TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2013) 43: 57-62
© TÜBİTAK
doi:10.3906/sag-1112-50

The effects of valsartan treatment on visfatin levels and lipid profiles in newly diagnosed hypertensives

İsmail ATACAN[1], Adem PARLAK[2,*], Ümit AYDOĞAN[3], Oktay SARI[3], Deniz Engin GÖK[4], Tuncer ÇAYCI[5], Kenan SAĞLAM[4]

[1]Department of Family Medicine, Erdek Naval District Command, Balıkesir, Turkey
[2]Department of Family Medicine, Ağrı Military Hospital, Ağrı, Turkey
[3]Department of Family Medicine, Gülhane Military Medical Faculty, Ankara, Turkey
[4]Department of Internal Medicine, Gülhane Military Medical Faculty, Ankara, Turkey
[5]Department of Biochemistry, Gülhane Military Medical Faculty, Ankara, Turkey

Received: 28.12.2011 • **Accepted:** 27.06.2012 • **Published Online:** 18.01.2013 • **Printed:** 18.02.2013

Aim: In this study, the curative effect of valsartan on hypertension based on its effect on visfatin levels and lipid profiles was investigated.

Materials and methods: Forty patients aged 38–60 with hypertension were included in the study. In order to determine initial visfatin levels and lipid profiles, blood samples were taken from the patients and all were started on 80-mg valsartan tablets. All patients were monitored for 12 weeks.

Results: By using multivariate regression analysis, it was determined that visfatin levels affected systolic blood pressure (SBP) ($P = 0.012$, beta; –0.43, 95% CI: –0.092 to –0.012). After the patients received the valsartan treatment for 12 weeks, a significant increase in visfatin levels was observed (pre- and posttreatment, respectively: 0.42 ± 0.22 ng/mL and 0.71 ± 0.36 ng/mL, $P < 0.001$). When the lipid profile changes of patients were examined, only low-density lipoprotein (LDL) levels showed a statistically significant change (pre- and posttreatment, respectively: 150.32 ± 13.22 mg/dL and 143.82 ± 7.53 mg/dL, $P = 0.008$).

Conclusion: In this study, it was found that visfatin levels affected SBP in newly diagnosed hypertensive patients and valsartan treatment increased visfatin levels. In addition, the use of valsartan reduced LDL levels.

Key words: Hypertension, valsartan, visfatin, lipid, multivariate regression analysis

1. Introduction

Hypertension is an important health problem that many people face at some point in their lives. Its prevalence differs based on geographic, cultural, demographic, nutritional, and genetic factors, and it is one of the most important health problems in developed countries. Hypertension has been accepted as one of the most important modifiable risk factors contributing to an increased risk of coronary artery disease and it can also damage the structure and function of organs when it is not controlled well (1,2).

The endothelium is a dynamic organ with a complex structure that can secrete and synthesize vasodilator and vasoconstrictor substances in response to environmental stimulation. In endothelial dysfunction, the balance of vasoactive substances is damaged and complications occur with the vascular structure and function (3). Consequently, by causing an increase in vascular resistance and damage, endothelial dysfunction has an important role in vascular pathogenesis, which is responsible for hypertension (4).

Visfatin, a recently discovered type of adipokine, sustains vascular dysfunction by causing vascular smooth muscle inflammation in some metabolic diseases (5). A relationship has been shown between the classic cardiovascular disease risk factors (cholesterol, smoking, hypertension, diabetes mellitus, and obesity) and increased visfatin levels (6).

Although paradoxical results have been obtained from research on the treatment of endothelial dysfunction with antihypertensive drugs, many studies have reported important improvements in endothelial function with antihypertensive treatment in hypertensive individuals (4). As a result, the decision to use drugs for antihypertensive treatment, thus bringing about a decrease in blood pressure and an improved efficiency of endothelial functions, is a rational approach.

* Correspondence: cipro0055@yahoo.com

This research study was mainly concerned with observing the changes in serum visfatin levels as a result of valsartan treatment in newly diagnosed hypertensive patients. Moreover, the effects of valsartan treatment on lipid profiles were observed.

2. Materials and methods

2.1. Study population

Forty patients newly diagnosed with hypertension stage 1 (according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure), who visited the Gülhane Military Medical Faculty Internal Medicine Outpatient Clinic between January 2010 and July 2010 and had not previously used any antihypertensive treatment, were included in this study. Patients with a history of secondary hypertension, renal dysfunction, diabetes, acute infection, polycystic ovary syndrome, preeclampsia, or other systemic illnesses were excluded. After the patients were diagnosed with hypertension, blood was drawn for fasting blood glucose (FBG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglyceride (TG), and serum visfatin levels. This research received approval from the Pharmaceutical Ethics Committee.

2.2. Drug administration

All patients were given a daily dose of 80 mg of valsartan orally and their adaptation to the treatment was monitored. The dose of valsartan was increased to 160 mg if needed. The patients were observed for 12 weeks; at the end of this period the observed parameters were measured again and changes were noted.

2.3. Determination of visfatin levels

Visfatin levels were measured from sera separated by centrifugation (10 min at 4000 rpm) from whole venous blood drawn in the morning after overnight fasting. Serum samples were kept at –80 °C until the measurements were performed and visfatin measurements were done at the same time for all the samples. The measurement of visfatin levels was done using the immunoassay method with a human quantitative visfatin enzyme immunoassay kit and a Bio-Tek reader.

2.4. Statistical analysis

Statistical evaluations of data were done using SPSS 15.0 with the help of a microchip. The differences between the groups were analyzed according to group numbers and data distribution with Student's t-test or the Mann–Whitney U test. Multivariate regression analysis was done for determining the relationship between visfatin levels and biochemical parameters. The data were calculated as mean ± standard deviation, median (min–max), beta, and 95% confidence interval (CI). P values less than 0.05 were accepted as valid in all the tests.

3. Results

Forty newly diagnosed hypertensive patients, 14 males (35%) and 26 females (65%), were included in the study. The sociodemographic characteristics and visfatin levels of the patients according to sex are shown in Table 1. There were no statistical differences observed in terms of height, weight, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and visfatin levels ($P > 0.05$ for all parameters) based on sex.

Visfatin levels affected SBP according to the multivariate regression analysis ($P = 0.012$, beta: –0.43, 95% CI: –0.092 to –0.012). A similar effect was not found for DBP, FBG, TC, HDL, or LDL levels, or for BMI ($P > 0.05$ for all parameters) (Table 2).

The blood pressure, visfatin, and lipid profile values of the patients who were given valsartan treatment from the time of diagnosis and after treatment are shown in Table 3. Visfatin levels were elevated in patients who used valsartan (pre- and posttreatment, respectively: 0.42 ± 0.22 ng/mL and 0.71 ± 0.36 ng/mL, $P < 0.001$). A meaningful decrease was determined for LDL level when the effects of valsartan treatment were observed on the lipid profile (pre- and posttreatment, respectively: 150.32 ± 13.22 mg/dL and 143.82 ± 7.53 mg/dL, $P = 0.008$). However, there were no similar findings for the levels of HDL, TC, and TG ($P > 0.05$ for all parameters). As expected, there were meaningful decreases in SBP and DBP after the valsartan treatment ($P < 0.001$ for each parameter) (Table 3).

4. Discussion

In this study, visfatin levels affected SBP in newly diagnosed hypertensive patients and valsartan treatment increased visfatin levels. In addition, the use of valsartan reduced LDL levels.

Currently, the topic of adipose tissue that works like an endocrine organ by secreting bioactive substances has drawn the attention of scientists. These substances whose origins are in adipose tissue take a part in energy hemostasis and inflammation. Visfatin, which is one of these substances, also plays a role in vascular damage and endothelial dysfunction (7). Visfatin was investigated in many cardiovascular diseases; visfatin levels were found to be low in some and high in others. We observed that visfatin levels in this study were similar to the levels seen linked to cardiovascular disease (8–11).

Although visfatin is generally produced from visceral fat tissue and its high circulation levels are related to obesity, there is some doubt about whether the criteria that evaluate obesity have been emphasized (9). Even though Chen et al. found a positive relationship between visfatin levels and waist-to-hip ratio, they did not confirm a similar relationship for visfatin and BMI (12). In other studies, no relationship was shown between visfatin and waist-to-hip

Table 1. Sociodemographic characteristics, SBP, DBP, and visfatin levels of patients participating in the study.

Parameters	Number	Average	P
Height, cm			
Women	26	166.88 ± 3.31	NS [a]
Men	14	168.85 ± 2.87	
Women and men	40	167.10 ± 6.48	
Weight, kg			
Women	26	72.57 ± 3.46	NS [a]
Men	14	74.14 ± 3.05	
Women and men	40	73.20 ± 6.35	
Age, years			
Women	26	47 (38–58)	NS [b]
Men	14	48 (43–60)	
Women and men	40	48 (38–60)	
BMI, kg/m^2			
Women	26	26.08 ± 1.51	NS [a]
Men	14	26.01 ± 1.08	
Women and men	40	26.06 ± 2.15	
SBP, mmHg			
Women	26	149.40 ± 3.62	NS [a]
Men	14	149.80 ± 3.85	
Women and men	40	149.55 ± 3.67	
DBP, mmHg			
Women	26	93.40 ± 3.45	NS [a]
Men	14	93.87 ± 2.53	
Women and men	40	93.57 ± 3.11	
Visfatin, ng/mL			
Women	26	0.41 ± 0.15	NS [a]
Men	14	0.44 ± 0.29	
Women and men	40	0.42 ± 0.22	

Data are presented as mean ± standard deviation for the parametric tests and median (min–max) value for the nonparametric tests and numbers. NS = nonsignificant, [a] = unpaired Student's t-test, [b] = Mann–Whitney U test, and BMI = body mass index. There were no differences in the sociodemographic properties of the patients based on sex.

Table 2. Multivariate regression analysis between visfatin levels and SBP, DBP, FBG, TG, TC, HDL, LDL, and BMI.

		SBP	DBP	FBG	TG	TC	HDL	LDL	BMI
Visfatin	P	**0.012**	NS	NS	NS	NS	NS	NS	NS
	beta	–0.43	0.04	–0.07	–0.26	0.11	0.09	–0.15	0.03
	95% CI	–0.092 to –0.012	–0.042 to 0.054	–0.025 to 0.016	–0.003 to 0.001	–0.005 to 0.008	–0.014 to 0.024	–0.009 to 0.005	–0.042 to 0.05

SBP = systolic blood pressure, DBP = diastolic blood pressure, FBG = fasting blood glucose, HDL= high density lipoprotein, LDL = low density lipoprotein, BMI = body mass index, and NS = nonsignificant (P > 0.05). Visfatin levels only affected SBP.

Table 3. Changes in SBP, DBP, lipid profile, and visfatin levels with valsartan treatment.

Parameters	At diagnosis	At 12th week	P
TC, mg/dL	195.20 ± 10.42	191.50 ± 12.99	NS [a]
LDL, mg/dL	150.32 ± 13.22	143.82 ± 7.53	**0.008** [a]
HDL, mg/dL	40.37 ± 3.11	40.22 ± 3.10	NS [a]
TG, mg/dL	186.52 ± 11.22	179.42 ± 20.58	NS [a]
SBP, mmHg	147.78 ± 1.27	124.80 ± 4.54	< **0.001** [a]
DBP, mmHg	96.20 ± 1.38	83.30 ± 2.04	< **0.001** [a]
Visfatin, ng/mL	0.42 ± 0.22	0.71 ± 0.36	< **0.001** [a]

Data are presented as mean ± standard deviation for the parametric tests. NS = nonsignificant (P > 0.05), [a] = paired Student's t-test, TC = total cholesterol, LDL = low density lipoprotein, HDL = high density lipoprotein, TG = triglyceride, SBP = systolic blood pressure, and DBP = diastolic blood pressure. LDL, SBP, DBP, and visfatin levels were significantly changed by the valsartan treatment.

ratio or BMI (9,13,14). In the studies by Berndt et al. and Taskesen et al., a relationship was found between plasma visfatin levels and BMI (15,16); however, in this study a relationship was not found between plasma visfatin levels and BMI.

In their study, Saddi-Rosa et al. determined that variations in the visfatin gene might affect glucose, lipid, and other metabolic and vascular events and can cause changes in visfatin levels (17). No relationship between visfatin levels and TC, HDL, LDL, or TG was determined in the study by Kadoglou et al. with coronary artery patients or the study by Dogru et al. with newly diagnosed young hypertensive patients without complications (9,18,19). Some studies showed that there is a strong relationship between visfatin levels and lipid parameters (20,21). In this study, a relationship between visfatin levels and lipid profile was not determined. For this reason, our study is similar to those of Kadoglou et al. and Dogru et al.

In this study, visfatin levels affected only SBP, regardless of other parameters. It is interesting that a similar effect on DBP was not detected.

Although there are currently many drugs affecting a multitude of different mechanisms in hypertension treatment, hypertension still retains its importance as a serious societal health problem. Antihypertensive drugs not only reduce blood pressure but also have a role in metabolic movements. This study observed the effects of valsartan, a type of AT-II receptor blocker (ARB), on visfatin levels as a new marker of vascular damage physiopathology. Storka et al. showed that the use of ARBs, angiotensin-converting enzyme inhibitors, and rosiglitazone increases the visfatin levels of patients with type 2 diabetes mellitus (22). In their research done on hypertensive patients with metabolic syndrome, Saraç et al. found that telmisartan decreases and valsartan increases visfatin levels, but these changes were not statistically significant (23). However, in this study we confirmed that valsartan treatment increases

visfatin levels. ARBs show their effects on visfatin secretion via binding to peroxisome proliferator-activated receptor gamma (PPAR) receptors with agonistic interaction. Therefore, visfatin levels increase via a PPAR-dependent pathway (22). The demonstrated effect of valsartan on visfatin levels is coherent with the literature.

Hypertension is not only a marker of cardiovascular damage but also a traditional risk factor for atherosclerosis related to age, sex, obesity, smoking, diabetes mellitus, and dyslipidemia. Antihypertensive drugs show their effects on the cardiovascular system not only by decreasing blood pressure but also by reducing metabolic diseases like hyperlipidemia. The use of high doses of diuretics and beta-blockers causes an increase in TC and TG levels and a decrease in HDL levels (24,25). Despite the studies that show losartan stays metabolically neutral from ARBs, some research shows that it provides healing for the lipoprotein profile (26,27). A definitive determination has not yet been made regarding the effects of ARBs on lipid metabolism. Therefore, this study's purpose was to research the effect of valsartan, an ARB, on the lipid profile. Trenkwalder et al. showed that candesartan, another ARB, had no effect on lipid profile in patients with type 2 diabetes mellitus or mild hypertension (28). However, some positive results were found in research on the effects on losartan on lipid profile (27,29,30). In the broad study by Kyvelou et al. that researched the effect of ARBs on the lipid profiles of untreated patients with no complications, patients that received candesartan had a decrease in total cholesterol and LDL levels, but the patients that received losartan and valsartan only had a decrease in triglyceride levels (31). In the research by Hanefeld et al. on the effect of valsartan treatment on lipid profile in mildly or severely hypertensive patients, it was noted that valsartan decreased TC and LDL levels but did not cause any changes in HDL or triglyceride levels (32). According to Barutçuoğlu et al., telmisartan therapy, acting as a partial PPARγ agonist, did not affect serum TC, TG, HDL, or LDL concentrations (33). In this study, a meaningful decrease was observed only in LDL levels. When the results of this study are compared to other research done on hypertensive patients who received the same drug therapy, similar decreases were observed. It should not be overlooked that ARB usage with hypertensive patients generally causes healing in the lipid profile, and so especially for patients with metabolic syndrome, it is a good alternative therapy.

In this study, no side effects were observed in the patients who received valsartan therapy, and it was well tolerated. Previous research has shown that valsartan can be tolerated well and used safely, and it is similar to a placebo in terms of side effects (27,34). Our study shows similar findings with earlier studies that were done to determine side effects.

We think that when this study is done with a randomized control and over a longer period, it will be more useful in terms of evaluating the effects of valsartan on visfatin levels over the long term.

Visfatin, an adipokine, has a role in endothelial dysfunction and increases with valsartan therapy. It is noted that valsartan can provide effective blood pressure control and have positive effects on lipid profiles as well as being well tolerated in terms of side effects.

References

1. Karamahmutoğlu F. Dirençli Hipertansiyonun Vücut Kitle İndeksi ile İlişkisi. Uzmanlık Tezi. Okmeydani Eğitim ve Araştırma Hastanesi, 1. Dahiliye Kliniği; 2007.
2. Bostan M, Şatıroğlu Ö, Uydu HA, Çicek Y, Çanga A, Karadağ Z et al. Distribution of coronary artery risk factors: a regional analysis. Turk J Med Sci 2011; 41: 317–24.
3. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases. Circ Res 2000; 87: 840–4.
4. Kırkpantur A, Altun B. Endotel disfonksiyonu ve hipertansiyon. Türk J Cardiol 2006; 9: 55–61.
5. Romacho T, Azcutia V, Vazquez-Bella M, Matesanz N, Cercas E, Nevado J et al. Extracellular PBEF/NAMPT/visfatin activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyltransferase activity. Diabetologia 2009; 52: 2455–63.
6. Liu SW, Qiao SB, Yuan JS, Liu DQ. Association of plasma visfatin levels with inflammation, atherosclerosis and acute coronary syndromes (ACS) in humans. Clin Endocrinol (Oxf) 2009; 71: 202–7.
7. Wozniak SE, Gee LL, Watchel MS, Frezza EE. Adipose tissue: the new endocrine organ? Dig Dis Sci 2009; 54: 1847–56.
8. Yilmaz MI, Saglam M, Carrero JJ, Quereshi AR, Caglar K, Eyileten T et al. Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. Nephrol Dial Transplant 2008; 23: 959–65.
9. Dogru T, Sonmez A, Tasci I, Yilmaz MI, Erdem G, Erturk H et al. Plasma visfatin levels in young male patients with uncomplicated and newly diagnosed hypertension. J Hum Hypertens 2007; 21: 173–5.
10. Grill S, Rusterholz C, Zanetti-Dallenbach R, Tercanli S, Holzgreve W, Hahn S et al. Potential markers of preeclampsia – a review. Reprod Biol Endocrinol 2009; 7: 70–84.
11. Arner P. Editorial: Visfatin – a true or false trail to type 2 diabetes mellitus. J Clin Endocrinol Metab 2006; 91: 28–30.
12. Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ et al. Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2006; 91: 295–9.

13. Hammerstedt A, Pihlajamaki J, Rotter Sopasakis V, Gogg S, Jansson PA, Laakso M et al. Visfatin is an adipokine, but it is not regulated by thiazolidinediones. J Clin Endocrinol Metab 2006; 91: 1181–4.

14. Haider DG, Schindler K, Schaller G, Prager G, Woltz M, Ludvik B. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. J Clin Endocrinol Metab 2006; 91: 1578–81.

15. Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schon MR et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005; 54: 2911–6.

16. Taskesen D, Kirel B, Us T. Serum visfatin levels, adiposity and glucose metabolism in obese adolescents. J Clin Res Pediatr Endocrinol 2012; 4: 75–9.

17. Saddi-Rosa P, Oliveira CSV, Giuffrida FM, Reis AF. Visfatin, glucose metabolism and vascular disease: a review of evidence. Diabetol Metab Syndr 2010; 2: 21.

18. Kadoglou NP, Gkontopoulos A, Kapelouzou A, Fotiadis G, Theofilogiannakos EK, Kottas G et al. Serum levels of vaspin and visfatin in patients with coronary artery disease – Kozani study. Clinica Chimica Acta 2011; 412: 48–52.

19. Gunes F, Akbal E, Cakir E, Akyurek O, Altinbas M, Ozbek M. Visfatin may be a novel marker for identifying stages of essential hypertension in advanced age patients. Intern Med 2012; 51: 553–7.

20. Wang P, Bai C, Xu QY, Xu TY, Su DF, Sassard J et al. Visfatin is associated with lipid metabolic abnormalities in Lyon hypertensive rats. Clin Exp Pharmacol Physiol 2010; 37: 894–9.

21. Olszanecka-Glinianowicz M, Kocełak P, Nylec M, Chudek J, Zahorska-Markiewicz B. Circulating visfatin level and visfatin/insulin ratio in obese women with metabolic syndrome. Arch Med Sci 2012; 8: 214–8.

22. Storka A, Vojtassako E, Mueller M, Kapiotas S, Haider DG, Jungbauer A et al. Angiotensin inhibition stimulates $PPAR_Y$ and the release of visfatin. Eur J Clin Invest 2008; 38: 820–6.

23. Saraç S, Saraç F, Tütüncüoglu P. Effects of telmisartan and valsartan on insulin resistance, visfatin and adiponectin levels in hypertensive patients with metabolic syndrome. Acta Endocrinologica (Buc) 2008; 4: 23–32.

24. Lardinois CK, Neuman SL. The effects of antihypertensive agents on serum lipids and lipoproteins. Arch Intern Med 1988; 148: 1280–8.

25. Grimm RG, Leon AS, Hunning DB, Lenz K, Hannan P, Blackburn H. Effects of thiazide diuretics on blood lipids and lipoproteins in mildly hypertensive patients: a double-blind controlled trial. Ann Intern Med 1981; 94: 7–11.

26. Moan A, Hoieggen A, Seljeflot I, Risanger T, Arnesen H, Kjeldsen SE. The effect of angiotensin II receptor antagonism with losartan on glucose metabolism and insulin sensitivity. J Hypertens 1996; 14: 1093–7.

27. Ogihara T, Yoshinaga K. The clinical efficacy and tolerability of the angiotensin II receptor antogonist losartan in Japanese patients with hypertension. Blood Press 1996; 5: 78–81.

28. Trenkwalder P, Mehtovirta M, Dahl K. Long-term treatment with candesartan cilexetil does not affect glucose hemostasis or serum lipid profile in mild hypertensives with type II diabetes. J Hum Hypertens 1997; 11: 81–3.

29. de Zeeuw D, Gansevoort RT, Dullaart RPF, Jong PE. Angiotensin II antagonism improves the lipoprotein profile in patients with nephrotic syndrome. J Hypertens 1995; 13: S53–8.

30. Lerch M, Teuscher U, Beissner P, Schneider M, Shaw SG, Weidmann P. Effects of angiotensin II receptor blockade with losartan on insulin sensitivity, lipid profile, and endothelin in normotensive offspring of hypertensive parents. J Cardiovasc Pharmacol 1998; 31: 576–80.

31. Kyvelou SMG, Vyssoulis GP, Karpanou EA, Adamopoulos DN, Zervoudaki AI, Pietri PG et al. Effects of angiotensin II receptor blockers on lipid profile: an open multidrug comparison trial. Hellenic J Cardiol 2006; 47: 21–8.

32. Hanefeld M, Abletshauer C. Effect of the angiotensin II receptor antagonist valsartan on lipid profile and glucose metabolism in patients with hypertension. J Int Med Res 2001; 29: 270–9.

33. Barutçuoğlu B, Parıldar Z, Mutaf MI, Özmen D, Alioğlu E, Habif S et al. Effect of telmisartan on vascular endothelium in hypertensive and type 2 diabetic hypertensive patients. Turk J Med Sci 2010; 40: 239–48.

34. Kirk JK. Angiotensin II receptor antagonists: their place in therapy. Am Fam Phys 1999; 59: 3140–8.