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Review Article:

Angiotensin-Converting Enzyme Inhibitors and Adipokines: The Role of Visfatin and Apelin in Cardiovascular Disease Management

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Abstract

Background: Angiotensin-converting enzyme (ACE) Inhibitors are medications pivotal in cardiovascular disease management, impacting the renin-angiotensin system which plays a critical role in cardiovascular health. These inhibitors not only modulate blood pressure and fluid balance but also influence adipose-derived hormones like visfatin and apelin. These adipokines are intricately linked with cardiovascular function and interact with the renin-angiotensin system, thereby affecting cardiovascular disease outcomes. Understanding the interplay between ACE inhibitors, visfatin, and apelin is crucial for optimizing therapeutic strategies in cardiovascular disease management. Visfatin is primarily expressed in visceral adipose tissue and is associated with hypertension, vascular inflammation, and insulin resistance. Elevated serum levels of visfatin correlate with increased systolic and diastolic blood pressure. Apelin, acting through the G protein-coupled receptor APJ, is implicated in cardiac system diseases and can lower arterial blood pressure, improving cardiac output. Different apelin isoforms have varying efficacies in arterial pressure regulation. ACE inhibitors, widely prescribed for hypertension and heart failure, are found to modulate serum levels of apelin and visfatin, potentially augmenting their cardioprotective effects. **Aim:** This review article aims to elucidate the effects of angiotensin-converting enzyme (ACE) inhibitors on the serum levels of visfatin and apelin and their implications for cardiovascular disease management. **Conclusion:** The interactions between ACE inhibitors, visfatin, and apelin present promising avenues for targeted therapies in hypertension and cardiovascular diseases. Despite some inconsistencies in the research, understanding these interactions could lead to novel therapeutic approaches and enhanced cardiovascular care.

1. Introduction

The Renin-Angiotensin System (RAS), crucial for regulating blood pressure and fluid balance, comprises elements like renin, angiotensin II, and aldosterone (1). Over time, it has been recognized as a complex system influencing cardiovascular, renal, and metabolic health, with the Angiotensin-Converting Enzyme 2 (ACE2/ Angiotensin (1-7)/Mas) axis revealing roles in inflammation and tissue repair (2, 3). Hypertension is closely associated with the RAS, a key determinant of vascular resistance and fluid homeostasis, impacting hypertension's onset and progression, as well as cardiovascular health (4).

The role of Angiotensin II in vasoconstriction and aldosterone-driven sodium retention underscores the RAS on blood pressure (5). ACE inhibitors, by mitigating these effects, also affect hormones like visfatin and apelin, with implications for hypertension's pathophysiology and cardiovascular outcomes (6). ACE inhibitors, pivotal in managing hypertension and related cardiovascular ailments, cut mortality, particularly in heart failure with reduced heart failure with reduced ejection fraction. (HFrEF) (7). They're preferred for hypertension with heart failure or diabetic nephropathy (8). Prescribers must monitor for adverse reactions and drug interactions (9).

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Visfatin and apelin, hormones secreted by adipose tissue, are implicated in cardiovascular disease. Apelin, a potential biomarker, is linked with hypertension and atherosclerosis when at low levels (10). One the other hand, high visfatin levels can induce vascular inflammation and destabilize plaques, particularly in essential hypertension and coronary events (11). Disparities in these adipokine levels in individuals with high normal blood pressure may contribute to their increased cardiovascular risk (12).

Adipose tissue, now considered an endocrine organ, secretes adipokines affecting more than just energy storage (13). These adipokines, identified through proteomic profiling (14). play roles in metabolic regulation (15). and are increasingly linked to cardiovascular diseases (16) with dysregulation associated with hypertension and vascular issues (17). Their dualistic roles in cardiovascular pathologies (18). and the debunking of old theories regarding adipocyte functions highlight adipokines' significance in managing hypertension and obesity (19). Adipokines are crucial regulators in blood pressure and metabolic health. Yiannikouris et al. outlined their roles: resistin in inflammation, the renin-angiotensin system in blood regulation, and leptin in energy control (20). Vlasova et al. connected adipokines like interleukin-6 and TNF-α to obesity-induced hypertension (21). Kim et al. explored new adipokines' effects on metabolism, with lipocalin-2, Secreted Frizzled-Related Protein 5. (SFRP5), omentin-1, asprosin, Family with Sequence Similarity 19 (Chemokine (C-C Motif)-like), Member A5 (FAM19A5), and neuregulin 4 influencing various aspects of cardiometabolic disorders (22).

1.1 Renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) is a crucial hormonal cascade in the regulation of blood pressure and fluid balance. It initiates with the synthesis of renin, an enzyme predominantly released by the kidneys in response to low blood pressure or sympathetic nervous system activation (23). Renin catalyzes the conversion of angiotensinogen, produced by the liver, into angiotensin. This is then transformed into angiotensin II, a potent vasoconstrictor, by angiotensin-converting enzyme (ACE), mainly found in the lungs (24). Angiotensin II exerts its effects by binding to angiotensin receptors in various tissues, leading to vasoconstriction, increased blood pressure, and stimulation of aldosterone secretion from the adrenal glands, which promotes sodium and water retention (25).

The inclusion of several components and mechanisms important for cellular and systemic functions has prompted the proposal that the RAS may have a part in the development of diseases that impact numerous organs and systems. Dysregulation of the RAS has been implicated in the pathophysiology of cardiovascular diseases, including hypertension, heart failure, and atherosclerosis (26). Inhibitors of the RAS, such as ACE inhibitors and angiotensin receptor blockers, are commonly used in the management of these conditions (24). The interactions between the RAS and peptides like apelin and visfatin are becoming clearer, highlighting their potential influence on cardiovascular health and disease (27).

The traditional concept of the RAS involves three key components: renin, angiotensin II, and aldosterone (28). First described over a century ago, the RAS has evolved from its initial discovery as a simple blood pressure-regulating system to a complex network with significant implications for cardiovascular, renal, and metabolic health (29). The majority of existing research has concentrated on the harmful effects of the RAS's vasoconstrictor arm constituents, including renin, angiotensin II, and aldosterone, on cardiovascular autonomic regulation (30). Over the years, the discovery of additional components and pathways within the RAS, such as the angiotensin-converting enzyme2 ACE2/Ang (1-7)/Mas receptor axis, has underscored its biological complexity and significance beyond mere blood pressure regulation, highlighting roles in inflammation, fibrosis, and tissue remodeling (31). **Figure 1** provides overview of the Renin-Angiotensin-Aldosterone System.

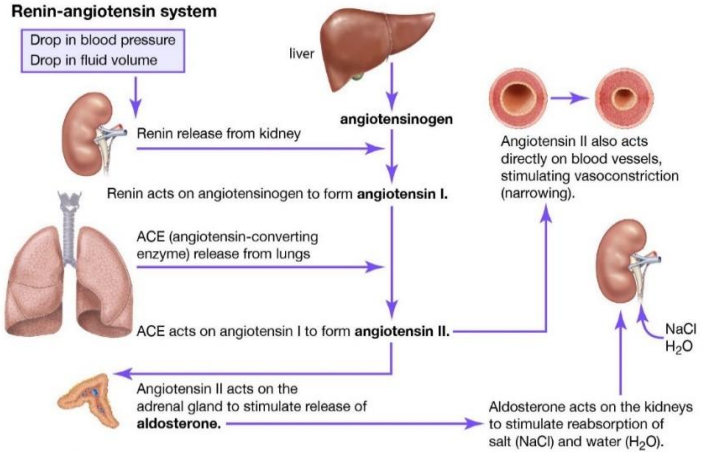

Figure 1. Overview of the Renin-Angiotensin-Aldosterone System (32)

1.2 Renin-angiotensin system and hypertension

Hypertension, a multifaceted cardiovascular disorder, is intricately linked with the renin-angiotensin system (RAS), a critical regulator of vascular resistance and fluid balance (33). The RAS, which is strongly linked to blood pressure regulation, plays a significant role in the development and progression of hypertension, as well as in ageing and cardiovascular diseases (34). Angiotensin II, a pivotal effector of the RAS, not only induces vasoconstriction but also stimulates aldosterone secretion, promoting sodium and water retention, which elevates blood pressure (35). Consequently, interventions targeting the RAS, particularly those inhibiting angiotensin-converting enzyme (ACE), have become fundamental in managing hypertension (36). These ACE inhibitors not only alleviate the hypertensive state but also modulate the systemic effects of hormones such as visfatin and apelin, which are emerging as significant factors in the pathophysiology of hypertension and its cardiovascular consequences (37).

1.3 Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors are medications used to treat and manage hypertension, which is a significant risk factor for coronary disease, heart failure, stroke, and a host of other cardiovascular conditions. ACE inhibitors reduce overall mortality, especially in patients with heart failure with reduced ejection fraction (0HFrEF) (38). They also reduce mortality even in asymptomatic patients with left ventricular dysfunction (39). ACE inhibitors are strongly recommended as first-choice therapy in patients with hypertension and coexistent conditions such as congestive heart failure and diabetic nephropathy (40). While effective, healthcare workers (nurse practitioners, physicians, and pharmacists) who prescribe these agents should be aware of their adverse drug reactions and contraindications. Patients must also be regularly monitored for drug-drug interactions (41).

1.4 Interplay between adipokines and the renin-angiotensin system

Adipose tissue is now recognized as an endocrine organ that releases bioactive substances known as adipokines, and is no longer thought of simply a triglyceride-storing depot (42). White adipose tissue produces these adipokines, which act as hormones or cytokines in the body (43). Using proteomic profiling methods, over 600 secreted proteins have been identified as adipokines (44). Various studies have revealed the role of adipokines in regulating and controlling metabolic disorders. Recent findings on the roles these adipokines play in cardiovascular diseases suggest a potential association between these bioactive substances and the cardiovascular system (45). Hypertension, endothelial dysfunction, and arterial stiffness were linked with dysregulation of serum adipokine levels (46, 47).
Interestingly, a previous study found that these bioactive proteins have a "yin-yang" role in the pathogenesis of cardiovascular diseases (48). Moreover, various substances that were previously thought to be largely stored and produced by adipocytes for the body's metabolic demands have since been identified, challenging the long-held theory that adipocytes are responsible for these functions (49). Production of adipocyte-derived factors controls the pathophysiological changes of hypertension and obesity (50). Yiannikouris et al. elucidated the biological activities of various adipokines in blood pressure regulation. Visfatin and apelin are adipokines, which are hormones produced by adipose tissue that have been linked to cardiovascular diseases (51). Resistin is involved in inflammation and insulin resistance, the renin-angiotensin system regulates blood volume and vascular resistance, vascular relaxation factors modulate blood vessel tone, adiponectin enhances insulin sensitivity and possesses anti-inflammatory properties, and leptin regulates appetite and energy expenditure .further investigated the role of adipokines in obesity-related hypertension, highlighting interleukin-6's pro-inflammatory effects, TNF-α's role in inflammation and endothelial function, resistin's association with insulin resistance, leptin's influence on sympathetic nervous system activity, adiponectin's cardiovascular protective effects, and apelin's role in blood pressure regulation (43).
The emerging data suggest that lower apelin and higher visfatin plasma levels in high normal blood pressure subjects compared to normal or optimal blood pressure individuals could partially explain the higher cardiovascular risk of the high normal blood pressure group (52). Additionally, Kim et al. assessed the pathophysiological impacts of emerging adipokines in cardiometabolic disorders and obesity. Lipocalin-2 is implicated in obesity and insulin resistance, Secreted Frizzled-Related Protein 5 (SFRP5) is involved in anti-inflammatory processes, omentin-1 enhances insulin sensitivity, asprosin regulates glucose homeostasis, Family with Sequence Similarity 19 (Chemokine (C-C Motif)-Like), Member A5 (FAM19A5) is linked with inflammatory processes, and neuregulin 4 plays a role in metabolic homeostasis (53).

1.5 Visfatin

Visfatin was discovered for the first time in 2005 by Fukuhara et al. (Fukuhara A). They showed that visfatin is mostly expressed by visceral adipose tissue and has actions similar to that of insulin (54). Visfatin, a 52 kDa mass adipokine, is a multifunctional protein with many functions, including adipokine, cytokine, and phosphoryltransferase (55). The mean visfatin level was considerably greater in hypertensive patients. Moreover, compared to those with normal healthy group, it was shown to be considerably greater in the prehypertensive group. Moreover, visfatin levels were found to be positively associated with systolic and diastolic blood pressure (56, 57).
High levels of visfatin plasma may promote vascular inflammation and atherosclerotic plaque destabilization, and have been evaluated as a marker for identifying stages of essential hypertension. A positive relationship between visfatin levels and unstable atherosclerotic lesions has been reported in patients with coronary artery disease and acute myocardial infarction (58). Visfatin has been demonstrated to produce vascular inflammation and atherosclerotic

plaque instability. Its role has been extensively researched as a potential biomarker for distinguishing phases of essential hypertension (16).

Plasma visfatin/nicotinamide phosphoribosyl transferase (NAMPT) concentrations exhibit a positive correlation with inflammation and insulin resistance and decline with age. In aged patients, plasma levels of visfatin/NAMPT were not associated with the prevalence of hypertension (59). There was an association between renal function and increased serum visfatin levels in nondiabetic hypertensive patients (60). Visfatin, high-density lipoproteins, and diastolic blood pressure, all have positive correlations (61). Visfatin levels in hypertensive individuals with hypertriglyceridemia were shown to be increased and linked to pro-inflammatory cytokines (62). Hypertension has been found to be the most common concomitant illness in cancer patients, and visfatin could serve as a novel potential therapeutic target for this condition in both cancer and hypertensive patients (63).

1.6 Apelin

Apelin, an endogenous bioactive peptide first identified in 1998, is a naturally formed ligand for the G protein-coupled receptor subfamily member APJ(64). Apelin has been shown to be a biomarker of cardiovascular diseases, and low levels of apelin plasma have been associated with arterial hypertension and atherosclerosis (65). The apelin gene code is located on chromosomal Xq25-q26.1 in humans, and the native apelin polypeptide is created by processing the 77 amino acid residues of the pre-proprotein's C terminus. Several active apelin molecules with 12, 13, 15, 16, 17, 19, 28, 31, or 36 amino acid residues, as well as the pyroglutamated apelin-13 (Pyr1)- apelin-13, are formed during posttranslational processing of pre-proprotein (66).

The 12-A.A apelin is the shortest fragment that may activate the apelin receptor, while the 36-A.A apelin variation appears to be the parent peptide. The intracellular trafficking of APJ is affected differently by apelin-13 and apelin-36 because of their distinct receptor binding affinities. Furthermore, apelin-36 has been identified as a less potent activator of the APJ receptor compared to its shorter apelin isoforms, indicating a variance in the functional impact of these isoforms on the cardiovascular system (67). Notably, both apelin and its receptor, APJ, are expressed in cardiac myocytes under normal physiological conditions. Apelin plays a pivotal role in cardiovascular physiology, as Snarska A's research has shown (68). It lowers arterial blood pressure by causing arterial vasodilation, improving cardiac output, and exerting a positive inotropic impact in vitro.

In 2003, a groundbreaking discovery by Starfield B established a link between apelin and cardiovascular diseases for the first time (69). Building upon this, a study by Földes et al. observed greater levels of apelin mRNA expression in human heart disease, indicating its relevance in pathological states (70). Interestingly, apelin's presence becomes more pronounced in abnormal tissue when the pathophysiology of human heart failure is influenced by various factors. Barnes G et al research has demonstrated that in individuals with heart failure, apelin not only improves cardiac output but also lowers blood pressure and the resistance of peripheral arteries (71).

The complexity of apelin's action is further highlighted by the fact that its different isoforms may act differently depending on the experimental model. Tatemoto K found that, in anesthetized normotensive rats, apelin-12 is more effective than apelin-13 and -36 at lowering mean arterial pressure (67). Delving deeper into the apelin/APJ receptor signaling pathway, studies by Mughal TI have elucidated its crucial role in directly regulating vascular tone, as well as proliferation, angiogenesis, and other aspects of vascular stability (72). Moreover, interaction of apelin with nitric oxide (NO) pathways adds another layer to its multifaceted role. It has been shown that apelin may have a net vasoconstrictor impact by inhibiting NO-induced relaxation. This effect is mediated through apelin's suppression of NO-induced activation of the large-conductance voltage-and Big Potassium Calcium-activated Channels (BKCa channels) in cerebral artery smooth muscle cells (73). **Figure 2** represents the biological pathways of Apelin and its role in cardiovascular regulation.

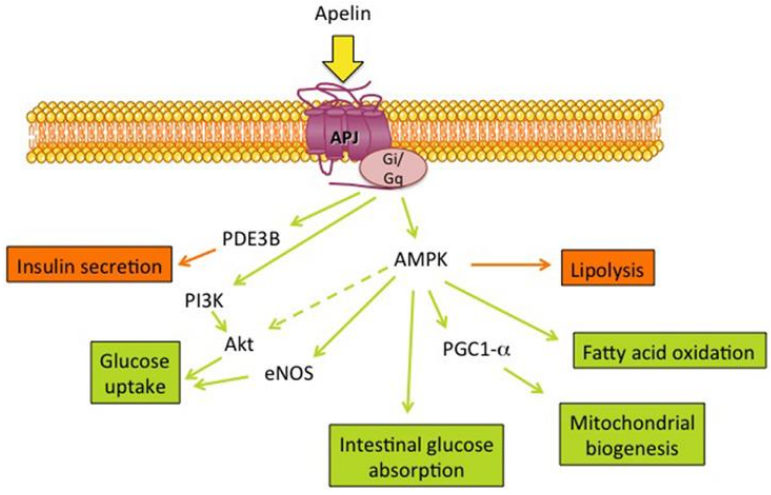

Figure 2. The Biological Pathways of Apelin and Its Role in Cardiovascular Regulation (74)

1.7 Angiotensin-converting enzyme (ACE) inhibitors and apelin

Both ACE inhibitors and apelin have important but complex roles in cardiovascular health. ACE inhibitors reduce blood pressure by inhibiting angiotensin II formation, and they may also elevate apelin levels, enhancing vasodilator and cardioprotective effects. On the other hand, the apelinergic system, broadly expressed in the body, offers cardiovascular benefits through mechanisms like vasodilation and improved metabolism (75). Apelin is a peptide that interacts with the renin-angiotensin system (RAS) by promoting the transcription of angiotensin-converting enzyme 2 (ACE2), which leads to increased ACE2 protein levels and activity. This interaction augments ACE2 activity, counteracting the effects of angiotensin II (Ang II). However, the impact of apelin is moderated due to its rapid degradation by proteolytic enzymes, including ACE2 itself and neprilysin (NEP) (38).

Despite lower apelin levels in pathological conditions, its diagnostic and therapeutic potential remains a subject of ongoing research. The review conducted by Chatterjee et al. showed the multifaceted interaction between ACE inhibitors, apelin, and ACE2, spotlighting their potential in treating a range of cardiovascular diseases (76). A study by Sato et al. showed that apelin, a cardioprotective peptide, enhances heart function by boosting ACE2 expression. In aged mice lacking apelin, the adverse effects of angiotensin II were intensified, causing worsened cardiac dysfunction and hypertrophy. The study highlights apelin's key role in mitigating heart issues (77). To understand the potential interactions between apelin and ACE2 in cardiovascular physiology, it is crucial to consider a seminal study that characterizes ACE2 as a unique and specific homologue of ACE primarily present in heart, kidney, and testis tissues (78) . ACE2 is a homologue of ACE, found primarily in the heart, kidney, and testis. Unlike ACE, ACE2 has a specialized role in hydrolyzing angiotensin I to angiotensin 1-9 and is not inhibited by common ACE inhibitors. ACE2 plays a unique, essential role in the local renin-angiotensin systems of the heart and kidney (79).

ACE2 is also expressed in nearly all human organs in varying degrees, and it is a cellular entry point for SARS-CoV-2, the cause of COVID-19. ACE2 catalyzes angiotensin II conversion to angiotensin-(1–7), and the ACE2/angiotensin-(1–7)/MAS axis counteracts the negative effects of the renin-angiotensin system (80). The different RAS blockers (captopril, perindopril) increased the mRNA expression and peptide synthesis of apelin (81). Whereas felodipine and enapril raises the level of apelin in hypertensive individuals (82).

1.8 Angiotensin-converting enzyme (ACE) inhibitors and visfatin

Visfatin is an adipokine that serves as a critical coenzyme in various cellular redox processes. Elevated visfatin levels are linked with metabolic syndrome and endothelial balance (52). A strong association has also been found between high levels of visfatin and the severity of peripheral arterial occlusive disease (PAOD) as well as carotid atherosclerosis. These effects, particularly when combined with other risk factors, could contribute to the vulnerability of atherosclerotic plaques and a higher likelihood of cardiovascular incidents (83). The interaction between ACE inhibitors and visfatin is an area of growing interest in cardiovascular research. ACE inhibitors are commonly used to treat hypertension and heart failure, primarily by inhibiting the conversion of angiotensin I to Ang II. On the other hand, visfatin is an adipokine involved in metabolic syndrome and endothelial homeostasis (84). Elevated visfatin levels have been linked to peripheral arterial occlusive disease and carotid atherosclerosis.

Preliminary studies suggest that ACE inhibitors may modulate visfatin levels, potentially enhancing their cardioprotective effects. Understanding this interaction could offer new insights into comprehensive cardiovascular disease management (85). A study by Kärberg et al. found that visfatin levels correlate with subclinical atherosclerosis markers, especially in male type 2 diabetic patients. Interestingly, this correlation changes when patients take ACE inhibitors, revealing a significant interaction between ACE inhibitors and visfatin that could influence cardiovascular disease management (86).

Research on how drugs affect circulating adipokines has shown inconsistent results, due to varying study populations and lab methods. These inconsistencies underline the importance of targeted research, like this paper's focus on the specific interaction between ACE inhibitors and visfatin (86, 87). A study investigated the binding affinity of various drugs, including ACE inhibitors and Angiotensin II Receptor Blockers (ARBs), to Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)—a receptor linked to antidiabetic effects. It found that telmisartan had the highest binding affinity, followed by lisinopril and valsartan. These drugs also enhanced phosphorylation in skeletal muscle cells and increased the release of the adipocytokine visfatin. The study concluded that telmisartan, valsartan, and lisinopril act as agonists on PPARγ, suggesting that their antidiabetic properties may vary based on pharmacokinetic differences. The production of the adipocytokine visfatin and the high affinity of ACE-I lisinopril for Peroxisome Proliferator-Activated Receptor show PPAR-mediated protein phosphorylation (88). Ramipril will be decrease blood pressure in hypertensive patient without any effect on visfatin level (89).

In a series of studies examining the effects of ACE inhibitors on apelin and visfatin as shown in

Table 1, captopril emerged with diverse outcomes. Preclinical in vivo studies in rats and mice demonstrated that captopril administration significantly increased apelin

gene expression in adipose tissue and elevated serum apelin levels (90-92). Notably, captopril also enhanced gene expression of the Ang 1-7/Mas receptor (90).However, in hypertensive patients, captopril treatment resulted in a significant reduction in serum apelin levels (93). Furthermore, a combined study using captopril and perindopril on 3T3-L1 cells revealed an increase in both apelin production and mRNA expression, but a decrease in mRNA expression of visfatin (94). In contrast, lisinopril treatment led to a 1.6-fold increase in visfatin release from various cell types, including adipocytes, umbilical vein endothelial cells, and skeletal muscle cells (95). Interestingly, ramipril did not exhibit any effect on visfatin levels in hypertensive patients (96). These findings highlight the varied and complex effects of ACE inhibitors on adipokines, underlining their potential implications in cardiovascular disease management.

Table 1. Comparison of the effects of ACE inhibitors on apelin and visfatin

ACE inhibitors	Type of study	Therapy regimen	Adipokine	Results
Captopril (97)	Preclinical *in vivo*, rats with diet-induced hypertension	Captopril 40mg/kg/day orally for 10 weeks	Apelin	A significant increase in gene expression of Ang 1-7/Mas receptor and apelin/APJ receptor in adipose tissue
Captopril (98)	Preclinical *in vivo*, wild type and apelin-deficient mice (99)	Captopril 50 mg/L in their drinking water	Apelin	Captopril suppressed cardiac contractility in apelin-deficient mice
Captopril (100)	Preclinical *in vivo*, adult male rats	Captopril 10mg/kg/day orally for 14 days before induction of peptic ulcer	Apelin	Significantly increased apelin level and gene expression of Ang 1-7.
Captopril ((101)	Clinical, hypertensive patients	Captopril 25-150 mg/day	Apelin	Serum levels of apelin were significantly reduced in hypertensive patients
Captopril and perindopril (94)	Preclinical *in vitro*, 3T3-L1 cells	Captopril 10^{-4} M and perindopril 10^{-3} M added to culture medium after differentiation	Apelin and visfatin	Significantly increased the production of apelin and mRNA expression of apelin while significantly reduced the mRNA expression of visfatin
Lisinopril (95)	Preclinical *in vitro*, isolated human umbilical vein endothelial cells, skeletal muscle cells and adipocytes	Lisinopril 2.9 µM	Visfatin	Visfatin release from adipocytes, umbilical vein endothelial cells, and skeletal muscle cells was 1.6-fold increased after treatment with lisinopril
Ramipril (96)	Clinical, hypertensive patients	Ramipril 5 mg/day for 1 month	Visfatin	No effect

2. Conclusion

The intricate relationships between ACE inhibitors, apelin, and visfatin in the cardiovascular system are subjects of evolving research. ACE inhibitors, well-known for their blood pressure-lowering effects, may also interact with adipokines like apelin and visfatin, offering potential cardioprotective benefits. Apelin is seen as a cardioprotective agent, while visfatin levels are notably influenced by ACE inhibitors, particularly in patients with hypertension. However, inconsistent findings attributed to varied study populations and methodologies call for more targeted research. Overall, understanding these interactions may offer nuanced approaches to cardiovascular disease management.

3. References

1. Ferrão FM, Lara LS, Lowe J. Renin-angiotensin system in the kidney: What is new? *World journal of nephrology*. 2014;3(3):64.

2. Queiroz-Junior CM, Santos ACPM, Galvão I, Souto GR, Mesquita RA, Sá MA, et al. The angiotensin converting enzyme 2/angiotensin-(1-7)/Mas Receptor axis as a key player in alveolar bone remodeling. *Bone*. 2019;128:115041.

3. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, et al. The ACE2/angiotensin-(1–7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1–7). *Physiological reviews*. 2017.

4. Onuh JO, Qiu H. Metabolic profiling and metabolites fingerprints in human hypertension: discovery and potential. *Metabolites*. 2021;11(10):687.

5. Craigie E, Mullins JJ, Bailey MA. Glucocorticoids and mineralocorticoids. *Cardiovascular hormone systems: from molecular mechanisms to novel therapeutics*. 2009:1-64.

6. Smekal A, Vaclavik J. Adipokines and cardiovascular disease: A comprehensive review. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc*. 2017;161(1).

7. Sara JD, Toya T, Taher R, Lerman A, Gersh B, Anavekar NS. Asymptomatic left ventricle systolic dysfunction. *European Cardiology Review*. 2020;15.

8. Williams AF, Manias E, Walker R. Adherence to multiple, prescribed medications in diabetic kidney disease: a qualitative study of consumers' and health professionals' perspectives. *International journal of nursing studies*. 2008;45(12):1742-56.

9. Schatz S, Weber RJ. Adverse drug reactions. *Pharmacy Practice*. 2015;1(1).

10. Ragino YI, Stakhneva EM, Polonskaya YV, Kashtanova EV. The role of secretory activity molecules of visceral adipocytes in abdominal obesity in the development of cardiovascular disease: a review. *Biomolecules*. 2020;10(3):374.

11. Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A, et al. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation*. 2007;115(8):972-80.

12. Abu-Farha M, Behbehani K, Elkum N. Comprehensive analysis of circulating adipokines and hsCRP association with cardiovascular disease risk factors and metabolic syndrome in Arabs. *Cardiovascular diabetology*. 2014;13:1-10.

13. Musi N, Guardado-Mendoza R. Adipose tissue as an endocrine organ. Cellular endocrinology in health and disease: Elsevier; 2014. p. 229-37.

14. Zhang Y, Yu M, Dong J, Wu Y, Tian W. Identification of novel adipokines through proteomic profiling of small extracellular vesicles derived from adipose tissue. *Journal of proteome research*. 2020;19(8):3130-42.

15. Booth A, Magnuson A, Fouts J, Foster MT. Adipose tissue: an endocrine organ playing a role in metabolic regulation. *Hormone molecular biology and clinical investigation*. 2016;26(1):25-42.

16. Taube A, Schlich R, Sell H, Eckardt K, Eckel J. Inflammation and metabolic dysfunction: links to cardiovascular diseases. *American Journal of Physiology-Heart and Circulatory Physiology*. 2012;302(11):H2148-H65.

17. Huertas A, Perros F, Tu L, Cohen-Kaminsky S, Montani D, Dorfmüller P, et al. Immune dysregulation and endothelial dysfunction in pulmonary arterial hypertension: a complex interplay. *Circulation*. 2014;129(12):1332-40.

18. Francisco V, Ruiz-Fernández C, Pino J, Mera A, Gonzalez-Gay MA, Gómez R, et al. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. *Biochemical pharmacology*. 2019;165:196-206.

19. Frasca D, Blomberg BB, Paganelli R. Aging, obesity, and inflammatory age-related diseases. *Frontiers in immunology*. 2017;8:1745.

20. de Farias Lelis D, de Freitas DF, Machado AS, Crespo TS, Santos SHS. Angiotensin-(1-7), adipokines and inflammation. *Metabolism*. 2019;95:36-45.

21. Vlasova M, Purhonen A, Jarvelin M, Rodilla E, Pascual J, Herzig K. Role of adipokines in obesity-associated hypertension. *Acta Physiologica*. 2010;200(2):107-27.

22. Rafaqat S, Nasreen S, Rafaqat S. Role of major adipokines in hypertension: A literature review. *World Journal of Hypertension*. 2023;11(1):1-11.

23. Nakagawa P, Gomez J, Grobe JL, Sigmund CD. The Renin-Angiotensin System in the Central Nervous

System and Its Role in Blood Pressure Regulation. *Current Hypertension Reports*. 2020;22(1):7.

24. Cutrell S, Alhomoud IS, Mehta A, Talasaz AH, Van Tassell B, Dixon DL. ACE-Inhibitors in Hypertension: A Historical Perspective and Current Insights. *Current Hypertension Reports*. 2023;25(9):243-50.

25. Yang R, Smolders I, Dupont AG. Blood pressure and renal hemodynamic effects of angiotensin fragments. *Hypertension Research*. 2011;34(6):674-83.

26. Mehta JK, Kaur G, Buttar HS, Bagabir HA, Bagabir RA, Bagabir SA, et al. Role of the renin-angiotensin system in the pathophysiology of coronary heart disease and heart failure: Diagnostic biomarkers and therapy with drugs and natural products. *Frontiers in Physiology*. 2023;14:1034170.

27. Ożegowska K, Bartkowiak-Wieczorek J, Bogacz A, Seremak-Mrozikiewicz A, Duleba AJ, Pawelczyk L. Relationship between adipocytokines and angiotensin converting enzyme gene insertion/deletion polymorphism in lean women with and without polycystic ovary syndrome. *Gynecological Endocrinology*. 2020;36(6):496-500.

28. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. *American Journal of Physiology-Heart and Circulatory Physiology*. 2019.

29. Raschke S, Elsen M, Gassenhuber H, Sommerfeld M, Schwahn U, Brockmann B, et al. Evidence against a beneficial effect of irisin in humans. *PloS one*. 2013;8(9):e73680.

30. Ziaja M, Urbanek KA, Kowalska K, Piastowska-Ciesielska AW. Angiotensin II and Angiotensin Receptors 1 and 2—Multifunctional System in Cells Biology, What Do We Know? *Cells*. 2021;10(2):381.

31. Zamai L. The Yin and Yang of ACE/ACE2 pathways: the rationale for the use of renin-angiotensin system inhibitors in COVID-19 patients. *Cells*. 2020;9(7):1704.

32. Raschke S, Elsen M, Gassenhuber H, Sommerfeld M, Schwahn U, Brockmann B, et al. Evidence against a beneficial effect of irisin in humans. *PloS One*. 2013;8(9):e73680.

33. Senatore F, Balakumar P, Jagadeesh G. Dysregulation of the renin-angiotensin system in septic shock: mechanistic insights and application of angiotensin II in clinical management. *Pharmacological research*. 2021;174:105916.

34. van Thiel BS, van der Pluijm I, te Riet L, Essers J, Danser AJ. The renin–angiotensin system and its involvement in vascular disease. *European journal of pharmacology*. 2015;763:3-14.

35. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AJ. Hypertension: renin–angiotensin–aldosterone system alterations. *Circulation research*. 2015;116(6):960-75.

36. Arendse LB, Danser AJ, Poglitsch M, Touyz RM, Burnett JC, Llorens-Cortes C, et al. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. *Pharmacological reviews*. 2019;71(4):539-70.

37. Katragadda S, Arora RR. Role of angiotensin-converting enzyme inhibitors in vascular modulation: beyond the hypertensive effects. *American Journal of Therapeutics*. 2010;17(1):e11-23.

38. Khalil ME, Basher AW, Brown EJ, Alhaddad IA. A remarkable medical story: benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *Journal of the American College of Cardiology*. 2001;37(7):1757-64.

39. Sara JD, Toya T, Taher R, Lerman A, Gersh BJ, Anavekar NS. Asymptomatic Left Ventricle Systolic Dysfunction. *European Cardiology Review 2020;15:e13*. 2020.

40. Patel BM, Mehta AA. Choice of anti-hypertensive agents in diabetic subjects. *Diabetes and Vascular Disease Research*. 2013;10(5):385-96.

41. Coleman JJ, Pontefract SK. Adverse drug reactions. *Clinical Medicine (London, England)*. 2016;16(5):481-5.

42. Kanugula AK, Kaur J, Batra J, Ankireddypalli AR, Velagapudi R. Renin-Angiotensin System: Updated Understanding and Role in Physiological and Pathophysiological States. *Cureus*. 2023;15(6):e40725.

43. Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators of Inflammation*. 2010;2010:802078.

44. Santos RAS, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. *American Journal of Physiology: Heart and Circulatory Physiology*. 2019;316(5):H958-h70.

45. Martyniak A, Tomasik PJ. A New Perspective on the Renin-Angiotensin System. *Diagnostics (Basel)*. 2022;13(1).

46. Miller AJ, Arnold AC. The renin-angiotensin system in cardiovascular autonomic control: recent developments and clinical implications. *Clinical Autonomic Research*. 2019;29(2):231-43.

47. Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes ESAC. The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. *Current Drug Targets*. 2017;18(11):1301-13.

48. Schouten LR, Helmerhorst HJ, Wagenaar GT, Haltenhof T, Lutter R, Roelofs JJ, et al. Age-Dependent Changes in the Pulmonary Renin-Angiotensin System Are Associated With Severity of Lung Injury in a Model of Acute Lung Injury in Rats. *Critical Care Medicine*. 2016;44(12):e1226-e35.

49. Burhans MS, Hagman DK, Kuzma JN, Schmidt KA, Kratz M. Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus. *Comprehensive Physiology*. 2018;9(1):1-58.

50. DeMarco VG, Aroor AR, Sowers JR. The pathophysiology of hypertension in patients with obesity. *Nature Reviews: Endocrinology*. 2014;10(6):364-76.

51. Yu D, Huang B, Wu B, Xiao J. Association of serum vaspin, apelin, and visfatin levels and stroke risk in a Chinese case-control study. *Medicine (Baltimore)*. 2021;100(12):e25184.

52. Liakos CI, Sanidas EA, Perrea DN, Grassos CA, Chantziara V, Viniou NA, et al. Apelin and Visfatin Plasma Levels in Healthy Individuals With High Normal Blood Pressure. *American Journal of Hypertension*. 2016;29(5):549-52.

53. Kim JA, Choi KM. Newly Discovered Adipokines: Pathophysiological Link Between Obesity and Cardiometabolic Disorders. *Frontiers in Physiology*. 2020;11:568800.

54. Romacho T, Sánchez-Ferrer CF, Peiró C. Visfatin/Nampt: an adipokine with cardiovascular impact. *Mediators of Inflammation*. 2013;2013:946427.

55. Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. *Current Medicinal Chemistry*. 2008;15(18):1851-62.

56. Gunes F, Akbal E, Cakir E, Akyurek O, Altunbas M, Ozbek M. Visfatin may be a novel marker for identifying stages of essential hypertension in advanced age patients. *Internal Medicine*. 2012;51(6):553-7.

57. Wang P, Bai C, Xu QY, Xu TY, Su DF, Sassard J, et al. Visfatin is associated with lipid metabolic abnormalities in Lyon hypertensive rats. *Clinical and Experimental Pharmacology and Physiology*. 2010;37(9):894-9.

58. Zheng LY, Xu X, Wan RH, Xia S, Lu J, Huang Q. Association between serum visfatin levels and atherosclerotic plaque in patients with type 2 diabetes. *Diabetology & Metabolic Syndrome*. 2019;11:60.

59. Kocelak P, Olszanecka-Glinianowicz M, Owczarek A, Bożentowicz-Wikarek M, Brzozowska A, Mossakowska M, et al. Plasma visfatin/nicotinamide phosphoribosyltransferase levels in hypertensive elderly - results from the PolSenior substudy. *Journal of the American Society of Hypertension*. 2015;9(1):1-8.

60. Hsu CY, Huang PH, Chen TH, Chiang CH, Leu HB, Huang CC, et al. Increased Circulating Visfatin Is Associated With Progression of Kidney Disease in Non-Diabetic Hypertensive Patients. *American Journal of Hypertension*. 2016;29(4):528-36.

61. Kärberg K, Forbes A, Lember M. Visfatin and Subclinical Atherosclerosis in Type 2 Diabetes: Impact of Cardiovascular Drugs. *Medicina*. 2023;59(7):1324.

62. Peng X, Wu H. Inflammatory Links Between Hypertriglyceridemia and Atherogenesis. *Current Atherosclerosis Reports*. 2022;24(5):297-306.

63. Parimelazhagan R, Umapathy D, Sivakamasundari IR, Sethupathy S, Ali D, Kunka Mohanram R, et al. Association between Tumor Prognosis Marker Visfatin and Proinflammatory Cytokines in Hypertensive Patients. *Biomed Research International*. 2021;2021:8568926.

64. Gandham R, Sumathi M, Dayanand C, Sheela S, Kiranmayee P. Apelin and its Receptor: An Overview. *Journal of Clinical & Diagnostic Research*. 2019;13(6).

65. Askin L, Askin HS, Tanrıverdi O, Ozyildiz AG, Duman H. Serum apelin levels and cardiovascular diseases. *Northern Clinical of Istanbul*. 2022;9(3):290-4.

66. Messerli FH, Bangalore S, Bavishi C, Rimoldi SF. Angiotensin-Converting Enzyme Inhibitors in Hypertension: To Use or Not to Use? *Journal of the American College of Cardiology*. 2018;71(13):1474-82.

67. Chapman NA, Dupré DJ, Rainey JK. The apelin receptor: physiology, pathology, cell signalling, and ligand modulation of a peptide-activated class A GPCR. *Biochemistry and Cell Biology*. 2014;92(6):431-40.

68. Snarska A, Wysocka D, Rytel L, Makowska K, Gonkowski S. Cytological Evaluation of the Influence of High and Low Doses of Bisphenol a on an Erythroblastic Cell Line of Porcine Bone Marrow. *Journal of Veterinary Research*. 2018;62(4):543-7.

69. Starfield B, Lemke KW, Bernhardt T, Foldes SS, Forrest CB, Weiner JP. Comorbidity: implications for the importance of primary care in 'case' management. *Annals of Family Medicine*. 2003;1(1):8-14.

70. Földes G, Horkay F, Szokodi I, Vuolteenaho O, Ilves M, Lindstedt KA, et al. Circulating and cardiac levels of apelin, the novel ligand of the orphan receptor APJ, in patients with heart failure. *Biochemical and Biophysical Research Communications*. 2003;308(3):480-5.

71. Barnes G, Japp AG, Newby DE. Translational promise of the apelin--APJ system. *Heart*. 2010;96(13):1011-6.

72. Mughal TI, Gotlib J, Mesa R, Koschmieder S, Khoury HJ, Cortes JE, et al. Recent advances in the genomics and therapy of BCR/ABL1-positive and -negative chronic myeloproliferative neoplasms. *Hematological Oncology*. 2018;67:67-74.

73. Mughal A, Sun C, O'Rourke ST. Apelin Reduces Nitric Oxide-Induced Relaxation of Cerebral Arteries by Inhibiting Activation of Large-Conductance, Calcium-Activated K Channels. *Journal of Cardiovascular Pharmacology*. 2018;71(4):223-32.

74. Wysocka MB, Pietraszek-Gremplewicz K, Nowak D. The role of apelin in cardiovascular diseases, obesity and cancer. *Frontiers in physiology*. 2018;9:557.

75. Wang W, McKinnie SMK, Farhan M, Paul M, McDonald T, McLean B, et al. Angiotensin-Converting Enzyme 2 Metabolizes and Partially Inactivates Pyr-Apelin-13 and Apelin-17. *Hypertension*. 2016;68(2):365-77.

76. Guang C, Phillips RD, Jiang B, Milani F. Three key proteases – angiotensin-I-converting enzyme (ACE), ACE2 and renin – within and beyond the renin-angiotensin system. *Archives of Cardiovascular Diseases*. 2012;105(6):373-85.

77. Chatterjee P, Gheblawi M, Wang K, Vu J, Kondaiah P, Oudit GY. Interaction between the apelinergic system and ACE2 in the cardiovascular system: therapeutic implications. *Clinical science*. 2020;134(17):2319-36.

78. Reboldi G, Gentile G, Angeli F, Verdecchia P. Choice of ACE inhibitor combinations in hypertensive patients with type 2 diabetes: update after recent clinical trials. *Vascular Health and Risk Management*. 2009;5(1):411-27.

79. Manoharan S. Is It Still Relevant to Discover New ACE Inhibitors from Natural Products? YES, but Only with Comprehensive Approaches to Address the Patients' Real Problems: Chronic Dry Cough and Angioedema. *Molecules*. 2023;28(11).

80. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *International Journal of Peptides*. 2012;2012:256294.

81. McLachlan CS. The angiotensin-converting enzyme 2 (ACE2) receptor in the prevention and treatment of COVID-19 are distinctly different paradigms. *Clinical Hypertension*. 2020;26:14.

82. Wysocka MB, Pietraszek-Gremplewicz K, Nowak D. The Role of Apelin in Cardiovascular Diseases, Obesity and Cancer. *Frontiers in Physiology*. 2018;9:557.

83. Erten M. Visfatin as a Promising Marker of Cardiometabolic Risk. *Acta Cardiologica Sinica*. 2021;37(5):464-72.

84. Lafontan M. Historical perspectives in fat cell biology: the fat cell as a model for the investigation of hormonal and metabolic pathways. *American Journal of Physiology: Cell Physiology*. 2012;302(2):C327-59.

85. Lehr S, Hartwig S, Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. *Proteomics: Clinical Applications*. 2012;6(1-2):91-101.

86. Brockman D, Chen X. Proteomics in the characterization of adipose dysfunction in obesity. *Adipocyte*. 2012;1(1):25-37.

87. Kim EY, Kim WK, Oh KJ, Han BS, Lee SC, Bae KH. Recent advances in proteomic studies of adipose tissues and adipocytes. *International Journal of Molecular Sciences*. 2015;16(3):4581-99.

88. Smekal A, Vaclavik J. Adipokines and cardiovascular disease: A comprehensive review. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*. 2017;161(1):31-40.

89. Solini A, Stea F, Santini E, Bruno RM, Duranti E, Taddei S, et al. Adipocytokine levels mark endothelial function in normotensive individuals. *Cardiovascular Diabetology*. 2012;11:103.

90. Youn JC, Kim C, Park S, Lee SH, Kang SM, Choi D, et al. Adiponectin and progression of arterial stiffness in hypertensive patients. *International Journal of Cardiology*. 2013;163(3):316-9.

91. Xu C, Wang F, Chen Y, Xie S, Sng D, Reversade B, et al. ELABELA antagonizes intrarenal renin-angiotensin system to lower blood pressure and protects against renal injury. *American Journal of Physiology: Renal Physiology*. 2020;318(5):F1122-f35.

92. Sato T, Suzuki T, Watanabe H, Kadowaki A, Fukamizu A, Liu PP, et al. Apelin is a positive regulator of ACE2 in failing hearts. *Journal of Clinical Investigation*. 2013;123(12):5203-11.

93. Gemici B, Birsen İ, İzgüt-Uysal VN. The apelin-apela receptor APJ is necessary for formation and healing of ischemia reperfusion-induced gastric ulcer in rats. *Peptides*. 2023;166:171027.

94. Bezci Aygun F, Kocabeyoglu S, Irkec M, Dikmen ZG, Umaroglu MM, Konstas AGP. Serum Apelin and Asymmetric Dimethylarginine Levels in Patients With Exfoliation Syndrome or Exfoliative Glaucoma. *Journal of Glaucoma*. 2020;29(7):593-7.

95. Hung WW, Hsieh TJ, Lin T, Chou PC, Hsiao PJ, Lin KD, et al. Blockade of the renin-angiotensin system ameliorates apelin production in 3T3-L1 adipocytes. *Cardiovascular Drugs and Therapy*. 2011;25(1):3-12.

96. Storka A, Vojtassakova E, Mueller M, Kapiotis S, Haider DG, Jungbauer A, et al. Angiotensin inhibition stimulates PPARgamma and the release of visfatin. *European Journal of Clinical Investigation*. 2008;38(11):820-6.

97. Derosa G, Maffioli P, Ferrari I, Palumbo I, Randazzo S, Fogari E, et al. Different actions of losartan and ramipril on adipose tissue activity and vascular remodeling biomarkers in hypertensive patients. *Hypertension Research*. 2011;34(1):145-51.

98. Mohamed RA, Sabry MM, Shawky HM, Tawadrous AF, Gharib D. Interaction between renin angiotensin system and apelin/APJ System in hypertensive rats. 2016;8:32-49.

99. Sato T, Kadowaki A, Suzuki T, Ito H, Watanabe H, Imai Y, et al. Loss of Apelin Augments Angiotensin II-Induced Cardiac Dysfunction and Pathological Remodeling. *International Journal of Molecular Sciences*. 2019;20(2).

100. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, et al. Polycystic ovary syndrome. *Nature reviews Disease primers*. 2016;2(1):1-18.

101. FATMA E. IBRAHIM MD, NANCY F. SAMIR, M.D., RASHED MD, LAILA A. The Interplay between Apelin/APJ System and Renin Angiotensin System in Protection Against Cold Restraint Stress Induced Gastric Ulcers in Adult Male Rats. *The Medical Journal of Cairo University*. 2018;86(December):4503-11.

102. Al-rubaye FG. Serum concentration of Apelin and Asymmetric Dimethylarginine in hypertensive patients on different modalities of treatment. *Cukurova Medical Journal*. 2013;38(1):1-6.

مثبطات الإنزيم المحول للأنجيوتنسين والأديبوكينات: دور الفسفاتين والأبيلين في إدارة أمراض القلب والأوعية الدموية

الخلاصة

المقدمة: مثبطات الإنزيم المحول للأنجيوتنسين (ACE) هي أدوية محورية في إدارة أمراض القلب والأوعية الدموية، مما يؤثر على نظام الرينين أنجيوتنسين الذي يلعب دورًا حاسمًا في صحة القلب والأوعية الدموية. لا تقوم هذه المثبطات بتعديل ضغط الدم وتوازن السوائل فحسب، بل تؤثر أيضًا على الهرمونات المشتقة من الدهون مثل الفسفاتين والأبيلين. ترتبط هذه الأديبوكينات بشكل معقد بوظيفة القلب والأوعية الدموية وتتفاعل مع نظام الرينين أنجيوتنسين، مما يؤثر على نتائج أمراض القلب والأوعية الدموية. يعد فهم التفاعل بين مثبطات الإنزيم المحول للأنجيوتنسين والفيسفاتين والأبيلين أمرًا بالغ الأهمية لتحسين الاستراتيجيات العلاجية في إدارة أمراض القلب والأوعية الدموية. يتم التعبير عن الفسفاتين بشكل أساسي في الأنسجة الدهنية الحشوية ويرتبط بارتفاع ضغط الدم والتهاب الأوعية الدموية ومقاومة الأنسولين. ترتبط مستويات المصل المرتفعة من الفسفاتين بزيادة ضغط الدم الانقباضي والانبساطي. الأبلين، الذي يعمل من خلال مستقبل البروتين G المقترن APJ، متورط في أمراض الجهاز القلبي ويمكنه خفض ضغط الدم الشرياني، مما يحسن النتاج القلبي. الأشكال الإسوية المختلفة للأبيلين لها فعالية متفاوتة في تنظيم الضغط الشرياني. تم العثور على مثبطات الإنزيم المحول للأنجيوتنسين، والتي توصف على نطاق واسع لارتفاع ضغط الدم وفشل القلب، لتعديل مستويات مصل الأبلين والفيسفاتين، مما قد يزيد من آثارها الوقائية للقلب.**الأهداف:** تهدف هذه المقالة المراجعة إلى توضيح آثار مثبطات الإنزيم المحول للأنجيوتنسين (ACE) على مستويات مصل الفسفاتين والأبيلين وآثارها على إدارة أمراض القلب والأوعية الدموية. **الاستنتاج:** توفر التفاعلات بين مثبطات الإنزيم المحول للأنجيوتنسين والفيسفاتين والأبيلين طرقًا واعدة للعلاجات المستهدفة لارتفاع ضغط الدم وأمراض القلب والأوعية الدموية. على الرغم من بعض التناقضات في البحث، فإن فهم هذه التفاعلات يمكن أن يؤدي إلى أساليب علاجية جديدة وتعزيز رعاية القلب والأوعية الدموية.

الكلمات المفتاحية: مثبطات الإنزيم المحول للأنجيوتنسين، أديبوكين، أبلين، فيسفاتين، الجهاز القلبي الوعائي.