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Role of major adipokines in hypertension: A literature review

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Abstract

The incidence and prevalence of hypertension are increasing as a consequence of the obesity epidemic. Adipocytes and their variety of factors make contributions to the long-term regulation of blood pressure. The pathophysiologic states of hypertension, including obesity, are regulated by the production of adipocyte-derived factors. Increased body mass index was closely linked to elevated blood pressure. Mostly the hypertensive subjects were obese as well as overweight. There are numerous adipokines, however, this review article only focuses on the major adipokines including chemerin, visfatin, retinol-binding protein 4, PAI-1, monocyte chemotactic protein-1, omentin-1, lipocalin-2, vaspin, progranulin, complement c1q tumor necrosis factor-related protein, and nesfatin-1 role in the pathogenesis of hypertension. This review article concludes the significant association of major adipokines in the pathogenesis of hypertensives. New research should be focused on other newly reported adipokine roles in hypertensive subjects and the management of these adipokines in hypertensive subjects. The discovery of this information could result in the creation of antihypertensive medications, particularly those that focus on obesity-related hypertension.

INTRODUCTION

The risk of hypertension and cardiovascular diseases increases due to obesity mainly central obesity. At least two-thirds of the prevalence of hypertension may be directly

attributed to obesity, according to many population-based studies that revealed the estimated risk of hypertension[1]. Many studies have reported the role of adipokines in hypertension. Adipocytes and their variety of factors make contributions to the long-term regulation of blood pressure. The pathophysiologic states of hypertension including obesity are regulated by the production of adipocyte-derived factors. In the same way, Yiannikouris et al (2010) explained the adipokines in blood pressure control. There were a few adipokines such as leptin, adiponectin, perivascular relaxation factor, renin-angiotensin system, and resistin [2]. Also, Vlasova et al (2010) studied the adipokines in obesity-associated hypertension such as interleukin-6, TNF-α, resistin, leptin, adiponectin, and apelin [3]. Likewise, Kim et al (2020) assessed a few newly discovered adipokines in obesity and cardiometabolic disorders including lipocalin-2, SFRP5, omentin-1, asprosin, FAM19A5, neuregulin 4 [4].

However, this review article only focuses on the major adipokines such as chemerin, visfatin, retinol-binding protein 4 (RBP4), plasminogen activator inhibitor-1 (PAI-1), monocyte chemotactic protein-1 (MCP-1), omentin-1, lipocalin-2 (LCN-2), vaspin, progranulin (PGRN), complement C1q tumor necrosis factor-related proteins (CTRPs), and nesfatin-1 role in hypertension which were not reported collectively as explained in figure 1.

There are many keywords which have been used including chemerin, visfatin, retinol-binding protein 4, plasminogen activator inhibitor-1, monocyte chemotactic protein-1, omentin-1, lipocalin-2, vaspin, progranulin, and nesfatin-1. Google Scholar, PubMed, Science Direct and other different databases were used to review the literature. 15 May 2022 was the last date for the search. The language of clinical studies was restricted to English.

Main text

There are numerous adipokines, but this review article only focuses on chemerin, visfatin, retinol-binding protein 4, plasminogen activator inhibitor-1, monocyte chemotactic protein-1, omentin-1, lipocalin-2, vaspin, progranulin, complement C1q tumor necrosis factor-related protein, and nesfatin-1 role in hypertension as explains in table 1.

1. Chemerin

Chemerin is a very recent adipokine. Chemerin was once categorized as a chemokine because of its immune system origins. Chemerin activates tissue macrophages as well as natural killer cells, plasmacytoid dendritic cells, and dendritic cells. According to several studies, circulating chemerin was substantially correlated with positive blood pressure, body mass index, and visceral fat. It was recognized as an adipokine in 2007, and the receptor via which it was discovered to function was known as chemerin chemokine-like receptor 1 (CMKLR1) or ChemR23, which is now known as Chemerin 1. In vascular smooth muscle cells, chemerin is a mitogen when infused in the mouse that elevates the blood pressure. The long-term remodeling of blood vessels in hypertension was the proliferative effect which might be influenced due to chemerin [5].

In the obesity and metabolic syndrome state, chemerin was a new adipokine with elevated concentration. Gu et al (2014) study stated the role of chemerin in hypertension which explained that a high chemerin level was an independent predictor of the presence of hypertension when metabolic variables were adjusted in the logistic regression analysis. In hypertensive subjects, components of the metabolic syndrome as well as markers of inflammation were strongly related to chemerin and independently linked to hypertension after adjustment for age, gender, and metabolic risk factors [6]. Additionally, an independent relationship was found between chemerin levels with an index of arterial function as well as early atherosclerosis in essential hypertension [7]. Also, Wojcik et al (2020) concluded that increased systolic blood pressure could be linked to elevated chemerin levels in obese children [8].

Chemerin elicits a variety of functions *via* chemokine-like receptor 1 (CMKLR1). Yamamoto et al (2021) reported increased protein expression of chemokine-like receptor 1 in the paraventricular nucleus (PVN) for the first time, which was at least partly

responsible for systemic hypertension in spontaneously hypertensive rats [9]. Moreover, Ferland et al (2019) study resulted that Chemerin, which is generated from adipose tissue rather than the liver, is a key factor in the relationship between hypertension and excessive fat intake. This information might influence the development of antihypertensive medications, particularly those that target obesity-related hypertension[10].

2. Visfatin

In hypertensive patients, the mean visfatin level was significantly higher. It was also found significantly higher in the prehypertensive group compared to participants with normal blood pressure. Visfatin levels, systolic blood pressure, and diastolic blood pressure were found significantly positive correlation [11]. Likewise, Wang et al. (2010) study demonstrated that Lyon hypertensive (LH) rats had elevated levels of serum visfatin which were linked with lipid metabolic abnormalities [12]. Similarly, Liakos et al (2015) the study reported significantly higher levels of visfatin in high normal BP subjects. It has been examined as a marker for detecting phases of essential hypertension and may induce vascular inflammation as well as the destabilization of atherosclerotic plaque [13]. In the same way, Yu et al (2019) the study concluded a higher level of plasma visfatin concentration in cerebrovascular accident and hypertension patients compared to healthy subjects [14].

Additionally, Kocelak et al (2014) found a positive correlation between plasma visfatin/nicotinamide phosphoribosyl transferase (NAMPT) concentrations with inflammation and insulin resistance and are decreased in the oldest. Plasma levels of visfatin/NAMPT were not linked to the presence of hypertension in elderly subjects [15]. Moreover, Hsu et al (2016) reported the association between a subsequent renal function with increased circulating visfatin in nondiabetic hypertensive patients [16].

Also, Parimelazhagan et al (2021) a positive correlation between visfatin and high-density lipoproteins as well as diastolic blood pressure. Visfatin levels were shown to be elevated and associated with pro-inflammatory cytokines in hypertensive individuals with hypertriglyceridemia. The most frequent comorbidity in cancer patients has been identified as hypertension, and visfatin may represent a unique potential therapeutic target for this condition in both cancer patients and survivors [17]. In the contribution to the pathogenesis of hypertension in patients with visceral obesity, increased plasma visfatin concentration could play a significant role. In patients with visceral obesity, activation of the Renin-Angiotensin-Aldosterone System (RAAS) by dietary salt restriction and upright positioning did not affect plasma visfatin levels [18].

3. Retinol Binding Protein 4

Retinol-binding protein 4 (RBP4) is mainly secreted by adipocytes with 21-KDa adipokines. It has a role in the induction of insulin resistance, also closely linked to cardiovascular diseases and other risk factors including coronary heart disease, obesity, hypertension, hyperlipidemia, and heart failure [19]. Increased prevalence of hypertension, as well as myocardial infarction, were correlated with elevated levels of serum retinol-binding protein 4 which also contribute to insulin resistance. Blood pressure increases due to elevated serum levels of retinol-binding protein 4 and lack of retinol-binding protein 4 reduce it, with commensurate changes in aortic eNOS (Ser1177) phosphorylation. To reduce blood pressure, retinol-binding protein 4 Levels can be lowered through enhanced eNOS- mediated vasodilatation and could be a novel therapeutic approach for hypertension [20].

Moreover, Li et al (2019) explained that hypertension is a leading cause of death as well as cardiovascular disease. The increased range of cardiovascular diseases is due to retinol-binding protein 4 which is an inflammatory factor. In individuals with essential hypertension, blood pressure levels were strongly connected with retinol-binding protein

4, which may be regulating left ventricular diastolic function[21]. Cardiovascular disease, as well as blood pressure, was correlated with circulating retinol-binding protein 4 [22-25], potentially also secondary to reduced renal clearance due to hypertensive nephropathy [26].

Furthermore, Deng et al (2014) elucidated that retinol-binding protein 4 is a novel adipokine which modulates the action of insulin in numerous diseases and insulin resistance correlated with cardiovascular disease. After adjusting for body mass index, waist circumference, and waist-hip ratio, a modestly linear relationship was observed between retinol-binding protein 4 Levels and systolic blood pressure, diastolic blood pressure and HOMA-β. In conclusion, the authors explain the elevated levels of retinol-binding protein 4 in naïve hypertension patients; no variations were seen in obese or non-obese hypertensive people. For the first time, researchers suggested that retinol-binding protein 4 was considerably elevated in newly diagnosed hypertensive Chinese patients but did not play a role in the development of insulin resistance [27].

Solini et al (2009) stated showed retinol-binding protein-4 levels were higher in nave hypertensive women and linked with the degree of carotid intima-media thickness (IMT), suggesting that this adipocytokine may be involved in the regulation of the atherosclerotic process exerted by adipose tissue as an endocrine organ[22]. Likewise, Zhang et al (2017) demonstrated that the retinol-binding protein 4 Level was independently linked with systolic blood pressure and diastolic blood pressure. serum retinol-binding protein 4 Level was significantly higher and closely linked with blood pressure in the prehypertensive Chinese population [28]. Moreover, Stuck et al (2010) concluded that In addition to the current conventional treatment for hypertension, which focuses on inhibiting the angiotensin system, reducing serum retinol-binding protein 4 may be a unique therapeutic strategy for the condition [29].

4. Plasminogen Activator Inhibitor-1

Over 35% increased risk of developing hypertension was linked to a higher level of plasma plasminogen activator inhibitor-1 (PAI-1) in a high-risk population. Peng et al. (2017) resulted that plasma plasminogen activator inhibitor-1 could contribute to the development of hypertension through pathways beyond traditional risk factors [30]. PAI-1 levels were correlated with plasma renin activity, aldosterone, and insulin resistance in hypertensive subjects. Therefore, the authors suggested that aldosterone could be a vital factor contributing to the variability of plasminogen activator inhibitor-1 Levels in hypertensive subjects [31]. Moreover, Kaikita et al. (2001) showed that In the presence of long-term NOS inhibition, PAI-1 impairment was sufficient to prevent the structural vascular alterations associated with hypertension. For the prevention of arteriosclerotic cardiovascular disease, direct inhibition of vascular plasminogen activator inhibitor-1 activity could provide a new therapeutic strategy [32].

5. Monocyte Chemotactic Protein-1

The pathogenesis of metabolic syndrome and various metabolic parameters including essential hypertension, obesity, and diabetes have involved the contribution of monocytes chemotactic protein-1 (MCP-1). The quantitative evaluation of MCP-1 was a diagnostic as well as a prognostic marker of atherosclerotic disease [33]. Both resistant (RH) and hypertensive subjects had similar levels of MCP-1 and decreased in hypertensive subjects with existing left ventricular hypertrophy. The authors suggested possible downregulation in MCP-1 levels in hypertensive patients with left ventricular hypertrophy, regardless of hypertension strata [34]. In the same line, Wang et al (2015) reported for the first time which indicated that the deletion of transient receptor potential vanilloid type 1 (TRPV1) aggravated the renal injury in salt-sensitive hypertension *via* enhancing monocytes chemotactic protein-1 (MCP-1)/CCR2 (C-C Motif Chemokine Receptor 2) signaling-dependent inflammatory responses [35].

6. Omentin-1

Omentin-1 is released from visceral adipose tissue, visceral fat, stromal vascular cells, and endothelial cells. It is a glycoprotein of the adiponectin family which has an anti-inflammatory effect. Waist circumference, body mass index, and insulin resistance were negatively correlated with circulating omentin-1. In addition, serum omentin-1 was employed as a biomarker for conditions such as metabolic syndrome, diabetes mellitus, coronary artery disease, cancer, atherosclerosis, and inflammatory illnesses. Both stage 1 and 2 HT subgroups had lowered levels of omentin-1 as compared with normotensive control (72.19 ± 54.33 ng/mL for the stage 1 HT subgroup; 62.45 ± 47.01 ng/mL for the stage 2 HT subgroup; and, 147.84 ± 58.55 ng/mL for healthy normotensive controls; overall $P < 0.001$). In addition, the authors demonstrated that serum omentin-1 Levels decreased in patients with hypertension as compared with normotensive controls which could be attributed to a combined outcome of endothelial dysfunction, inflammation as well as renal injury in the setting of hypertension [36].

Tetrahydroxystilbene glycoside (TSG) exhibits a preventive as well as hypotensive impact on endothelial dysfunction and obesity-related hypertension through increased level of omentin-1. Omentin-1 plays a vital role in the process of endothelial dysfunction and obesity-related hypertension. In conclusion, the authors explained that the down-regulation of omentin-1 induces endothelial dysfunction and hypertension in obesity. Tetrahydroxystilbene glycoside treatment (at least partially) increases omentin-1 *via* promoting the binding of peroxisome proliferator-activated receptor-γ (PPAR-γ) and intelectin-1 (*Itln-1)* promoter in adipose tissues, subsequently exerts protective effects on endothelial function *via* activating Akt/eNOS/NO signaling and attenuating oxidative/nitrative stress. According to the findings, TSG may be developed as a potent anti-hypertension drug that prevents endothelial dysfunction and obesity-related cardiovascular disorders [37]. On the other hand, Cetin et al (2022) suggested that Circulating omentin-1 levels are negatively correlated with the existence of metabolic

syndrome and may serve as an accurate diagnostic to anticipate the onset of metabolic syndrome in hypertensive individuals [38].

7. Lipocalin-2

Lipocalin- is a proinflammatory adipokine which is upregulated in obese humans as well as animals. The harmful involvement of lipocalin-2 in people with hypertension was proposed by the authors. Mice lacking lipocalin-2 were shielded against the cardiovascular impairment brought on by diet-induced obesity. Mice fed a high-fat diet have aberrant vasodilator responses after receiving lipocalin-2. The removal of lipocalin-2 was facilitated by Polyamination, whereas the buildup of deamidated lipocalin-2 in arteries results in vascular inflammation, endothelial dysfunction, and hypertension [39]. Obesity and inflammation are risk factors for hypertension and lipocalin-2 has recently been recognized as a biomarker of these two diseases. Haplotype GGTCC was linked to the progress of higher blood pressure at follow-up after adjusting for baseline age, sex, systolic blood pressure, and follow-up duration. Among subjects not taking antihypertensive medication, carriers of the haplotype GGTCC had higher systolic blood pressure compared to noncarriers. For the first time, the researchers presented the results and hypothesized that blood pressure may be impacted by genetic variations in LCN2. More research is needed to better understand how lipocalin-2 controls blood pressure [40]. Whereas, Chen et al (2020) examined the contributing role of LCN2 in liver fibrosis as well as portal hypertension in alcoholic hepatitis (AH) and might represent a new therapeutic target [41].

8. Vaspin

Vaspin is a relatively novel adipocytokine and visceral adipose tissue-derived serine protease inhibitor which has a protective effect against metabolic diseases such as type II diabetes as well as obesity. Vaspin exerts a role in anti-migratory as well as anti-inflammatory through antioxidative effects in vascular smooth muscle cells. For the pathogenesis of hypertension, inflammatory responses, as well as migration of smooth muscle in the peripheral vascular wall, are key mechanisms. The prevention of elevated

SBP was significantly prevented by long-term vaspin treatment at 8 weeks of age. No reactivity of isolated mesenteric artery did not affect vaspin in spontaneously hypertensive rats (SHR). Oppositely, Vaspin dramatically reduced mesenteric artery wall hypertrophy in SHR, as well as the expression of tumor necrosis factor-alpha and the generation of reactive oxygen species in isolated SHR mesenteric arteries. In conclusion, the authors showed for the first time that vaspin reduces the rise in SBP in SHR by preventing peripheral vascular hypertrophy, probably through antioxidative and anti-inflammatory mechanisms [42].

In contrast, Fathey et al. (2022) reported vaspin levels and high blood pressure are inversely correlated. The newly diagnosed uncomplicated hypertensive patients' group had serum vaspin levels that were lower than those of the control group, and those with macrovascular and/or microvascular complications had serum vaspin levels that were significantly lower than those of both the uncomplicated hypertensive and control groups. The early diagnosis of macrovascular and/or microvascular hypertension problems may be possible using plasma vaspin as a standalone predictive biomarker [43].

9. Progranulin

Progranulin, one of the adipokines produced by adipose tissue, is a multifunctional regulatory protein having neuroprotective, growth-promoting, and anti-inflammatory properties. Visceral adipose tissue expresses it, and obesity raises the level of circulating progranulin, which plays a role in the pathophysiology of insulin resistance linked to obesity [44].

Kaur et al (2020) have examined that elevated progranulin (PGRN) levels in response to elevated tumor necrosis factor-α (TNF-α) levels depict the counter-regulation by progranulin to neutralize tumor necrosis factor-α. Findings of reduced PGRN/TNF ratio, and it was an independent predictor of SBP, ascertain the key role of imbalance in the pro-and anti-inflammatory environment in hypertension. As a result, the vicious network idea linking immunity, obesity, inflammation, and blood pressure is strengthened. Moreover, long-term studies must be conducted to examine this SBP and progranulin

cross-link. Finding a balance between the pro- and anti-inflammatory states in future research would allow for the exploration of novel target areas for the treatment of hypertension rather than just focusing on the effects of the pro-inflammatory environment [45].

10. C1q tumor necrosis factor-related proteins

The adipokine superfamily's C1q tumor necrosis factor-related proteins (CTRPs), which are homologs of adiponectin and have a variety of roles as well as a tight association with metabolic illnesses such improper lipid metabolism, high blood sugar, and diabetes. Moreover, CTRPs have highly participated in the regulation of various pathological processes as well as physiological processes such as protein kinase pathways, inflammation, cell proliferation, glycolipid metabolism, and cell apoptosis [46]. Additionally, Han et al (2018) reported that CTRP1 involvement in the regulation of blood pressure homeostasis by preventing dehydration-induced hypotension for the first time [47].

In this regard, Su et al (2019) concluded a potential biomarker for the prognosis of patients with essential hypertension may be CTRP1 levels, which were found to be elevated and associated with subclinical target organ damage (STOD) in essential hypertension, including damage to the heart and kidney [48]. Recently discovered adipokine CTRP1 was found to increase aldosterone synthesis in the adrenocortical carcinoma cell line H295R, suggesting that it may be a pathophysiologic connection between hyperaldosteronism and hypertension in overweight and obese individuals. Also, Seccia et al reported that CTRP-1 expression extends beyond adipocytes and occurs in both healthy and abnormal adrenocortical tissues supporting the idea that CTRP-1 modulates aldosterone synthesis in both the healthy zona glomerulosa and in adenomas that produce aldosterone, albeit *via* unidentified receptors and signalling mechanisms. The fact that CTRP-1 was expressed in myelolipomas together with adenomas that produce aldosterone raises the possibility that CTRP-1 may cause an excess of aldosterone and the growth of ZG cells [49].

11. Nesfatin-1

In addition to the central mechanism, the brain and peripheral tissues also play a role in the control of blood pressure in vivo via altering vascular contractility. Patients with type 2 diabetes or metabolic syndrome may experience hypertension due to nesfatin-1 or its precursor protein, nesfatin/NUCB2. Nesfatin-1, a novel essential molecule, may have a role in hypertension and be utilized to treat obesity and type 2 diabetes [50].

In the same way, Zhao et al (2015) found that nesfatin-1 levels in fasting plasma were shown to be significantly higher in hypertension patients than in control groups, particularly in patients who were overweight or obese. Nesfatin-1 may be crucial in the development of obesity-related hypertension and may also raise the chance of developing this condition [51]. In the same context, Güneş et al (2020) concluded that Nesfatin-1 concentrations were elevated and an independent predictor of hypertension in obese patients. The hypertension group had greater body mass index, weight, and serum Nesfatin-1 concentrations [52]. Also, Lu et al (2018) investigated nesfatin-1 as a key modulator in vascular remodeling and hypertension by facilitating vascular smooth muscle cell phenotypic switching and proliferation [53].

CONCLUSION

This review concludes with the association between major adipokines with elevated blood pressure. Likewise, numerous studies have reported the elevated concentration of chemerin, visfatin, retinol-binding protein 4, plasminogen activator inhibitor-1, monocyte chemotactic protein-1, lipocalin-2, progranulin, complement c1q tumor necrosis factor-related protein, and nesfatin-1 in the hypertension patients. In contrast, omentin-1 and vaspin had lowered concentrations in hypertensive subjects. There are other newly reported adipokines including follistatin-like 1, secreted protein acidic and rich in cysteine, secreted frizzled-related protein 5, a family with sequence similarity to 19 members A5, wingless-type inducible signaling pathway protein-1 need to focus on the association with hypertension. Further studies require to find the exact mechanism of action of these adipokines in hypertensive subjects and therapeutic approaches are

required to control the increasing prevalence of hypertension with obesity, which ultimately reduces the incidence of obesity-associated hypertension and cardiovascular diseases.

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