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**Title:** A Regulatory Peptide: Nesfatin-1 and Its Relationship with Metabolic Syndrome

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## Abstract

Abdominal obesity, high triglyceride levels, decline in low-density lipoprotein, increased blood pressure and increased fasting blood glucose are the components of metabolic syndrome. As it includes these components, the metabolic syndrome poses a risk for type 2 diabetes and cardiovascular diseases. The prevalence of metabolic syndrome is increasing with age. Nesfatin-1, which has effects on different systems, has recently been discovered as a regulatory peptide molecule. With the first discovery of Nesfatin-1, it has been reported to inhibit the intake of nutrients and to have significant regulatory effects on energy metabolism. Nesfatin-1 is present in both central and peripheral tissues. It is thought to have many functions due to its presence in both central and peripheral tissues. In addition to its

suppressive effect on food intake, nesfatin-1 has also been reported to have an effect on the blood glucose level, to regulate cardiological functions and to have effects on obesity by providing weight loss. Considering the effects of nesfatin-1, it may be associated with metabolic syndrome.

**Key Words:** Metabolic Syndrome, Nesfatin-1, Obesity, Peptide

## Introduction

Today, obesity has become a public health problem affecting more than one billion people worldwide and poses an increased risk for insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, atherosclerosis and cardiovascular diseases. The presence of these abnormalities along with obesity is called insulin resistance syndrome or metabolic syndrome [1]. Metabolic syndrome increases the risk of type 2 diabetes and cardiovascular disease [2]. Almost a third of the adult population in the world and in our country has metabolic syndrome. The increase in the prevalence of metabolic syndrome with age causes an increased morbidity and mortality, and therefore metabolic syndrome has become a growing social health problem [3]. The mechanism of the formation of metabolic syndrome is not fully understood; however, it has recently been thought that some new regulatory adipokines may play a key role in the pathogenesis of metabolic syndrome. Adipokines are secreted from adipose tissue with significant endocrine functions. Among these adipokines, nesfatin-1, retinol-binding protein 4, omentin-1, vaspin and progranulin are secreted from adipose tissues through a broad secretion network, and take part in pathologies directly related to the metabolic syndrome [1,4].

Nesfatin-1 is secreted from neurons (hypothalamic paraventricular nucleus, supraoptic nucleus, arcuate nucleus, lateral hypothalamic area, spinal cord) and peripheral tissues (pancreas, liver, subcutaneous and visceral fat tissues, brown adipose tissue, skeletal muscles) [5]. Due to this distribution feature in the body, nesfatin-1 is thought to affect many functions. Previous studies have reported that nesfatin-1 has regulatory effects on energy metabolism by suppressing food intake. In addition to the effect of Nesfatin-1 on food intake, it has been reported that nesfatin-1 regulates cardiological functions, decreases blood glucose levels, acts

as a neuroendocrine regulator and provides weight loss along with reduction in energy intake [6]. The present study analyzes the relation of nesfatin-1 with metabolic syndrome and its components.

**Definition of Metabolic Syndrome and Its Components**

Metabolic syndrome is defined as an abnormality accompanied by a decrease in high-density lipoprotein (HDL) level, hypertension along with the increase in triglyceride (TG), insulin resistance, hyperglycemia and abdominal obesity [7]. The prevalence of metabolic syndrome gradually increases in parallel with the increase in the consumption of foods with high fat and sugar content, the inadequacy of physical activity and increased prevalence of central obesity [8]. Metabolic syndrome is a metabolic disease caused by a group of diseases adding to each other [9]. Abdominal obesity, atherogenic dyslipidemia, high blood pressure, insulin resistance-glucose intolerance are the components of metabolic syndrome [10].

**The Discovery and Structure of Nesfatin-1**

Nesfatin-1, was first described as a peptide consisting of 82 amino acids by Oh-I et al. [11] in 2006. In this study, a protein secreted in the hypothalamic nuclei of mice was discovered. This protein, which corresponds to Nucleobindin2 (NUCB2), consists of 396 amino acids. NUCB2 prohormone is divided into three as a result of proteolytic processes. The N-terminal fragment constitutes nesfatin-1 (1-82), and the C-terminal fragment constitutes nesfatin-2 (85-163) and nesfatin-3 (166 -396). Among peptides consisting of NUCB2, only nesfatin-1 was found to have an effect on food intake and appetite control [11, 12]. However, the functions in which nesfatin-2 and nesfatin-3 are effective are not yet known [13].

The structure of Nesfatin-1 consists of three parts. The first part begins from the N-terminal end, continues to the 23$^{rd}$ amino acid and is called as N23. The second part contains amino acids between 23 and 53 and is defined as M30. The third part is located from the amino acids between 53 and 82 towards the carboxy terminal and is called as C29. In the food intake and appetite control, the middle segment called M30 is considered to be effective [13]. Figure 1 shows the structure of NUCB2 protein and the formation of nesfatin-1 [14].

## The Expression of Nesfatin-1

The mRNA and protein expression of NUCB2 have been detected in rats in the lateral hypothalamic area as well as in the arcuate nucleus, para ventricular nucleus, and supraoptic nucleus in the brain nucleus located in the section of the brain responsible for nutrition. These expressions have been confirmed by further studies, and NUCB2/nesfatin-1 expression has been found to be present in insular cortex, central amygdaloid nucleus, peri-ventricular nucleus, tubular hypothalamic area, dorsomedial hypothalamic nucleus, Edinger-Westphal nucleus and ventrolateral medulla. In the first study in which Nesfatin-1 was described, it was reported to be located in the cerebrospinal fluid and hypothalamic nuclei. However, in subsequent studies, it was also found in different peripheral tissues of rats such as the anterior pituitary gland, adipose tissue, heart, pancreas, gastric mucosa and testis. In addition, NUCB2 mRNA expression in the stomach was found to be ten-fold higher than the expression in the brain. In the pancreas, NUCB2/nesfatin-1 located in the cells of the islets of Langerhans together with insulin. When the widespread peripheral distribution of NUCB2/nesfatin-1 is examined, it shows homeostatic functions in addition to modulation of food intake [15].

## Effect Mechanism of Nesfatin-1

It shows anorexigenic activity with an intracerebroventricular application for the hypothalamus. The intracerebroventricular injection of nesfatin-1 significantly stimulates food intake. The central anorexigenic function induced by Nesfatin-1 is achieved with the help of a mechanism dependent on the melanocortin ¾ receptor independently of the release of leptin in the hypothalamus [16, 17]. The immunoreactivity of nesfatin-1 is localized in the forebrain and posterior brain nuclei along with various neurotransmitters regulating pituitary hormone regulation and stress. Thus, nesfatin-1 has a variety of potentially extended biological effects, including nutritional intake, as well as neuroendocrine regulation, pain, stress, and autonomic control of internal organs [18].

In addition to its anorexigenic effect, studies have shown some other central effects (Figure-2) [19]. In addition to the anorexigenic effect of Nesfatin-1 injection into the brain, it reduces gastric emptying and gastric motility. After the injection of Nesfatin-1 into the third cerebral

ventricle, it was observed to improve peripheral glucose intake and insulin sensitivity in rats. Furthermore, there is evidence that it stimulates body temperature by activating sympathetic nerve activity and plays a role in the regulation of cardiovascular function [20].

**The Relationship Between Nesfatin-1 and Metabolic Syndrome**

Nesfatin-1 has been reported to have effects on obesity by providing food intake, glucose metabolism, cardiological functions and weight loss [6]. These effects of nesfatin-1 were investigated in the studies by associating with metabolic syndrome and its components. In a study by Algül et al. [21], serum nesfatin-1 level was shown to be 0.885±0.01 ng/ml in individuals with metabolic syndrome and 1.094±0.07 ng/ml in control group. In another study on rats with metabolic syndrome as a result of fructose exposure, serum nesfatin-1 levels of both male and female rats with metabolic syndrome were found to be higher than the control group [22]. In a study by Aksu et al. [23], patients with obstructive sleep apnea syndrome were divided into two groups as those with and without metabolic syndrome. Serum nesfatin-1 levels were found to be lower in individuals with metabolic syndrome (3.97±1.42 pg/ml) than those without metabolic syndrome (4.98±1.84 pg/ml). The data obtained from the studies suggest that nesfatin-1 may play a role in the pathogenesis of metabolic syndrome.

**The Relationship Between Nesfatin-1 and Metabolic Syndrome Components**

**The Relationship Between Nesfatin-1 and Obesity**

As Nesfatin-1 has potential effects on nutrient intake and energy metabolism, several studies have been conducted on the relationship between the NUCB2/nesfatin-1 and obesity to identify its potential effects on regulation of body weight [17]. In a study investigating the relationship of the nucleotide polymorphism of the NUCB2 gene with obesity genetically, 1049 obese and 315 normal individuals were included. As a result of the study, nucleotide polymorphism of NUCB2 gene was found to be related to body mass index (BMI), body weight and lean body tissue. It was concluded that obesity and NUCB2 gene polymorphisms may play an important role in the protection of obesity in males and may have an effect on energy metabolism [24]. In another study conducted on obesity, seven variants of the NUCB2

gene were observed in a population of 471 obese children and adolescents. This situation may cause NUCB2/nesfatin-1 to lead to the development of obesity by bringing about possible changes in the brain physiology [25]. In an animal study on obesity, it was thought that the decrease in NUCB2 mRNA and protein levels in the hypothalamus may contribute to hyperphagia seen in obese diabetic mice [26]. Considering these results, NUCB2/nesfatin-1 expression may increase the risk of developing obesity in case of some genetic conditions [15].

Plasma nesfatin-1 levels were found to be significantly lower in individuals diagnosed with anorexia nervosa and who had chronic nutritional intake restrictions compared to healthy controls [27]. Plasma nesfatin-1 levels have been shown to be associated with BMI, insulin resistance, fasting blood glucose and fasting insulin levels, and body weight and fat mass [28,29]. These data indicate that nesfatin-1 derived especially from fat can play an important role on metabolism and nutrient intake [30]. In a study conducted by Başar et al. [31], a negative correlation was determined between serum nesfatin-1 levels and fasting blood glucose and BMI. Serum nesfatin-1 concentrations of obese individuals were found to be significantly lower when compared with non-obese individuals. Similar results were obtained in another study investigating the relationship between obesity and nesfatin-1. Obesity individuals were found to have lower fasting nesfatin-1 levels than those who are not obese. Nesfatin-1 levels and BMI, body fat percentage, body fat weight and blood glucose levels showed a negative correlation [32].

In several studies, it was revealed that NUCB2/nesfatin-1 plasma levels were positively correlated with BMI, and an increase was observed in the number of gastric NUCB2/nesfatin-1 expressing cells in obese patients with increased BMI [33, 34]. It is assumed that there is a connection between body weight and NUCB2/nesfatin-1, but the results obtained from the studies differ [20].

Obesity is a risk factor for many diseases. Also, the most important risk factor for obstructive sleep apnea syndrome (OSAS) is obesity [35]. Obesity is observed in 60-70% of patients with OSAS [36]. Plasma nesfatin-1 levels were investigated in obesity related diseases after the

relationship between obstructive obesity and Nesfatin-1. In a study, plasma nesfatin-1 levels were significantly found to be lower in OSAS patients than in healthy controls. There was also found a negative correlation between apnea hypopnea index and nesfatin-1 levels. In addition, a negative correlation was found between neck circumference and nesfatin-1 levels in OSAS patients [37]. Similar results were obtained in another study, and serum nesfatin-1 levels were found to be significantly lower in subjects with OSAS. In this study, the nesfatin-1 levels in individuals with severe OSAS were lower than those with mild and moderate OSAS. A negative correlation was found between serum nesfatin-1 levels and BMI, waist-hip ratio, HOMA-IR score and apnea hypopnea index [38)]. Different results were obtained in another study. No significant relationship was found between the nesfatin-1 levels of individuals with mild, moderate and severe OSAS and that of healthy controls [23]. It is observed that there is a relationship between low nesfatin-1 level and OSAS. In the light of future research, the relationship between nesfatin-1, obesity and OSAS will be clearly understood.

**The Relationship Between Nesfatin-1 and Glucose Metabolism**

In addition to regulating nutrient intake, NUCB2/nesfatin-1plays a role in the regulation of glucose metabolism, as well. The presence of NUCB2/nesfatin-1 and insulin together in human and rodent pancreas explains this condition. Following glucose release, NUCB2 / nesfatin-1 has been shown to be released from pancreatic cells. In-vitro studies have shown that nesfatin-1 increases the expression of pre-proinsulin mRNA and also increases glucose-induced insulin secretion by stimulating calcium flow involving L-type channels [15].

In a study investigating the effect of nesfatin-1 on glucose metabolism, the anti-hyperglycemic effect of nesfatin-1 has been demonstrated. Intravenous administration of nesfatin-1 significantly reduced blood glucose levels in hyperglycemic db/db mice (mimics of the type 2 diabetes model). In the same study, intracerebroventricular administration of nesfatin-1 to db/db mice prevented food intake, but high blood glucose levels were not affected. The results revealed that the anti-hyperglycemic effect of nesfatin-1 was dependent on peripheral administration, time, dose and insulin [39].

In another study, it was observed that blood glucose levels decreased as a result of continuous subcutaneous nesfatin-1 infusion into mice during oral glucose tolerance test (OGTT). In the same study, it was also seen that infusion of intracerebroventricular nesfatin-1 did not have an effect on blood glucose levels. These findings suggest that peripherally administered nesfatin-1 rather than central nesfatin-1 administration was effective in glucose metabolism [40]. The continuous subcutaneous infusion of Nesfatin-1 resulted in an increase in circulating insulin level and a decrease in glucagon level in the first 30 minutes of OGTT in male Fischer 344 rats. These findings suggest that nesfatin-1 affects insulin sensitivity [41].

In the study conducted in patients with type 2 diabetes, plasma nesfatin-1 levels decreased in patients with type 2 diabetes compared to healthy controls or patients with type 1 diabetes [42]. In another study, serum nesfatin-1 levels were found to be lower in pregnant women with gestational diabetes mellitus than in healthy controls [43].

**The Relationship Between Nesfatin-1 and Cardiovascular System**

Nesfatin-1 plays a role in the regulation of cardiovascular function. Nesfatin-1 distribution at the central level shows that it may play an important role in the regulation of cardiovascular functions and mechanisms that contribute to cardiovascular homeostasis [44]. For example, intra-cerebrospinal injection of nesfatin-1 increases arterial blood pressure. Nesfatin-1, which is localized with oxytocin in the paraventricular nucleus, stimulates the release of oxytocin by depolarization. It is also known that nesfatin-1 activates the melanocortin pathway through oxytocin. Therefore, hypertensive effect is thought to be related to either central oxytocin or melanocortin pathways [45].

In an animal study where nesfatin-1 was administered intravenously, administration of nesfatin-1 was shown to cause vasoconstriction and high blood pressure, inhibiting nitric oxide (NO) production. Intravenous administration of Nesfatin-1 produces a potentially hypertensive effect both in central nervous system and by modulating arterial resistance. [46]. When the human studies were examined, 40 hypertensive patients and 40 healthy control groups were compared. Plasma nesfatin-1 levels were found to be higher in hypertensive patients [47]. In another study, it has been shown that high plasma nesfatin-1 levels may be

associated with increased systolic and diastolic blood pressure values and increased heart rate in polycystic ovary syndrome [48]. In an in-vitro study, mRNA of nesfatin-1 protein and of its precursor NUCB2 was detected in rat heart. In the same study, it was revealed that nesfatin-1 levels decreased in the heart tissue under ischemia/reperfusion injury. As a result, it has been shown that nesfatin-1 causes a significant decrease in infarction size against ischemia/reperfusion injury and induces functional recovery after ischemic contraction [49].

**The Relationship Between Nesfatin-1 and Lipid Metabolism**

A recent study has shown that in addition to involvement in insulin and glucose metabolism, nesfatin-1 plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism in mice. In the study, it was observed that chronic infusion of nesfatin-1 decreased plasma triglyceride level in mice fed with normal or high fat diet. Moreover, compared to the control group, the infusion of nesfatin-1 reduced the diameter of lipid droplets, infiltration of inflammatory cells and epididymal fat mass and decreased plasma cholesterol level in mice fed with high-fat diet. The lipogenesis-related enzymes, such as PPARϒ in the epididymal fat mass of mice fed with a high-fat diet, were significantly reduced. As a result of in-vitro experiments in which primary hepatocytes were used, the stimulation with nesfatin-1 reduced the lipogenesis-related and β-oxidation-induced genes. This situation has also been shown to reduce hepatic lipid content and decrease lipid droplet size [50].

**Conclusion and Suggestions**

The data obtained from the studies indicate that nesfatin-1 is associated with metabolic syndrome and its components. The studies examining the relationship between obesity and nesfatin-1 have revealed that plasma nesfatin-1 levels are associated with BMI, body weight and fat mass. The peripheral application of nesfatin-1 has been proven to have an antihyperglycemic effect on glucose metabolism. When the effects of nesfatin-1 on cardiovascular system were examined, it has been proven that nesfatin-1 has effects on blood pressure, and it plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism. When these results were evaluated, nesfatin-1 was seen to have many roles as

regulator in metabolism and to have an effect on metabolic syndrome and its components. Nesfatin-1 is thought to be a pioneer in the diagnosis and treatment of diseases such as metabolic syndrome, obesity, diabetes and cardiovascular diseases.

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Figure List

Figure 1. Structure of NUCB2 Protein and Nesfatin-1 Formation

Figure 2. Nesfatin-1 and its Effects

Description of The Abbreviations in Figure 2: CCK, cholecystokinin; FSH, follicle-stimulating hormone; GLP-1, glucagon-like peptide 1; GLUT4,glucose transporter 4; hCG, human choriogonadotropin; LH, luteinizing hormone; PPARg, peroxisome proliferator-activated receptor gamma; PYY, peptide YY; SREBP1, sterol-regulatory element-binding protein.



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