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Serum adiponectin level in hypertensive patients and its association with atherosclerotic risk factors

Hipertansif hastalarda serum adiponektin düzeyi ve ateroskleroz risk faktörleri ile ilişkisi

Bülent Uygungelen, Serhat İçağasıoğlu, Fettah Acıbucu*, Fatih Kılıçlı, Ali Uğur Uslu, İbrahim Gül

Department of İnternal Medicine (B. Uygungelen, MD, Assist. Prof. S. İçağasıoğlu, MD, A. U. Uslu, MD), Department of Endocrinology and Metabolism (F. Acıbucu, MD, Assist. Prof. F. Kılıçlı), Department of Cardiology (Assoc. Prof. İ. Gül), Cumhuriyet University School of Medicine, TR-58140 Sivas

Abstract

Aim. Hypertension is one of the major risk factors for atherosclerosis. Adiponectin is mainly synthesized by white adipose tissue; it is known to have anti-atherogenic and anti-inflammatory effects on endothelial cells and macrophages. **Methods.** A total of 80 individuals including 48 hypertensive and 32 normotensive individuals were included in the study. Groups were separated as obese and non-obese. **Results.** It was found out that the patient group had statistically higher systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, triglyceride, low density lipoprotein, high sensitive C reactive protein and microalbuminuria values than the control group while high density lipoprotein values were significantly lower ($p<0.05$). When adiponectin levels of the groups were compared, the patient group had an adiponectin level of 8.66±2.75 µg/mL and the control group had an adiponectin level of 15.01±3.99 µg/mL. There was a statistically significant difference between two groups ($p<0.05$). There was a negative correlation between adiponectin level and atherosclerotic risk factors. **Conclusion.** Adiponectin level was lower in hypertensive group when compared to the control group; there was also a significant association between adiponectin and atherosclerotic risk factors. A low adiponectin level constitutes an important risk for development of atherosclerosis.

Keywords: Atherosclerosis, hypertension, adiponectin

Özet

Amaç. Hipertansiyon aterosklerozun majör risk faktörlerindendir. Adiponektin başlıca beyaz adipoz dokudan sentez edilmekte ve endotelyal hücreler ve makrofajlar üzerinde antiaterojenik ve antiinflamatuar etkileri olduğu bilinmektedir. **Yöntem.** Çalışmaya 48'i hipertansif 32 tanesi normotansif 80 birey alındı. Gruplar kendi arasında obez ve nonobez olarak ayrıldı. **Bulgular.** Hasta grubunun kontrol grubuna göre sistolik kanbasıncı, diastolik kanbasıncı, açlık kan şekeri, total kolesterol, trigliserit, low density lipoprotein-C, hs-CRP ve mikroalbuminüri değerleri istatistiksel olarak anlamlı yüksek, high density lipoprotein-C değerleri ise anlamlı düşük bulundu ($p<0,05$). Grupların adiponektin düzeyleri karşılaştırıldığında; hasta grubunda 8,66±2,75 µg/mL, kontrol grubunda 15,01±3,99 µg/mL olarak bulundu. Aradaki farklılık istatistiksel olarak anlamlı idi ($p<0,05$). Adiponektin seviyesi ile aterosklerotik risk faktörleri arasında negatif yönlü bir korelasyon bulundu. **Sonuç.** Sonuç olarak adiponektin düzeyi hipertansif grupta kontrole göre daha düşüktü ve ateroskleroz risk faktörleri ile aralarında anlamlı ilişki vardı. Adiponektin düzeyinin düşük olması ateroskleroz gelişimi için önemli bir risk oluşturmaktadır.

Anahtar sözcükler: Ateroskleroz, hipertansiyon, adiponektin

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***Corresponding author:**

Dr. Fettah Acıbucu, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Cumhuriyet Üniversitesi Tıp Fakültesi, TR-58140 Sivas. E-mail: dr.feto@hotmail.com

Introduction

Atherosclerotic vascular diseases are considered to be among significant reasons for morbidity and mortality. Hypertension (HT) is a major risk factor for atherosclerosis together with obesity, dyslipidemia and diabetes mellitus (DM). HT increases the risk of developing cerebrovascular and cardiovascular disease (CVD) by two times [1-3]. HT results in thickening of intima and media layers, increases the distance of diffusion and results in hypoxia. In this case, formation of free oxygen radicals is increased in blood vessel wall and oxidative stress occurs. These free radicals trigger inflammatory cell migration [4]. The resulting atherosclerosis is a complex, multi-factorial and inflammatory disease.

Fatty tissue is the major source of energy in body and acts as an endocrine organ. Adiponectin is mainly synthesized by white adipose tissue and it is available in serum in high concentrations (2-30 microgram/milliliter) [5]. Although adiponectin's physiological role is not clearly identified, it is known to have anti-atherogenic and anti-inflammatory effects on endothelial cells and macrophages [6]. Besides, it was shown that adiponectin had a protective role in early stage of atherosclerosis [7]. There are not sufficient number of studies on serum adiponectin level in hypertensive patients. In this study, we aimed to study the adiponectin level in hypertensive cases and its association with factors such as fasting plasma glucose (FPG), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TG), total cholesterol (T.Chol), high sensitive C reactive protein (hs-CRP), body mass index (BMI) and microalbuminuria (MAU).

Material and method

This study was carried out in 80 individuals between the age of 24 and 64, who applied to the outpatient clinic of Internal Medicine in Cumhuriyet University Hospital. Permission was obtained from the Local Board of Ethics and informed consent forms were received from all individuals for this study. Those with the history of DM, coronary artery disease (CAD) and cardiac failure, rheumatic disease, malignity, alcohol use, use of anti-obesity and anti-lipidemic drugs, history of secondary hypertension, and an acute or chronic disease except for HT were excluded from the study.

Physical examination, height, weight and waist circumference (cm) measurements were performed for the individuals, who were included in the study. BMI was calculated through division of weight by square of height (kg/m2). The individuals, whose BMI was ≥30 kg/m2, were considered to be obese while the individuals, whose BMI was <30 kg/m2, were considered to be non-obese. Blood pressures of the patients were measured with an ideal sphygmomanometer for twice in an interval of 5 minutes in a proper environment in a sitting position following a rest of 20 minutes and the average of these two values was taken. Those whose blood pressure was higher than 140/90 mmHg and those who received anti-hypertensive treatment were considered to be hypertensive patients. As for blood samples taken following a 12-hour fasting; FPG, TG, T.Chol, HDL-C, LDL-C and hs-CRP levels were studied. A blood sample was centrifuged in "hettich eba 35 fixed head desktop centrifuge" at 3,000 rpm for 5 minutes and its serum was taken. The allocated serum was transferred to a 1.5 cc eppendorf tube. Numerated serum tubes were stored in a freezer at -80 C for adiponectin analysis. A 24-hour urine sample was taken from the patients for determination of microalbuminuria. The patients, whose urinary albumin excretion quantity was lower than 30 mg/day, were considered to be normoalbuminuric while the patients, whose urinary albumin excretion quantity was in the range of 30-300 mg/day, were considered to be microalbuminuric. Laboratory procedures in relation to the study were performed in Biochemistry and Microbiology Laboratories of our center. Fasting plasma glucose was studied in Syncihron LX20 autoanalyzer through Glucose Oxidase / O2 Depletion method by using Syneron System Plasma Glucose kit (Beckman Coulter, Brea, CA, USA). Triglyceride was studied in Syncihron LX20 autoanalyzer through enzymatic / GPO Trinder method by using

Syneron System Plasma Triglyceride kit (Beckman Coulter, Brea, CA, USA). Total cholesterol was studied in Syncihron LX20 autoanalyzer through enzymatic method by using Syneron System Cholesterol kit (Beckman Coulter, Brea, CA, USA). HDL cholesterol was studied in Syncihron LX20 autoanalyzer through homogenous calorimetric method by using Syneron System HDL Cholesterol kit (Beckman Coulter, Brea, CA, USA). LDL cholesterol was calculated through Friedewald formula [LDL = T.Chol - (HDL + Tg/5)]. Microalbumin was studied in Syncihron LX20 autoanalyzer through immunoturbudimetric method by using Syneron System Microalbuminuria kit. Hs-CRP was studied in Beckman Coulter Image (USA) device and kits through turbidimetric method in a full-automatic way. RayBio Human Adiponectin / Acrp30 ELISA kit of RayBiotech Inc. firm was used for adiponectin analysis. Normal measurement range of our adiponectin kit was determined to be 3.5–29.6 µg/mL. Data of this study was transferred to SPSS (ver:13.0) software and "Chi-square test", "Mann-Whitney U test", "Significance test between two points" and "Correlation analysis test" were used for evaluation of this data. The data was specified as average ± standard deviation, number of individuals and percentage in tables and level of significance was taken as 0.05.

Results

Of 80 individuals, who were included in the study, 48 (24 male, 24 female) were hypertensive while 32 (16 male, 16 female) were normotensive. When the patient group was compared to the control group in terms of age, waist circumference and BMI, two groups were similar. It was found out that the patient group had statistically significantly higher systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, T.Chol, TG, LDL-C, hs-CRP and MAU values than the control group while HDL-C values were statistically significantly lower ($p<0.05$) than the control group. When average adiponectin levels of the patient group and the control group were compared, the patient group had an adiponectin level of 8.66±2.75 µg/mL and the control group had an adiponectin level of 15.01±3.99 µg/mL. There was a statistically significant difference between the two groups ($p=0.000$; $p<0.05$) (Table I).

In order to make a comparison between obese and non-obese patients, both the patient group and the control group were divided into two groups as obese and non-obese. The patients were studied in four groups as obese hypertensive group (n=24, male:10, female:14), non-obese hypertensive group (n=24, male:14, female:10), obese normotensive group (n=16, male:7, female:9) and non-obese normotensive group (n=16, male:9, female:7).

It was found out that the individuals in the obese hypertensive group had significantly higher FPG, TG and MAU values when compared to the individuals in the obese normotensive group while HDL-C values and adiponectin levels were significantly lower ($p<0.05$). When two groups were compared in terms of Hs-CRP, LDL-C and T.Chol values, there was not a significant difference ($p>0.05$) (Table II).

It was found out that the individuals in the non-obese hypertensive group had significantly lower adiponectin levels when compared to the individuals in the non-obese normotensive group while FPG and MAU levels were significantly higher ($p<0.05$). When two groups were compared in terms of LDL-C, hs-CRP, HDL-C and T.Chol values, there was not a significant difference ($p>0.05$) (Table II).

We found out an adiponectin level of 7.51±2.12 µg/mL in the obese hypertensive group while it was 9.82±2.87 µg/mL in the non-obese hypertensive group. There was a statistically significant difference between two groups ($p=0.000$; $p<0.05$). When adiponectin levels of obese and non-obese individuals in the normotensive group, adiponectin level of the obese group was found to be 13.28±2.07 µg/mL while it was 16.74±4.71 µg/mL in the non-obese group.There was a statistically significant difference between two groups ($p=0.007$; $p<0.05$).

While there was a negative correlation between adiponectin values and waist circumference, BMI, SBP, DBP, FPG, T.Chol, LDL-C, hs-CRP and MAU in the obese hypertensive group, a positive correlation was observed between adiponectin values and HDL-C (Table IV).

There was a negative correlation between adiponectin values and waist circumference, BMI, SBP, DBP, FPG, T.Chol, LDL-C, hs-CRP and MAU in the non-obese hypertensive group (Table IV).

When the individuals in the MAU(+) (n:10) and MAU(–) (n:14) sub-groups of the obese hypertensive group were compared in terms of adiponectin values; it was found to be 6.62±1.36 μg/mL in MAU(+) sub-group while it was 8.15±2.37 μg/mL in MAU(–) sub-group. This difference was not statistically significant ($p=0.074$, $p>0.05$).

When the individuals in the MAU(+) (n:6) and MAU(–) (n:18) sub-groups of the non-obese hypertensive group were compared in terms of adiponectin values; it was found to be 7.65±1.79 μg/mL in MAU(+) sub-group while it was 10.91±2.71 μg/mL in MAU(–) sub-group. This difference was statistically significant ($p=0.003$, $p<0.05$).

Discussion

Fatty tissue is a complex organ with endocrine, inflammatory and metabolic functions. It is shown that adiponectin, which is secreted from fatty tissue, plays an important role in regulation of glucose and lipid metabolism in insulin-sensitive tissues. Application of adiponectin results in an increase in insulin sensitivity and a reduction in glucose levels [8-11]. Adiponectin increases use of glucose and oxidation of fatty acid in muscles and liver [12]. It also decreases flow of fatty acid into liver and results in a reduction of hepatic triglyceride content and a decrease in gluconeogenesis [11]. Another important effect of adiponectin is that it plays a protective role against vascular damage. It has been shown through many experimental studies that adiponectin has anti-atherogenic and anti-inflammatory characteristics. Adiponectin suppresses release of macrophages from TNF-α and similar cytokines [13-16]. In a study, it was shown that adiponectin prevented macrophages from transformation into foamy cells. In the same study, it was shown that adiponectin also prevented migration of smooth muscle cells through proliferation. Adiponectin increases NO production from endothelial cells and stimulates angiogenesis. Adiponectin is an anti-inflammatory cytokine, which regresses atherosclerosis, and it has protective effects against atherosclerosis [7, 16-19].

HT is an important factor for development of atherosclerosis, CAD and stroke. HT may develop damage in vascular endothelium and result in a rise of transition into blood vessel wall for lipoproteins. Besides, HT causes thickening in intima and media layers of arteries. As a result of this, there is an increase in relation to the distance of diffusion and free oxygen radicals are formed in the blood vessel wall. These free radicals form oxidative stress and results in inflammatory cell migration [4].

There are many studies on adiponectin levels of hypertensive patients. In these studies, it was found out that there was an apparent negative correlation between adiponectin levels and SBP-DBP measurements [20-22].

In this study, it was shown that adiponectin levels of the hypertensive patients were lower than those of non-HT individuals. Besides, average adiponectin levels were also determined in the individuals of the hypertensive obese and non-obese group and the individuals in the normotensive obese and non-obese group. Adiponectin level was found to be 7.51±2.12μg/mL in the obese hypertensive group while it was 13.28±2.07μg/mL in the obese normotensive group. Adiponectin level was found to be 9.82±2.87μg/mL in the non-obese hypertensive group while it was 16.74±4.71μg/mL in the non-obese normotensive group. These differences were statistically significant ($p<0.05$). In our study, we specified a statistically significant negative correlation between adiponectin levels and SBP-DBP in the obese and non-obese hypertensive group. Our results are compatible with the results of the study performed by Adamczak M. et al. [21]. As a

result of our study, we determined that serum adiponectin levels in both the obese and non-obese hypertensive groups were significantly lower than those of the control groups independently of age, BMI and waist circumference measurements. Our findings show that serum adiponectin levels in hypertensive cases are significantly lower independently of obesity.

In a study, in which in-vitro isoproterenol was used for β–adrenergic agonists, it was shown that adiponectin mRNA decreased by 75% [23]. A reason for reduced adiponectin levels in HT could be elevated sympathetic activation in hypertensive patients. In a study, it was observed that sub-endothelial adiponectin accumulated in a spot, in which blood vessel damage was formed with a catheter. However, this accumulation was not observed in normal blood vessel spots. As a result of this, it was reported that serum adiponectin levels decreased. Possible reason for reduced adiponectin levels could be atherosclerotic lesions. Because adiponectin accumulated in atherosclerotic blood vessel wall and prevents inflammatory cell migration induced by TNF-α [15, 24].

There is a negative relation between adipose tissue content and adiponectin level in people. It was shown that there was a negative association between plasma adiponectin levels and BMI measurements [25]. There are many studies on the changes in adiponectin levels in the body as a result of lifestyle change, medical or surgical intervention for obese individuals. While no change was observed in relation to adiponectin level in some of these studies, there was an increase in adiponectin level in other studies [26-32]. In our study, we made a comparison in relation to adiponectin levels of obese and non-obese individuals in the hypertensive group. We measured the adiponectin level as 7.51±2.12µg/mL in the obese group while it was 9.82±2.87µg/mL in the non-obese group. The difference was statistically significant. When we compared adiponectin levels of obese and non-obese individuals in the normotensive group, we observed an adiponectin level of 13.28±2.07µg/mL in the obese group while it was 16.74±4.71µg/mL in the non-obese group. The difference was statistically significant. Consequently, individuals in the obese group had lower adiponectin levels than individuals in the non-obese group independently of hypertension. In addition, adiponectin levels decreased in case of hypertension accompanied by obesity. In our study, we found a negative correlation between adiponectin values and waist circumference, BMI measurements in the obese and non-obese hypertensive groups. As waist circumference and BMI values increased, adiponectin values decreased. Our findings indicate that serum adiponectin levels significantly decrease in correlation with elevated abdominal fatty tissue mass and waist circumference in obese cases in accordance with the literature.

In clinical studies, it was proven that low serum adiponectin levels were closely associated with atherogenic lipid profile. Adiponectin levels have a negative correlation with fasting plasma insulin concentration, FPG, T.Chol, TG, LDL-C, SBP, DBP and uric acid levels while it has a positive correlation with insulin sensitivity and HDL-C levels [22, 33-35].

In our study, FPG and TG values of individuals in the obese hypertensive group were significantly higher than those of individuals in the obese normotensive group while HDL-C values were significantly lower. Although LDL-C and T.Chol values were higher in the hypertensive group, the difference between the groups was not statistically significant. FPG values of individuals in the non-obese hypertensive group were significantly higher than those of individuals in the non-obese normotensive group. Although LDL-C, TG and T.Chol values of individuals in the non-obese hypertensive group were higher than those of individuals in the non-obese normotensive healthy group and HDL-C values were lower, there was no statistically significant difference between two groups in terms of these parameters. Besides, in our study, we found out a negative correlation between adiponectin values and FPG, T.Chol, LDL-C values ($p=0.003$, $p=0.014$, $p=0.003$, respectively) and a positive correlation between adiponectin values and HDL-C level ($p=0.007$). In this group, there was a negative relation between

adiponectin levels and TG levels, but this relation was not statistically significant (p=0.500). In the non-obese hypertensive group, we found out a negative correlation between adiponectin values and FPG, T-Chol, LDL-C values (p=0.002, p=0.002, p=0.003, respectively). There was a negative correlation between adiponectin levels and TG (p=0.085) while there was a positive correlation between adiponectin levels and HDL-C (p=0.054), but these correlations were statistically insignificant. As a result of our study, we found out that serum adiponectin levels were lower in hyperlipidemic individuals in line with the literature. One of the possible reasons for reduced serum adiponectin levels in individuals with hyperlipidemia could be existent atherosclerotic lesions. In a study performed by Tsioufis C. et al. [20] on non-diabetic individuals with recently diagnosed HT, association between adiponectin levels and hs-CRP levels, urinary albumin excretion levels was studied. As a result of this study, it was shown that the group with hypertensive microalbuminuria had significantly lower adiponectin levels than both the group with normoalbuminuria and the control group. In that study, a positive correlation was observed between the microalbuminuria levels and hs-CRP levels. Correlation of microalbuminuria and hs-CRP was associated with sub-clinical inflammation that resulted in direct injury to renal glomerulus. In our study, when the obese hypertensive group was divided into two sub-groups as MAU(+) and MAU(–), we specified an adiponectin level of 6.62±1.36 µg/mL in MAU(+) subgroup while it was 8.15±2.37µg/mL in MAU(–) subgroup. Although adiponectin levels were higher in MAU(–) subgroup, this difference was not statistically significant (p=0.074). Besides, there was a negative correlation between adiponectin levels and MAU levels (p=0.037). When the non-obese hypertensive group was divided into two sub-groups as MAU(+) and MAU(–), we specified an adiponectin level of 7.65±1.79µg/mL in MAU(+) subgroup while it was 10.91±2.71µg/mL in MAU(–) subgroup. This difference was statistically significant (p=0.003). Besides, there was a negative correlation between adiponectin levels and microalbuminuria levels (p=0.005). Our results were compatible with the results of the study performed by Tsioufis C. et al. [20]. As circulatory adiponectin regulates vascular endothelium functions and inflammatory reactions, it would not be wrong to say that reduced adiponectin levels could be partly responsible for inflammatory events observed in the cases with hypertension and microalbuminuria. In our study, we compared the average hs-CRP values of the obese hypertensive group-obese normotensive group and the non-obese hypertensive group-non-obese normotensive group. We could not find a statistically significant difference between these groups in terms of hs-CRP values (p>0.05).

In a study performed by Ouchi N. et al. [36], a negative correlation was observed between plasma adiponectin levels and plasma hs-CRP levels. When compared to the control group, it was found out that the individuals with coronary artery disease had higher hs-CRP levels while adiponectin level was found to be lower. In the same study, a negative correlation was observed between hs-CRP mRNA and adiponectin mRNA in percutaneous fatty tissue of the patients with angiographically diagnosed coronary artery disease. In another study performed by Yamamoto Y. et al. [22], a negative correlation was specified between adiponectin levels and hs-CRP levels. Similarly, we found out a negative correlation between adiponectin levels and hs-CRP (p=0.028, p=0.010, respectively) in the obese and non-obese hypertensive groups. This reciprocal association between adiponectin and hs-CRP supports the idea that adiponectin has a protective role against atherosclerosis and vascular inflammation. Reduced adiponectin levels could respond to systemic inflammation events. This finding is compliant with the elevated hs-CRP levels.

Consequently, serum adiponectin level was lower in the hypertensive group independently of age, BMI and waist circumference measurements when compared to the control group. Besides, there was a significant relation between adiponectin levels and atherosclerotic risk factors. Low adiponectin level may constitute an important risk for development of atherosclerosis. Further studies are needed to determine this relation.

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