

***Keywords**:* leptin, metabolic diseases, obesity, diabetes mellitus, cardiovascular diseases

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## Introduction

Leptin is a protein-structured hormone consisting of 167 amino acids released from adipose tissue. It is encoded by the ob/ob gene in humans (1). This hormone has important effects on energy balance and food intake (2). It has been shown that leptin, which is synthesized mainly from adipose tissue in the body, is secreted to some extent by the placenta, gastric epithelium, skeletal muscle, pituitary and mammary gland (3).

Leptin, mainly synthesized and secreted by adipose tissue, shows function as a kind of antiobesity factor by regulating the balance between energy intake and energy expenditure by acting on its specific receptors in the hypothalamus. It has been demonstrated that leptin have many functions such as reproduction, hematopoiesis, regulation of gastrointestinal functions, angiogenesis, regulation of sympathetic nervous system activation, determination of bone density, thermogenesis and brain development (3).

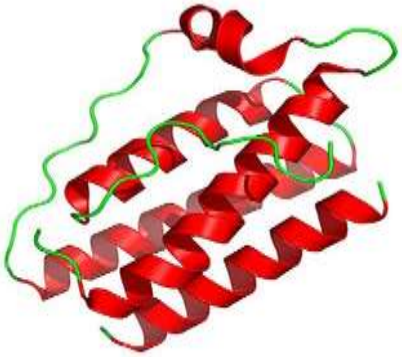
## Structure of Leptin

Leptin has a quadruple helix structure and it structurally resembles members of the type 1 helical family (4).

All receptor types of leptin are encoded by the Lepr gene, but they exist in 6 forms, namely OBRa, OBRb, OBRc, OBRd, OBRe and OBRf, depending on cytoplasmic domains of different lengths as a result of alternative mRNAs used in translation and proteolytic processes. These receptors are members of the class 1 cytokine receptor family (5).

Leptin receptors are expressed in brain and peripheral tissues. Binding of leptin to its receptors leads to stimulation of receptors associated with the Janus kinase 2 pathway, resulting in phosphorylation of two tyrosine residues. Expression of leptin receptors such as ObRa and ObRb is seen in all tissues in mammals, but ObRb is only highly expressed in the hypothalamus (4).

**The Tertiary Structure of Leptin. (6).**



## Secretion of Leptin

Leptin secretion is regulated by a several hormones, including insulin, glucocorticoids, and leptin itself. As lipid stores in the body increase, leptin secretion

in adipocytes increases accordingly. Therefore, changes in adipose tissue directly affect the change in leptin level in the blood (7). The secreted leptin is removed from the system via the kidneys and liver. The amount of circulating leptin is primarily energy stores in adipose tissue, but also varies according to hormonal balance, body fat ratio, skin thickness and gender (5).

Leptin is a besides secreted at low levels in other tissues such as bone marrow, ovary, placenta, stomach, and lymphoid tissue. Short isoforms of leptin, ObRa and ObRc, are thought to have effects on the transport of leptin across the blood-brain barrier. ObRb, the long isoform of leptin, is present everywhere in the central nervous system and plays a primary role in leptin signaling. The ObRb receptor is incredibly important in the hypothalamus as it regulates energy balance and neuroendocrine functions. In humans, the release of leptin into the circulation is pulsatile. Leptin concentrations follow a circadian rhythm and are affected by sleep patterns. It has been shown that the highest leptin levels are between midnight and early morning, and the lowest leptin levels are between morning and afternoon. (8).

The secretion of leptin hormone from the adipose tissue is determined by the level of the hormone in the circulation. This hormone primarily decreases food intake through its hypothalamic receptors and increases metabolic rate. Leptin is found in the circulation both free and bound to leptin-binding proteins. The free/total leptin ratio is independent of physiological states such as hunger and satiety. However, there is probably a dynamic balance between binding proteins and free leptin, which can be affected by metabolic events. It has been reported that most of the leptin is found in bound form in thin people and in free form in obese people (9).

**Metabolic and Physiopathological Effects of Leptin**

Leptin exerts its metabolic effects by interacting with receptors in the central nervous system and peripheral tissues (lung, kidney, liver, heart, endocrine part of the pancreas, adrenal glands, uterus, ovary, testis, hematopoietic cells, skeletal muscle, etc.). Leptin receptors, whose main area of action is the hypothalamus; it is located within the hypothalamic area, which is related with the control of appetite, reproduction and growth (10).

After the leptin gene was discovered, it was understood that leptin inhibits the synthesis and release of neuropeptide Y (NPY) in the arcuate nucleus (ARC). With this effect, it has been understood that leptin regulates appetite and metabolism (11).

While leptin increases glucose uptake and expenditure in brown adipose tissue, it decreases glucose uptake by suppressing glucose transporters in white adipose tissue. It stimulates glycogen synthesis by reducing insulin resistance in liver tissues, while muscle increases fatty acid oxidation by decreasing glycogen synthesis. Leptin increases fatty acid uptake and oxidation by inhibiting the activities of regulatory enzymes involved in fatty acid synthesis. In general, it increases the use of oxygen in the tissues and induces the use of fats as an energy source. In addition, it provides lipid balance in the body by reducing the intracellular lipid level in skeletal muscle, liver and pancreas (5).

**Leptin and Obesity**

Obesity is described as an excessive increase in body fat mass relative to fat-free mass. Obesity is a serious public health problem as it is associated with insulin resistance, diabetes, atherosclerosis, hypertension, chronic kidney disease, and increased cardiovascular morbidity and mortality (12).

The hormone leptin plays an substantial role in producing energy and regulating food intake. Deficiency of this hormone or formation of leptin resistance causes obesity in humans (13).

Many studies have found a strong positive relationship between serum leptin levels and body fat percentage. As the amount of adipose tissue increases, leptin levels in the body increase rapidly, and by binding to its receptor in the hypothalamus, it reduces appetite, but does not completely stop eating. Leptin stimulates lipolysis in adipose tissue and inhibits insulin release from beta cells in the pancreas (13).

Leptin levels decrease in situations that cause a decrease in fat mass, such as calorie restriction, hunger, and illness. As a result, the sympathetic nervous system response is reduced, the hypothalamus is stimulated, and signals that inhibit appetite are reduced. In obesity, leptin resistance occurs, which is characterized by the inability to detect the amount of leptin in the body by the brain, and the lack of feeling of satiety and the inability to suppress the feeling of hunger. Although circulating leptin is high, the brain cannot receive satiety signals and this causes hyperphagia (14).

With the decrease in fat stores, leptin decreases, increasing appetite and food intake. In other words, with a decrease in leptin level, food intake increases while energy expenditure decreases. The increase in fat stores reduces appetite by increasing leptin, and in this way, food intake is reduced (10).

Leptin secretion increases in obesity and leptin resistance develops due to inflammation. Insulin and leptin signaling pathways are the main pathways that regulate the nutrient and energy balance in the body. Leptin exerts insulin-like effects on glucose metabolism. Basically, it provides body weight control by showing an appetite suppressant effect. Some studies have shown that acute injection of leptin into mice improves glucose metabolism and insulin sensitivity (15).

In the study conducted by Yigitbası T et al, it was determined that the leptin level in overweight and obese patients was higher than in normal individuals. In the same study, the relationship between leptin level and insulin resistance seen in obesity was also investigated. The leptin levels in the insulin resistance positive obese group and the insulin resistance negative obese group were compared and no statistically significant difference was observed between them. As a result of this study, it has been demonstrated that leptin is associated with body mass index (16).

**Leptin and Diabetes Mellitus**

Diabetes mellitus (DM) is a metabolic disorder that usually occurs as a result of a combination of hereditary and environmental factors and results in an excessively high blood glucose level (hyperglycemia). The regulation of blood sugar in the body is achieved as a result of the complex interaction of many chemicals and hormones. The most important hormone that plays a role in the regulation of sugar metabolism is

insulin, which is secreted from the beta (β) cells of the pancreas. DM may occur as a result of either a deficiency in insulin secretion or a defect in the action of insulin. In summary, DM is a complex disease characterized by defect in carbohydrate, fat and protein metabolism, various microvascular and macrovascular complications occurring simultaneously, and an increase in glucose changes in the blood. All subtypes of DM result from inadequate insulin supplementation or from a lack of tissue response due to the insulin being unable to exert its effect. Diabetes is generally divided into two types as type I diabetes and type II diabetes. Type I diabetes results from the destruction of β-cells involved in insulin production in pancreatic is lets by autoimmune pathway. Type II diabetes, on the other hand, is a progressive disease that results from the combination of insulin resistance and β-cell system dysfunction (17).

Studies in recent years have shown that leptin has effects such as regulating blood glucose levels and increasing insulin sensitivity (9). In a study conducted with type 2 DM patients, insulin was given to the patient and it was revealed that the leptin level increased after a long time, although not acutely. It is thought that the reason for this is the increase in the synthesis of leptin, a stimulating factor in adipocytes, by feeding the adipose tissue with insulin taken from the outside. In another study, it was demonstrated that leptin levels in type 2 DM patients with the same body mass index and non-diabetic individuals were not statistically different (5).

**Leptin and Coronary Heart Diseases**

Coronary artery disease (CAD) is the main cause of death in our country as well as in industrial western societies. Obesity is one of the most important risk factors for hypertension and atherosclerosis. It is stated that adipokines secreted from adipose tissue are very important for the development of obesity-related diseases such as CAD, diabetes and cancer (18).

In a prospective study examining the relationship between leptin and CAD, it was suggested that leptin may be an independent risk factor for CAD. These data suggest that leptin may affect the vascular structure. In vitro and in vivo studies have shown that leptin has an angiogenic effect and contributes to arterial thrombosis through platelet leptin receptors (18).

Studies have reported that individuals with coronary heart disease have higher leptin levels than controls. However, contrary to these studies, there are also studies supporting that there is no relationship between leptin and CAD (19).

**Leptin and Cancer**

Cancer is a serious health problem that ranks second among the causes of death in the world, has a high mortality and morbidity rate, causes anxiety about the future and uncertainty, and threatens life (20).

Studies have shown that obesity increases the risk of cancer formation. Leptin is thought to regulate the expression of genes associated with cancer progression. This suggests that it directly supports the growth of adipocytes in the tumor microenvironment. Leptin receptors are highly abundant in many tumors compared to

normal tissues, such as leptin-responsive mammary carcinoma and gastrointestinal malignancies. With this feature, leptin signal creates synergy with many different oncogenes, cytokines and growth factors that affect the same signaling pathways (21). Leptin may affect the risk of breast cancer by increasing estrogen synthesis or decreasing follicular estradiol synthesis. Leptin shows its effect by increasing cell survival and proliferation together with estrogen receptor-α. This explains the positive relationship between estrogen and leptin systems in human breast cancer development. It has been reported that circulating adiponectin levels are lower in overweight and obese adults, while leptin levels are higher than in thin individuals. Low adiponectin and increased leptin levels were related with an increase in breast cancer. Studies have shown that an increase in the ratio of adiponectin to leptin reduces the proliferation of breast cancer cells; no such effect was observed when the ratio of leptin to adiponectin was increased. Therefore, it is thought that the ratio between leptin and adiponectin is more important in the regulation of breast cancer development rather than the effect of a single adipokine (22).

Adipose tissue dysfunction caused by obesity plays an important role in carcinogenesis by affecting the production of various adipokines. Among these adipokines, leptin has been shown to play an important role in the progression and recurrence of cancer in epidemiological, pathophysiological and mechanistic studies (22).

## Conclusion

Leptin is closely related to many metabolic diseases and it is an important adipokine that affects the entire metabolism. Leptin is not only a hormone that controls body weight and energy homeostasis, but also plays an important role in blood glucose regulation, inflammation, and cancer formation. It is important to elucidate leptin signal molecules and their mechanisms of action, as well as to investigate the diseases they cause. More studies are needed to understand the molecular and physiological mechanisms of the effect of leptin on these diseases.

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