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Comparative evaluation of serum apelin, visfatin, and lipid levels in overweight hypertensive patients on enalapril versus telmisartan therapy

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ABSTRACT

Objectives. *Visfatin and apelin are two adipokines that recently gained a special interest in hypertension research as they may have a role in the pathogenesis of hypertension and are closely related to the renin-angiotensin system. This study aimed to evaluate the serum levels of apelin and visfatin in uncontrolled newly diagnosed hypertensive patients, controlled hypertensive patients managed by enalapril and controlled hypertensive patients managed by telmisartan.*

Patients and methods. *The study population included 126 participants, who were divided into four groups established as healthy participants, newly diagnosed hypertensive patients, hypertensive patients managed by enalapril and hypertensive patients managed by telmisartan.*

Outcomes. *Serum apelin levels reduced significantly in newly diagnosed hypertensive patients, with a significant increase in visfatin levels compared with control group. Enalapril-treated patients expressed significantly higher apelin levels with a significant reduction in visfatin levels compared with newly diagnosed. Apelin levels were significantly increased in enalapril-treated patients compared telmisartan-treated group. Additionally, a significant reduction in visfatin levels were found in telmisartan group compared with newly diagnosed hypertensive patients. Moreover, a significant positive correlation was found between HDL and visfatin in patients receiving treatment. Additionally, visfatin was negatively correlated with triglycerides and VLDL in the same patient group.*

Conclusions. *In light of the data collected so far, whether visfatin and apelin play roles in the pathophysiology of hypertension remains unclear and further research is still required to fully understand its relevance. Nevertheless, high visfatin and low apelin levels appear to be intrinsic characteristics of uncontrolled hypertension, indicating that these adipokines could be potential biomarkers for this disease.*

Keywords: Apelin, Hypertension, Visfatin, Telmisartan, Enalapril

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INTRODUCTION

Hypertension is a significant cardiovascular risk factor; by 2025, 1.56 billion people are expected to have this disease, which can be described as an average systolic blood pressure of more than 140 mm Hg and an average diastolic blood pressure of more than 90 mm Hg [1]. Because hypertension has a multifactorial etiology, investigations must evaluate multiple risk factors, and an important risk factor for resistant hypertension is the presence of obesity. Obesity is consistently described as the presence of chronic inflammation. Adipokines generally increase in the presence of increased inflammation and may provide insight mechanistic differences in the development of hypertension. Hypertension and obesity are linked as metabolic syndrome components [2,3]. Under normal physiological conditions, adipocytes release anti-inflammatory adipokines that also have anti-atherogenic, cardio-protective, and insulin-sensitivity-enhancing properties. However, in pathological states such as obesity, dysfunctional adipocytes proliferate and create pro-inflammatory and atherogenic adipokines [4,5]. Apelin is an adipose tissue-derived adipokine binds to apelin receptor (APJ), which is widely expressed in marked concentration in cardiovascular tissues, exerting potent vasodilator and positive inotropic effects. APJ is a member of G-protein coupled receptor (GPCR) shares 31% of its amino acid (AA) sequence with the human AT1 receptor. Nevertheless, it cannot bind to radiolabeled Ang II. Apelin concentration significantly decreased in hypertensive patients [6]. Visfatin, also referred to as Pre-B-cell colony-enhancing factor 1 (PBEF-1), is an adipokine secreted from visceral fats. Visfatin is a proinflammatory mediator, considered to be associated with plaque destabilization, atherosclerosis, insulin receptor activation, and cardiovascular disease. Previous studies showed that hypertensive patients exhibited higher plasma visfatin levels [7]. Nicotinamide phosphoribosyltransferase (Nampt), which is released by cardiomyocytes, encourages the development of detrimental ventricular remodeling and cardiac hypertrophy, two characteristics that are crucial to hypertension [8].

The pathophysiology of hypertension is mostly caused by excessive and prolonged over activation of the renin-angiotensin system (RAS).

There are two basic strategies to inhibit the RAS: direct blockage of the angiotensin receptors or inhibition of the ACE. The apelin system counteracts the effects of the renin-angiotensin system, and apelin and AT1 receptors are expressed together throughout the cardiovascular system. Additionally, the systems might control one another reciprocally. Seo et al. [9] demonstrated that blockage of AT1 receptor, down-regulating cardiac apelin and apelin receptor mRNA in an animal model of heart failure is recovered. Similarly, an AT1 blocker restores the down-regulated cardiac apelin mRNA caused by angiotensin II infusion. ACE2 is an important negative modulator of angiotensin II, which transforms angiotensin II into angiotensins1-7 that stimulate vasodilatation. Apelin peptides are degraded by ACE2 into ge-nerally less active substances in failing heart, additionally apelin regulates the RAS cardioprotective axis, which consists of ACE2/Ang1-7/Mas signaling, by increasing the transcription and levels of Ace2 mRNA in a negative feedback loop (10). According to RAS and visfatin association, Chang et al. [11] demonstrated that visfatin expression was mostly upregululated via the JAK\STAT pathway, during the AT1-R mediated cardiomyocyte hypertrophy which was induced by angiotensin II. Enalapril (ACE inhibitor) and telmisartan (ARB), have been the focus of much research due to their potential to lower blood pressure and improve cardiovascular function. Within the renin-angiotensin-aldosterone system, limited researches had linked the antihypertensive effect of these drugs to the levels of apelin, visfatin, and lipid profile in hypertensive patients. The present study was designed to evaluate the comparative effects of telmisartan and enalapril on apelin and visfatin levels, and lipid profile in hypertensive patients.

PATIENTS AND METHODS

Study design inclusion and exclusion criteria

This case-control study was designed to target three patient groups: newly diagnosed hypertensive patients, enalapril-treated hypertensive patients, and telmisartan-treated hypertensive patients. Exclusion criteria comprised pregnant and lactating women, individuals with liver or kidney diseases, any participant who had allergy or contraindication to either enalapril or telmisartan, individuals currently participating in another clinical trial or those who have participated in a trial in the past 3 months, individuals unable to comply with study procedures or visits. Participants were asked to sign a permission document following full explanation of the trial's protocol and approval. Control group participants should have no known history of hypertension, cardiovascular diseases, or any other significant chronic diseases. Participants of newly diagnosed hypertension should not be on any antihypertensive medication. Participants on antihypertensive medications (enalapril or telmisartan) should be on treatment for at least 5 weeks, and they asked to be able to adhere to study protocol and medication schedule.

Study participants

The study involved 126 participants with an age range between 35-62 years, 29 healthy people were enrolled as a control group, and 32 newly diagnosed hy-

pertensive patients, 29 hypertensive patients managed by enalapril, and 29 hypertensive patients managed by telmisartan. For all participants, body mass index (BMI) was calculated from the measured weight and height.

Biochemical measurement

Five milliliters blood sample were obtained from all participants and tubes were gently inverted many times to ensure proper mixing with the clotting factor and allowed to stand for 15 minutes. Then, tubes centrifuged at 2500 RPM for 20 minutes to obtain the sera. The obtained serum from each blood sample were divided into 4 eppendorf tube of 0.5 ml, then stored at -20°C for estimation of apelin, visfatin, TC, LDL, TG, VLDL and HDL.

Concentrations of apelin and visfatin were demonstrated by application of ELISA technique using the devise BioTek ELx800 Absorbance Microplate Reader. The kits used were provided by Bioassay Technology Laboratory BT LAB (Shanghai Korain Biotech Co.).

Serum levels of TC and TG are determined by enzymatic colorimetric method using BIOLABO kit, while VLDL and LDL levels were determined using Friedewald's equation [12].

Statistical analysis

All data are expressed as an average value ± standard deviation (SD). Data were analysed using non parametric (kruskal-wallis) test followed by comparison of all groups data using dunn's multiple comparison test. Spearman's correlation was utilized to determine the presence of correlation between the parameters under study. Using GraphPad Prism version 10.0 (San Diego, California, USA).

RESULTS

Demographic characteristics of the study population

The demographic characteristics of the study population at baseline were matched between control and patient groups and no significant variation were found. However, analysis of clinical characteristics that include systolic and diastolic blood pressure are considered significantly higher in patient groups compared to control group Table 1.

Lipid profile, apelin and visfatin

Analysis of lipid profile parameters, apelin and visfatin were summarized in Table 2. TC is found to be significantly higher in newly diagnosed group in comparison to control group (p value=0.0103). Conversely, there is no significant variation between control, patient groups on enalapril and telmisartan. Additionally, TG exhibited

TABLE 1. *Demographical and clinical characteristics in patients and control groups*

Parameters	Control (n=31)*	Newly diagnosed hypertensive (n=31)#	Enalapril (n=32)^	Telmisartan (n=32)
Age (years)	47.27±5.589	50.40±7.347	51.50±6.546	51.60±8.467
BMI (kg/m^2)	26.56±4.205	28.87±7.065	27.34±3.945	27.89±2.855
Gender	13F	12F	15M	18M
	17M	18M	15F	12F
SBP (mmHg)	120.1±2.68	149.9±13.40****	123.4±4.96####	122.1±2.23####
DBP (mmHg)	79.67±2.20	98.79±7.75**	83.59±3.95	84.57±3.79

Results are expressed as mean ± standard deviation and are significantly different where indicated (*p <0.05, ***p <0.001, ****p <0.0001; in comparison to control; ##p <0.01 in comparison to newly diagnosed; ^ in comparison to enalapril) using kruskal wallis test followed by Dunn's multiple comparison test. N: number of participants. HT: hypertension, BMI: body mass index, M; male, F: female, SBP; systolic blood pressure, DBP; diastolic blood pressure. Mean and standard deviation were obtained by descriptive statistics/prism.

TABLE 2. *Serum apelin, visfatin and lipid profile of the studied population*

Parameters	Control*	Newly diagnosed#	Enalapril^	Telmisartan
TC (mg/dl)	150.1±16.85	176±38.05*	159.4±36.55	171.6±32.72
TG (mg/dl)	109.6±34.24	202±68.15****	219.2±199.1**	214.1±121.6****
LDL (mg/dl)	77.89±16.35	100±31.55*	78.80±27.21	97.64±24.79*
VLDL (mg/dl)	21.37±6.292	28.95±13.20	30.36±8.279**	30.53±13.08*
HDL (mg/dl)	48.59±4.759	41.13±6.942**	43.77±8.434	39.06±6.655****
Apelin (ng\L)	240.8±56.23	176.3±72.65*	244.6±82.85#	191.5±111.7^
Visfatin (ng\ml)	13.68±3.003	17.52±3.783*	11.86±5.292###	12.14±7.382###

TC: total cholesterol. LDL: low-density lipoprotein. TG: triglyceride. VLDL: very low-density lipoprotein. HDL: high-density lipoprotein. Values set as mean ± standard deviation (SD), where (*p < 0.05, **p <0.01, ***p <0.001, ****p <.0001; in comparison to control; #p <0.05, ###p < 0.001, ####p<.0001 in comparison to newly diagnosed; ^p <0.05, ^^^p <0.001 in comparison to enalapril), variations between parameters were determined by kruskal wallis test, followed by Dunn s multiple comparison test.
Mean and standard deviation calculated by descriptive statistics.

a high significant elevation in newly diagnosed hypertensives and patients using telmisartan (p value >0.0001) in comparison to control group, and to a lesser extent, a significant (p value=0.0010) increment in patients using enalapril compared with control group. LDL was expressed a significant elevation in newly diagnosed hypertensives (p value=0.0143) and in patients using telmisartan (p value=0.0227) when compared with control group. Moreover, VLDL values were significantly elevated in patients using enalapril (p value=0.0036) and in patients using telmisartan (p value=0.0239). HDL expressed variable values in the studied population. When compared with healthy control, HDL was significantly decreased in newly diagnosed hypertensives (p value=0.0013) and patients using telmisartan (p value >0.0001). Additionally, statistical analysis of adipokines, apelin and visfatin were revealed a significant variation among the population of the entire study. Apelin was shown to be significantly decreased in newly diagnosed group (p value=0.0202) when compared to control. Furthermore, apelin exhibited a significant elevation in patients using enalapril when compared with newly diagnosed hypertensive group (p value=0.013) and patients using telmisartan (p value=0.0388), respectively. While visfatin expressed a significant elevation in newly diagnosed group (p value = 0.0335) in comparison with control. Moreover, visfatin exhibited a high significant reduction in patients using enalapril (p value =0.0002) and those using telmisartan (p value=0.0003) when compared with newly diagnosed hypertensives.

TABLE 3. *Correlation of visfatin in controlled hypertensive group*

Parameters	Telmisartan		Enalapril	
	R	P value	R	P value
TG	-0.3577	0.0364*	-0.3503	0.034*
HDL	0.3675	0.0324*	0.3842	0.022*
VLDL	-0.3553	0.0374*	-0.3574	0.031*

Results were computed by using non parametric spearman correlation with one tailed P value and 95% confidence interval. Significant *p value <0.05.

DISCUSSION

The study groups were matched in terms of age and gender based on their baseline characteristics. Furthermore, the BMI values retained matched throughout all groups to eliminate any potential influence of these factors on the examined parameters.

The primary findings of the current study indicate a significant reduction in serum apelin levels among newly diagnosed individuals with hypertension compared with control group. Previous studies had indicated that apelin may have a potential involvement in the pathogenesis of hypertension [13,14]. In both animal models and clinical research, it has been observed that participants with hypertension exhibit reduced levels of apelin in comparison to those with normal blood pressure [15,16]. A study performed by Najafipour H et al. [17] exhibited that hypertensive rats express decreased amounts of both mRNA and protein APJ receptors in their heart, kidney, and aorta Apelin and AngII have contrasting effects on blood vessels. Regarding this matter, it has been observed that the administration of either apelin has a hypotensive impact, suggesting that this peptide may have a therapeutic role in reversing hypertension [18]. Furthermore, apelin has the ability to enhance ACE2 expression, serving as an additional mechanism to counteract RAS. In addition, it has been shown that apelin acts as a positive regulator of ACE2, which in turn promotes the degradation of Ang-II. [10]. Consistent with the findings from laboratory experiments, mice lacking the apelin gene also exhibited a decrease in ACE2 expression and, as a result, a reduced amount of ACE2 protein [19]. Additionally, ACE2 functions as an adverse controller of vasoconstriction and diastolic dysfunction generated by Ang-II, through the process of breaking down Ang-II into Ang-(1-7). Furthermore, ACE2, being a multipurpose enzyme, has been found to metabolize apelin [20]. Another mechanism by which apelin counteract the renin-angiotensin system (RAS) involves the production of heterodimers through the interaction of APJ and AT1R. This interaction leads to the blockage of angiotensin II binding to its receptor and the activation of the signaling cascade [21]. Apelin KO mice expressed reduced ACE2 level, elevated superoxide formation and increased NADPH oxidase action [19].

There is a biphasic role of apelin in vasomotor tone comprising two distinct components: endothelium-dependent and endothelium-independent activities. The activation of endothelial nitric oxide synthase (eNOS) via phosphorylating Akt is facilitated by the binding of Apelin-13 to APJ in vascular endothelial cells. Vasodilation is induced by the diffusion of nitric oxide (NO) from the endothelial cell to the vascular smooth muscle cells (VSMCs) [22,23]. In contrast, concerning animal studies, researches demonstrated that apelin directly interacts with its receptor APJ on VSMCs, leading to vasoconstriction and worsening hypertension in the presence of induced endothelial dysfunction [24]. ACE inhibitors have been proven to enhance endothelial function in animals suffering from heart failure [25] and in individuals diagnosed with coronary artery disease [26]. This impact is associated with a decrease in angiotensin II levels and an increase in the production of bradykinin. Furthermore, ACE inhibitors induce an increase in eNOS expression in animals [26]. The impact of ACE inhibitors on eNOS expression is facilitated by

bradykinin B2-receptors. ACE inhibitors and AT1 blockers also suppress the generation of reactive oxygen species (ROS) and vasoconstrictors resulting from COX-2, which have a role in the protective effects of these drugs on the endothelium [27].

Hypertensive patients using enalapril express significant elevation in apelin in comparison with newly diagnosed hypertensive patients. Our finding is in line with the study conducted by Hongxian Wu et al. [28] This study demonstrated a significant reduction in plasma apelin, apelin mRNA and APJ mRNA in perirenal adipocyte of OH-rats (obesity induced hypertension) and they were restored by perindopril treatment. Moreover, our study is also agreed with the finding of hung et al. [29] which demonstrated a significant elevation of apelin peptide released from 3T3-L differentiated adipocyte after treatment with captopril and peridinopril.

The current study conducted that patients using telmisartan has significant reduction in apelin levels when compared with patients using enalapril, suggesting that apelin may undergo degradation by ACE2 [30]. Therefore, our finding is supported by Jessup's study which expressed that losartan significantly enhanced ACE2 activity in the heart of hypertensive mRen2 rat, while Lisinopril stimulated cardiac ACE2 to a lesser extent than losartan [31]. It has been found that telmisartan decreased the levels of profilin-1 and elevated the levels of ACE2 in hypertensive rats. This is accompanied by a significant decrease in blood pressure and a reduction in aortic hypertrophy [32]. Thus, apelin modulation of RAS was thought to be limited due to rapid degredation by elevated ACE2 in patients using telmisartan, while enalapril exhibits lower ACE2 expression. Therefore, patients using enalapril demonstrated higher apelin than patients using telmisartan due to lower ACE2 level obtained with ACEi compared with ARBs.

In our study, visfatin is significantly increase in newly diagnosed hypertensives compared with control group. Out of the 8 case control studies that had been demonstrated, 6 of them were agreed with our study, indicated that visfatin levels were considerably elevated in hypertensive individuals compared to normotensive individuals [33-40].

The current study revealed that visfatin is significantly reduced in patients groups using enalapril and those on telmisartan in comparison with newly diagnosed hypertensive group. Our finding is agreed with hung et al. (29) which revealed that captopril, peridinopril and losartan exhibited reduction in the mRNA expressions of visfatin in 3T3 L1 adipocyte, captopril expressed highest inhibition of visfatin mRNA expression followed by peridinopril and losartan, respectively.

Our findings is also agreed with a study conducted by Eyileten et al. [41] that shown that the administration of an ACE inhibitor, known for its ability to lower plasma aldosterone levels, resulted in a reduction in circulating visfatin levels among individuals diagnosed with diabetic nephropathy. Ma junhana et al. [42] demonstrated that aldosterone may inhance visfatin expression via the GR-ERK1/2 signal pathway in 3T3-L1 adipocytes. This study enhance our findings that enalapril and telmisartan reduce serum visfatin as a result of inhibition of aldosterone in RAAS. Chang liang et al, conducted a study that agreed with our study. This study revealed that the induction of cardiac hypertrophy in cultured neonatal rat cardiomyocytes by Ang II was linked to an upregulation of visfatin expression mostly via the AT1R-JAK/STAT pathway. A dose- and time-dependent increase in the expression of visfatin and brain natriuretic peptide was seen in cardiomyocytes produced by Ang II. However, the administration of AT1R antagonist (telmisartan) prior to Ang II treatment effectively prevented the rise in visfatin expression induced by Ang II [11].

Additionally, there is a positive correlation between visfatin and HDLc and a negative correlation between visfatin and TG in patients treated with enalapril. This finding is agreed with jin,hua et al. [43]. This study demonstrated a positive correlation between visfatin and HDLc in obese adolescents. Furthermore, wang et al.'s study found a correlation between plasma NAMPT concentration and HDL-cholesterol levels, as well as low triglyceride levels, in non-diabetic Caucasian patients. Additionally, obese people with a lower plasma NAMPT content had lower HDL-cholesterol levels and greater triglyceride levels in comparison to lean individuals. This study elucidated the association between visfatin and lipid profile by considering the cytosolic role of PBEF as a nicotinamide phosphoribosyltransferase (NAMPT) [44].

CONCLUSION

However, most of the findings concerning adipokines from in vivo and in vitro studies are limited until now. Because of apelin and visfatin involvement in blood pressure regulation, fluid balance, and angiogenesis, current findings clearly suggests that apelin and visfatin are involved in the pathophysiology of hypertension, encouraging prospective studies to assess whether visfatin and apelin can be predictive of hypertension.

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