DOI: 10.4274/MMJ.galenos.2024.16098
Medeni Med J 2024;39:204-210

Original Article

Comparative Effects of Candesartan Versus Enalapril on Apelin, Visfatin, and Lipid Levels in Non-obese Hypertensive Patients

Obez Olmayan Hipertansif Hastalarda Kandesartan ve Enalaprilin Apelin, Visfatin ve Lipid Düzeyleri Üzerindeki Karşılaştırmalı Etkileri

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ABSTRACT

Objective: Apelin and visfatin are adipokines secreted from adipose tissue that play important roles in regulating blood pressure. Therefore, the current study aimed to investigate the effects of candesartan versus enalapril on apelin, visfatin, and lipid profiles in hypertensive patients.

Methods: In this case-control study, 120 participants were enrolled in four groups; Healthy people, newly diagnosed hypertensive patients, and enalapril- and candesartan-treated patients.

Results: Serum apelin levels were significantly lower and visfatin levels were significantly higher in newly diagnosed hypertensive patients compared with the control group (p=0.0015, p=0.0175 respectively). Moreover, apelin levels were higher and visfatin levels were lower in the candesartan-treated patients compared with the newly diagnosed group (p=0.0487, p<0.0001 respectively). Interestingly, apelin levels were non-significantly higher and visfatin levels were significantly lower in enalapril-treated patients compared with the newly diagnosed group (p<0.0001).

Conclusions: Lower apelin and higher visfatin levels are associated with newly diagnosed patients with hypertension. Interestingly, the findings suggest that ACE inhibition and angiotensin receptor blockade by enalapril and candesartan, respectively, positively regulate apelin and visfatin levels in hypertension. Specifically, candesartan regulates these adipokine to a greater extent than enalapril.

Keywords: Apelin, visfatin, lipid, hypertension, candesartan, enalapril

ÖZ

Amaç: Apelin ve visfatin, yağ dokusundan salgılanan ve kan basıncının düzenlenmesinde önemli rol oynayan adipokinlerdir. Bu nedenle, bu çalışmada hipertansif hastalarda kandesartan ve enalaprilin apelin, visfatin ve lipid profilleri üzerindeki etkilerinin araştırılması amaçlanmıştır.

Yöntemler: Bu olgu-kontrol çalışmasında 120 katılımcı dört gruba ayrıldılar; sağlıklı kişiler, yeni tanı konmuş hipertansif hastalar, enalapril ile tedavi gören hastalar ve kandesartan ile tedavi gören hastalar.

Bulgular: Yeni tanı konmuş hipertansif hastalarda, kontrol grubuna kıyasla, serum apelin düzeyleri anlamlı derecede düşük ve visfatin düzeyleri anlamlı derecede yüksekti (sırasıyla p=0,0015, p=0,0175). Ayrıca, kandesartan ile tedavi edilen hastalarda, apelin düzeyleri yeni tanı konulan gruba kıyasla daha yüksek ve visfatin düzeyleri daha düşüktü (sırasıyla p=0,0487, p<0,0001). İlginç bir şekilde, yeni tanı konulan grup ile kıyaslandığında, enalapril ile tedavi edilen hastalarda apelin düzeyleri anlamlı olmayan bir şekilde daha yüksek ve visfatin düzeyleri anlamlı bir şekilde daha düşüktü (p<0,0001).

Sonuçlar: Düşük apelin ve yüksek visfatin düzeyleri yeni tanı konmuş hipertansiyon hastalarıyla ilişkili bulunmuştur. İlginç bir şekilde, bulgular sırasıyla enalapril ve kandesartan ile ACE inhibisyonu ve anjiyotensin reseptör blokajının, hipertansiyonda apelin ve visfatin seviyelerini olumlu yönde düzenlediğini göstermektedir. Özellikle, kandesartan bu adipokinleri enalaprilden daha çok düzenlemektedir.

Anahtar kelimeler: Apelin, visfatin, lipid, hipertansiyon, kandesartan, enalapril

INTRODUCTION

Hypertension is a prevalent condition characterized by persistently elevated blood pressure that increases the risk of developing cardiovascular diseases (CVDs) and other serious health complications[1]. The main causes of hypertension include genetic predisposition, a sedentary lifestyle, high salt intake, alcohol consumption, psychological stress, and obesity. Alternative methods for treating hypertension should be considered due to

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Received: 12 June 2024
Accepted: 26 August 2024
Online First: 05 September 2024

Cite as: Jumaah YK, Fathi ZH, Mohammad JA. Comparative Effects of Candesartan Versus Enalapril on Apelin, Visfatin, and Lipid Levels in Non-obese Hypertensive Patients. Medeni Med J. 2024;39:204-210

its multifactorial etiology. One potential risk factor of hypertension in patients with obesity is chronic mild inflammation. Adipose tissues release adipokine in response to inflammation, and these molecules may be associated with hypertension.

Apelin, visfatin, and several other peptides have been recognized as adipokines[2]. By activating the G-protein-coupled receptor angiotensin II (AngII) protein J receptor (APJ), apelin increases diuresis by opposing arginine vasopressin, causing vasodilation with a corresponding reduction in blood pressure through a nitric oxide-dependent mechanism and has a positive inotropic effect on the myocardial[3]. Interestingly, apelin decreases the release of free fatty acids, increases the thickness of the perilipin layer around lipid vacuoles, and increases its stability against lipase[4]. Elevated low-density lipoprotein-cholesterol (LDL-c) levels are associated with lower apelin levels[5].

Visfatin was identified in 2005. It is unclear how visfatin contributes to hypertension pathophysiology. Visfatin produces oxidative pressure, which damages NO and increases endothelin factor 1 levels, possibly leading to atherosclerosis and vasoconstriction[6]. Interestingly, visfatin increases the synthesis of interleukin 6, which is a potential inhibitor of adipogenesis, and influences the metabolism of humane adipocytes by lowering lipoprotein lipase activity[7].

Low plasma apelin levels are associated with arterial hypertension and atherosclerosis. In contrast, elevated visfatin levels can induce vascular inflammation, destabilize atherosclerotic plaques, and serve as markers for determining the stages of essential hypertension[8].

Apelin and visfatin were previously reported to affect food intake and lipid metabolism. The salivary and serum levels of these adipocytokine have been extensively evaluated as biomarkers for the early diagnosis of CVDs[9,10]. Visfatin has a specific appeal for researchers due to its role in the pathogenesis of hypertension and the possibility of using its serum levels as a prognostic biomarker for hypertension detection. Visfatin may alter metabolic processes involved in lipid and glucose metabolism via its NAMPT enzyme-like activity. Furthermore, apelin has been reported to block lipolysis and enhance the stability of lipid vacuoles by rendering them resistant to lipases. Interestingly, apelin is related to higher lipid levels and can be used as an indicator of premature atherosclerosis in hypertensive patients[11].

There are conflicting studies on the comparative effects of candesartan and enalapril on adipokine levels in hypertensive patients[12]. Therefore, the aim of this study was to determine whether treatment with enalapril or candesartan influences plasma apelin, visfatin, and lipid profiles in non-obese hypertensive patients.

MATERIALS and METHODS

Subjects and Study Designs

This comparative case-control study included 120 subjects (controls and hypertensive of both sexes) aged between 38 and 65 years and was classified into four groups (30 samples each); group A: healthy subjects as controls, group B: hypertensive patients (newly diagnosed), group C: enalapril-treated patients (20 mg once daily) for 1 year, and group D: candesartan-treated patients (16 mg once daily) for 1 year. The current case-control study conducted between September 2023 and February 2024 in the Kirkuk governorate included the following hospitals (Hawija General Hospital, Azadi Teaching Hospital in Kirkuk, and Kirkuk General Hospital). The ethical integrity of this study was paramount and was conducted under ethical guidelines and with approval from the Kirkuk Health Province Department Knowledge Management and Research Division (approval no.: 631, date: 05/10/2023). Their endorsement for the study was documented in a letter dated October 5, 2023, bearing reference number 631, and informed consent was obtained from all participants. Pregnant and lactating women, patients taking drugs other than candesartan or enalapril, those taking dietary supplements, patients with acute or chronic health conditions other than hypertension, patients changing medications during the study year, smokers, patients with a history of drinking, and anyone unable to follow the study procedures were excluded from the study. Body mass index (BMI) was determined from anthropometric data (height and weight) for each group.

Collection of Specimens

Venous blood samples (5 mL) were collected after an overnight fast from the control and patient subjects. The blood samples were immediately transferred to gel tubes from each participant and incubated for 10 min at 37 °C in a water bath. After that, samples were centrifuged for 10 min at 2000-3000 xg to separate the serum. Serum samples were divided into 3 parts and transferred promptly by micropipette into Eppendorf tubes, labeled, and refrigerated at 20 °C for later analysis.

Estimation of Serum Apelin and Visfatin Levels

Apelin and visfatin hormone levels were estimated using the enzyme-linked immunosorbent assay technique

at 450 nm using a kit supplied by Bioassay Technology Laboratory (Shanghai Korain Biotech Company).

Estimation of Serum Lipid Profile

Cobas c311 was utilized to quantify serum total cholesterol (TC), high-density lipoprotein (HDL), and triglycerides by enzymatic colorimetric techniques using the detergent cholesterol esterase, cholesterol, and its esters are released from lipoprotein which formed H_2O_2 and hydrolyzes the esters.

LDL and very low-density lipoprotein (VLDL) were estimated using Friedewald's equation[13].

Statistical Analysis

GraphPad Prism software was used to conduct statistical analyses. The Mann-Whitney U and Kruskal-Wallis tests, which were followed by Dunn's multiple comparisons test, were used to conduct two or multiple comparisons. Apelin and visfatin levels were correlated with other laboratory parameters using Spearman rank correlation analysis. The statistical significance level was set at $p<0.05$, and all quantitative data were presented as medians (minimum-maximum). Version 10 of the GraphPad Prism software (San Diego, California, USA) was used in all experiments.

RESULTS

Demographic information for Study Groups

Table 1 shows the ages, sex, BMI, and systolic and diastolic blood pressures of the hypertensive patients and controls. No significant differences were found between the study groups.

Validation of Serum Apelin and Visfatin

Serum level of apelin was significantly lower in newly diagnosed hypertensive patients than in the control group with p-value 0.0015. The circulating level of apelin was significantly higher in the candesartan-treated patients compared with the newly diagnosed hypertensive group at p-value 0.0487. However, no statistically significant differences were observed in the enalapril-treated group compared with the other groups and the candesartan-treated group compared with the control group, as shown in Figure 1. Additionally, serum levels of visfatin showed significantly elevated in the newly diagnosed hypertensive patients compared with the control group (p=0.0175) and lower in both the candesartan- and enalapril-treated patients compared with the newly diagnosed hypertensive group with p-value <0.0001. However, compared with the control group, no statistical significance was found for enalapril- and candesartan-treated patients, as shown in Figure 2.

Table 2 shows the serum levels of apelin, visfatin, and lipids in the control, newly diagnosed, and hypertensive-treated groups. It was observed that serum TC, TG, LDL, and VLDL levels were significantly higher in newly diagnosed hypertensive patients with p-value, <0.0001, 0.001, 0.0003, 0.0001 respectively, along with low HDL-cholesterol (HDL-c) levels, compared with the control group with p-value 0.0146. Concomitant serum levels of TC and LDL-c were significantly lower in enalapril-treated patients with p-value 0.0095 for TC and 0.0182 for LDL-c, while serum levels of other lipid parameters were non-significantly lower compared with newly diagnosed hypertensive patients. Moreover, analysis of the results revealed that compared with newly diagnosed hypertensive groups, the candesartan-treated group had lower levels of TC (p=0.0187) and non-significantly lower levels of other lipid parameters.

Compared with the control group, enalapril-treated patients showed significantly higher levels of serum TG, VLDL with p-value 0.036, 0.0005 respectively, with no significant variations in other lipid parameters.

Our data showed that circulating levels of TC, TG, LDL, and VLDL were significantly higher in the candesartan-treated patients compared with the control group

Table 1. Demographic characteristics of hypertensive patients and control subjects.

Parameters	Control n (30)	Newly diagnosed HT n (30)	Enalapril n (30)	Candesartan n (30)
Age (years)	45 (38-54)	43 (39-65)	48 (40-62)	46 (39-65)
Sex (M, F)	16, 14	19, 11	15, 15	11, 19
BMI (kg/m^2)	24.62 (22.47-24.7)	24 (22.09-25)	24.36 (18.49-25)	24.75 (20.6-24.97)
Blood pressure				
SBP (mmHg)	120 (115-121)	155 (139-155)	123 (120-130)	120 (118-125)
DBP (mmHg)	79 (79-81)	95 (95-110)	82 (81-83)	80 (78-82)

Values are presented as medians (minimum-maximum) BMI: Body mass index, M: Male, F: Female, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

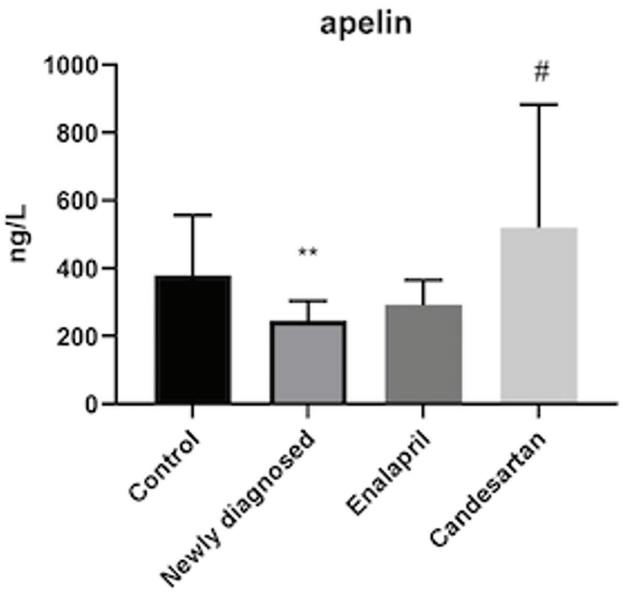

Figure 1. Effects of enalapril and candesartan on serum level of apelin. *Indicates statistically significant differences compared with the control group, and # indicates statistically significant differences compared with the newly diagnosed hypertensive group (#p<0.05, **p<0.01), as shown by Dunn's multiple comparisons post-hoc test upon completion of the Kruskal-Wallis test.

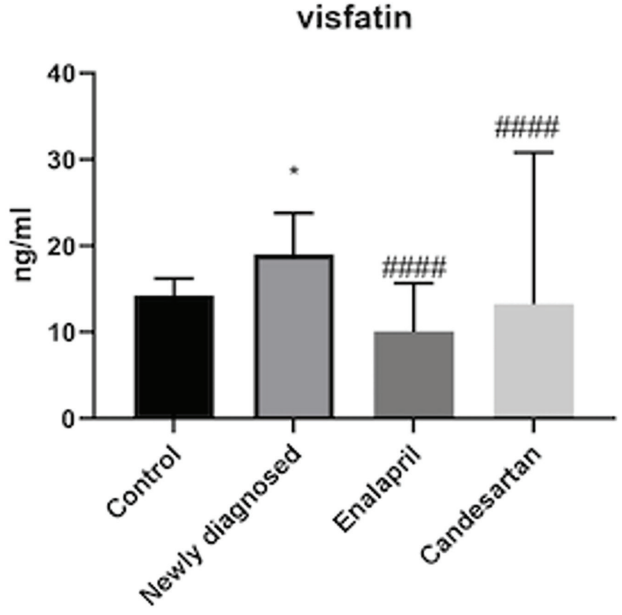

Figure 2. Effects of enalapril and candesartan on serum level of visfatin. *Indicates statistically significant differences compared with the control group, and # indicates statistically significant differences compared with the newly diagnosed hypertensive group (*p<0.05; ####p<0.0001), as shown by Dunn's multiple comparisons post-hoc test upon completion of the Kruskal-Wallis test.

(p=0.0189, 0.017, 0.001, and 0.0002), respectively, with no significant variations in the HDL-c levels. Furthermore, no statistical significance was observed between the candesartan- and enalapril-treated groups for any of the following parameters (Table 2).

DISCUSSION

While candesartan and enalapril have frequently been used for hypertension, studies focused on their effects on adipokine and lipids have shown conflicting results. Concerning apelin levels, our findings are consistent with those of Mahmoud Kadry et al.[14], which showed that apelin levels were lower in hypertensive patients than in the control. Furthermore, Derosa et al.[15] found elevated apelin levels after administration of candesartan in the animal model. In contrast, Skoczylas et al.'s[16] study showed no statistically significant difference in the apelin levels between candesartan-treated patients. Apelin is easily degraded by proteases, which limits its effectiveness. However, hypertension may be a result of elevated AngII and an increase in ACE2 expression as compensated, so there may be an increase in the metabolism of apelin[17]. However, the effect of apelin/APJ on hypertension. Concerning the enalapril group, our results disagreed with Ahmad et al.'s[18] study, which found that combining felodipine and enalapril for treating essential hypertension and coronary artery disease can reduce blood pressure, enhance their effectiveness, and improve peripheral blood circulation apelin.

Recent developments in the field suggest that visfatin could function as either a "friend" or a "foe", contingent upon the circumstances. Generally, arterial hypertension, obesity, and type 2 diabetes are associated with elevated visfatin levels[19]. Our findings were in agreement with the study by Yu et al.[20], which revealed higher visfatin levels in hypertensive participants than in healthy controls. This increase may partly explain the cardiovascular risk in the hypertensive group. In contrast, Dogru et al.[21] Did not find any significant variation in visfatin levels between the hypertensive and control groups. Although endothelial dysfunction may occur in essential hypertension and visfatin may cause endothelial dysfunction, the causal relationship between visfatin and essential hypertension remains unclear. Furuya et al.[22] revealed that candesartan can improve visfatin levels in patients undergoing peritoneal dialysis. Kärberg et al.[23] showed no significant effect on visfatin levels in patients with type 2 diabetes treated with candesartan. Candesartan's anti-inflammatory effect of candesartan was primarily produced by inhibiting AngII-induced reactive oxygen species production and blocking AT1R. Our findings revealed that serum visfatin levels were low after

Table 2. Clinical parameters in healthy and hypertensive patients.

Parameters	Control (a)	Newly diagnosed (b)	Enalapril (c)	Candesartan (d)	Significant	p-value
Apelin (ng/L)	323.3 (215.3-810)	257.3 (106-363.3)	263 (205.3-506.7)	268 (200.7-1146)	a & b** b & d*	(0.0015) (0.0487)
Visfatin (ng/mL)	14 (12-17)	18 (13-27)	10 (1-19)	9 (2-70)	a & b* b & c**** b & d****	(0.0175) (<0.0001) (<0.0001)
TC (mg/dL)	148.3 (124.6-179.2)	195.5 (133.3-250.8)	157.4 (118.1-227.3)	166.9 (100-228)	a & b**** a & d* b & c** b & d*	(<0.0001) (0.0189) (0.0095) (0.0187)
TG (mg/dL)	100.7 (67-185.2)	200.6 (124.7-340.7)	161.1 (111.9-935.3)	180 (90-380)	a & b** a & c* a & d*	(0.001) (0.036) (0.017)
LDL (mg/dL)	65.7 (49.9-75.4)	96.4 (41.9-158.1)	71.3 (22.2-126.3)	61.3 (49.4-95)	a & b*** b & c* b & d***	(0.0003) (0.0182) (0.0004)
HDL (mg/dL)	48.7 (40.5-56.9)	40.9 (28.8-46.4)	45.1 (28.9-61.4)	41.2 (25-70.7)	a & b*	(0.0146)
VLDL (mg/dL)	20.1 (13.4-37)	39.5 (14.3-68.1)	31.6 (22.4-65.9)	40 (21-76)	a & b*** a & c*** a & d***	(0.0001) (0.0005) (0.0002)

Values are presented as medians (minimum-maximum). *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001 represented statistically significant variations, as set by the Kruskal-Wallis test followed by Dunn's multiple comparisons. TC: Total cholesterol, LDL: Low-density lipoprotein, TG: Triglyceride, VLDL: Very low-density lipoprotein, HDL: High-density lipoprotein.

treatment with enalapril for over 1 year. Bryniarski et al.'s[24] study showed that enalapril inhibits pro-inflammatory cytokine production.

Dyslipidemia and BMI are markers of human health that are frequently linked to hypertension. Tasci et al.[5] demonstrated that plasma apelin levels were lower in individuals with hypercholesterolemia that were non-obese, non-diabetic, and normotensive. Our results are consistent with Zhang et al.'s[25] study, indicating that overweight individuals with dyslipidemia are at a greater risk of developing hypertension. Dyslipidemia can alter the permeability of cell membranes by altering their structure, and it can also result in damage to the renal microvascular system, thereby inducing hypertension[26]. Moreover, our results are compatible with Dharwadkar's[27] findings that found serum levels of TC and LDL-c were lower in hypertensive patients treated with enalapril. Enalapril decreases AngII production, thereby reducing TC and LDL. Furthermore, dyslipidemia induces overexpression of the AT1 receptor. Keidar et al.[28] demonstrated that AngII significantly enhances cellular cholesterol biosynthesis following AngII injection. Both the AT1 receptor blocker and ACE inhibitor reduced the formation of cholesterol in response to AngII. Interestingly, AngII failed to increase cholesterol production in cells lacking AT1 receptors. However, candesartan blocks the AT1 receptor, resulting in decreased blood pressure and may affect lipid profiles[29]. Simultaneously, Quesada-Caballero et al.[30] found that the serum level of HDL-c was lower in hypertensive patients. It is unclear which processes underlie high HDL-c and low blood pressure. However, HDL-c may increase the availability of nitric oxide in the endothelial cells, thereby relaxing blood vessels and reducing blood pressure. However, it is possible that variations in blood pressure might have a reverse causal relationship with HDL-c levels. Interestingly, the possibility of a reverse causal relationship in which changes in blood pressure affect serum HDL cannot be ruled out[31].

CONCLUSION

In conclusion, apelin and visfatin appear to have clinical significance and promising diagnostic, prognostic, and therapeutic applications in CVDs. Additionally, we concluded that blocking of renin-Ang system may

represent a major positive regulator of apelin and visfatin actions in the vasculature and heart, unlocking novel potential therapeutic targets for these anti-inflammatory and proinflammatory adipokine in the treatment of hypertension. Specifically, candesartan regulates adipokine to a greater extent than enalapril.

Ethics

Ethics Committee Approval: The ethical integrity of this study was paramount and was conducted under ethical guidelines and with approval from the Kirkuk Health Province Department Knowledge Management and Research Division approval no.: 631, date: 05/10/2023).

Informed Consent: Informed consent was obtained from all participants.

Author Contributions

Surgical and Medical Practices: Y.K.J., J.A.M., Concept: Z.H.F., Design: Z.H.F., Data Collection and/or Processing: Y.K.J., Z.H.F., J.A.M., Analysis and/or Interpretation: Y.K.J., Z.H.F., J.A.M., Literature Search: Y.K.J., Writing: Y.K.J., J.A.M.

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

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

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