Original Article

The Relationship between Serum Adiponectin Levels with the Presence and Severity of Coronary Artery Disease

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Abstract

Background: Adiponectin plays important roles in the endocrine and cardiovascular systems, in fat and carbohydrate metabolism, and inflammation. In this study the relationship between adiponectin levels with the presence and severity of coronary artery disease (CAD) is evaluated.

Methods: This was a cross-sectional study that enrolled 213 persons who referred for coronary angiography. One cardiologist reported the results of each coronary angiography by using two scoring systems [number of vessel disease (usual method) and Gensini scoring system]. Then, the relationship between adiponectin levels with the presence and severity of CAD as well as predictive factors for CAD were evaluated.

Results: There was a significant negative association between mean serum adiponectin levels and presence of CAD (P = 0.04) after adjustment for all conventional risk factors for CAD. Also there was a significant negative correlation between serum adiponectin levels and severity of CAD based on the usual method for reporting coronary angiograms (P = 0.01). After adjustment for all conventional risk factors for CAD the serum adiponectin level tended to be inversely associated with the Gensini score (P = 0.09). Logistic regression analysis showed that a higher serum adiponectin level was negatively and independently associated with CAD (odds ratio: 0.94; 95% confidence interval: 0.88–1.00; P < 0.05). The variables predictive of serum adiponectin levels were determined as follows: HDL-cholesterol (P = 0.001); age (P = 0.002); insulin resistance (P = 0.005) and triglycerides (P = 0.036).

Conclusions: This cross-sectional study showed a significant negative association between serum adiponectin levels to the presence and severity of CAD.

Keywords: Adiponectin, coronary artery disease, coronary angiography

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Introduction

Adiponectin, a peptide hormone and member of the family of adipokines is strictly expressed in and secreted by adipocytes and adipose tissue.[1] Since its discovery in the mid-1990s, many roles have been determined for adiponectin. This hormone plays important roles in the endocrine and cardiovascular systems, in fat and carbohydrate metabolism, and inflammation. Adiponectin is an insulin sensitizer and hypoadiponectinemia is associated with insulin resistance.[2–6] Metabolic syndrome, lipodystrophy, obesity and body mass index (BMI) are negatively correlated with adiponectin levels.[7–9] In addition, adiponectin has anti-diabetic and anti-inflammatory properties that include inhibition of tumor necrosis factor (TNF)-α production in lipopolysaccharide-treated macrophages, reduction of TNF-α-induced monocyte adhesion, nuclear factor-κB signaling, and expressions of intracellular adhesion molecule-1, endothelial cell adhesion molecule-1 and E-selectin in endothelial cells in vitro.[10–12] Adiponectin level is a predictor of hypertension, increases in chronic renal failure and has a negative correlation with C-reactive protein (CRP).[13–15]

Adiponectin has anti-atherogenic effects and hypoadiponectinemia has been associated with atherosclerosis, coronary artery disease (CAD) and myocardial infarction (MI).[12,16–24] This effect is attributed partly to its anti-inflammatory effects.[4] In an animal model and in humans, adiponectin has been detected only in the walls of catheter-injured vessels but not in intact vascular walls,[16] where it binds to collagen I, III, and V to perform anti-inflammatory activities.[25] This peptide hormone also promotes nitric oxide production in endothelial cells,[26] neointimal and smooth muscle cell proliferation,[27] lipid accumulation on the vascular wall, foam cell formation,[28] and thrombus formation.[29] Adiponectin improves angiogenic repair[30] and its levels have a negative correlation with progression of coronary artery calcification.[31]

The aim of this study was to show the relationship between serum adiponectin levels with the presence and severity of CAD based on two scoring systems used to report coronary angiograms [number of vessel disease (usual method) and Gensini scoring system].

Patients and Methods

In a cross-sectional study, a total of 240 persons who referred to Shahid Faghihi and Nemazee Hospitals for coronary angiography were entered consecutively into the study. Exclusion criteria were: no history of coronary artery bypass graft (CABG) surgery or angioplasty, renal failure, and absence of any acute inflammatory conditions that included infections, trauma or fever. After obtain-

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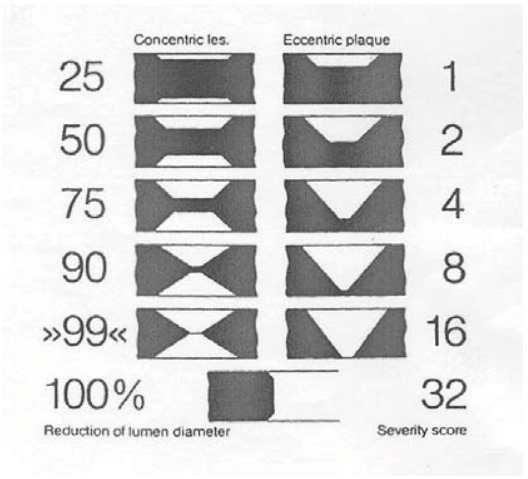
Table 1. Results of the coronary angiograms based on usual method (No. of vessel disease) in 213 participants.

Coronary Status	*n* (%)	No. of vessel disease	*n* (%)
No CAD*	54 (25.35)	—	54 (25.35)
CAD*	159 (74.65)	One vessel disease	64 (30.05)
		Two vessel disease	46(21.60)
		Three vessel disease	33(15.49)
		Left main disease	16(7.51)
Total	**213 (100)**	**Total**	**213(100)**

* CAD = coronary artery disease.



Vessel		Stenosis (%)	Score
Lt main (×5)			
LAD	Proximal (×2.5)		
	Mid part (×1.5)		
	Distal (×1)		
D1 (×1)			
D2(×0.5)			
LCX	Proximal (× 2.5)		
	Mid part (×2)		
	Distal (×1)		
OM1 (×1)			
OM2 (×0.5)			
RCA	Proximal (×1)		
	Mid part (×1)		
	Distal (×1)		
PDA (×1)			
Final score			

Figure 1. Gensini scoring system.

ing informed consent, a questionnaire that contained demographic characteristics including age, sex, cardiovascular risk factors and drug history was completed. Patients' weight, height, waist and hip circumferences were measured and recorded. After at least 12 hours of fasting, 10 mL of blood was taken from the vascular catheter at the beginning of angiography and sent immediately to the laboratory of the Endocrinology and Metabolism Research Center for separation of serum after which the samples were frozen at -70ºC. All angiographies were reported by one cardiologist who was unaware of the adiponectin levels of the participants. Assessment of the severity of CAD for each coronary angiogram was done with two methods, the usual method and the Gensini scoring system, a method that assigns a different severity score depending on the degree of luminal narrowing and the geographical importance of its location (Figure 1).[32]

Serum adiponectin, lipid profiles, fasting blood glucose (FBS), fasting insulin and creatinine levels were measured. Serum adiponectin levels were measured using radioimmunoassay (DRG Instruments GmbH, Germany), which had inter- and intra-assay coefficients of variation of 6.9% and 6.21%, respectively. Serum insulin levels were measured by immunoradiometric assay (Bio-Source, Belgium). Inter- and intra-assay coefficient of variations were 6.5% and 2.1%, respectively. The lipid profiles and FBS were measured with enzymatic and creatinine levels using colorimetric methods. The degree of insulin resistance was estimated by the homeostasis model assessment (HOMA) index, which was computed using the formula: FBS (mg/dL) × serum insulin (μU/mL)/405. Then, the correlation of the serum adiponectin levels with the presence and severity of CAD as well as other variables were evaluated.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL). Independent samples *t*-test was used for comparison of quantitative variables. The distribution of qualitative variables was investigated by Chi-square analysis. Analysis of covariance was used for comparison of mean serum adiponectin levels between participants with and without CAD after adjustment for all conventional risk factors for CAD. Spearman's rho test was used to assess the correlation between serum adiponectin levels and severity of CAD. Pearson's correlation coefficient was used to assess the correlation between serum adiponectin levels and other variables. We used the logistic regression model to determine independent predictors for CAD. Conventional risk factors for CAD were included in the analysis. Finally, linear regression analysis was applied for determination of factors predictive of serum adiponectin levels. The variables used in the model were age, sex, smoking, presence of diabetes mellitus and hypertension, weight, BMI, waist and hip circumferences, waist hip ratio, FBS, insulin levels, insulin resistance (HOMA), and serum lipid levels. A P value of < 0.05 was considered significant.

Results

There were 213 participants with a mean age of 57.9 ± 11.07 years (131 males and 82 females) who remained in the study, following exclusion of 27 subjects who had serum creatinine levels of more than 1.2 mg/dL. The mean serum adiponectin level was 11.4 ± 6.29 ng/mL and the mean Gensini score was 33.2 ± 38.29. According to the usual method of reporting coronary angiograms, about 25% of participants had normal results (Table 1). Demographic, clinical and biochemical characteristics of participants are shown in Table 2.

There was a significant negative association between mean serum adiponectin levels and the presence of CAD. The mean serum adiponectin level was 13.3 ± 5.66 ng/mL in those with normal coronary angiograms and 10.8 ± 6.40 ng/mL in those with

Table 2. Demographic, clinical and biochemical characteristics of participants divided by the absence/presence of coronary artery disease (CAD) according to the number of vessel disease (usual method) and Gensini scoring system.

	Coronary status Number of vessel disease (usual method)			Coronary status (Gensini score)		
Variables	**No CAD* (54)**	**CAD* (159)**	***P*-value**	**Gensini score = 0 No CAD* (47)**	**Gensini score > 0 CAD* (166)**	***P*-value**
Age (yrs.)	54.4 ± 9.54	59.1 ± 11.33	0.007	53.7 ± 9.65	59.1 ± 11.18	0.003
Sex (M/F)	(21/33)	(110/49)	0.0001	(17/30)	(114/52)	0.0001
Smoking, *n* (%)	24 (44.4)	84 (52.8)	0.287	20 (42.6)	88 (53.0)	0.205
Diabetes mellitus, *n* (%)	6 (11.1)	49 (30.8)	0.004	5 (10.6)	50 (30.1)	0.007
Hypertension, *n* (%)	27 (50.0)	62 (39.0)	0.315	24 (51.0)	70 (42.2)	0.278
Hyperlipidemia, *n* (%)	23 (42.6)	74 (46.5)	0.615	19 (40.4)	78 (47.0)	0.425
BMI (kg/m^2)	25.7 ± 4.11	25.9 ± 4.22	0.78	25.9 ± 4.27	25.9 ± 4.17	0.92
Waist circumference (cm)	91.6 ± 12.08	92.8 ± 12.06	0.53	90.7 ± 11.41	93.0 ± 12.20	0.21
Hip circumference (cm)	100.1 ± 9.51	98.7 ± 10.88	0.37	99.3 ± 8.86	98.9 ± 10.99	0.861
Waist:hip ratio	0.9 ± 0.07	0.9 ± 0.06	0.011	0.91 ± 0.07	0.94 ± 0.06	0.01
Insulin resistance (HOMA index)	2.1 ± 2.25	3.0 ± 3.49	0.079	2.1 ± 2.16	2.9 ± 3.47	0.118
Adiponectin (ng/mL)	13.3 ± 5.66	10.8 ± 6.39	0.012	13.2 ± 5.75	10.9 ± 6.38	0.031
Total cholesterol (mg/dL)	175.0 ± 42.54	172.8 ± 47.19	0.768	170.6 ± 39.75	174.2 ± 47.67	0.642
LDL-cholesterol (mg/dL)	116.3 ± 38.79	116.8 ± 40.05	0.937	112.5 ± 35.60	117.9 ± 40.75	0.381
Triglycerides (mg/dL)	99.8 ± 50.57	117.5 ± 76.73	0.114	96.6 ± 49.63	117.7 ± 75.83	0.073
HDL-cholesterol (mg/dL)	38.7 ± 12.94	32.8 ± 12.81	0.005	38.8 ± 13.28	33.1 ± 12.76	0.008
*CAD = Coronary artery disease						

Table 3. Logistic regression analysis of independent predictors for coronary artery disease (CAD).

Predictor	**Crude model**		**Adjusted model**	
	Odds ratio	**95% Confidence interval**	**Odds ratio**	**95% Confidence interval**
Age	1.04	1.01–1.07	1.06	1.02–1.10
Female gender	0.28**	0.15–0.54	0.21**	0.01–0.49
Diabetes mellitus	3.56**	1.43–8.88	7.63**	2.21–26.31
HDL-cholesterol	0.97**	0.94–0.99	0.97**	0.95–1.01
Adiponectin	0.94*	0.90–0.99	0.94*	0.88–1.00
*P < 0.05, **P < 0.01				

CAD based on the usual method after adjustment for all conventional risk factors for CAD such as age, sex, smoking, presence of diabetes mellitus, hypertension, hyperlipidemia, BMI, waist and hip circumferences, waist hip ratio, insulin resistance (HOMA), and serum lipid levels (P = 0.04). There was a significant negative correlation between serum adiponectin levels and severity of CAD (r = -0.183; P = 0.01) based on the usual method for reporting coronary angiograms. The mean serum adiponectin level tended to be significantly higher in the Gensini group that scored zero (no CAD) than those whose Gensini scores were more than zero (with CAD) after adjustment for all conventional risk factors for CAD (13.2 ± 5.75 ng/mL vs. 10.9 ± 6.38 ng/mL; P = 0.09); (Figure 2). No linear correlation existed between serum adiponectin levels and Gensini score.

Logistic regression analysis showed that female gender (odds ratio: 0.21; P < 0.01), serum adiponectin (odds ratio: 0.94; P < 0.05) and HDL-cholesterol (odds ratio: 0.97; P < 0.01) levels were negatively associated with CAD while diabetes mellitus (odds ratio: 7.63; P < 0.01) was positively correlated with CAD. The results revealed that a decrease in serum adiponectin level by 1 ng/mL

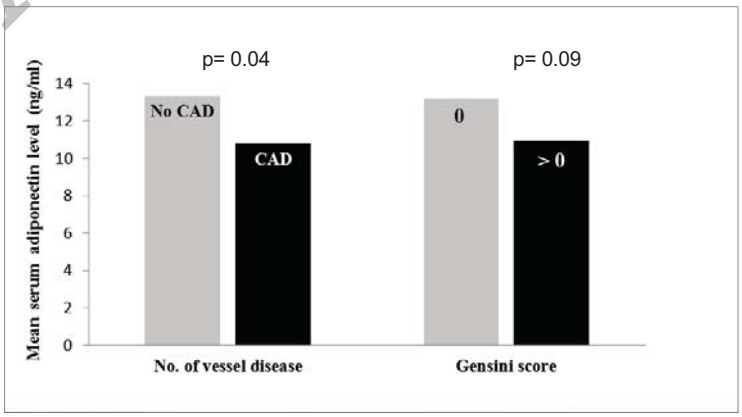


Figure 2. Comparison of the mean serum adiponectin levels between participants with normal coronary angiography and those with documented coronary artery disease (CAD) according to the number of vessel disease (usual method) and Gensini scoring system.

Table 4. Correlates of serum adiponectin levels.

Variables	r *	*P*-value
Age (yr)	0.239	0.001
Weight (kg)	-0.167	0.019
Height (m)	-0.044	0.54
BMI (kg/m^2)	-0.069	0.34
Waist circumference (cm)	-0.169	0.017
Hip circumference (cm)	-0.169	0.018
Waist:hip ratio	-0.059	0.41
FBS (mg/dL)	-0.202	0.004
Insulin (μU/mL)	-0.192	0.007
Insulin resistance (HOMA index)	-0.216	0.002
Total cholesterol (mg/dL)	0.011	0.87
LDL-cholesterol (mg/dL)	0.00	0.99
HDL-cholesterol (mg/dL)	0.247	0.0001
Triglycerides (mg/dL)	-0.191	0.007
Gensini score	-0.063	0.38

*: r = Pearson's correlation coefficients

Table 5. Predictors of serum adiponectin levels.

Variables	β* Coefficients	*t*	*P*-value
HDL-cholesterol	0.234	3.537	0.001
Age	0.209	3.154	0.003
Insulin resistance (HOMA index)	-0.191	-2.854	0.005
Triglycerides	-0.141	-2.109	0.036

* β Coefficients = linear regression analysis

resulted in a 0.94 times higher risk of CAD (Table 3).

Serum adiponectin levels had a significant negative linear correlation with weight, waist and hip circumferences, insulin resistance (HOMA index) and triglyceride levels; however, there was a significant positive linear correlation with age and HDL-cholesterol levels (Table 4). The variables (HDL-cholesterol, age, insulin resistance, and triglyceride levels) that predicted adiponectin levels were determined by regression analysis (Table 5).

Discussion

This study revealed a significant negative association between serum adiponectin levels with the presence and severity of CAD according to the usual method. These results supported other studies that showed the relationship between low serum adiponectin levels and atherosclerosis, CAD and MI.[4,16–24] As with previous studies,[5,6,17] our study revealed a positive correlation between serum adiponectin levels and HDL-cholesterol levels, and a negative correlation with triglyceride levels and insulin resistance. Also this study demonstrated that HDL-cholesterol levels, age, insulin resistance and triglyceride levels were significant predictors of serum adiponectin levels. The positive correlation between age and serum adiponectin levels was shown in other studies.[33–35]

In our study serum adiponectin level was identified as a significant independent determinant for CAD. In a prospective study, doubling of adiponectin levels was accompanied by a 30% reduced risk of MI after eliminating the confounding factors.[23] Kumada et al. showed that hypoadiponectinemia (below 4 μg/mL) was associated with a double increase in CAD prevalence in males after adjustment for traditional risk factors.[22] Another study elucidated the association of low (< 4 μg/mL) serum adiponectin levels with multiple coronary artery stenoses.[36] von Eynatten et al. and Liang et al. explained the inverse correlation of high molecular weight (HMW) adiponectin and the HMW/total adiponectin ratio with the extent of CAD.[37,38] Sattar and colleagues in a prospective study and meta-analysis have shown that the association between adiponectin levels and CAD is comparatively moderate and requires further investigation.[39]

Other studies on the association between serum adiponectin levels and prediction of the outcome in patients with CAD or recurrent cardiovascular events, and the relationship between adiponectin levels with the severity of CAD show conflicting results.[40–46] To the best of our knowledge, there are limited studies that have evaluated the relationship between serum adiponectin level and CAD that simultaneously used two scoring system to determine the extent of CAD. The strength of our study was the use of two methods to evaluate coronary artery angiograms for all participants, the usual method and the Gensini scoring system. A significant negative association was documented between serum adiponectin levels and the presence/severity of CAD only with the usual method. After adjustment for all conventional risk factors for CAD the mean serum adiponectin levels tended to be inversely associated with Gensini score. The literature review on studies that compared the serum adiponectin levels and severity of coronary angiograms based on Gensini scoring system revealed that the majority of studies used a different cut-off point for the Gensini score to determine the severity of CAD.[35,47,48]

Our study had several limitations. The lack of association between serum adiponectin level and Gensini score was likely due to the relatively small number of participants and the narrow cut-off point for the presence (Gensini score > 0) and absence (Gensini score = 0) of CAD. Another limitation was that this study consisted of persons who referred for coronary angiography with symptoms of CAD, which have led us to overestimate the association between serum adiponectin levels and CAD.

In conclusion, this cross-sectional study has shown a significant negative association between serum adiponectin levels with the presence and severity of CAD. However, there is no linear correlation between serum adiponectin levels and Gensini score. More studies in a larger population are needed to evaluate the association between serum adiponectin levels and Gensini score and to explore the mechanisms for the protective effects of adiponectin against CAD.

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