

# THE RELATIONSHIP BETWEEN NESFATIN-1 LEVELS AND VARIOUS DISEASES

## Abstract

Nesfatin-1(NES-1) is a multifunctional polypeptide made up of 82 amino acids and derived from nucleobindin2 (NUCB2) which is a protein. It has 3 parts and the second part consisting of 23-53 amino acids is the active part, which has an anorexigenic effect on food intake and also affects glucose hemostasis, and has an anti-apoptotic and anti- inflammatory effect. Studies have shown that NES-1 is secreted from hypothalamus which are responsible for controlling appetite and also from the peripheral tissues which induces vasoconstriction and decrease gastric motility. The level of NES-1 is decreased in Type 2 Diabetes Mellitus patients compared to the apparently healthy individuals. It has a role in the glucose metabolism, justified by the presence of NES-1 and insulin together in human pancreas. The suggested mechanism here is it increases insulin sensitivity and decreases its resistance. The level of NES-1 has a negative correlation with the body mass index (BMI), HOMA-IR (homeostatic model assessment of insulin resistance), waist-hip ratio and apnea hypopnea index in Metabolic Syndrome patients.

The value of NES-1 of Polycystic Ovarian Syndrome patients were lower compared to the healthy individuals. In a study of epilepsy patients, serum NES-1 levels before prescribing antiepileptic treatment were 160 times higher in newly diagnosed patients of generalized seizure than the healthy individuals. The value reduced after the treatment but was still higher than the values of the controls. Hence, nesfatin-1 can be a potential biomarker for the diagnosis and monitoring of epilepsy patients in response to anti- epileptic treatment. The level of NES-1 has a negative relationship with the incidence and severity of coronary artery disease.

**Keywords:** Nesfatin-1, nucleobindin2, anorexigenic

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## I. INTRODUCTION

Nesfatin-1 (NES-1) is a multifunctional peptide made up of 82 amino acids with 9.8 kDa as its approximate weight and has 23.5 minutes as its half-life. Oh I and his colleagues in 2006 discovered the peptide for the first time. It consists of 3 parts, the second part consisting of 23-53 amino acids is the active part which has anorexigenic, anti-inflammatory, anti-apoptotic effects and has a role in glucose homeostasis.<sup>1</sup>

It is secreted by the hypothalamus and brainstem which is responsible for the mechanism of appetite and also secreted from the peripheral tissues like gastric mucosa,  $\beta$ -cells of pancreas, adipose tissue, ovaries, uterus, epididymis, cardiomyocytes and testis tissue which induces vasoconstriction and reduces gastric motility with many other effects. It crosses the blood brain barrier in both directions. The central release of NES-1 fluctuates with changes in metabolic activities.

NES-1 is also found to be involved in the leptin pathway which is an appetite suppressant.

After 24 hours fasting, transcription and translation of NES-1 is decreased in the paraventricular hypothalamic nucleus (PVN) & supraoptic nucleus (SON) and then re-feeding afterwards found that production and secretion is activated in SON meaning NES-1 is involved in the satiety signalling by affecting the feeding peptides.

The effects of NES-1 have been studied in various diseases like diabetes, metabolic syndrome, 'obstructive sleep apnoea syndrome', epilepsy, cardiovascular diseases, thyroid disorders, gastrointestinal disorders.

**1. Nesfatin-1 in 'endocrine disorders':** The presence of nesfatin-1 in the pancreas suggests that it may be associated in the metabolism of insulin and glucose. And that it increases the insulin sensitivity and decreases its resistance. Several studies have found that the level of NES-1 decreases in diagnosed type 2 diabetes mellitus patients and in 'gestational diabetes mellitus' but is increased in the newly diagnosed patients.

The levels of NES-1 in patients with metabolic syndrome have found to be lesser than the controls in some studies. Individuals diagnosed with anorexia nervosa and who had chronic nutritional intake restrictions were found of have significantly lesser plasma nesfatin-1 levels compared to healthy controls.<sup>3</sup> Serum nesfatin-1 concentrations in obese individuals decreased significantly compared to non-obese individuals.

A recent study has shown that NES-1 plays a part in the control of peripheral lipid accumulation and liver lipid metabolism in mice. In another study the plasma triglyceride level increased in mice fed with normal or a high-fat diet after the infusion of NES-1 chronically.

**2. Nesfatin-1 in cardiovascular disorders:** It has been studied that NES-1 which is secreted from the brain has a part in the regulation of cardiovascular response under stress conditions. The injection of NES-1 in the intra-cerebro-spinal elevates arterial blood pressure.

NES-1 stimulates the release of oxytocin by depolarization which localizes with oxytocin in the para-ventricular nucleus. Additionally, NES-1 activates the melanocortin pathway through oxytocin. Therefore, the hypertensive effect is associated to either central oxytocin or melanocortin pathways.<sup>4</sup>

In another study of microinjection of NES-1 into the nucleus ambiguus, there was reduction in the heart rate with no change in blood pressure. Another study where intravenous injection of NES-1 in rats induced vasoconstriction via inhibition of NO and eventually raised the blood pressure. The level of serum nesfatin-1 has a negative relationship with both the incidence and the severity of coronary artery disease.

- 3. Nesfatin-1 in the gastrointestinal disorders:** The expression of NES-1 is twenty times more in oxyntic mucosa cells than in the brain. And, also it reduces the antral and duodenal motility which reduces gastric emptying.

In patients of anorexia nervosa and those having weight loss due to cancer, the level of nesfatin-1 is remarkably lesser than the ones without weight loss.

Injection of indomethacin subcutaneously in a rat model induced ulcer in the gastric mucosa, and afterwards injection of NES-1 intraperitoneally or intravenously lead to the reduction of epithelial desquamation of the mucosa of stomach, lesser neutrophil infiltration, reduction of erosion and bleeding, decreased the generation of pro-inflammatory factors and there was an increase in the regeneration of the mucosa.

And it inhibited the pro-inflammatory mediators like myeloperoxidase, malondialdehyde, chemiluminescence, tumor necrosis factor  $\alpha$  and interleukin-1. Similar results were obtained in cases of Acute mesenteric ischaemia and Necrotising enterocolitis of small intestine.<sup>5</sup>

The intraperitoneal administration of nesfatin-1 for 10 days in another model of chronic gastric ulcer induced rats significantly improved the regeneration of mucosa and healing which may be arbitrate by nitric oxide. Taken together, these findings suggest that the ulcer healing NES-1 may also be locally secreted, and perhaps the enteric nervous system controls it which is a widely known as a source of sensory and nitrergic neurons. In a study of gastric cancer patients, concentration of nesfatin-1 markedly increased in patients with gastric cancer as compared to the healthy individuals.

- 4. Nesfatin-1 in Epilepsy:** In a study of temporal lobe epilepsy patients with no drug resistance as one group, a second group of drug resistant patients and a group of controls, the levels of serum nesfatin-1 increased in the group with no drug resistance but was ultimately inconsequential when compared to the controls.

In another study conducted in epilepsy patients, the levels of saliva and serum nesfatin-1 increased by 160 times higher approximately in newly diagnosed primary generalized epilepsy patients than the healthy individuals; although, the level decreased after treatment with antiepileptic drugs but was still higher than the values of the controls. Therefore, it indicates that increased levels of nesfatin-1 might play a part in the

pathophysiology of epilepsy and nesfatin-1 may be a promising biomarker for both the diagnosis of epilepsy and for monitoring the response to the treatment of epilepsy.<sup>7</sup>

- 5. Reproductive system:** NES-1 is found in the testis and is associated next to the interstitium of seminiferous tubules. During the progression from puberty to adulthood, pituitary LH stimulates the increase levels of nesfatin-1. Also, the levels of NES-1 increased in girls with premature thelarche compared to the prepubertal state, leading to the speculation of nesfatin-1 taking part in the gonadal development.

Production of NES-1 in rat's stomach is found to be variable with age to modulate energy homeostasis during the different stages of development, especially it increases during weaning and puberty.

- 6. Malnutrition:** Individuals suffering from anorexia nervosa and those patients with chronic restrictions of consumption of nutrition particularly on anticancer medications had remarkably reduced nesfatin-1 levels compared to healthy individuals. In another study, there were decreased NES-1 levels in obese individuals compared to non-obese individuals.

The serum NES-1 level in underweight children with poor appetite and no systemic disease was found to be significantly higher than the controls. High levels of nesfatin-1 may possibly a reason for poor appetite by reducing the feel of hunger as it is a satiety molecule.

But a controversial study concluded that nesfatin-1 levels were lesser remarkably in the underweight children than in the healthy group and it may be a preventive response to protect against worsening nutritional status.

## II. CONCLUSION

Nesfatin-1 is found to have several effects on various systems of the body as in glucose homeostasis and also plays a role in the pathogenesis of anxiety and depression. It is also associated with the cardiovascular system by increasing in contractility, reduction in heart rate and as well as a cardioprotective biomarker which still stands to be a controversy with other studies. In addition, nesfatin-1 is a risk for patients with cardiovascular diseases as it increases the blood pressure. It is also involved in the reproductive system, mostly during puberty. In the near future, with the understanding of the mechanism and receptor of NES-1, it may become a potential therapeutic agent for various major public health concern diseases like diabetes mellitus, cardiovascular diseases, obesity, epilepsy and gastric ulcers.

## REFERENCES

- [1] Ayada C, Toru U, Korkut Y. Nesfatin-1 and its effects on different systems. *Hippokratia* 2015; 19(1):4–10.
- [2] Yamada M, Horiguchi K, Umezawa R, Hashimoto K, Satoh T, Ozawa A, et al. Troglitazone, a Ligand of Peroxisome Proliferator-Activated Receptor, Stabilizes NUCB2 (Nesfatin) mRNA by Activating the ERK1/2 Pathway: Isolation and Characterization of the Human NUCB2 Gene. *Endocrinology*. 2010; 151: 2494-2503.

- [3] Ogiso K, Asakawa A, Amitani H. Plasma nesfatin-1 concentrations in restricting-type anorexia nervosa. *Peptides* 2011; 32; 150-3.
- [4] Yosten GL, Samson WK. Nesfatin-1 exerts cardiovascular actions in brain: possible interaction with the central melanocortin system. *Am J Physiol Regul Integr Comp Physiol* 2009; 297: 330-6.
- [5] Kolgazi M, Ozturk C, Deniz R, Kumral O, NZ, Yuksel M et al. Nesfatin-1 alleviates gastric damage via direct antioxidant mechanisms. *J. Surg. Res.* 2015, 193, 111–118.
- [6] Erkec OE, Milanlioğlu A, Komuroglu AU, Kara M, Huyut Z, Keskin S. Evaluation of serum ghrelin, nesfatin-1, irisin, and vasoactive intestinal peptide levels in temporal lobe epilepsy patients with and without drug resistance: a cross-sectional study. Original article 2021; <https://doi.org/10.1590/1806-9282.67.02.20200521>
- [7] Aydin S, Dag E, Ozkan Y, Erman F, Dagli AF, Kilic N et al. Nesfatin-1 and ghrelin levels in serum and saliva of epileptic patients: hormonal changes can have a major effect on seizure disorders. *Mol Cell Biochem.* 2009; 328: 49-56.