

Assessment of Serum Apelin Level in Patients with Erectile Dysfunction

Areeg.M.Elnoby¹, Osama.H.Alkady¹, Ghada.M.Abdel Khalik¹, Amira.O.Abd El ghafar²

¹Dermatology, Venereology and Andrology Dept., Faculty of Medicine, Benha University

²clinical and chemical Pathology Dept., Faculty of Medicine, Benha University

E-mail: areegmoawad@gmail.com

ABSTRACT

Objectives: Analyzing the relationship between serum Apelin-13 levels and erectile dysfunction severity **Background:** Both hypercholesterolemic and hyperglycemic mice, two well-known vasculogenic ED models, have recently been revealed to have an elevated Apelin system, and intracavernosal acute injection of Apelin has been proven to restore erectile functioning in both animals (19). **Data Sources:** We did this by searching and examining the Medline databases (Pub Med and Medscape) and looking for studies that looked at the probable link between serum Apelin-13 and erectile function and its connection to severity of erectile dysfunction up to 2020. **Study Selection:** The quality of each study was evaluated separately before being accepted. If they met any of the following criteria, we considered them for inclusion: 1. It's written in English and published. 2. Appearing in publications with a strict peer-review process. Third, explain how the level of serum Apelin-13 may be linked to erectile function and how this may affect the severity of erectile dysfunction. **Data Extraction:** Studies were not included if they did not meet the inclusion criteria. Ethical permission, eligibility criteria, controls, information, and well-defined evaluation measures were all factors in determining the study's quality. Our concerned research results were captured by independently abstracting data utilising a data collecting form from each qualifying study. **Conclusions:** Serum Apelin -13 levels are lower in individuals with erectile dysfunction, and this drop is associated with elevated triglyceride and body-mass index levels.

Key words: Erectile Dysfunction, Serum Apelin-13.

1. Introduction

When a man has erectile dysfunction (ED), he struggles to get or keep an erection long enough for sexual satisfaction. Organic, psychological, and a combined cause of ED are all recognised. Vasculogenic, Hormonal, and Neurogenic Etiologies (20).

Many factors contribute to ED's development. Major causes of ED include metabolic disorders that promote endothelial dysfunction, such as diabetes mellitus (DM), hypertension, and coronary artery disease (CAD) (24).

An endogenous ligand for the G-protein-coupled receptor is apelin (APJ). Both apelin and its receptor are widely distributed, however they are most prominent in heart and blood vessel endothelial and smooth muscle cells (25).

It has been hypothesised that the apelin-APJ pathway has a dual purpose in endothelial cells. Initially, apelin triggers a nitric oxide (NO)-dependent vasodilation in the endothelium. Also, apelin stimulates the proliferation of endothelial cells. Given the association between ED and vascular risk factors, our data points to apelin signalling as a possible treatment target for ED. (14)

Since erectile function (EF) is a neurovascular phenomena dependent on an unimpaired vascular endothelium, any condition that compromises the health of the arterial vasculature has the potential to

adversely influence a man's ability to have an erection (13).

One of the most important factors in initiating and keeping an erection going is nitric oxide (NO), a relaxing substance produced by the endothelium. Endothelial NO synthase (NOS) uncoupling might lead to lower NO levels (2).

The incidence of ED varies widely, but it affects more than 100 million men globally. The prevalence of erectile dysfunction rises with age, from 20-40% in males aged 60-69 to 50-100% in those aged 70 and beyond (14).

Vascular abnormalities are responsible for approximately 80% of ED cases, which suggests that the existence of vascular risk factors (hypertension, hyperlipidemia, atherosclerosis, and diabetes) strongly correlates with the severity of ED (15).

2. Materials and methods

The literature on the putative link between serum Apelin-13 and erectile function and its connection to severity of erectile dysfunction up till 2020 was sourced via a search of the Medline databases (Pub Med and Medscape).

Studies were chosen after being subjected to a rigorous, objective, and transparent selection process. If they met any of the following criteria, we considered them for inclusion: 1. It's written in English and published. 2. Appearing in publications with a

strict peer-review process. Third, explain how the level of serum Apelin-13 may be linked to erectile function and how this may affect the severity of erectile dysfunction.

Extraction of Data: Research Studies were not included if they did not meet the inclusion criteria. Ethical permission, eligibility criteria, controls, information, and well-defined evaluation measures were all factors in determining the study's quality. Information on our relevant research results was retrieved from each qualifying study by hand utilising a data collecting form.

3. Review of literature

The inability to get or keep an erection that's good enough to have sexual satisfaction is what we mean when we talk about erectile dysfunction. Quality of life may be negatively impacted by such dysfunction, which may have an effect on both the individual's physical and social environments (Hatzimouratidis et al, 2019).

Fifty percent of men in their forties and fifties will have erectile dysfunction, and ten percent will have a severe case. In males between the ages of 40 and 49, the prevalence of ED is 2–9%; in men between the ages of 20 and 69, it rises to 20–40%; and the frequency of ED increases further in men in their 70s and 80s (16).

Since it is not a life-threatening disorder and because men with ED seldom seek care, ED is often under-reported in many underdeveloped nations. The issue of diagnosing and treating the causes of ED at an early stage also arises (18).

Erectile dysfunction: the underlying pathology

Whether or not the penis is flaccid or erect depends on a delicate balancing act between the central and peripheral neural systems, as well as the health of the penile vasculature. As a result of dopamine stimulation, the hypothalamus is responsible for triggering an erection in response to sexual stimulation in the central nervous system. The paraventricular nucleus is where dopaminergic neurons collide with oxytocinergic cell bodies and send their projections out to the hippocampus, ventral medulla, and spinal cord (7).

Touching the penis transmits an erection-inducing signal to the sacral spinal cord, where it excites sensory neurons in the S2-S4 area. From the sacral neural foramina, efferent neurons go to the hypogastric plexus, where they make synapses with postganglionic nonadrenergic, noncholinergic (NANC) fibres (6).

It is at the level of the crura that NANC fibres reach the cavernous bodies through the cavernous nerves. Cavernous nerves in the corpus cavernosum emit nitrous oxide (NO) in response to a central or reflexogenic impulse (5).

The vascular endothelium also produces nitric oxide (NO) in response to parasympathetic stimulation, which causes the release of acetylcholine, and to shear stress caused by an increase in blood flow to the cavernosal sinusoids.

In response, NO increases the conversion of guanosine triphosphate into cyclic guanosine monophosphate in cavernosal smooth muscle cells (cGMP). Arteriolar vasodilation and relaxation of the cavernosal smooth muscle are mediated by a protein kinase cascade, hyperpolarization, and intracellular calcium sequestration (5).

Concurrently, venous outflow blockage and completion of the erectile cascade occur due to the compression of the subtunical venular plexuses caused by sinusoidal engorgement. Hydroxylation of cyclic GMP by phosphodiesterase type 5 (PDE-5) causes resumption of laxity. Parasympathetic adrenergic nerve fibres also run in the cavernous nerves, providing a counterweight to the parasympathetic pro-erectogenic process described. By stimulating 1-G protein linked receptors on the cavernosal smooth muscle, tonic release of norepinephrine from sympathetic neurons causes detumescence and keeps flaccidity at bay. This causes phospholipase C to launch a cascade that culminates in elevated calcium in the cytoplasm and smooth muscle contraction (5).

Impairment of erection function due to vasculature

The vascular endothelium is a highly dynamic and active tissue that controls several processes, including proliferation, local homeostasis, vascular tone modulation, perfusion maintenance, coagulation, and inflammatory reactions. Endothelial dysfunction has been linked to age-related and other risk factors, suggesting that the ageing process itself might harm blood vessels (14).

Vascular abnormalities are responsible for approximately 80% of ED cases, which suggests that the existence of vascular risk factors (hypertension, hyperlipidemia, atherosclerosis, and diabetes) strongly correlates with the severity of ED (11).

Less prevalent causes of vasculogenic ED, such as veno-occlusive illness, severe trauma, and cavernosal fibrosis, are notoriously difficult to cure with standard medical care. It is possible for radiation

treatment, priapism, trauma, or surgery to enhance extracellular matrix and fibrosis of the cavernosal smooth muscle and endothelial cells (22).

Excessive outflow of lacunar blood via the subtunical venules may lead to veno-occlusive failure owing to structural abnormalities in the corporal smooth muscle, trabecular framework, or tunica albuginea. Poor penile stiffness and short erection length may come from age, high cholesterol, and atherosclerosis (21).

Persistent hypoxemia, which is often the outcome of obstructive sleep apnea and chronic lung illness, seems to be an independent risk related with ED. Vasoconstriction occurs as a result of hypoxia because vascular growth factors are produced in response to low oxygen levels. These growth factors prevent endothelial-mediated relaxation. The corpus cavernosum's NO production may also be regulated by oxygen (22).

Apelin

The apelin receptor was first characterised as an orphan G-protein-coupled receptor; apelin is an endogenous peptide that binds to this receptor (1).

Pre-pro-apelin undergoes proteolysis to generate distinct fragments varying in size from 36 to 13 amino acids; the 12 C-terminal amino acids are conserved throughout all apelin isoforms, albeit the precise mechanism of this conservation is not yet known (1).

While all of these isoforms have the potential to activate APJ, the physiologic response induced by apelin-13 is more robust (25)

Apelin's Impact on the Blood Vessels

The existence of an unbroken endothelium is necessary for apelin to exert both of its actions in animal and human tissues (15)

Depending on the vascular bed and the underlying circumstances, apelin may have either vasodilatory or vasoconstrictive vasomotor effects. Since APJ receptors are found on endothelium and smooth muscle cells, apelin may operate on both the inner and outer layers of blood vessels. Directly on vascular smooth muscle cells, inducing contraction or relaxation; on endothelial cells, which can secrete substances that mediate vasodilation (e.g., NO, prostacyclin) and vasoconstriction (e.g., endothelin); and on vascular smooth muscle cells, which can contract or relax in response to vasoactive agents (19).

Many vascular and metabolic illnesses have responded well to apelin treatment.

Treatment with apelin decreased mean arterial pressure and levels of vasoconstrictor mediators such as angiotensin-II and endothelin-1 in animal models of pulmonary hypertension and diabetes (4).

Moreover, apelin signalling through APJ - KOR heterodimers induced a depressor response in renovascular hypertension, and intravenous bolus injection of apelin significantly decreased mean pulmonary arterial pressure in patients with acute pulmonary embolism (Feng, et al., 2010). (23).

In addition, apelin restored normal acetylcholine relaxation response and abolished aberrant Ang II-induced contractile tone in the intrarenal arteries of diabetic rats through boosting eNOS phosphorylation (27).

Apelin's possible role in erectile dysfunction

Most occurrences of erectile dysfunction (ED) may be traced back to an underlying condition characterised by an increase in fibrosis of the corpora cavernosa and the media of penile arteries (20)

Increased vasoconstrictor tonus and decreased nitric oxide (NO) bioavailability have been linked to oxidative stress in the corpus cavernosum, which has been proposed as a significant cause (8)

Long-term exposure to oxidative stress in the corpus cavernosum causes hypoxia and an inflammatory response, which in turn leads to the production of mitogenic and pro-fibrotic cytokines and, eventually, fibrosis. When there is an imbalance between the amount of collagen that is deposited as stiff fibres and the amount that is deposited as elastic fibres, erections in the penile region suffer (9)

One example is how Apelin reduces ventricular dysfunction in an aortic banding model by blocking TGF β -stimulated activation of cardiac fibroblasts and halting structural remodelling and fibrosis of the myocardium (17)

Moreover, Apelin has been demonstrated to decrease fibrosis in various clinical circumstances, including renal damage and pulmonary hypertension (10)

Both hypercholesterolemic and hyperglycemic mice, two well-known vasculogenic ED models, have recently been revealed to have an elevated Apelin system, and intracavernosal acute injection of Apelin has been proven to restore erectile functioning in both animals (19)

One of the most common causes of vasculogenic ED is hypercholesterolemia, which may lead to atherosclerosis of the penile vasculature (20)

Atherosclerosis is a vascular disease caused by the buildup of lipids in the artery wall, which leads to the development of foam cells and eventually atherosclerosis (26)

Collateralization of the coronary arteries in individuals with stable angina is correlated with increased plasma apelin levels (3)

By activating the PI3K/Beclin-1 pathway, Apelin 13 reduces foam cell lipid buildup and triggers autophagy (5)

4. Conclusion

In conclusion, the present investigation showed that the blood apelin-13 level is lower in patients with ED, and that this drop is connected to serum lipids and BMI, which may represent a novel step in understanding the pathophysiology of ED and aiding in its treatment.

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