The association between serum adiponectin levels and the severity of coronary artery lesions on the angiogram

Serum adiponektin düzeyleri ile anjiyogramda koroner lezyon ciddiyeti arasındaki ilişki

Hidayet Goksoy, M.D., Dursun Dursunoglu, M.D., Mehmet Ozturk, M.D., Simin Rota, M.D.,[1]

Pamukkale University, Faculty of Medicine, Department of Cardiology [1]Department of Biochemistry, Denizli

Objectives: Decreased serum adiponectin levels have been shown in patients with coronary artery disease (CAD). We evaluated the association between serum adiponectin levels and CAD severity on the angiogram.

Study Design: The study included 86 patients (70 males, 16 females; mean age 60 years) with angiographically documented CAD (≥50% stenosis). The patients were divided into three groups according to the number of vessels affected; thus 18 had single-vessel, 16 had two-vessel, and 52 had multiple-vessel disease. The severity of coronary lesions was assessed using the modified Gensini score. Serum adiponectin levels were measured in the CAD group and in a control group of 33 subjects (16 males, 17 females; mean age 54.8 years) who were found to have normal coronary arteries on angiography.

Results: The mean age, the number of male patients, and the number of smokers were significantly higher in the CAD group (p=0.01). Patients with CAD exhibited significantly lower serum levels of adiponectin compared to the control group (2.0±2.0 μg/dL vs. 3.2±2.7 μg/dL; p=0.01). There were no significant differences in adiponectin levels between patients with single-, two, and multiple-vessel disease. Compared to the controls, patients with two-and multiple-vessel disease had significantly lower adiponectin levels (1.5±0.9 μg/dL vs. 2.0±2.0 μg/dL, respectively), whereas those with single-vessel disease (2.6±2.5 μg/dL) did not differ from the controls in this respect. The mean Gensini score was 3.8±1.7 in the CAD group. There was a weak inverse correlation between serum adiponectin levels and the Gensini score (r=-0.209; p=0.02).

Conclusion: Serum adiponectin levels are decreased in CAD patients compared to controls. This decrease is more prominent with increasing levels of CAD severity, which may be a helpful clue of multivessel disease.

Key words: Adiponectin; biological markers; coronary angiography; coronary artery disease/blood/classificaition.

Amaç: Koroner arter hastalığı (KAH) olanlarda serum adiponektin düzeylerinin düştüğü gösterilmiştir. Bu çalışmada, serum adiponektin düzeyleri ile anjiyogramda koroner lezyon ciddiyeti arasındaki ilişki değerlendirildi.

Çalışma planı: Çalışmaya koroner anjiyografide koroner arterlerinde ciddi lezyon (≥%50 darlık) saptanan 86 hasta (70 erkek, 16 kadın; ort. yaş 60) alındı. Koroner lezyonlu damar sayısına göre hastalar üç gruba ayrıldı; 18 hastada tek damar, 16 hastada 2 damar, 52 hastada çok damar hastalığı vardı. Koroner lezyonların ciddiyeti modifiye Gensini skoru ile değerlendirildi. Serum adiponektin düzeyleri hasta grubunda ve anjiyografide koroner arterleri normal bulunan 33 kişiden (16 erkek, 17 kadın; ort. yaş 54.8) oluşan kontrol grubunda ölçüldü ve karşılaştırıldı.

Bulgular: Hasta grubunda ortalama yaş, erkek hastaların ve sigara içenlerin sayısı kontrol grubundan anlamlı olarak daha yüksekti (p=0.01). Serum adiponektin düzeyleri hasta grubunda (2.0±2.0 μgr/dl) kontrol grubuna (3.2±2.7 μgr/dl) göre anlamlı derecede düşük bulunurken (p=0.01), lezyonlu damar sayısına göre altgruplar arasında serum adiponektin düzeyleri anlamlı farklılık göstermedi. Serum adiponektin düzeyi tek damar lezyonlu grupta (2.6±2.5 μgr/dl) kontrol grubundan anlamlı fark göstermedi; iki damar (1.5±0.9 μgr/dl) ve çok damar (2.0±2.0 μgr/dl) lezyonlu gruplarda ise kontrol grubundan anlamlı derecede düşüktü (p=0.01). Hasta grubunda Gensini skoru ortalaması 3.8±1.7 bulundu. Korelasyon analizinde, serum adiponektin düzeyi Gensini skoru ile, zayıf da olsa, anlamlı negatif bir ilişki gösterdi (r=-0.209; p=0.02).

Sonuç: Serum adiponektin düzeyleri, KAH'de kontrollere göre anlamlı düşüş göstermektedir. Koroner lezyon ciddiyeti arttıkça belirginleşen bu düşüş çok damar hastalığı için bir ipucu olabilir.

Anahtar sözcükler: Adiponektin; biyolojik belirteç; koroner anjiyografi; koroner arter hastalığı/kan/sınıflandırma.

Received: 13.01.2009 *Accepted:* 23.03.2009

Corresponding address: Dr. Dursun Dursunoğlu. Pamukkale Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 20200 Kınıklı Kampüsü, Denizli
Tel: +90 - 258 - 444 07 28 e-mail: dursundursunoglu@yahoo.com

The most common cause of death due to cardiovascular diseases is coronary artery disease (CAD), which is a progressive inflammatory disease with underlying atherosclerosis in its etiology.[1,2] In addition to major risk factors such as smoking, hypertension, diabetes mellitus (DM) and hyperlipidemia, adiponectin which is secreted from adipose tissue has recently been shown to be associated with CAD and other risk factors.[3,4] Although the physiological role of adiponectin has not been fully understood, several studies have demonstrated antiatherogenic and anti-inflammatory effects of adiponectin in endothelial cells and macrophages,[4-6] and that adiponectin levels decreased in presence of hypertension, DM and metabolic syndrome.[7-10] It has been also suggested that normal or high levels of adiponectin may prevent development of cardiovascular diseases and complications in healthy individuals.[11]

In this study, we assessed serum adiponectin levels of those diagnosed with CAD angiographically in different patient groups and investigated the association between levels and the severity of coronary atherosclerosis.

PATIENTS AND METHODS

The study included 86 patients (70 males, 16 females) who visited the cardiology department and who were detected with severe lesions (≥50% stenosis) in the coronary arteries by coronary angiography. On the other hand, the control group consisted of 33 subjects (16 males, 17 females) with completely normal coronary arteries. Prior to coronary angiography, a detailed medical history was obtained from every subject and risk factors of CAD were established. Subjects were also evaluated by physical examination and 12-lead electrocardiography.

Patients with heart failure and atrial fibrillation and those with an infectious disease or conditions which may affect metabolic parameters (those with thyroid dysfunction, anemia, and malignancy, renal and liver dysfunction based on medical history or laboratory tests) were excluded from the study. Hypertensives and diabetics continued to benefit from drug therapy. Obesity was defined as body mass index (BMI) of >30 kg/m^2.

Routine biochemistry analyses of all the subjects were performed using 12-hour fasting venous blood samples. 10-mL venous blood samples which were collected to assess serum total adiponectin levels were centrifuged at 4000 rpm for 7 minutes and the supernatant was decanted into an eppendorf. The serum samples were stored at -20^0C in the laboratory and levels of serum total adiponectin were measured by ELISA method (Adiponectin ELISA, BioVendor Laboratory Medicine Inc., Czech Republic).

Selective coronary angiography by standard Judkins technique was performed on all subjects with the right femoral approach and patients who were found to have severe coronary stenoses were divided into three groups according to the number of vessels affected: single-vessel lesion (n=18: 13 males, 5 females), two-vessel lesions (n=16: 15 males, 1 female) and multi (≥3) -vessel lesion (n=52: 42 males, 10 females).

The severity of coronary lesions was assessed using the modified Gensini score.[12] Scoring was applied as follows: 5 scores for left main coronary lesion; 2.5 scores for proximal left anterior descending (LAD) artery and the left circumflex artery (LCx); 1.5 scores for the mid-LAD artery lesion; 1 score for the first diagonal branch (D1) and the obtuse marginal branches and right coronary artery; 0.5 score for the second diagonal (D2) and the LCx posterolateral branch. Gensini scores were calculated by adding up the respective scores for each patient.

Informed consents were obtained from all patients and the study protocol was approved by the local ethics committee of our hospital.

Statistical analyses were performed by SPSS package program (version 11.0 for Windows) and the results were presented as mean ± standard deviation. In the caparison of measurable data the Student t-test was used in the assessment of subjects with/without CAD, while Kruskal-Wallis test was used in the comparison of subgroups of CAD patients (single-vessel, two-vessel and (≥3) vessel). The Mann-Whitney U-test and the Students T tests were used in binary comparison of control group and patient subgroups according to the number of vessels affected. Pearson correlation test was also used in the assessment of the correlation between serum adiponectin levels and certain parameters including age, BMI and Gensini score. $P<0.05$ was considered to be statistically significant.

RESULTS

Table 1 shows comparison of the basic characteristics of patients and the control group. Mean age and the number of male patients and smokers were significantly higher in the patient group than the controls (p=0.01). There was no significant difference between the groups with regards to body mass index and prevalence of hypertension, DM and obesity . Serum adiponectin levels were found to be significantly lower in the patient group (2.0±2.0 µg/dL) compared to the control group (3.2±2.7 µg/dL) (p=0.01). The mean Gensini score

Table 1. Comparison of basic characteristics and serum adiponectin levels in the patient and control groups

	Control group (n=33)			Patient group (n=86)			
	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	*p*
Sex							**0.01**
Male	16	48.5		70	81.4		
Female	17	51.5		16	18.6		
Age			54.8±10.7			60.0±9.5	**0.01**
Body mass index (kg/m^2)			27.8±3.5			26.8±4.9	NS
Hypertension	14	42.4		39	45.4		NS
Diabetes mellitus	14	42.4		34	39.5		NS
Cigarette smoking	8	24.2		33	38.4		**0.01**
Obesity (BMI >30 kg/m^2)	14	42.4		35	40.7		NS
Previous myocardial infarction	-			56	65.1		
Coronary artery bypass grafting	-			26	30.2		
Percutaneous coronary intervention	-			26	30.2		
Adiponectin (µg/dL)			3.2±2.7			2.0±2.0	**0.01**

NS: not significant

which indicates prevalence of coronary lesions in the patient group was found to be 3.8±1.7.

No significant difference was found between patient subgroups according to the number of vessels affected with respect to mean age, BMI, hypertension, DM and serum adiponectin levels.

In the binary comparison of patient subgroups and control group, mean age was not significantly different in patient subgroups with single-vessel (61.1±9.3) and two-vessel lesion (59.7±11.4) compared to the controls, whereas mean age was significantly higher in the patient subgroup with multi-vessel (≥3) lesion (59.7±9.29 years) (p=0.01). Serum adiponectin levels were not significantly different between patient subgroup with single-vessel disease (2.6±2.5 µg/dL) and control group, while it was found to be significantly lower in the patient subgroup with two-vessel (1.5±0.9 µgr/dL) and multi-vessel lesion (2.0±2.0 µg/dL) compared to the control group (p=0.01).

Serum adiponectin level was not significantly related to age and BMI, whereas a significant and negative relation was found in the correlation analysis, despite poor Gensini score (r=-0.209; p=0.02; Figure 1).

DISCUSSION

Some recent studies have shown that adiponectin which is secreted from adipose tissue is associated with CAD.[3,4] Similarly, our study also showed that serum adiponectin levels were significantly lower in patients with angiographically diagnosed CAD compared to the controls. In addition, serum adiponectin levels were not significantly different in single-vessel lesions compared to the control group, whereas it was found to be significantly lower in patients with two-vessel and ≥3-vessel lesions. As a result, it may be suggested that low serum adiponectin levels may indicate multi-vessel (≥2 vessels) disease rather than single-vessel disease. In other words, it may be concluded that serum adiponectin level decreases in CAD patients with multi-vessel involvement, whereas no significant difference was found in CAD patients with single-vessel disease.

Despite a poor but significantly negative association of Gensini score in the patient group indicating the extent (prevalence) of the coronary lesions, with serum adiponectin level, it is suggested that there is decreased

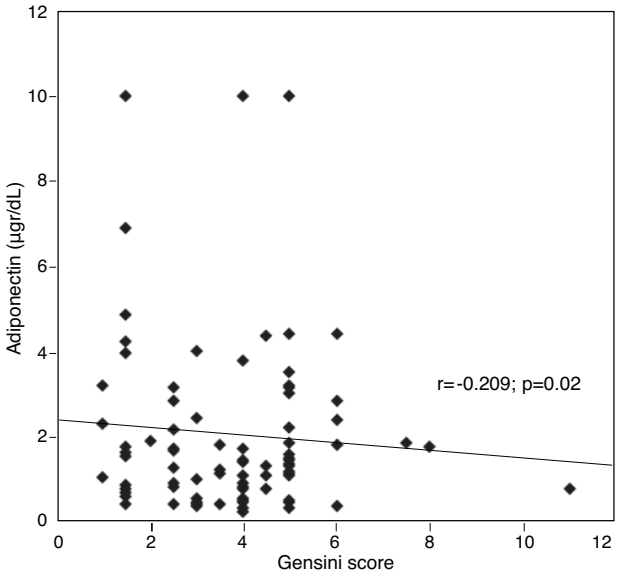

Figure 1. The relationship between serum adiponectin levels and Gensini score

serum adiponectin levels with CAD progression or that more severe and prevalent coronary lesions are observed in patients with lower levels of serum adiponectin. The physiological role of adiponectin has not been fully understood; however, it has been demonstrated that adiponectin has an antiatherogenic and antiinflammatory effect on endothelial cells and macrophages.[4-6] Moreover, it has been suggested that normal and even higher serum adiponectin levels may prevent the development of cardiovascular diseases and complications in healthy individuals.[11] Recently, Liang et al.[13] revealed that there was an association between the progression of CAD diagnosed angiographically and decreased serum adiponectin level in patients with angina pectoris following a 5-year follow-up. In, another study in which coronary angiography was performed on 325 male patients with stable angina pectoris, unstable angina pectoris and non-ST elevation myocardial infarction (MI) it was found that low serum adiponectin levels were a predictor of acute MI and cardiac mortality.[14] It has been suggested that CAD patients with complex lesions have lower serum adiponectin levels and that decreased adiponectin levels may indicate sensitivity of plaque.[15]

High molecular weight (HMW) adiponectin which is an active form of adiponectin makes up the majority of intracellular adiponectin and has more effective role in glucose and lipid metabolism compared to total adiponectin.[14] In a study conducted by Inoue et al.[16] on 149 patients it was shown that decreased HMW adiponectin level was associated with vasospastic angina pectoris, stable angina pectoris and MI. The study showed that HMW adiponectin levels were lower in CAD patients with multi-vessel disease compared to those with single-vessel disease and that decreased HMW adiponectin level together with DM, insulin resistance and high sensitivity CRP was a predictor of cardiovascular events.[16] On the other hand, serum adiponectin levels were measured in our study, but their molecular forms were not evaluated. However, decreased total adiponectin levels in CAD patients with multi-vessel in our study suggest that HMW adiponectin level may also be decreased.

Whether decreased serum adiponectin level in patients with multi-vessel coronary disease is the reason or a result is still uncertain. In this regards, it is obvious that there is a need for randomized, prospective studies, as well as experimental studies. Some recent studies have thrown light on this subject, although partially. In a prospective study conducted by Pischon et al.[17] it was found that the risk of MI was lower in men with high adiponectin level, independent of other risk factors. In their experimental study, Okamoto et al.[18] demonstrated that there was subendothelial adiponectin accumulation at the site of catheter-related vascular damage, whereas no such accumulation was found in intact vascular sites. As a consequence, it was reported that there was a decrease in serum adiponectin levels. It has been also shown that adiponectin acts as an endogenous regulator of endothelial cells in response to inflammatory stimuli, inhibits cell proliferation and migration of vascular smooth muscles and has antiinflammatory and antiatherogenic effects on macrophages together with endothelial cells,[19] and has also been shown to increase nitric oxide production in endothelial cells.[20]

In conclusion, serum adiponectin levels have been shown to decrease significantly in CAD patients compared to controls. It has been demonstrated that serum adiponectin levels are significantly lower in patients with two or multi-vessel lesions compared to controls. As a consequence, low serum adiponectin levels may indicate single-vessel disease rather than multi-vessel disease (≥2 vessels). In addition, despite a poor but significantly negative association of Gensini score, which indicates the extent of the coronary lesions, with serum adiponectin level it is suggested that there is decreased serum adiponectin levels with CAD progression or that more severe and prevalent coronary lesions are observed in patients with lower serum adiponectin levels.

Our study did not include any methodology (objectives, methods, etc.) investigating the effect of serum adiponectin level on possible new cardiovascular events, which was one of the limitation of the study. Therefore, further randomized and prospective studies as well as experimental studies are obviously required. Absence of multivariate analysis between serum adiponectin levels and age, sex, BMI, hypertension and DM was another limitation in our study. Although a significant relation between serum adiponectin levels and age was not found in our study, it is known that age has an effect on serum adiponectin levels and that there exists a positive relationship between age and serum adiponectin level.[21] On the other hand, the ages of CAD patients were significantly higher compared to the control group. As a result, it is interesting that serum adiponectin levels decreased significantly when the levels were expected to increase with age. This is associated with CAD. The poor but significantly negative association of Gensini score with serum adiponectin level also supports this relationship. We conclude that our study is important since it allowed evaluation of serum adiponectin levels in the subgroup of patients with angiographically documented coronary lesions and demonstration of the relationship between prevalence of coronary lesions and serum adiponectin levels.

REFERENCES

1. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med 1999;340:115-26.
2. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
3. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85-9.
4. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. J Am Coll Cardiol 2007;49:531-8.
5. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
6. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96:939-49.
7. Salmenniemi U, Ruotsalainen E, Pihlajamäki J, Vauhkonen I, Kainulainen S, Punnonen, et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 2004;110:3842-8.
8. Matsushita K, Yatsuya H, Tamakoshi K, Wada K, Otsuka R, Takefuji S, et al. Comparison of circulating adiponectin and proinflammatory markers regarding their association with metabolic syndrome in Japanese men. Arterioscler Thromb Vasc Biol 2006;26:871-6.
9. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
10. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
11. Giannessi D, Maltinti M, Del Ry S. Adiponectin circulating levels: a new emerging biomarker of cardiovascular risk. Pharmacol Res 2007;56:459-67.
12. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. Am J Cardiol 1983;51:606.
13. Liang KW, Sheu WH, Lee WL, Liu TJ, Ting CT, Hsieh YC, et al. Decreased circulating protective adiponectin level is associated with angiographic coronary disease progression in patients with angina pectoris. Int J Cardiol 2008;129:76-80.
14. Çavuşoğlu E, Ruwende C, Chopra V, Yanamadala S, Eng C, Clark LT, et al. Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. Eur Heart J 2006;27:2300-9.
15. Otsuka F, Sugiyama S, Kojima S, Maruyoshi H, Funahashi T, Matsui K, et al. Plasma adiponectin levels are associated with coronary lesion complexity in men with coronary artery disease. J Am Coll Cardiol 2006;48:1155-62.
16. Inoue T, Kotooka N, Morooka T, Komoda H, Uchida T, Aso Y, et al. High molecular weight adiponectin as a predictor of long-term clinical outcome in patients with coronary artery disease. Am J Cardiol 2007;100:569-74.
17. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA 2004;291:1730-7
18. Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res 2000;32:47-50.
19. Shimada K, Miyazaki T, Daida H. Adiponectin and at herosclerotic disease. Clin Chim Acta 2004;344:1-12.
20. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem 2003;278:45021-6.
21. Patel JV, Abraheem A, Dotsenko O, Creamer J, Gunning M, Hughes EA, et al. Circulating serum adiponectin levels in patients with coronary artery disease: relationship to atherosclerotic burden and cardiac function. J Intern Med 2008;264:593-8.