Erciyes Med J 2022; 44(1): 8–11 • DOI: 10.14744/etd.2021.23571
REVIEW – OPEN ACCESS



# Serum Adropin: Pathogenesis and Clinical Research in Cardiovascular Disease

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ABSTRACT

Adropin is a peptide hormone that acts as a stabilizing factor in body energy metabolism and may be a marker for cardiovascular disease (CVD). The serum adropin level has been shown to be positively correlated with the nitrite/nitrate level and adropin appears to provide a protective endothelial function. Adropin has been reported to play a protective role in heart failure and hypertension. The underlying mechanism may help to reduce obesity and insulin resistance, improve endothelial dysfunction, and modulate the activity of the nervous system. Adropin regulates the cardiac energy cycle through a series of reactions, such as insulin signaling, glucose, and fat oxidation. This regulation of the energy circuit may represent a source of an alternative therapy for obese diabetes. The objective of this review was to contribute to the literature by examining research of the expression, processing, biological function, and role of adropin in the prevention of CVD.

**Keywords:** Adropin, cardiovascular disease, endothelial dysfunction, metabolic syndrome, obesity

**Cite this article as:**
Aşkın L, Aşkın HŞ, Tanrıverdi O, Hoşoğlu Y. Serum Adropin: Pathogenesis and Clinical Research in Cardiovascular Disease. Erciyes Med J 2022; 44(1): 8-11.

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**Submitted**
24.12.2020

**Accepted**
12.03.2021

**Available Online**
11.11.2021

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## INTRODUCTION

Adropin has a role in regulation of energy balance and insulin secretion. Adropin is encoded by the energy homeostasis-related gene (Enho) and expressed by liver, brain, and endothelial cells (1, 2). A relationship between adropin, dyslipidemia, and insulin resistance has been demonstrated in experimental studies. Adropin reduced insulin resistance in obese mice (3).

In addition to having a regulatory effect on body energy metabolism, adropin may be an adjunct marker in the diagnosis of CVD. Adropin enhances endothelial cell abilities, such as proliferation, migration, and endothelial nitric oxide synthase expression (2). Celik et al. (4) reported that the mean adropin level was lower in cardiac syndrome X (CSX) patients than in a control group. Coronary microvascular dysfunction is a possible mechanism for CSX (5).

Adropin also affects the progression of vascular atherosclerosis (6). A decreased serum adropin level may be a precursor of coronary atherosclerosis and a reason for acute myocardial infarction (AMI) (7).

The aim of this review was to summarize the relationship between serum adropin and CVD. A search of the PubMed, Web of Science, and Google scholar databases was conducted using the keywords "adropin," "cardiovascular diseases," "endothelial dysfunction," "metabolic syndrome," and "obesity." Reviews, original articles, and case reports or case series published in English within the last 10 years were selected and evaluated.

### Serum Adropin Levels in Patients with Stable Coronary Artery Disease

Adropin has a positive effect on endothelial function by increasing endothelial nitric oxide synthase (eNOS) release. Adropin can upregulate the eNOS level via adropin phosphoinositide 3-kinase (PI3K/Akt), extracellular signaling-regulated kinases 1 and 2 (ERK1/2), and vascular endothelial growth factor receptor 2 (VEGFR2) (2, 8) (Fig. 1). Nitric oxide formation and bioavailability may be regulated by interactions with adropin, Akt Ser473, and endothelial nitric oxide synthase Ser1177. A low adropin level was found to be related to endothelial dysfunction in type 2 diabetes (9).

The positive correlation between serum adropin level and nitrite/nitrate level may reveal a mechanism of endothelial protection in patients with CSX (4). Adropin may be a new agent to prevent atherosclerotic vascular diseases through metabolic modulation.

Patients with stable angina have been shown to have a lower serum adropin level (10). The pathogenesis of myocardial infarction (MI) is usually platelet aggregation, thrombus formation, and artery occlusion occurring following the rupture of sensitive coronary plaques. Inflammatory reactions in the endothelium increase oxidative stress

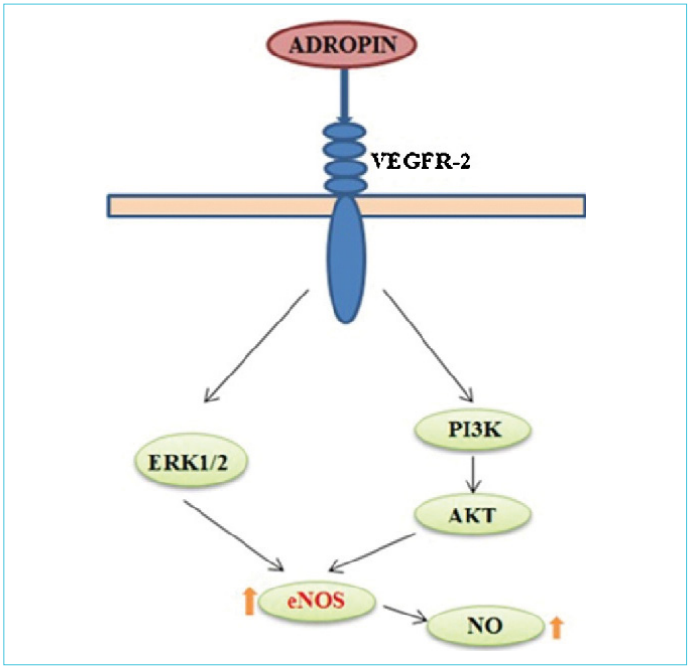


**Figure 1. A flowchart of the effect of adropin on the signaling pathway in the endothelium. Up-regulation of endothelial nitric oxide synthase (eNOS) via adropin phosphoinositide 3-kinase (PI3K/Akt), extracellular signal-regulated kinases 1 and 2 (ERK1/2), and vascular endothelial growth factor receptor 2 (VEGFR2)**

and coronary plaque instability, prompting endothelial dysfunction (11). A high serum adropin level may play a critical role in reducing atherosclerotic plaque (12).

Stress factors can trigger stable angina pectoris due to a mismatch in the supply and demand of reversible myocardial oxygen. Zhao et al. (12) showed that a low adropin level was significantly associated with a high SYNTAX score. A diffuse coronary spasm is a possible reason for CSX.

A low level of adropin has been observed to be a risk factor for HT; the regulatory role of adropin on endothelial function affects blood pressure (13). Atherosclerosis is a common cause cardiac events in diabetes (14). The mechanisms of atherosclerosis include vascular inflammation and smooth muscle cell (VSMC) proliferation, monocyte infiltration, differentiation into macrophages, and transformation to foam cells (15).

A low level of adropin is thought to be a cause of endothelial dysfunction in obstructive sleep apnea syndrome (16). Topuz et al. (9) found that a low adropin level was associated with endothelial dysfunction.

Butler et al. (17) demonstrated that the consumption of fructose increased the level of plasma adropin concentration in comparison to glucose. Furthermore, they noted that dietary fat intake may also increase the adropin level. Lian et al. (18) observed that adropin may directly affect gene expression at the cellular level. Adropin was found to stimulate lipoprotein lipase (LPL) expression in cultured tilapia hepatocytes via multiple signaling mechanisms.

## Adropin Level in Heart Failure

Heart failure (HF) is recognized worldwide as a critical public health problem (19, 20). Adropin may increase simultaneously with natriuretic peptide (BNP) in patients with HF (21). Lian et al. (22) found that the plasma adropin level was elevated in HF patients and that BNP had an independent impact on the adropin level, suggesting that the release of adropin may be a marker in the HF process (22).

## Adropin Level in Hypertension

The endogenous vasodilator property of nitric oxide is well known. Paracrine and neuroendocrine factors regulate blood pressure by affecting metabolic hemostasis, energy consumption, and endothelial function (23). Adropin seems to play a multifactorial role, contributing to the reduction of insulin resistance as well as having an effect on endothelial function and the nervous system in hypertension (HT) (24). Gu et al. (13) reported that the plasma level of adropin had an inverse correlation to that of endothelin-1 (ET-1) in patients with HT. Increased ET-1 contributes to endothelial dysfunction, which may contribute to an elevated systolic blood pressure (25). Adropin may regulate blood pressure by improving endothelial function (26).

## Other Systemic Studies

Zhao et al. (27) observed an inverse relationship between homocysteine and adropin in coronary artery disease. A high homocysteine level has been associated with a higher SYNTAX score. Altintas et al. (28) demonstrated that ischemic preconditioning modulating the expression of adropin and oxidative damage markers yielded neuroprotective effects in rats with induced focal ischemia. This may provide useful information for the evaluation of therapeutic options to prevent stroke.

Gulen et al. (29) suggested that an increased adropin level in patients with HT may not be a predictive marker for the detection of end-organ damage in the emergency department. Ertem et al. (30) found that the adropin level was inversely related to the SYNTAX score in MI. Adropin may contribute to the formation of the atherosclerotic process.

Bolayir et al. (31) reported that the adropin level negatively affected the absolute blood pressure level. Adropin was found to be independently associated with a non-dipper pattern in HT patients. The authors suggested that there may be a correlation between a longer duration of day-night high blood pressure and low adropin level in non-dipper HT patients. Therefore, adropin may be a potential marker to measure endothelial dysfunction in HT patients with a high risk of target organ damage.

Peak adropin synthesis and activity in the liver may be associated with periods of maximum nutrient cycle and lipid production. Further research is needed to ascertain the effect of hepatic carbohydrate lipid metabolism on adropin and to investigate the rhythmicity of adropin expression in rheumatic tissue. Nonetheless, research has indicated that the adropin level may be useful for risk stratification in obese individuals with a low level of low-density lipoprotein (32).

Sato et al. (33) demonstrated that adropin has anti-atherosclerotic qualities, such as the ability to suppress inflammatory responses in endothelial cells and monocyte/macrophages, inhibit monocyte-

endothelial adhesion, and suppress the migration and proliferation of VSMCs. Thus, the authors posited that adropin analogs and receptor agonists may prove a useful contribution to the prevention of atherosclerosis.

Zhao et al. (34) found low serum adropin levels in patients with coronary slow flow phenomenon (CSFP). Adropin appears to be a biomarker that could provide a useful and different perspective in CSF prediction.

Wang et al. (35) demonstrated a decrease in serum adropin concentration in patients with atrial fibrillation (AF). Adropin was inversely related to the AF subtype. Also, adropin correlated inversely with the left atrial diameter. They concluded that adropin was associated with AF and atrial remodeling. Pre-clinical studies of adropin may encourage future clinical research to investigate diabetic cardiomyopathy (36).

## CONCLUSION

While there are still doubts about the effects of adropin, current evidence suggests that this biomarker will be valuable to the prevention of CVD. However, most of the existing research on the cardiovascular protection of adropin are animal studies. Adropin may be a promising agent for improving treatment in patients with metabolic syndrome, obesity, and diabetes. Further studies of adropin in CVD will shed further light on potential uses, but adropin may be beneficial to the prevention of CVD for therapeutic purposes and in cardiovascular risk classification.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – LA, OT; Design – LA, OT, HŞA; Supervision – LA, OT, HŞA, YH; Resource – LA, OT; Materials – LA, OT, HŞA; Data Collection and/or Processing – LA, OT; Analysis and/or Interpretation – LA; Literature Search – LA, OT; Writing – LA, OT, HŞA; Critical Reviews – LA, OT.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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