**Relationship between Nesfatin-1 levels and various diseases**

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ABSTRACT

 Nesfatin-1(NES-1) is a multifunctional 82 amino acid length polypeptide derived from the protein nucleo-bindin 2(NUCB2). 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 anti-apoptotic and anti- inflammatory effect. Studies have shown that NES-1 is secreted by hypothalamic nuclei which are responsible for controlling appetite and from the peripheral tissues which induces vasoconstriction and decrease gastric motility. The level of NES-1 is found to be decreased in Type 2 Diabetes Mellitus than the controls. NES-1 plays a role in the regulation of 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. NES-1 levels has a negative correlation between neck circumference and, also with body mass index (BMI), waist-hip ratio, HOMA-IR & apnea hypopnea index in Metabolic Syndrome patients.

 The value of NES-1 of Polycystic Ovarian Syndrome patients were found to be lower compared to the controls. Before antiepileptic treatment, both saliva and serum NES-1 levels were found to be 160 fold higher in newly diagnosed patients of generalized seizure than the controls. The value decreased with treatment but still remained 10 fold higher than the values of controls. They concluded that nesfatin-1 can be a candidate biomarker for the diagnosis of epilepsy and also to monitor the response to anti- epileptic treatment. Serum nesfatin-1 levels have negative association with the incidence and severity of coronary artery disease.

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

 **I. INTRODUCTION**

Nesfatin-1(NES-1) is a multifunctional peptide made up of 82 amino acids with an approximate weight of 9.8 kilo Dalton and a half-life of 23.5 minutes. It was first discovered by Oh I and his colleagues in 2006. 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.1

NES-1 is secreted by the hypothalamus and brainstem (paraventricular nucleus, arcuate nucleus, and nucleus of the solitary tract) which is responsible for controlling appetite and also secreted from the peripheral tissues like gastric mucosa, pancreatic β-cell, 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 alters depending on the variations of metabolic activities.

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

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

Effect of NES-1 has been studied in various diseases like diabetes, metabolic syndrome, obstructive sleep apnoea syndrome, epilepsy, cardiovascular diseases, thyroid disorders, gastrointestinal disorders.

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1. **Nesfatin-1 in endocrine disorders**

 Its presence in the pancreas indicates that it may be involved in insulin and glucagon-mediated glucose metabolism. And that it increases the insulin sensitivity and decreases its resistance.2 Several studies have found that the level of NES-1 decreases in diagnosed type 2 diabetes mellitus patients and in gestational diabetes mellitus but found to be 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 lower plasma nesfatin-1 levels compared to healthy controls.3 Serum nesfatin-1 concentrations in obese individuals decreased significantly compared to non-obese individuals.

A recent study has shown that NES-1 plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism in mice. There was another study of chronic infusion of nesfatin-1 which reduced the plasma triglyceride level in mice fed with normal or a high-fat diet.

1. **Nesfatin-1 in cardiovascular disorders**

It has been studied that brain NES-1 also plays a role in the regulation of cardiovascular response under stress conditions, like in a study by injection of NES-1 in the intra-cerebro-spinal elevates arterial blood pressure. NES-1, which is localized with oxytocin in the para-ventricular nucleus, stimulates the release of oxytocin by depolarization. It is also known that NES-1 activates the melanocortin pathway through oxytocin. Therefore, the hypertensive effect is thought to be related to either central oxytocin or melanocortin pathways.4

In another study, microinjection of NES-1 into the nucleus ambiguous when being monitored by telemetric and tail-cuff method lead to reduction in heart rate but 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. Serum nesfatin-1 levels have found to have a negative association with both the incidence and the severity of coronary artery disease.

1. **Nesfatin-1 in the gastrointestinal disorders**

It has been found that the expression of NES-1 is 20 times higher in the gastric oxyntic mucosa cells than that of the brain. And, also it reduces the antral and duodenal motility which reduces gastric emptying.

In patients with anorexia nervosa and those having cancer-related weight loss, NES-1 level is significantly lesser than those without weight loss.

In a rat model of ulceritis (induced by administration of indomethacin subcutaneously or a low level of acetic acid by gavage), after injection of NES-1 intraperitoneally or intravenously, there was

1. Reduction of epithelial desquamation of the gastric mucosa
2. Decreased neutrophil infiltration
3. Reduced erosion
4. Reduced bleeding
5. Decreased generation of pro-inflammatory factors
6. Mucosa regeneration was found to be increased

And also it inhibited the pro-inflammatory mediators like myeloperoxidase, malondialdehyde, chemiluminescence, tumor necrosis factor α, and interleukin-1. Similar findings were noted in cases of Acute mesenteric ischaemia and Necrotising enterocolitis of small intestine.5

In another model of chronic gastric ulcer induced rats (by serosal application of concentrated acetic acid), intraperitoneal administration of nesfatin-1 for 10 days substantially improved mucosa regeneration and healing, this protective effect was mediated by nitric oxide or by sensory neuropeptides. Taken together, these findings suggest that ulcer-healing NES-1 may also be locally secreted, and the process may be is controlled by the enteric nervous system, which is well known as a source of sensory and nitrergic neurons.

In a study, concentration of nesfatin‑1 were found to be significantly increased in patients with gastric cancer as compared to the controls.

1. **Nesfatin-1 in Epilepsy**

In a study with temporal lobe epilepsy patients without drug resistance as one group, a second group with drug resistant patients and a group of controls, serum nesfatin-1 levels were found to be increased in the group without drug resistance but was ultimately non-significant when compared to the controls.

In another study conducted in epilepsy patients, the saliva and serum nesfatin-1 levels were reported to have increased by 160 fold higher approximately in newly diagnosed primary generalized epilepsy patients than the controls; however, the level was decreased after treatment with antiepileptic drugs but remained approximately 10-fold higher than that of the control. Therefore, it was suggested that elevated nesfatin-1 levels might contribute to the pathophysiology of epilepsy and remarkably increased nesfatin1 may be a candidate biomarker both for the diagnosis of epilepsy and for monitoring the response to anti-epileptic treatment.7

1. **Reproductive system**

Expression of NES-1 has been detected in the testes and has been identified next to the interstitium of seminiferous tubules,8 and increased levels of nesfatin-1 were seen during the transition from puberty to adulthood stimulated by pituitary LH. Also, circulating nesfatin-1 levels were increased in girls with premature thelarche compared to the prepubertal state, leading to the hypothesis of a role for nesfatin-1 in gonadal development

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

1. **Malnutrition**

Individuals with anorexia nervosa and those with chronic nutritional intake restrictions like patients on anticancer medications were found to have significantly reduced nesfatin-1 levels compared to healthy controls. In another study, serum NES-1 in obese individuals were found to be significantly reduced 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. The high nesfatin-1 levels might have caused poor appetite by blocking the feel of hunger as it is a satiety molecule.

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

**Conclusion**

Nesfatin-1 is found to have various effects on different systems of the body as in glucose homeostasis and also in the development of anxiety and depression. It is also found to be related to the cardiovascular system by increasing in contractility, reduction in heart rate and being cardioprotective which still stands to be a controversy with other studies, nesfatin-1 being a risk for patients with cardiovascular diseases as it is found to increase the blood pressure. It is also found to be 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.

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