



ROLE OF SERUM APLEIN AND NITRIC OXIDE IN PRIMARY HYPERTENSION PATIENTS

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ABSTRACT:

A frequent health problem that aggravates renal problems and other cardiovascular illnesses is hypertension. The significance of serum apelin and nitric oxide in controlling blood pressure and endothelial function has been identified by recent research. An endogenous peptide called apelin has been linked to cardiovascular homeostasis and has been demonstrated in hypertensive individuals to positively correlate with blood pressure levels. Increased apelin levels in the serum are frequently linked to hypertension and related side effects, including microalbuminuria.

Key Words: Serum apelin, Nitric oxide, Primary Hypertension.

INTRODUCTION

Hypertension is characterized by an increase in either the systolic or diastolic blood pressure (BP). Most major guidelines provide specific criteria for diagnosing hypertension. When SBP of a patient in the clinic or office is ≥ 140 mmHg and/or DBP is ≥ 90 mmHg after repeated evaluations, hypertension should generally be diagnosed ¹. A major contributor to cardiovascular and cerebrovascular diseases (CVDs), hypertension is the primary cause of premature death globally. The estimated prevalence of hypertension in the adult population worldwide was 1.39 billion in 2010 and is still rising². In order to lower cardiovascular disease-related premature mortality risk, treating and preventing hypertension is an essential global public health strategy ³.

DEFINITION AND PREVALENCE OF PRIMARY HYPERTENSION: Blood pressure that is consistently elevated without a clear cause is referred to as primary hypertension, also called essential hypertension. This syndrome accounts for 90-95% of all hypertension cases and usually develops gradually over several years. It is diagnosed when blood pressure readings exceed 130/80 mmHg; persistent readings of 140/90 mmHg or above frequently necessitate therapy ⁴. The prevalence of primary hypertension, also known as essential hypertension, varies greatly between populations and geographies. Here are a few key statistics:

Global Prevalence: In people 30-79 years of age, the global age-standardized prevalence of hypertension was approximately 32% for women and 34% for men in 2019. Since 1990, the prevalence has been generally steady, with variances seen between countries with higher and lower incomes ⁵.

In the United States: From 2013 and 2016, the age-standardized prevalence for BP readings of 140/90 mmHg or higher was approximately 32% for men and 31% for women ².

Regional variations: Hypertension is more prevalent in some locations than others. For example, Eastern Europe and Central Asia have recorded prevalence rates as high as 39%, while Sub-Saharan Africa has considerable rates as well ².

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Demographic Factors: As people get older, their risk of developing hypertension increases. For example, in a study conducted in Germany, the age-standardized prevalence was determined as 74.3% for males and 70.2% for women among older persons⁶.

OVERVIEW OF SERUM APELIN AND NITRIC OXIDE:

An endogenous peptide hormone called apelin was recently identified. Tatemoto discovered it in 1998 while examining an extract from the bovine stomach. The apelin gene in humans produces a prepropeptide with 77 amino acids that can be cleaved into multiple active forms with lengths of 36, 17, 13, and 12 amino acids. The most frequently expressed isoform in a number of organs, such as adipocytes and small artery endothelial cells, is 36 amino acids⁷. An in-vitro investigation suggested that Apelina might modify the angiotensin II type 1 receptor, hence suppressing the angiotensin II signaling cascade⁸. Angiotensin-converting enzyme 2, a negative regulator of the Renin-Angiotensin-Aldosterone System (RAAS), uses apelin as a catalytic substrate⁹. Renin-angiotensin-aldosterone cascade activation is a known primary cause of hypertension (HTN)¹⁰.

It has been demonstrated that nitric oxide suppresses RAAS activation as well as can counteract angiotensin II-induced peripheral vasoconstriction because of its vasodilatory properties. More sympathetic output and oxidative stress can result from the prohypertensive impacts of the SNS (Sympathetic Nervous System) being heightened by reduced NO bioavailability¹¹. Apelina and nitric acid are thought to be involved in endothelial dysfunction as well as the intensity of HTN¹². According to a 2002 WHO research, among individuals with essential HTN, microalbuminuria is a reliable indicator of cardiovascular morbidity and mortality¹³. Five to fifteen percent of patients may get microalbuminuria or proteinuria as a result of essential HTN. Albumin excretion in urine of 30-300mg/24 hours is known as microalbuminuria. Microalbuminuria may be a reliable indicator of cardiovascular morbidity as well as death in individuals with essential HTN¹⁴.

IMPORTANCE OF STUDYING SERUM APELIN AND NITRIC OXIDE IN PRIMARY HYPERTENSION:

SERUM APELIN:

Apelin is a peptide that controls blood pressure and other aspects of the cardiovascular system. Apelin undoubtedly has a role in the pathophysiology of HTN and heart conditions associated with elevated BP¹⁵. Additionally, it supports smooth muscle and endothelial cell death and angiogenesis. There is also an antivasular endothelial growth factor present. Apelin inhibits the vasoconstriction brought on by angiotensin II and causes vasodilation by changing the expression of endothelial nitric oxide synthase (eNOS). It has advantageous inotropic and heart-protective benefits as a result. Positive inotropes and vascular endothelial-dependent vasodilation are influenced by the protein apelin. Apelin has been shown to reduce ventricular afterload as well as preload while also increasing cardiac contraction strength. Apelin plasma levels are a useful indicator for assessing heart failure severity¹⁶.

This peptide is remarkably similar to angiotensin II and acts on the Apelin receptor (APJ receptor). Apelin is mostly found in vascular endothelium¹⁷. The Apelin/APJ System affects water and electrolyte balance, bodily safety, blood sugar control, as well as nutrition, but its primary function is to regulate the cardiovascular system¹⁸.

Apelin exerts physiological effects at the plasma level in addition to producing autocrine and paracrine actions. The plasma concentration of apelin is approximately 10 g/mL, and its half-life is shorter than five minutes. Apelin has been shown to exhibit gradual, steady, and inotropic effects even at low concentrations, making it the strongest endogenous inotrope molecule, exceeding adrenomedullin and endothelin^{19,20}.

NITRIC OXIDE:

It has been determined that nitric oxide is an endogenous signaling molecule with strong vasodilatory effects that affect organ perfusion and vascular compliance. Nitric oxide synthase (NOS) is an enzyme that produces NO which is essential for many biological functions, including the regulation of sympathetic activity, smooth muscle contraction, kidney sodium excretion, renin secretion, and extracellular volume preservation ²¹.

Reduced NO bioavailability, a sign of endothelial dysfunction, is a robust predictor of both hypertension and cardiovascular disease, possibly establishing a connection between the two diseases. BP regulation is largely dependent on NO, and HTN is associated with reduced NO bioactivity. Clinical research has shown that NOS inhibition increases BP and that people with HTN respond less well to endothelium-dependent vasodilators in their arteries ²¹.

PATHOPHYSIOLOGY OF PRIMARY HYPERTENSION:

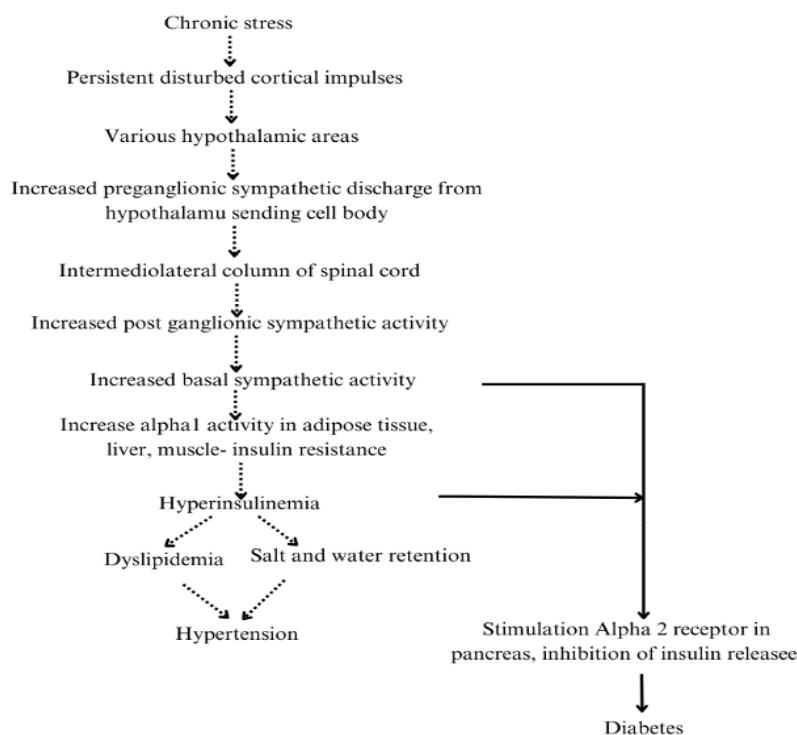


Figure 1. Pathophysiology of Primary Hypertension

INTERPLAY BETWEEN APELIN AND NITRIC OXIDE IN PRIMARY HYPERTENSION:

Vascular tone is regulated by the apelin system both in vivo and in vitro. Apelin peptides activate the apelin receptor on vascular endothelial cells, which increases nitric oxide generation and causes vasodilation. β-arrestin recruitment is also involved in this process ²². This occurs in both healthy and sick arteries, although in sick conditions prostanoids rather than nitric oxide may cause vasodilation ^{23,24}. In hypertensive rats, apella mRNA is decreased in the renal medulla, whereas apelin receptor message and protein are decreased in the heart, aorta, and kidney ²⁵. Elabela deficiency accelerates the development of hypertension, while apelin and elabela provide protection against it ²⁶. In the hypertensive DOCA-salt rat, once-daily treatment of the long-acting apelin analogue LIT01-196 successfully lowered BP without adversely altering sodium concentration or renal function ²⁷. Nitric oxide is required for apelin-induced vasodilation, according to clinical investigations in healthy volunteers ²⁸. When [Pyr1] apelin-13 is infused systemically, peripheral vascular resistance and BP in

both healthy and heart failure patients decrease by about 5%²⁹. In particular, apelin promotes vasodilatation regardless of activation of the renin-angiotensin system and patients with hypertension have lower apelin circulating concentrations³⁰. It has been established that nitric oxide is an endogenous signaling molecule whose potent vasodilatory effects regulate organ perfusion and vascular compliance. Many biological processes, including the sympathetic activity's regulation in vasomotor centers, renin secretion, vascular smooth muscle contraction, kidney sodium excretion, and preservation of extracellular volume, are now known to be dependent on NO, which is produced by the nitric oxide synthase (NOS) enzyme³¹.

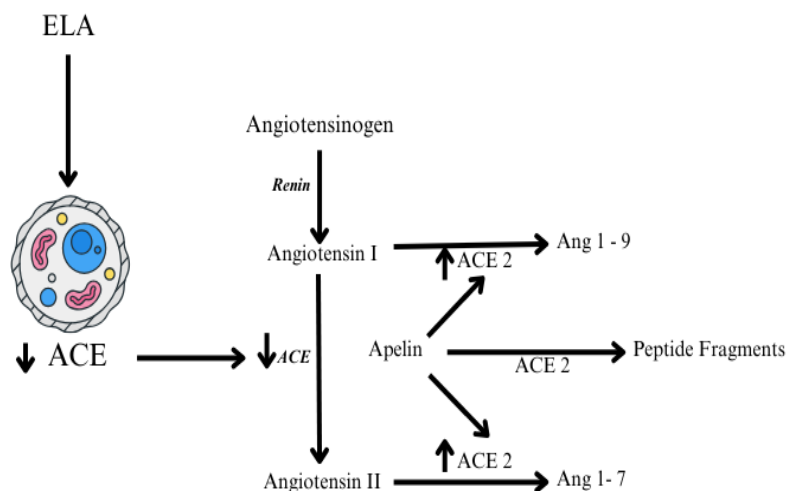


Figure 2

DIAGNOSTIC ASSESSMENT OF SERUM APELIN AND NITRIC OXIDE:

SERUM APELIN: Serum apelin is determined using an enzyme immunoassay method, that combines two extremely specific monoclonal antibodies in a "sandwich ELISA" format: one antibody that is conjugated with human apelin - HPP, and the other that is biotinylated human Apelin (APLN)/AP³².

NORMAL RANGE: 37 – 121 ng/L

SERUM NITRIC OXIDE: Serum nitric oxide (NO) is determined by sandwiching a human NO antibody as well as a NO-HRP conjugated antibody together, a technique known as "sandwich ELISA." The absorbance was plotted against the corresponding human apelin and NO concentrations of each standard on a point-to-point curve during the ELISA estimate of serum apelin and serum NO to generate a standard curve. The quantities of human apelin and NO in the patient samples and controls had been computed using the standard curve that was produced³³.

NORMAL RANGE: 10.3 – 66.8 μmol/L

THERAPEUTIC IMPLICATIONS TARGETING APELIN AND NITRIC OXIDE PATHWAYS:

Drugs that target the apelin/APJ system have emerged as potential therapeutic targets (94), and they may be used to treat a variety of illnesses³⁴. The first identified non-peptide agonist of the APJ receptor, E339-3D6, has the ability to lower arterial blood pressure and prevent from release of antidiuretic hormone upon water-dependent induction³⁵. Another APJ small molecule chemical ligand, ML233, has the ability to specifically block AT1 receptors, which in turn can stimulate vasoconstriction by activating phospholipase C³⁶. E339-3D6 and ML233 have the ability to block the cAMP pathway's release of forskolin-activated rennin, which can be a significant factor in the onset of hypertension³⁷. The medication ALX40-4C, an antagonist of the APJ and

CXCR4 receptors with nine arginine residues, works by blocking the APJ receptor to prevent ligand-induced intracellular calcium mobilization and receptor internalization, which lowers blood pressure³⁸. Apelin analogues have the potential to lower blood pressure either directly or by stimulating the Akt-eNOS/NO pathway³⁹.

CONCLUSION:

This study found that patients with essential hypertension had lower serum apelin levels. The specific mechanisms of apelin and NO in hypertension, including their roles in endothelial function and vascular remodeling, require further investigation. It will be essential to conduct long-term studies evaluating their levels in connection to the development of hypertension as well as the outcomes of treatment. Clinical trials assessing the effectiveness of NO modulators and apelin-based treatments may also open the way to novel approaches to the treatment of hypertension.

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