Effects of Angiotensin Receptor Blockers on Apelin and Visfatin in Hypertension

Mina K. Mohammed, Zainab H. Fathi,* and Jehan A. Mohammad
Department of Pharmacognosy and Medicinal Plants,
College of Pharmacy, University of Mosul, Mosul, Iraq.

ABSTRACT

Angiotensin receptor blockers (ARBs) are crucial in the management of cardiovascular diseases, by targeting the renin-angiotensin system, which plays a vital role in cardiovascular health. These drugs control hypertension and fluid imbalance, as well as influence adipose-derived hormones such as visfatin and apelin. The renin-angiotensin system is affected by these adipokines, which are closely associated with cardiovascular health and, consequently, can influence the complications of cardiovascular diseases. Understanding the relationship between ARBs, apelin, and visfatin is essential to optimizing therapeutic approaches to controlling cardiovascular diseases. Apelin stimulates vasodilation through two mechanisms including either building a heterodimer with G-protein-coupled receptors (GPCRs) or increasing the release of nitric oxide (NO) through enhancing the expression of angiotensin-converting enzyme 2. Visfatin is an adipocytokine with several interesting characteristics. Initially identified as a pre-B cell colony-enhancing factor, it later revealed enzymatic roles in nicotinamide adenine dinucleotide (NAD) synthesis. Researchers correlated higher visfatin levels with the risk of developing severe hypertension. Studies have demonstrated that ARBs influence the serum levels of apelin and visfatin, potentially enhancing their cardioprotective effects. This review article aims to highlight the roles and mechanisms of apelin and visfatin in hypertension, as well as the effects of ARBs on these adipokines.

Keywords: Angiotensin Receptor Blockers; Adipokine; Visfatin; Apelin; Hypertension.

INTRODUCTION

Hypertension, a major cardiovascular risk factor, affects one billion people worldwide, and projections indicate that this number will rise to 1.56 billion patients by 2025 [1]. The pathophysiology of hypertension correlates with many variables, such as kidney disturbances [2], vasculature disturbances [3], and central nervous system (CNS) perturbations [4]. The same mechanism occurs in all of these disorders: decreased nitric oxide (NO) levels, diminished antioxidant capacity in the arteries, heart, brain, and kidney, and increased bioavailability of reactive oxygen species (ROS) as a result of excess ROS generation [5].

Researchers are still investigating the exact processes that link obesity and hypertension as components of the metabolic syndrome. There are a trio of elements involved: renin-angiotensin-aldosterone system (RAAS) activation, increased sympathetic nervous system (SNS) activity, and reduced sodium excretion [6]. Adipose tissue serves as both an energy storage organ and an active endocrine tissue, producing a variety of biologically active proteins known as adipokines [7]. Adipokines are crucial in controlling inflammation, immunity, metabolism, cardiovascular health, and tumors. Nevertheless, dysregulation of adipokines may exacerbate diseases associated with obesity [8]. The adipocytes' colour (brown or white) and their number, size, arrangement, and connections to other cells affect how many adipokines are made by adipose tissue [9]. In obese individuals, researchers have demonstrated a link between higher levels of brown adipose tissue (BAT) and weight loss, as well as a correlation between higher differentiation of brown fat cells and increased energy expenditure in diet-induced obesity. BAT also enhances insulin tolerance and controls glucose homeostasis [10]. Conversely, an excessive buildup of white adipose tissue (WAT) is known to harm the progression of metabolic illnesses, including car-

---

* Corresponding author: E-mail: zainabh@uomosul.edu.iq

diovascular disorders and diabetes mellitus [11]. Interestingly, researchers found brown fat-like cells, sometimes referred to as beige cells, in WAT, and observed a reduction in beige cell features in obese individuals' WAT. Obese patients have elevated levels of most adipokines [12].

Many studies have suggested the role of adipocytes, adipokines, and adipocyte-derived factors in hypertension pathogenesis and long-term blood pressure regulation, as shown in Figure 1. Some adipokines, like resistin, the renin-angiotensin system, perivascular relaxation factor, adiponectin, and leptin , have been shown to help control blood pressure by Yiannikouris et al. [13]. Additionally, Vlasova et al. investigated the role of adipokines such as apelin, resistin, TNF-α, leptin, adiponectin, and interleukin-6 in obesity-associated hypertension [14]. Similarly, Kim et al. also looked at a lot of new adipokines, like lipocalin-2, SFRP5, omentin-1, asprosin, FAM19A5, and neuregulin 4, in heart disease, obesity, and metabolic diseases [15].

Leptin, the first discovered adipokine, plays an endocrine role in adipose tissue. Clinical studies showed that obese individuals experienced elevated levels of leptin along with specific leptin resistance situations, which possibly contributed to obesity-related hypertension. Macrophages mostly produce the protein resistin, which is also present in adipose tissue and elevated in inflammatory circumstances. According to many studies, the concentrations of resistin had been elevated in obesity and hypertension [16]. Adiponectin (APN) has anti-inflammatory effects and serves as a protective mechanism against diseases linked to obesity, such as hypertension [17]. Adipose tissue contains the local renin-angiotensin system (RAS), which produces angiotensin II (Ang II), the most potent vasoactive peptide of the RAS. According to many studies from several different experimental obesity models, the adipose tissue of obese hypertensive patients has shown increased expression of RAS components, including Ang II [18]. Thus, this review article aimed to assess apelin and visfatin's functions and processes in hypertension as well as how ARBs affect these adipokines.
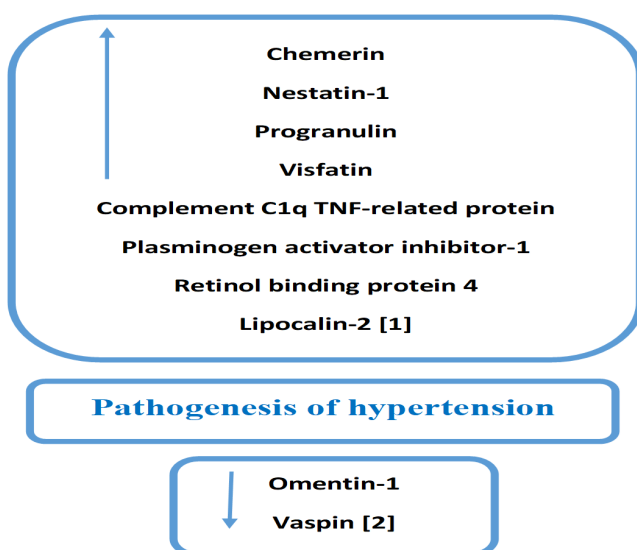

Figure 1. Role of major adipokines in the pathogenesis of hypertension.

APELIN

Apelin (APLN) is biosynthesized from a 77 amino acid (AA) precursor called preproapelin. The apelin history started in 1993 with the cloning of a cDNA from a human genomic library for an orphan receptor known as the "APJ receptor" (putative receptor protein related to the type 1 (AT1) angiotensin receptor). APJ is a member of the GPCR family A [19]. APJ is detected in organs like heart, brain, kidney, lung, and spinal cord. It is also in the vascular endothelium, cardiomyocytes, and vascular smooth muscle cells [20]. Ma et al. showed the first crystal structure of APJR connected to a cyclic apelin-like peptide called AMG3054 at a level of detail of 2.6 angular units. PJR structure is linked to a single-domain antibody with agonist characteristics, and many site-directed mutagenesis investigations have provided insights into the ligand-binding manner and likely activation mechanism. Novel peptides and cyclic analogues are being researched for their possible therapeutic uses because APJR is involved in several physiological processes [21]. APJ connects to Gi proteins, and when it interacts with apelin, it stops adenylate cyclase (AC) from working and lowers the amount of cAMP inside cells. Apelin stimulates the activation of the extracellular signal-regulated protein kinase 1/2 (ERK1/2) mechanisms. It induces vasorelaxation in the endothelium using distinct processes, including ERK1/2, AMP-activated protein kinase (AMPK), phosphatidylinositol 3-kinase/protein kinase B (PI3K-AKT) pathways, and nitric oxide synthase (NOS). Nevertheless, apelin induces vasoconstriction when it acts on vascular smooth muscle cells, but in cardiomyocytes, activation of APJ encourages inotropy through several pathways. A gene on chromosome 11 expresses this seven-transmembrane domain G-protein coupled receptor (GPCR), which shares 31% AA sequence similarity with the human AT1 receptor [19]. Additionally, the cell line expressed the rat apelin receptor, which negatively coupled to adenylate cyclase. Angiotensin II and III were not working, but apelin fragment K17F stopped the production of cAMP at very small levels. The inhibitory effect of K17F on cAMP generation remained unchanged upon N-terminal elongation with a tyrosine or N-terminal deletion of the first four amino acids [22]. In 1998, researchers isolated the endogenous ligand of the APJ receptor from bovine stomach tissue extract. Using specific mutations, the structure-function relationship of the apelin peptide has been thoroughly investigated. Receptor binding is lost when the N-terminal 2RPRL5 motif in the apelin-13 is substituted with an amino acid [23]. The same study demonstrated that minor disruptions in receptor binding result from modifications in the Q1, S6, and H7 residues. These findings highlight the critical function of the 2RPRL5 motif in the activation of APJR. Cyclic analogues of apelin-13 peptide further highlighted the structural and conformational significance of this region. In comparison to other peptide analogues without cyclization of the motif, cyclization of the 2RPRL5 motif resulted in a greater affinity for the receptor. The apelin isoforms demonstrated by the nuclear magnetic resonance (NMR) study reveal that the Arg4–Leu5 and Leu5–Ser6 at the C-terminus (RPRL motif) in the apelin-13 generate a distinctive β-turn that may be important in specific identification by the receptor [24].

Despite slightly inconsistent studies, the C-terminal F13 residue of the apelin isoform appears to be important in activating the receptor. The C-terminal modified residue 4-Cl-F is seen to form many highly conserved interactions with

the receiver's transmembrane region in the AMG3054 bound APJR crystal structure [25]. Alanine substitution of the conserved F13 in the apelin peptide resulted in loss of receptor internalization, indicating its primary role in mediating structural changes that activate the β-arrestin pathway but did not affect its binding to the receptor or activation of the cAMP pathway. Accordingly, F13's binding affinity and ability to reduce blood pressure in mice models increased when hydrophobic, artificial amino acids were substituted for it [26]. Furthermore, apelin peptides were discovered to be inactivated by angiotensin-converting enzyme-2 (ACE2) through the specific cleavage of two C-terminal residues, P12, F13 (number based on apelin-13. By replacing the C-terminal M11 and F13 residues, Wang et al. created peptide analogues that were resistant to ACE2 cleavage; these modified 12-residue peptides demonstrated cardioprotective properties [27].

The apelin gene produces a 77-amino acid precursor peptide that is broken down into 12-to 36-amino acid active fragments, which include pyroglutamate (pyr)-apelin-13, apelin-36, apelin-17, and apelin-13. It has been determined that apelin-13 and apelin-36, to a lesser extent, are the most active isoforms having the greatest activity on the cardiovascular system [28]. Apelin-13 is the predominant isoforms in the heart, while apelin 36 is predominantly present in the lung, testis, and uterus. Both apelin 13 and apelin 36 are substrates of ACE2 (Figure 2) [29].

ACE 2 has a wide range of peptide substrate catalysis abilities. Apelin and ACE2 interact functionally, as evidenced
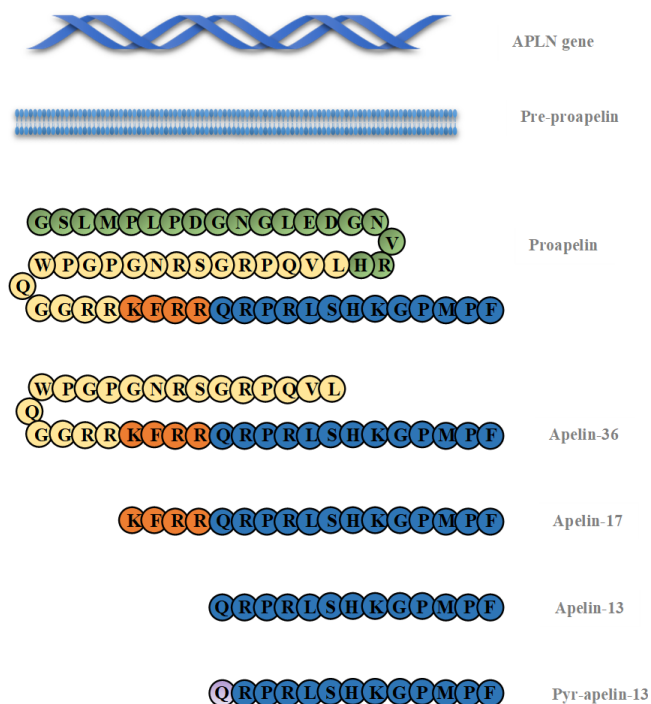

Figure 2. Apelin peptides and the sequences of their isoforms. Pre-proapelin, which is produced by the translation of the APLN gene, is hydrolyzed by many different enzymes to produce apelin-36, 17, and 13. Pyroglutamylate can be generated by modifying apelin-13's N-terminal glutamine, resulting in pyr-apelin-13. The purple accent indicates the altered amino acid [30].

by higher ACE2 activity in vitro and increased ACE2 production in failing hearts in vivo upon apelin therapy [31]. It is interesting to note that researchers observed variations in the development, growth, and cardiac phenotypes of APJ KO and apelin knockout (KO) mice. These findings suggest the existence of another biologically active endogenous ligand for APJ prior to apelin. Two different study groups then discovered a short-secreted peptide that attaches to APJ, giving it the moniker elabela/Toddler [32]. Patients with general and essential hypertension showed a significant decrease in circulatory apelin and elabela concentrations. Upon intraperitoneal injection of apelin, sedated typical rats exhibit decreased systolic and diastolic blood pressure value [33]. A while later, apelin administered intravenously was demonstrated to have decreased blood pressure impact and vasodilation. Apelin administration increases NO production in rats and mice with hypertension [34]. Apelin's hypotensive effects were inhibited by L-NAME, apelin prevented vascular smooth muscle cells (VSMCs) from becoming calcified and eliminated aberrant elevated activation of phosphatidylinositol 3-kinase (PI3K)/ protein kinase-B/endothelial nitric oxide synthase (eNOS) s causes Ang II-induced contraction in diabetic mice's intrarenal arteries [35]. These results suggested that apelin acts through a mechanism that is dependent on NO to produce vasodilation.

Apelin administration also causes vasodilation in human mammary arteries, which can be reversed by cyclooxygenase inhibitors. Furthermore, in diseased state, apelin induces vasodilatation through a prostanoid-dependent mechanism rather than NO [34]. The plasma half-lives of apelin 13 and apelin 36 are no longer than 8 minutes. Apelin is highly unstable in plasma due to its fast decomposition by endogenous protease [36].

However, the rapid degradation of the natural apelin peptides in vivo restricts their application as medicinal agents. Accordingly, many studies investigated the simple homologue substitutions of apelin. A study by Fernandez et al. demonstrated the metabolic stability of APJR agonistic peptides (homoarginine-and cyclohexylalanine-) substitution of apelin analogues with effective anti-hypertensive effects [37]. Furthermore, McKinnie et al. modified the neprilysin degradation part (RPRL motif) of apelin, resulting in an improvement in proteolytic stability (in vitro) with the same receptor-binding affinity and effective cardiovascular activity for potential therapeutic use [38]. Additionally, O'Harte et al. demonstrated the in vitro and in vivo potency of the apelin-13 analogue as an insulinotropic and glucose-lowering agent [39]. Interestingly, Wang et al. developed a novel APLN analogue resistant to ACE2 cleavage with a marked protective effect against in vivo and ex vivo myocardial ischemia-reperfusion injury and angiogenesis promotion [40].

ROLE OF APELIN IN HYPERTENSION

Apelin can block the effects of Ang II, which means that it could have a positive influence on blood pressure and be an appropriate goal for antihypertensive medication. The RAAS plays a key role in the development and progression of hypertension [41]. Both in healthy individuals and heart failure patients, apelin-induced depressor and vasodilation responses remain unchanged throughout RAAS activation. Additionally, stimulation of the apelin-APJ axis has a negative impact on the AT1R-mediated actions via enhancing NO-dependent signalling or building heterodimers with the receptor [42].

APJ is typically associated with AT1R and, in the blood vessel wall, works as an endogenous counter-regulator. Furthermore, apelin stimulates vasodilatation, that even though the renin-angiotensin system is functioning. APJ can combine to create heterodimers with κ-opioid receptors, bradykinin receptors, and neurotensin receptor-1, In contrast to APJ monomers, APJ homodimers-oligomers may trigger distinct signaling processes.

The majority of the research that is now available suggests that apelin significantly lowers blood pressure in hypertensive animal models [43]. Several in vitro studies, however, have documented the impact of apelin administered systemically on raised blood pressure. For instance, administering apelin intravenously to conscious lambs resulted in a brief initial drop in arterial pressure, followed by a subsequent rise in blood pressure and peripheral vascular resistance [44]. As a result, the vasomotor effect of apelin is complex because, depending on the vascular bed and underlying circumstances, it can cause either vasodilation or constriction. Aperin has two effects, which are caused by APJ receptors being present in the smooth muscle and endothelial layers of the blood vessel wall.Vasoactive drugs can directly produce contraction or relaxation in vascular smooth muscle cells, or they can operate on endothelial cells, which can discharge chemicals that mediate both vasoconstriction and vasodilation (such as, prostacyclin and NO [45]. The renin-angiotensin system plays a major role in the development and progression of heart failure, hypertension, and other CVDs. Although apelin does not bind AT1-receptors and angiotensin II (Ang II) does not bind to APJ receptors, APJ and AT1-receptors share a comparable tissue distribution pattern and significant sequence homology [46]. However, stimulation of the apelinergic system has an antagonistic effect on responses mediated by the AT1 receptor, either through increased NO-dependent signaling or through allosteric modulation of the receptor [47]. In both healthy individuals and heart failure patients, apelin-induced vasodilation and depressor responses are maintained throughout renin-angiotensin system activation [48]. According to Chun et al. [49], apelin also prevented Ang II-induced atherosclerosis in ApoE-deficient mice by boosting the production of NO, which reacted to superoxide-induced alterations in the arterial wall. Apelin reduced Ang II-induced contractions in pulmonary arteries from normoxic mice, but not in arteries from animals subjected to chronic hypoxia, suggesting that apelin's antagonistic effects on Ang II signaling may depend on the underlying pathologic situation. According to Sato et al. [50], Apelin-APJ receptor signaling can also enhance the expression of the ACE-2 gene, which may enhance the conversion of Ang II to Angiotensin 1–3 and affect cardiovascular activities.

Apelin may elicit either vasodilation or vasoconstriction, depending on the vascular bed and accompanying circumstances [51]. The presence of APJ in the endothelium and vascular smooth muscle cell layers, as well as the integrity of endothelial cells, are thought to be responsible for apelin's multimodal effects [34]. While apelin receptors are found in vascular smooth muscle cells (VSMC) and vascular endothelium, adipocytes and endothelium appear to be the primary sources of apelin [52]. Apelin's function in the pathophysiology of hypertension has also drawn a lot of interest. Patients with essential hypertension have lower circulating apelin levels, which is correlated with more severe cardiac dysfunction [53], apelin loss increases the development of myocardial damage caused by angiotensin II, and apelin ther-

apy reverses such alterations [54]. Using apolipoprotein E (Apoe) KO mice, apelin enhances NO production to counteract superoxide-induced arterial wall alterations, thereby preventing Ang II-induced atherosclerosis [55]. The apelin-APJ axis strengthened ACE2 expression in failing hearts in vivo and increased ACE2 promoter activity in vitro, which may enhance the transformation of Ang II to Angiotensin 1–7 [31]. Ang 1–7 has been found to have cardioprotective and vasodilator action in animal models by acting on Mas receptors that are present in the heart, brain, kidneys, and blood vessels. Apelin-mediated ACE2 overexpression is a crucial mechanism that prevents the renin-angiotensin system. Additionally, apelin proteins degrade by ACE2 to largely destressed molecules, and they also increase ACE2's synthesis [56].

In rats, water deprivation or central vasopressin administration causes apelin-positive axons to grow along the hypothalamo-hypophyseal tract, increases the number and density of apelin-immunoreactive hypothalamic cells, and reduces apelin release into the bloodstream [57]. Conversely, vasopressin-immunoreactive hypothalamic cells, axons, and vasopressin release are affected negatively. Antagonists of the vasopressin V1 receptor (V1R) reduce these effects. Intravenous or central apelin therapy raises diuresis and reduces serum levels of vasopressin. Moreover, apelin blocks vasopressin V2 receptor agonist-induced cyclic AMP synthesis and calcium influx and reduces insertion into the apical membrane [58]. Apelin receptor was discovered to exist in a mouse CD cell line, and apelin inhibited vasopressin-induced cyclic AMP synthesis. Additionally, apelin increased the calcium signal that came from stimulating vasopressin V1 receptor, indicating that vasopressin V1 receptor's physiological antagonistic actions were intensified. The finding that apelin causes the vasorelaxation of Ang II-preconstricted efferent and afferent arterioles in the rat kidney by blocking Ang II-induced calcium signals offers more proof that apelin has an impact on renal haemodynamics. Both in vivo and human cell model data are insufficient. It has been demonstrated that in healthy volunteers, rising plasma osmolality raises plasma vasopressin and lowers plasma apelin levels, whereas falling plasma osmolality following water loading raises circulating apelin levels and inhibits vasopressin [59].

VISFATIN

WAT primarily produces and secretes visfatin, a recently identified hormone [60]. We also refer to it as Pre-B-cell colony-enhancing factor 1 (PBEF-1), an adipokine that may have a glucose-lowering effect due to its nicotinamide phosphoribosyl transferase activity. It is also known as nicotinamide phosphoribosyl transferase (NAMPT). NAMPT converts nicotinamide into nicotinamide mononucleotide (NMN), and this is transformed to NAD+ by nicotinamide/nicotinic acid mononucleotide adenylyl transferase (Nmnat) [61].

Visfatin is a multifunctional protein that serves a variety of functions. It acts as an adipokine, cytokine, and phosphoribosyltransferase. In the apo, FK-866 (anti-cancer agent)-complexed, and nicotinamide mononucleotide-complexed structures, respectively, there are 915, 934, and 934 amino acid residues out of a total of 982 in the crystal structure of rat (Rattus norvegicus) visfatin. Visfatin's catalytic activity as nicotinamide hosphoribosyltransferase (NAmPRTase) depends on the dimerization process [62]. The presence of nicotinamide phosphoribosyltransferase (NAm-

PRTase) activity in rat visfatin indicates that nicotinamide and phosphoribosyl pyrophosphate (PRPP) may combine to form nicotinamide mononucleotide, and that visfatin can catalyze this process. Furthermore, it has both adipocytokine and cytokine characteristics [63]. Chen et al.s' study showed that pig visfatin has a molecular weight of 52 kDa and 491 amino acids. Its human orthologs have the exact identical exon/intron structure as its three alternative splicing variants, each with 11 exons [64]. Variants 1 and 3 exhibit widespread expression in pig tissues. Human (491), chimpanzee (491), rhesus monkey (490), pig (491), dog (588), cattle (491), sheep (285), rat (491), mouse (491), and chicken (493) are the total amount of amino acids in the chosen mammalian visfatin protein.

Visfatin hormone is a vital candidate in the development of diabetes, obesity, and dyslipidemia since it is an adipocytokine that is currently linked to regulating insulin resistance and showing insulin-mimicking behavior via interacting with the insulin receptor-1 [65]. In 1994, visfatin determined by methods of cloning to be widely expressed and secreted in the lungs, placenta, heart, muscles, liver, bone marrow, and kidney tissues. The highest quantities of expression were found in the muscles and liver, with the liver expressing the most [66]. As a result of visfatin's dual cytokine-like extrinsic activity (pre-B-cell colony-enhancing factor PBEF) and enzymatic intrinsic activity [nicotinamide phosphoribosyltransferase (NAMPT)], researchers have been looking into whether it may have a function in the physiology and pathophysiology of cardiovascular-metabolic diseases [67]. The rate-limiting enzyme for the production of NAD+ in mammalian cells is referred to as intracellular Nampt or iNampt. Extracellular Nampt, or eNampt, is a multifunctional cytokine-like molecule that is produced and secreted via adipocytes as well as additional cell types, such as vascular cells, that are provoked by pro-inflammatory triggers [68].

Visfatin is a cytokine that is elevated in neutrophils under septic circumstances and in the bronchoalveolar lavage fluid of animal models. Neutrophils create PBEF/visfatin in response to endotoxin stimulation, which prevents the apoptosis of neutrophils [69]. A potentially significant novel function of visfatin in the setting of metabolic illness was recently identified in a study by Ezzati-Mobaser et al. [70]. According to the study, visfatin increases the levels of extracellular matrix (ECM) proteins in pre-adipocytes like osteopontin, collagen type VI, MMP-2, and MMP-9 [70]. The salvage process of NAD biosynthesis includes using the intracellular version of visfatin, or iNAMPT. It has been demonstrated that NAD production is essential for fundamental cellular function. Visfatin is a major regulator of multiple cellular components, including sirtuins (SIRTs), poly (ADP-ribose) polymerase (PARPs), CD157, and CD38, due to its capacity to control NAD+ production [71].

ROLE OF VISFATIN IN HYPERTENSION

Adipose tissue is not only an autocrine or paracrine system, but it can also act as a metabolic and non-metabolic organ, leading to cardiovascular diseases (CADs) and related cardiometabolic diseases [72]. Adipose tissues can enter circulatory areas such as the heart or arteries and release hormones to regulate their function. Through the paracrine release of adipokines, adipose storage within the cardiovascular system (CVS), such as perivascular and epicardial adipose tissue, directly influences the vascular barrier and myocardium

[73]. This can have a vasocrine effect on vascular tone, inflammation, endothelial function, and the redox state of the blood vessels [74]. Given their close relationship, both the myocardial and the epicardial (or subepicardial) adipose tissue (EAT) participate in the same microcirculation vasculature and the coronary highways that the EAT lines [75]. So, EAT affects the heart's electrical activity in a paracrine way, and the adipokines it produces change conductivity and make atrial fibrillation (AF) more likely in a number of clinical settings [76]. Perivascular adipose tissue (PVAT), which creates vasculature throughout the body except the cerebral vessels, is another fat deposit that encompasses the coronary arteries. Additionally, PVAT is significantly higher in rotund people and secretes proinflammatory adipokines [77]. It is well-recognized that PVAT malfunction is linked to blood vessel contractility dysregulation, which eliminates natural inflammatory and antioxidant functions and subsequently plays a role in the progression of hypertension (HT) [78].

Visceral rotund is referred to as "visfatin" since it is mostly released from this type of rotund in mice and humans instead of subcutaneous rotund. Nonetheless, research has also indicated that visfatin released in the visceral and subcutaneous fat as well as the perivascular and epicardial fat, has a paracrine influence on CVS [79]. Several findings revealed that patients with hypertension had higher plasma visfatin concentrations [80]. Visfatin is thought to be detrimental to the blood vessels because it promotes the growth of vascular smooth muscle cells (VSMCs), as well as the activation and recruitment of monocytes and macrophages. Visfatin has been shown to have a negative correlation with vascular endothelial activity [81].

Visfatin is an inflammatory protein that raises the levels of IL-6, MMP-3, CAMs, ICAM-1, and VCAM-1, which are all inflammatory and adhesion molecules. Researchers have demonstrated a significant association between visfatin levels and blood levels of IL-4 [82]. The study also showed that treating human VSMCs with visfatin raises the production of inducible nitric oxide synthase (iNOS) [83]. Elevated visfatin stimulates the growth of fibroblasts and vascular smooth muscle cells and contributes to cardiac remodelling and myocardial fibrosis, two significant hypertension factors [84]. Yang et al. demonstrated that the AT1-R-JAK/STAT pathway was primarily responsible for the increase in visfatin expression during the Ang II-induced cardiomyocyte hypertrophy process using the cultured neonatal rat cardiomyocytes [85].

ADIPOKINES AND ANGIOTENSIN II RECEPTOR BLOCKERS

Every category of antihypertensive medicines is associated with significantly reducing the probability of stroke and significant cardiovascular events, but some classes, such as those targeting the RAAS, have excelled in terms of efficacy and safety, making them some of the most commonly prescribed and advised drugs for hypertension [86]. Research and discovery of antihypertensive drugs have primarily targeted the RAAS.

This system implicates four groups of drugs: angiotensin II receptor blockers, ACE inhibitors, direct renin inhibitors, and aldosterone antagonists. The effects of angiotensin II on the vascular system, renal salt and water management, and cellular proliferation are the reasons for the interest in this pathway[87]. Table 1 displays the comparative effects of ARBs on apelin and visfatin. 1995 saw the introduction of

Table 1. Comparisons of the effects of angiotensin receptor blockers (ARBs) on visfatin and apelin.

ARBs	Type of study	Therapy regimen	Adipokine	Results
Losartan [88]	Clinical, hypertensive patients	50 mg once a day	Apelin	Increase serum apelin as a result of inhibition of the renin angiotensin aldosterone system
Losartan [89]	Preclinical in vivo study	30 mg/kg/day	Apelin	A significant increase in apelin mRNA expression
Valsartan [90]	Clinical, hypertensive patients	80 mg tablets for 12 weeks	Visfatin	Increased serum visfatin and decreased LDL levels
Telmisartan [91]	Preclinical in vivo study, female db/db mice	2 mg/kg/day for 11 weeks	Apelin	A significant increase in Kidney APJ and preproapelin mRNA expression
Losartan [92]	Preclinical in vitro, 3T3-L1 cells	10–100 μm for 48 hr.	Apelin	A significant increase in apelin secretion and mRNA expression
Telmisartan [93]	Clinical, non-diabetic essential hypertensive patients with and without insulin resistance	80 mg/day for 6 months	Visfatin	Increased serum levels of visfatin
Candesartan & olmesartan [94]	Clinical, type II diabetic hypertensive patients Candesartan	8 mg/day or olmesartan 10 mg/day for 1 month, then 16 mg and 20 mg candesartan and olmesartan, respectively; for 1 year	Visfatin	There was a significant increase in serum visfatin on candesartan, but no changes on olmesartan therapy
Olmesartan & irbisartan [95]	Clinical, hypertensive obese women	Irbesartan 300 mg/day or olmesartan 40 mg/day for 3 months	Visfatin	A significant decrease in visfatin levels was observed olmisartan and, to a lesser extent, irbisartan

Losartan as the first ARB. At first, it appeared obvious how an ARB works—by inhibiting the angiotensin type 1 (AT1) receptor. However, as more people received therapy and new experimental findings emerged, the confusion around how an ARB functions has grown significantly more complex. Consequently, the analysis of ARB functions has incorporated numerous neurohumoral, cellular, and tissue-based factors. Scientists found that telmisartan stopped Ang II from making visfatin overexpressed. This meant that visfatin was overexpressed through AT1-R but not through AT2-R [85].

CONCLUSION

As research continues to evolve, it elucidates the potential role of apelin and visfatin as independent prognostic factors for cardiovascular disease. While ARBs significantly affect visfatin levels, especially in hypertensive patients, apelin is considered a cardioprotective agent. However, given the contradictory findings attributed to different study populations and methodologies, targeted research is necessary. In general, awareness of these relationships may provide more sophisticated approaches to control hypertension.

ETHICAL DECLARATIONS

Acknoweldgements

None.

Ethics Approval and Consent to Participate

Not required.

Consent for Publication

None.

Availability of Data and Material

None.

Competing Interests

The authors declare that there is no conflict of interest.

Authors' Contributions

All authors were responsible for the literature review and writing the manuscript. The authors read and approved the final version of the manuscript.

REFERENCES

[1] P. Devos and J. Menard. Bibliometric analysis of research relating to hypertension reported over the period 1997- 2016. *J Hypertens*, 37(11):2116–2122, 2019.

[2] O. Z. Ameer. Hypertension in chronic kidney disease: What lies behind the scene. *Front Pharmacol*, 13:949260, 2022.

[3] Y. Hu, M. Chen, M. Wang, and X. Li. Flow-mediated vasodilation through mechanosensitive g protein-coupled receptors in endothelial cells. *Trends Cardiovasc Med*, 32(2):61–70, 2022.

[4] C. Bellocchi *et al.* The interplay between autonomic nervous system and inflammation across systemic autoimmune diseases. *International Journal of Molecular Sciences*, 23(5):2449, 2022.

[5] K. Sugamura and J. F. Keaney Jr. Reactive oxygen species in cardiovascular disease. *Free radical biology and medicine*, 51(5):978–992, 2011.

[6] C. Koliaki, S. Liatis, and A. Kokkinos. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism*, 92:98–107, 2019.

[7] K. J. Moore and I. Tabas. Macrophages in the pathogenesis of atherosclerosis. *Cell*, 145(3):341–355, 2011.

[8] M. Fasshauer and M. Blüher. Adipokines in health and disease. *Trends in pharmacological sciences*, 36(7):461–470, 2015.

[9] P. Mancuso. The role of adipokines in chronic inflammation. *ImmunoTargets and therapy*, 23(5):47–56, 2016.

[10] L. Cheng *et al.* Brown and beige adipose tissue: a novel therapeutic strategy for obesity and type 2 diabetes mellitus. *Adipocyte*, 10(1):48–65, 2021.

[11] M. Longo *et al.* Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. *Int J Mol Sci*, 20(9), 2019.

[12] K. Ohashi, R. Shibata, T. Murohara, and N. Ouchi. Role of anti-inflammatory adipokines in obesity-related diseases. *Trends in endocrinology & metabolism*, 25(7):348–355, 2014.

[13] F. Yiannikouris, M. Gupte, K. Putnam, and L. Cassis. Adipokines and blood pressure control. *Curr Opin Nephrol Hypertens*, 19(2):195–200, 2010.

[14] M. Vlasova, A. K. Purhonen, M. R. Jarvelin, E. Rodilla, J. Pascual, and K. H. Herzig. Role of adipokines in obesity-associated hypertension. *Acta Physiol (Oxf)*, 200(2):107–27, 2010.

[15] J. A. Kim and K. M. Choi. Newly discovered adipokines: Pathophysiological link between obesity and cardiometabolic disorders. *Front Physiol*, 11:568800, 2020.

[16] F. Chang *et al.* Association of higher resistin levels with inflammatory activation and endothelial dysfunction in patients with essential hypertension. *Chinese medical journal*, 126(4):646–649, 2013.

[17] T. M. D. Nguyen. Adiponectin: Role in physiology and pathophysiology. *Int J Prev Med*, 11:136, 2020.

[18] P. Devos and J. Menard. Bibliometric analysis of research relating to hypertension reported over the period 1997–2016. *Journal of hypertension*, 37(11):2116, 2019.

[19] B. F. O'Dowd *et al.* A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11. *Gene*, 136(1-2):355–360, 1993.

[20] C. Read *et al.* International union of basic and clinical pharmacology. cvii. structure and pharmacology of the apelin receptor with a recommendation that elabela/toddler is a second endogenous peptide ligand. *Pharmacological reviews*, 71(4):467–502, 2019.

[21] S. Murali and G. K. Aradhyam. Structure-function relationship and physiological role of apelin and its g protein coupled receptor. *Biophys Rev*, 15(1):127–143, 2023.

[22] G. Hu, Z. Wang, R. Zhang, W. Sun, and X. Chen. The role of apelin/apelin receptor in energy metabolism and water homeostasis: A comprehensive narrative review. *Front Physiol*, 12:632886, 2021.

[23] A. D. Medhurst *et al.* Pharmacological and immunohistochemical characterization of the apj receptor and its endogenous ligand apelin. *J Neurochem*, 84(5):1162–72, 2003.

[24] D. N. Langelaan, E. M. Bebbington, T. Reddy, and J. K. Rainey. Structural insight into g-protein coupled receptor binding by apelin. *Biochemistry*, 48(3):537–48, 2009.

[25] Y. Ma *et al.* Structural basis for apelin control of the human apelin receptor. *Structure*, 25(6):858–866.e4, 2017.

[26] A. Murza *et al.* C-terminal modifications of apelin-13 significantly change ligand binding, receptor signaling, and hypotensive action. *J Med Chem*, 58(5):2431–40, 2015.

[27] W. Wang *et al.* Angiotensin-converting enzyme 2 metabolizes and partially inactivates pyr-apelin-13 and apelin-17: Physiological effects in the cardiovascular system. *Hypertension*, 68(2):365–77, 2016.

[28] A. Folino, P. G. Montarolo, M. Samaja, and R. Rastaldo. Effects of apelin on the cardiovascular system. *Heart failure reviews*, 20:505–518, 2015.

[29] W. Wang *et al.* Angiotensin-converting enzyme 2 metabolizes and partially inactivates pyr-apelin-13 and apelin-17: physiological effects in the cardiovascular system. *Hypertension*, 68(2):365–377, 2016.

[30] M. Dawid *et al.* Apelin, apj, and elabela: Role in placental function, pregnancy, and foetal development—an overview. *Cells*, 11(1):99, 2022.

[31] T. Sato *et al.* Apelin is a positive regulator of ace2 in failing hearts. *The Journal of clinical investigation*, 123(12):5203–5211, 2013.

[32] A. Pauli *et al.* Toddler: an embryonic signal that promotes cell movement via apelin receptors. *Science*, 343(6172):1248636, 2014.

[33] D. Lee *et al.* Characterization of apelin, the ligand for the apj receptor. *Journal of neurochemistry*, 74(1):34–41, 2000.

[34] J. Song, J. Tang, Z. Zhang, Y. Liu, and J. Zhong. Targeting the elabela/apelin-apelin receptor axis as a novel therapeutic approach for hypertension. *Chinese Medical Journal*, 135(09):1019–1026, 2022.

[35] J.-C. Zhong *et al.* The novel peptide apelin regulates intrarenal artery tone in diabetic mice. *Regulatory peptides*, 144(1-3):109–114, 2007.

[36] E. Y. Zhen, R. E. Higgs, and J. A. Gutierrez. Pyroglutamyl apelin-13 identified as the major apelin isoform in human plasma. *Analytical biochemistry*, 442(1):1–9, 2013.

[37] K. X. Fernandez *et al.* Metabolically stable apelin-analogues, incorporating cyclohexylalanine and homoarginine, as potent apelin receptor activators. *RSC Med Chem*, 12(8):1402–1413, 2021.

[38] S. M. K. McKinnie *et al.* Synthetic modification within the "rprl" region of apelin peptides: Impact on cardiovascular activity and stability to neprilysin and plasma degradation. *J Med Chem*, 60(14):6408–6427, 2017.

[39] F. P. M. O'Harte, V. Parthsarathy, C. Hogg, and P. R. Flatt. Apelin-13 analogues show potent in vitro and in vivo insulinotropic and glucose lowering actions. *Peptides*, 100:219–228, 2018.

[40] W. Wang *et al.* Loss of apelin exacerbates myocardial infarction adverse remodeling and ischemia-reperfusion injury: Therapeutic potential of synthetic apelin analogues. *Journal of the American Heart Association*, 2(4):e000249, 2013.

[41] C. Xu *et al.* Elabela antagonizes intrarenal renin-angiotensin system to lower blood pressure and protects against renal injury. *American Journal of Physiology-Renal Physiology*, 318(5):F1122–F1135, 2020.

[42] K Siddiquee, J Hampton, D McAnally, Lauren Therese May, and Layton H Smith. The apelin receptor inhibits the angiotensin ii type 1 receptor via allosteric transinhibition. *British journal of pharmacology*, 168(5):1104–1117, 2013.

[43] C. U. Andersen, O. Hilberg, S. Mellemkjær, J. E. Nielsen-Kudsk, and U. Simonsen. Apelin and pulmonary hypertension. *Pulm Circ*, 1(3):334–46, 2011.

[44] C. J. Charles, M. T. Rademaker, and A. M. Richards. Apelin-13 induces a biphasic haemodynamic response and hormonal activation in normal conscious sheep. *Journal of endocrinology*, 189(3):701–710, 2006.

[45] M. Creager and S. Henkin. *Vascular Medicine, An Issue of Cardiology Clinics, E-Book: Vascular Medicine, An Issue of Cardiology Clinics, E-Book*, volume 39. Elsevier Health Sciences, 2021.

[46] A. Mughal and S. T. O'Rourke. Vascular effects of apelin: Mechanisms and therapeutic potential. *Pharmacol Ther*, 190:139–147, 2018.

[47] K. Siddiquee *et al.* Apelin protects against angiotensin ii-induced cardiovascular fibrosis and decreases plasminogen activator inhibitor type-1 production. *J Hypertens*, 29(4):724–31, 2011.

[48] G. D. Barnes *et al.* Sustained cardiovascular actions of apj agonism during renin-angiotensin system activation and in patients with heart failure. *Circ Heart Fail*, 6(3):482–91, 2013.

[49] H. J. Chun *et al.* Apelin signaling antagonizes ang ii effects in mouse models of atherosclerosis. *J Clin Invest*, 118(10):3343–54, 2008.

[50] T. Sato *et al.* Apelin is a positive regulator of ace2 in failing hearts. *J Clin Invest*, 123(12):5203–11, 2013.

[51] Y. Rikitake. The apelin/apj system in the regulation of vascular tone: friend or foe? *The journal of biochemistry*, 169(4):383–386, 2021.

[52] J.-C. Zhong *et al.* Targeting the apelin pathway as a novel therapeutic approach for cardiovascular diseases. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, 1863(8):1942–1950, 2017.

[53] M. Przewlocka-Kosmala, T. Kotwica, A. Mysiak, and W. Kosmala. Reduced circulating apelin in essential hypertension and its association with cardiac dysfunction. *Journal of hypertension*, 29(5):971–979, 2011.

[54] T. Sato *et al.* Loss of apelin augments angiotensin ii-induced cardiac dysfunction and pathological remodeling. *International journal of molecular sciences*, 20(2):239, 2019.

[55] H. J. Chun *et al.* Apelin signaling antagonizes ang ii effects in mouse models of atherosclerosis. *The Journal of clinical investigation*, 118(10):3343–3354, 2008.

[56] E. Marsault *et al.* The apelinergic system: a perspective on challenges and opportunities in cardiovascular and metabolic disorders. *Annals of the New York Academy of Sciences*, 1455(1):12–33, 2019.

[57] A. Reaux-Le Goazigo, A. Morinville, A. Burlet, C. Llorens-Cortes, and A. Beaudet. Dehydration-induced cross-regulation of apelin and vasopressin immunoreactivity levels in magnocellular hypothalamic neurons. *Endocrinology*, 145(9):4392–400, 2004.

[58] A. Hus-Citharel, L. Bodineau, A. Frugière, F. Joubert, N. Bouby, and C. Llorens-Cortes. Apelin counteracts vasopressin-induced water reabsorption via cross talk between apelin and vasopressin receptor signaling pathways in the rat collecting duct. *Endocrinology*, 155(11):4483–93, 2014.

[59] M. Azizi *et al.* Reciprocal regulation of plasma apelin and vasopressin by osmotic stimuli. *J Am Soc Nephrol*, 19(5):1015–24, 2008.

[60] T. Di Raimo *et al.* Adipokines and their involvement as a target of new drugs. *Journal of Pharmacovigilance*, 3(3):166, 2015.

[61] T. Romacho *et al.* Visfatin/enampt induces endothelial dysfunction in vivo: A role for toll-like receptor 4 and nlrp3 inflammasome. *Scientific reports*, 10(1):5386, 2020.

[62] A. Dakroub *et al.* Visfatin: A possible role in cardiovasculo-metabolic disorders. *Cells*, 9(11):2444, 2020.

[63] A. A. Grolla *et al.* Nicotinamide phosphoribosyltransferase (nampt/pbef/visfatin) is a tumoural cytokine released from melanoma. *Pigment Cell Melanoma Res*, 28(6):718–29, 2015.

[64] H. Chen *et al.* Gene organization, alternate splicing and expression pattern of porcine visfatin gene. *Domest Anim Endocrinol*, 32(3):235–45, 2007.

[65] K. L. Stromsdorfer *et al.* Nampt-mediated nad+ biosynthesis in adipocytes regulates adipose tissue function and multi-organ insulin sensitivity in mice. *Cell reports*, 16(7):1851–1860, 2016.

[66] B. Samal *et al.* Cloning and characterization of the cdna encoding a novel human pre-b-cell colony-enhancing factor. *Molecular and Cellular Biology*, 14(2):1431–1437, 1994.

[67] T. B. Dahl, S. Holm, P. Aukrust, and B. Halvorsen. Visfatin/nampt: a multifaceted molecule with diverse roles in physiology and pathophysiology. *Annual review of nutrition*, 32:229–243, 2012.

[68] C. Ruiz-Fernández. Molecular relationships among obesity, inflammation and intervertebral disc degeneration: are adipokines the common link? *International journal of molecular sciences*, 20(8):2030, 2019.

[69] N González, Z Moreno-Villegas, A González-Bris, J Egido, and Ó Lorenzo. Regulation of visceral and epicardial adipose tissue for preventing cardiovascular injuries associated to obesity and diabetes. *Cardiovascular diabetology*, 16:1–11, 2017.

[70] S. Ezzati-Mobaser *et al.* The up-regulation of markers of adipose tissue fibrosis by visfatin in pre-adipocytes as well as obese children and adolescents. *Cytokine*, 134:155193, 2020.

[71] E. Verdin. Nad+ in aging, metabolism, and neurodegeneration. *Science*, 350(6265):1208–1213, 2015.

[72] A. Rodríguez, S. Becerril, A. W. Hernández-Pardos, and G. Frühbeck. Adipose tissue depot differences in adipokines and effects on skeletal and cardiac muscle. *Current opinion in pharmacology*, 52:1–8, 2020.

[73] Y. K. Jumaah, Z. H. Fathi, and J. A. Mohammad. Angiotensin-converting enzyme inhibitors and

adipokines: The role of visfatin and apelin in cardiovascular disease management. *Iraqi Journal of Pharmacy*, 20(Supplementary Issue 1):250–260, 2023.

[74] M. F. Landecho *et al.* Relevance of leptin and other adipokines in obesity-associated cardiovascular risk. *Nutrients*, 11(11):2664, 2019.

[75] M. Packer. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *Journal of the American College of Cardiology*, 71(20):2360–2372, 2018.

[76] M. Zhou, H. Wang, J. Chen, and L. Zhao. Epicardial adipose tissue and atrial fibrillation: possible mechanisms, potential therapies, and future directions. *Pacing and Clinical Electrophysiology*, 43(1):133–145, 2020.

[77] H. Hu, M. Garcia-Barrio, Z.-. Jiang, Y. E. Chen, and L. Chang. Roles of perivascular adipose tissue in hypertension and atherosclerosis. *Antioxidants & Redox Signaling*, 34(9):736–749, 2021.

[78] E. DeVallance *et al.* Exercise training prevents the perivascular adipose tissue-induced aortic dysfunction with metabolic syndrome. *Redox biology*, 26:101285, 2019.

[79] S. Ali, R. Alam, H. Ahsan, and S. Khan. Role of adipokines (omentin and visfatin) in coronary artery disease. *Nutrition, metabolism and cardiovascular diseases*, 33(3):483–493, 2023.

[80] A. Shaheen, R. Nazli, S. Fatima, R. Ali, I. Khan, and S. Khattak. Adipokine serum visfatin level in pregnancy induced hypertension and uncomplicated pregnancy. *Pak J Med Sci*, 32(6):1419–1424, 2016.

[81] K. Takebayashi, M. Suetsugu, S. Wakabayashi, Y. Aso, and T. Inukai. Association between plasma visfatin and vascular endothelial function in patients with type 2 diabetes mellitus. *Metabolism*, 56(4):451–458, 2007.

[82] P.-l. Yu, C. Wang, W. Li, and F.-X. Zhang. Visfatin level and the risk of hypertension and cerebrovascular accident: a systematic review and meta-analysis. *Hormone and Metabolic Research*, 51(04):220–229, 2019.

[83] K. L. Shi *et al.* Atorvastatin antagonizes the visfatin-induced expression of inflammatory mediators via the upregulation of nf-κ b activation in hcaecs. *Oncology Letters*, 12(2):1438–1444, 2016.

[84] J. Xiao *et al.* Involvement of dimethylarginine dimethylaminohydrolase-2 in visfatin-enhanced angiogenic function of endothelial cells. *Diabetes/metabolism*

research and reviews, 25(3):242–249, 2009.

[85] L. Chang *et al.* Angiotensin ii type-1 receptor-jak/stat pathway mediates the induction of visfatin in angiotensin ii-induced cardiomyocyte hypertrophy. *The American journal of the medical sciences*, 343(3):220–226, 2012.

[86] D. Ettehad *et al.* Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *The Lancet*, 387(10022):957–967, 2016.

[87] T. K. Ma, K. K. Kam, B. P. Yan, and Y. Y. Lam. Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. *Br J Pharmacol*, 160(6):1273–92, 2010.

[88] M. Hemmati, F. Abharzanjani, T. Kazemi, and F. Estanesti. Comparing the apelin level in hypertensive patients who received hypertension drugs. *Modern Care Journal*, 17(4), 2020.

[89] M. Nishida *et al.* The role of apelin on the alleviative effect of angiotensin receptor blocker in unilateral ureteral obstruction-induced renal fibrosis. *Nephron Extra*, 2(1):39–47, 2012.

[90] I. Atacan *et al.* The effects of valsartan treatment on visfatin levels and lipid profiles in newly diagnosed hypertensives. *Turkish Journal of Medical Sciences*, 43(1):57–62, 2013.

[91] T. Müller *et al.* Apelinergic system in the kidney: implications for diabetic kidney disease. *Physiological reports*, 6(23):e13939, 2018.

[92] Do. Y. Kim *et al.* Angiotensin at1 receptor antagonism by losartan stimulates adipocyte browning via induction of apelin. *Journal of Biological Chemistry*, 295(44):14878–14892, 2020.

[93] J. Lan *et al.* The relationship between visfatin and homa-ir in hypertensive patients, and the effect of antihypertensive drugs on visfatin and homa-ir in hypertensive patients with insulin resistance. *Diabetes research and clinical practice*, 94(1):71–76, 2011.

[94] G. Derosa *et al.* Differential effects of candesartan and olmesartan on adipose tissue activity biomarkers in type ii diabetic hypertensive patients. *Hypertension Research*, 33(8):790–795, 2010.

[95] D. De Luis *et al.* Effects of olmesartan vs irbesartan on metabolic parameters and visfatin in hypertensive obese women. *Eur Rev Med Pharmacol Sci*, 14(9):759–763, 2010.