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Renin-Angiotensin System Blockage for Reduction of Plasma Adiponectin Level in Maintenance Hemodialysis Patients
A Randomized Controlled Trial

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Introduction. Plasma adiponectin level is markedly increased among patients on hemodialysis. This investigation aimed to evaluate the relationship between renin-angiotensin system blockade and serum adiponectin concentration in nondiabetic patients on hemodialysis.
Materials and Methods. This randomized double-blind controlled trial was conducted on a group of nondiabetic patients on regular hemodialysis. The first group received losartan, 12.5 mg twice per day for the 1st week, 25 mg twice per day during the 2nd week, and 75 mg/d from the 3rd week to the end of the 16th week. Patients of the control group received placebo. Blood samples from all of the patients were collected at the beginning and at the end of the study to measure serum adiponectin.
Results. Seventy-three hemodialysis patients were divided randomly into the losartan group (40 patients) and the control group (33 patients). The mean adiponectin level in all of the patients was 10.6 ± 3.9 µg/mL. A significant decrease of serum adiponectin level was observed after 4 months of treatment with losartan (8.86 ± 3.43 µg/mL for losartan group versus 10.71 ± 3.94 µg/mL for the control group; P = .04). None of the patients had a serum potassium value greater than 5 mg/dL or hypotension during the intervention. There was no significant difference in serum potassium levels between the two groups.
Conclusions. The decrease in serum adiponectin level in nondiabetic patients on regular hemodialysis by losartan might offer a potential protective approach in these patients. Mechanisms responsible for this reduction remain to be investigated.

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INTRODUCTION

Adiponectin is synthesized by white adipose tissue as a collagen-like protein.[1] Adiponectin plays an important role in the regulation of body weight, lipid metabolism, insulin sensitivity, and inflammatory response.[1,2] Also, adiponectin was demonstrated to have anti-inflammatory and anti-atherogenic properties. Its anti-inflammatory effect is possibly conducted through the suppression and the attachment of monocytes to endothelial cells.[1-3] Plasma adiponectin levels were shown to be inversely related to plasma insulin level, leptin and triglyceride levels, and also body mass index.[2,3] It is also associated with vascular function independent of insulin sensitivity.[2,3]

Recent findings have shown a protective function for adiponectin for the cardiovascular system, suggesting an inverse association with cardiovascular disease risks.[1-8] Plasma adiponectin level is dependent on kidney function, being

markedly increased among patients with kidney impairment, and also in patients with end-stage renal disease and those on regular hemodialysis.[3-9] The underlying cause for the higher levels of circulating adiponectin in kidney disease patients is still unclear. It has been suggested that decreased renal clearance is the cause of increased plasma levels of adiponectin in patients with failing kidney function.[1-8] While adiponectin might be a potential modulator of cardiovascular risk, epidemiological evidence has not consistently supported elevated levels being protective in hemodialysis patients.[2-9]

Data on the association between adiponectin and outcomes in chronic kidney failure patients are scares. It has been shown that high serum adiponectin level predicts progression of end-stage kidney disease and mortality in type 1 diabetic patients.[4,8,10-14] In kidney injury, some adipokines are involved through mediating endothelial dysfunction, triggering oxidative stress and inflammation, as well as stimulating renal sympathetic nervous activity, which diminishes cancellous bone but conversely increases cortical bone.[4,8,10-14] Adipokines may also be involved in the development of renal anemia.[2,4,8] Studies have shown that angiotensin II, as the main effector peptide of renin-angiotensin system,[4,8,15] is implicated in the development of renal, cardiac, and vascular pathologies.[16] Recent studies have explored the relationship between angiotensin II, renin-angiotensin system, and adiponectin level.[15-21] One study has shown the beneficial effects of losartan (angiotensin II type 1 receptor blocker) on plasma adiponectin level in patients with diabetic nephropathy.[21] This investigation was designed to find out the relationship between renin-angiotensin system blockade and serum adiponectin concentration in a group of nondiabetic patients on regular hemodialysis.

MATERIALS AND METHODS

Study Population

This randomized double-blind controlled trial (registered by the Iranian Registry of Clinical Trials, 2013112515535N1) was conducted on a group of nondiabetic patients on regular hemodialysis. The study was conducted at the hemodialysis section of Shahrekord University of Medical Sciences in 2013 for a period of 4 months. All enrolled patients were on hemodialysis 3 times a week for 4 hours using low-flux dialysis filters with polysulfone membranes and reverse osmosis purified water and bicarbonate-base dialysis solution. Exclusion criteria were presence of diabetes mellitus, active or chronic infection, and taking angiotensin-converting enzyme or renin-angiotensin blockers.[22] Also, patients receiving antibiotics, corticosteroids, pentoxifylline, or nutritional supplements, including various vitamins except for folic acid, within 3 months prior to this trial, were excluded from the study.[23]

Measurement of Blood Pressure

Blood pressure was measured before each dialysis session and the results were recorded. It was measured on the right arm in a sitting position after at least 20 minutes rest with a mercury sphygmomanometer. Resting systolic blood pressures and 5th phase diastolic blood pressures were measured 3 times, while the participants were seated, and the 2nd and 3rd measurements were averaged.[23-25] Hypertension was defined as systolic blood pressure of 130 mm Hg and higher or diastolic blood pressure of 85 mm Hg and higher.[23-25]

Study Protocol

The patients were assigned into 2 groups. The first group received losartan (purchased from Razak Co, Iran), 12.5 mg twice per day for the 1st week, 25 mg twice per day during the 2nd week, and 75 mg/d (50 mg in the morning and 25 mg for the evening) from the 3rd week to the end of the 16th week. Patients of the control group received placebo in the same divisions. Blood samples from all patients were collected at the beginning and at the end of the study to measure plasma adiponectin. To avoid hypotension, other antihypertensive drugs were decreased or replaced with losartan (losartan group) during the treatment, especially when the dose of losartan increased as per the study protocol. During the 16 weeks of the study, serum potassium levels were checked every 2 weeks to avoid hyperkalemia. Blood pressure was also checked intensively before each dialysis session to avoid hypotension. After the end of 4 months, fasting serum samples were obtained to measure plasma adiponectin level. Body mass index was calculated as weight divided by squared height (kg/m^2).

Laboratory Analysis

Blood samples were taken after a long dialysis-free weekend interval before the next hemodialysis, at 07:30 AM after a minimum 8-hour overnight fast to avoid the circadian and feeding impact on serum adiponectin fluctuations. Prior to the study and after intervention, serum adiponectin was measured in all of the patients by an enzyme-linked immunosorbent assay method, using the kits and protocol from Oegenium Laboratories (AviBion Human Adiponectin ELISA Kit, Helsinki, Finland). Blood urea nitrogen (BUN) and serum creatinine, potassium, sodium, calcium, and phosphorus were measured using standard kits and was done with standard automated techniques.

Ethics

The research protocol followed the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained the participants and the protocol was approved by the ethics committee of Shahrekord University of Medical Sciences.

Statistical Analysis

Results were expressed as mean ± standard deviation and comparisons were considered significant when the *P* value was less than .05. The independent *t* test was used for comparison of continuous variables between the two groups. Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Seventy-three nondiabetic hemodialysis patients (33 women and 44 men) were divided randomly into the losartan group (40 patients) and the control group (33 patients). The age range of the patients was from 13 to 91 years. Table 1 illustrates the patients' characteristics before intervention. The mean adiponectin level in all of the patients was 10.6 ± 3.9 µg/mL (range, 0.32 µg/mL to 17.41 µg/mL). Table 2 shows the significant decrease of serum adiponectin level after 4 months of treatment with losartan (8.86 ± 3.43 µg/mL for losartan group versus 10.71 ± 3.94 µg/mL for the control group; $P = .04$), as compared with those in the control group. None of the patients had a serum potassium value greater than 5 mg/dL. None of the patients had hypotension during the intervention. There was no significant difference in serum potassium levels between the two groups. The Figure shows serum potassium fluctuations in the two groups. Table 3 shows the hemoglobin levels and KT/V values before and after treatment with losartan. There was no significant difference in KT/V before and after the treatment ($P = .29$).

Table 1. Clinical and Demographic Characteristics of Nondiabetic Hemodialysis Patients Before Intervention*

Characteristic	Losartan Group (n = 40)	Control Group (n = 33)	*P*
Age, y	59.65 ± 19.02	53.94 ± 20.90	.93
Male sex, %	55	54	.97
Body weight, kg	59.86 ± 13.40	56.58 ± 15.39	.33
Body mass index, kg/m^2	3.85 ± 22.42	3.99 ± 21.31	.22
Systolic blood pressure, mm Hg	123.5 ± 21.90	125.45 ± 22.37	.71
Diastolic blood pressure, mm Hg	69.50 ± 9.59	71.21 ± 10.20	.46
Serum sodium, mg/dL	140.15 ± 2.87	141.88 ± 2.30	.007
Serum potassium, mg/dL	4.84 ± 0.56	5.16 ± 0.79	.06
Serum calcium, mg/dL	8.92 ± 0.55	9.09 ± 0.54	.20
Serum phosphorus, mg/dL	5.31 ± 1.16	4.88 ± 1.07	.10

*Values are mean ± standard deviation, except for sex distribution, which is percentage.

Table 2. Adiponectin Level Before and After Treatment With Losartan*

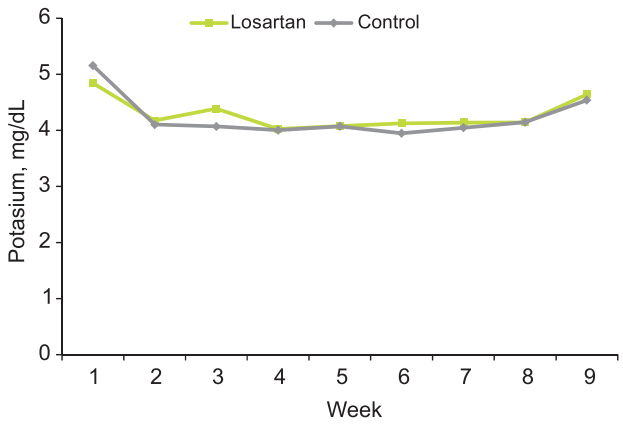
Adiponectin	Losartan Group (n = 40)	Control Group (n = 33)	*P*
Before treatment, µg/mL	10.52 ± 3.72 (0.3 to 17.4)	10.60 ± 4.12 (1.0 to 16.9)	.93
After treatment, µg/mL	8.86 ± 3.43 (0.5 to 15.0)	10.71 ± 3.94 (1.0 to 16.9)	.04

*Values are mean ± standard deviation (range).

Table 3. Hemoglobin Levels and KT/V Values of All Participants Before and After Treatment With Losartan*

Parameter	Before Treatment	After Treatment
Hemoglobin, g/dL	10.51 ± 1.96 (6.6 to 15.3)	9.35 ± 1.69 (5.7 to 14.1)
KT/V	1.43 ± 0.32 (0.5 to 2.7)	1.48 ± 0.22 (0.7 to 1.9)

*Values are mean ± standard deviation (range).



Serum potassium fluctuations during the study.

DISCUSSION

This study documented a decline in serum adiponectin level after 4 months of losartan therapy. To evaluate the effects of adiponectin on appearance of protein-energy wasting, Kaynar and colleagues examined 150 patients with chronic kidney disease.[26] They found an elevated level of adiponectin in hemodialysis, predialysis, and peritoneal dialysis patients in comparison to their control group. They showed a significant positive correlation between presence of protein-energy wasting and serum adiponectin level. They concluded that high serum adiponectin level might have a role in the development of protein-energy wasting among dialysis patients.[26] Recently, Okuno and colleagues conducted a study to assess the possible role of adiponectin in mineral and bone disorders of dialysis patients. The study conducted on 114 Japanese male hemodialysis patients.[27] They found a significant positive correlation between plasma adiponectin and serum N-telopeptide of type I collagen. They concluded that increased levels of serum adiponectin were associated with a decrease in bone mineral density in male hemodialysis patients.[27]

Furthermore, adiponectin may play a role in bone and mineral disorder, possibly in bone resorption of patients on dialysis.[27-31] Likewise, in a study on 44 hemodialysis patients, Lee and colleagues found that plasma adiponectin level was significantly higher in malnourished patients than in well-nourished patients.[31] They concluded that plasma adiponectin level reflected the nutritional-inflammation status of hemodialysis patients and also adiponectin might also be accompanied with dyslipidemia, insulin resistance, and the inflammatory response in these patients.[31] To examine the association between plasma adiponectin and mortality in the earlier stages of chronic kidney disease, Menon and associates conducted a study with a 10-year follow-up and found that high, rather than low, plasma adiponectin concentration was associated with increased mortality in patients with chronic kidney disease stages 3 to 4.[32] Recent studies suggest that in patients with nondiabetic chronic kidney disease, elevated adiponectin may be a novel predictor for chronic kidney disease progression in men.[1-6,20,33-34] Furthermore, it has been proposed that adiponectin enhances energy expenditure, and high plasma adiponectin levels might not be a valuable marker in chronic kidney disease.[35]

Hence, it seems that any attempts to decrease the adiponectin level may influence the survival of hemodialysis patients. In a study on 80 patients with type 2 diabetic nephropathy who were randomly divided into 2 groups for losartan and amlodipine, Gou and colleagues found declines in fasting insulin and adiponectin levels by losartan therapy.[21] They concluded that this effect of losartan might offer potential protection in diabetic nephropathy. Similar results were also obtained in our investigation. However, few studies have published regarding the capacity of angiotensin receptor blockers to increase or decrease the plasma adiponectin concentration. To the best of our knowledge, this is the first double-blind clinical trial on the effect of losartan on adiponectin level in hemodialysis patients. We assumed that decreased plasma adiponectin by losartan was a beneficial effect in hemodialysis patients. It has been found that increased adiponectin levels are strongly associated with all-cause and cardiovascular mortality in patients with chronic kidney failure

or hemodialysis patients.[36-46] However, further studies are required to confirm this finding and to reveal the underlying mechanisms.

CONCLUSIONS

Our results demonstrate for the first time that adiponectin level in nondiabetic patients on regular hemodialysis is decreased by the angiotensin receptor blockers, which might offer a protective role in hemodialysis patients. The mechanisms responsible for this decrement during short-course treatment with losartan remain to be investigated.

CONFLICT OF INTERESTS

None declared.

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REFERENCES

1. Yu Y, Bao BJ, Fan YP, Shi L, Li SQ. Changes of adiponectin and its receptors in rats following chronic renal failure. Ren Fail. 2014;36:92-7.
2. Ekramzadeh M, Sohrabi Z, Salehi M, et al. Adiponectin as a novel indicator of malnutrition and inflammation in hemodialysis patients. Iran J Kidney Dis. 2013;7:304-8.
3. Martinez Cantarin MP, Waldman SA, Doria C, et al. The adipose tissue production of adiponectin is increased in end-stage renal disease. Kidney Int. 2013;83:487-94.
4. Yang J, Lin SC, Chen G, et al. Adiponectin promotes monocyte-to-fibroblast transition in renal fibrosis. J Am Soc Nephrol. 2013;24:1644-59.
5. Tamadon MR, Ardalan MR, Nasri H. World Kidney Day 2013; acute renal injury; a global health warning. J Parathyr Dis. 2013;1:27-8.
6. Rastegari E, Nasri H. Association of serum leptin with serum C-reactive protein in hemodialysis patients. J Nephropharmacol. 2012;1:19-21.
7. Tamadon MR. Secondary hyperparathyroidism and chronic kidney disease. J Parathyr Dis. 2013;1:15-6.
8. Rüster C, Wolf G. Adipokines promote chronic kidney disease. Nephrol Dial Transplant. 2013;28 Suppl 4:iv8-iv14.
9. Rahimi Z, Mansouri Zaveleh O, Rahimi Z, Abbasi A. AT2R -1332 G:A polymorphism and diabetic nephropathy in type 2 diabetes mellitus patients. J Renal Inj Prev. 2013;2:97-101.
10. Hajivandi A, Amiri M. World Kidney Day 2014: Kidney disease and elderly. J Parathyr Dis 2014; 2(1):3-4.
11. Baradaran A. Lipoprotein (a), type 2 diabetes and nephropathy; the mystery continues. J Nephropathol. 2012;1:126-9.
12. Amiri M, Nasri H. Secondary Hyperparathyroidism in chronic kidney disease patients; current knowledge. J Parathyr Dis. 2014; 2:1-2.
13. Rafieian-Kopaei M, Nasri H. Correlation of serum leptin with levels of hemoglobin in hemodialysis. J Nephropharmacol. 2012;1:23-6.
14. Nasri H. Elevated serum parathyroid hormone is a heart risk factor in hemodialysis patients. J Parathyr Dis. 2013;1:13-4.
15. Kollerits B, Fliser D, Heid IM, Ritz E, Kronenberg F. Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. Kidney Int. 2007;71:1279-86.
16. Maesaka JK, Sodam B, Palaia T, et al. Prostaglandin D2 synthase: Apoptotic factor in alzheimer plasma, inducer of reactive oxygen species, inflammatory cytokines and dialysis dementia. J Nephropathol. 2013;2:166-80.
17. Ardalan MR, Sanadgol H, Nasri H, Baradaran A, Tamadon MR, Rafieian-Kopaei R. Vitamin D therapy in diabetic kidney disease; current knowledge on a public health problem. J Parathyr Dis. 2014;2:15-7.
18. Rafieian-Kopaei M, Nasri H. Association of serum lipids with level of lept in in hemodialysis patients. J Nephropharmacol. 2013; 2:17-20.
19. Nasri H. Elevated serum parathyroid hormone is a heart risk factor in hemodialysis patients. J Parathyr Dis. 2013;1:13-4.
20. Nasri H, Rafieian-Kopaei M. Association of serum vitamin D level with age in individuals with normal renal function. J Nephropharmacol. 2012;1:7-9.
21. Guo LL, Pan Y, Jin HM. Adiponectin is positively associated with insulin resistance in subjects with type 2 diabetic nephropathy and effects of angiotensin II type 1 receptor blocker losartan. Nephrol Dial Transplant. 2009;24:1876-83.
22. Ghorbani A, Jasemi-Zergani F. Ticlopidine to prevent primary arteriovenous fistula failure in hemodialysis patients; a randomized controlled trial. J Renal Inj Prev. 2013;2:109-11.
23. Rafiean-Kopaie M, Nasri H. Impact of inflammation on anemia of hemodialysis patients who were under treatment of recombinant human erythropoietin. J Renal Inj Prev. 2013;2:93-5.
24. Behradmanesh S, Nasri H. Association of serum calcium with level of blood pressure in type 2 diabetic patients. J Nephropathol. 2013;2:254-7.
25. Rafieian-Kopaei M, Nasri H. Carotid intima-media thickness and left ventricular hypertrophy in hemodialysis patients. J Renal Inj Prev. 2013;2:129-32.
26. Kaynar K, Kural BV, Ulusoy S, et al. Is there any interaction of resistin and adiponectin levels with protein-energy wasting among patients with chronic kidney disease. Hemodial Int. 2014;18:153-62.
27. Okuno S, Ishimura E, Norimine K, et al. Serum adiponectin and bone mineral density in male hemodialysis patients. Osteoporos Int. 2012;23:2027-35.
28. Ardalan MR, Nasri H. Acute kidney injury; the focus of world kidney day in 2013. J Nephropharmacol. 2013;2:15-6.

29. Nasri H. The awareness of chronic kidney disease and aging; the focus of world kidney day in 2014. J Nephropharmacol. 2014;3:1-2.
30. Nasri H. Impact of diabetes mellitus on parathyroid hormone in hemodialysis patients. J Parathyr Dis. 2013;1:9-11
31. Lee YJ, Cho S, Kim SR. The association between serum adiponectin levels and nutritional status of hemodialysis patients. Ren Fail. 2011;33:506-11.
32. Menon V, Li L, Wang X, et al. Adiponectin and mortality in patients with chronic kidney disease. J Am Soc Nephrol. 2006;17:2599-606.
33. Rafieian-Kopaei M, Nasri H. Vitamin D therapy in diabetic kidney disease. J Nephropharmacol. 2014;3:3-4.
34. Hajivandi A, Amiri M. World diabetes day: diabetes mellitus and nephrology. J Nephropharmacol. 2013;2: 31-2.
35. Qi Y, Takahashi N, Hileman SM, et al.Adiponectin acts in the brain to decrease body weight. Nat Med. 2004;10: 524-9.
36. Sabir S, Mubarak M, Ul-Haq I, Bibi A. Pattern of biopsy proven renal diseases at PNS SHIFA, Karachi: A cross-sectional survey. J Renal Inj Prev. 2013;2:133-7.
37. Nasri H, Rafieian-Kopaei M. Significant difference of serum 25-hydroxyvitamin D level in male hemodialysis patients with our without diabetes; a single center study. J Nephropharmacol. 2012;1:3-4.
38. Nasri H. Impact of diabetes mellitus on parathyroid hormone in hemodialysis patients. J Parathyr Dis. 2013;1:9-11.
39. Dehghan Shahreza F. From oxidative stress to endothelial cell dysfunction. J Prev Epidemiol. 2016;1:e04.
40. Dehghan Shahreza F. Renal tubular cell injury and its protection by antioxidants; new trends. J Inj Inflamm. 2016;1:e01.
41. Lokely A, Shoukry A, Ghonemy TA, Atia M, Amr G. Association of adiponectin with cardiovascular events in diabetic and non-diabetic hemodialysis patients. Saudi J Kidney Dis Transpl. 2012;23:736-42.
42. Rafieian-Kopaei M, Baradaran A. On the occasion of world diabetes day 2105; act today to change tomorrow. J Renal Endocrinol. 2015;1:e02.
43. Nasri H, Abedi-Gheshlaghi Z, Rafieian-Kopaei M. Curcumin and kidney protection; current findings and new concepts. Acta Persica Pathophysiol. 2016;1:e01.
44. Khodadadi S. Role of Herbal Medicine in Boosting Immune System. Immunopathol Persa. 2015;1:e01.
45. Lala MA, Nazar CMJ, Lala HA, Singh JK. Interrelation between blood pressure and diabetes. J Renal Endocrinol. 2015;1:e05.
46. Rafieian-Kopaei M, Nasri H. Serum lipoprotein (a) and atherosclerotic changes in hemodialysis patients. J Renal Inj Prev. 2013;2:47-50.

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