The Relationship Between Adiponectin Serum Level and Coronary Artery Disease in Type 2 Diabetic Patients

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Abstract- Adiponectin is an adipocytokine that has a higher serum level in healthy people. In type 2 diabetes, insulin resistance, hypertension, MI, and dyslipidemia, the serum level of adiponectin is lower than 4 µg/mL. Adiponectin is proved to have a protective role against atherosclerotic changes where its low serum levels in type 2 diabetes can lead to the progression of atherosclerotic lesions. In this study, we aimed to survey the possible effects of adiponectin in the development of coronary artery disease in type 2 diabetics. Thirty diabetic cases with coronary artery disease, 30 diabetic cases without known coronary artery disease, and a group of 30 healthy volunteers, all of them were between 18-65-year-old, were entered our study. We gathered demographic data by performing a physical examination followed by filling a checklist and a set of laboratory tests. All the groups were sex and age-matched (P=0.284 and P=0.163 respectively). CAD group had the lowest HBA1C (P<0.001). Both LDL and HDL were also lower in the CAD group (P<0.001). Adiponectin was also lower in the CAD group when compared to other groups (P<0.008) or when compared with only normal diabetics (P<0.002). We found a correlation between adiponectin and HDL (r=0.348, P=0.008), suggesting each unit of reduction in serum level of adiponectin could increase the chance of coronary artery disease by 38% in diabetics. In this study, we showed that the lower serum level of adiponectin is correlated with an increased risk of coronary artery disease in type 2 diabetics.

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Keywords: Type 2 diabetes; Adiponectin; Coronary artery disease

Introduction

Type 2 diabetes is one of the most common types of chronic metabolic disorders that causes many chronic complications with morbidity and mortality. Regarding the probable relationships which exist between many metabolic factors and chronic complications of diabetes, surveying these factors could play an effective role in the early and accurate diagnosis of these disabling complications of diabetes. It is also probable to use these factors in the process of developing new anti-diabetes medications.

Adiponectin is an adipocytokine with 244 amino acids that are very similar to collagen VIII, X, and complement protein C_{1q}, which secrete from mature adipocytes (1). This adipokine has a higher serum level in healthy people who have a healthy metabolic status (2,3). Normal adiponectin serum levels are reported between 4-30 µg/mL, when lower than 4 µg/mL could be related to type 2 diabetes, insulin resistance, hypertension, MI, and dyslipidemia (2-7). Adiponectin is proved to have a protective role against atherosclerotic changes where its low serum levels in type 2 diabetes can lead to the progression of atherosclerotic lesions (1,8). This protein also acts as a potent insulin enhancer in peripheral tissues (1). Recent studies have shown that the serum levels of

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adiponectin are reversely correlated with the ratio of visceral adipose tissue to total fatty tissue. This finding reveals that the serum level of adiponectin is not only related to adipose tissue amount, but it is also associated with its distribution pattern (3). It is proved that adiponectin enhances insulin sensitivity and promotes the metabolism of lipids. It is also reported to have anti-inflammatory effects (9).

Coronary artery complications are one of the most important causes of morbidity and mortality among diabetic patients. When compared to the non-diabetic population, cardiovascular events, including atherosclerosis and its related complications such as stroke, MI, and PVD, are three times more frequent in diabetic people (2). Type 2 diabetes-related metabolic dysfunctions that are effective in atherosclerosis development include hyperglycemia, the formation of glycogen end-products, severe platelet aggregation, coagulation abnormalities, increased oxidative stress, and chronic inflammation (2,7,10-12).

Materials and Methods

Study participants

This study aimed to determine the association between serum levels of adiponectin and coronary artery complications in type 2 diabetic patients. In this regard, 30 diabetic cases with coronary artery disease, 30 diabetic cases without known coronary artery disease, and a group of 30 healthy volunteers, who all were in the age group of 18-65-year-old, were entered our study.

Diabetic patients who were normal in physical examinations and did not report any chest pain who had a normal ECG were subjected to an Electrocardiogram Exercise Test; if their test results were normal, they were placed in the normal diabetic group. People with diabetes who were suspected of having coronary involvement and undergone angiography, but their results were normal also placed in the normal diabetic group.

For the coronary artery-involved diabetic group, we have selected diabetic patients with proven coronary artery disease or those who had a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG).

Inclusion and exclusion

All our subjects were selected from diabetic patients with the age group of 18 to 65-year-old.

We have excluded patients who had the following complications:

- Patients who had renal failure or patients who undergo hemodialysis
- Patients with hepatic failure
- Patients with sepsis
- Patients who had a history of stroke
- Patients who had a systemic inflammatory disease
- $HBA_1C>10\%$
- Professional athletes
- People who are using glucocorticoids, pioglitazone, and orlistat.

Data gathering

Using a checklist, we have gathered all required demographic information through physical examination by a physician. This checklist included the: age of diabetes onset, duration of diabetes, any familial history of diabetes or coronary artery complications, chest pain or shortness of breath during rest or exercise, any type of medical therapy. In physical examination, we also gathered height and weight, the age of the subject, the presence of acanthosis nigricans, and systolic and diastolic blood pressure.

Sampling method

10 ml of fasting venous blood sample was gathered from all subjects to check the following factors: FBS, 2hPPG, hs-CRP, Creatinine, HDL, LDL, Triglyceride, HBA_1C, Insulin, Adiponectin. We also gathered a morning urine sample from all subjects to control for microalbuminuria.

Ethics

We obtained written informed consent from patients. This study was approved by the ethical committee of the Mashhad University of Medical Science.

Statistical analysis

The data were statistically analyzed using IBM SPSS software (V.21). We have used the Kolmogorov-Smirnov test to identify if the samples follow a normal distribution pattern. In case that a sample was not followed a normal distribution pattern, we have used non-parametrical tests, including Mann-Whitney and Kruskal-Wallis, and for those who followed a normal distribution, we have used ANOVA. We have used Independent Sample T-Test for quantitative variables while the Chi-Square test has been used for qualitative ones. To survey correlations, we used Spearmen and Pearson correlation tests. In the case of independent variables that affect the outcome, we have used logistic regression. In all reports, a *P* less than 0.05 was considered significant.

Results

Twenty-seven people (30%) out of 90 were male. In the normal diabetic group, 9 (30%) were male, and in the diabetics with coronary artery complications group, 13 (43.3%) were male. There was no significant difference found between the two groups in the case of gender (P=0.284 and X=1.14). Table 1 shows the distribution of medication usage among diabetic groups. There was only a significant difference found between the two groups in the case of taking anticoagulant medications (P=0.001) and antihypertensive therapy (P=0.018).

Table 1. Distribution of Medication usage among the normal diabetic group and a group of diabetics who had coronary artery complications

	Diabetic without CAD	Diabetic with CAD
	Count (Percentage)	Count (Percentage)
Anti-Hypertensive Medication	8 (26.7%)	17 (56.7%)
Anti-Coagulant Medications	4 (13.3%)	18 (60.0%)
Insulin	8 (26.7%)	9 (30.0%)
Atorvastatin	21 (70.0%)	21 (70.0%)

CAD: Coronary artery diseases

There was a significant difference in age between the three groups (P<0.001), but when we compared normal diabetic groups and diabetics with coronary artery complications, we did not found any significant difference (P=0.163). The waist circumference was significantly different in the three groups (P<0.001). The groups also had a considerable difference in their body mass indexes (P=0.036), but when we compared normal diabetic groups and diabetics with coronary artery complications, we did not found any significant difference (P=0.432).

Laboratory investigations revealed a significant difference in HBA_1C levels (P<0.001). Diabetic patients who had coronary artery complications had reported having the HBA_1C levels lower than the diabetic group without CAD (P=0.033). In the case of LDL, there was also a significant difference revealed between groups (P<0.001) where diabetics with coronary artery complications had the lowest LDL level compared to other groups. FBS was also significantly different between the three groups (P<0.001), where the diabetics with the coronary artery complications had shown the highest FBS among the others, but when we compared the two diabetic groups with each other, we have seen no significant difference between them (P=0.107). HDL was also significantly different between the three groups (P<0.001), where diabetics with coronary artery complications had the lowest HDL level among others. When we compared two diabetic groups for HDL, the results for diabetics with coronary artery complications were significantly lower than the normal diabetics (P<0.001). Adiponectin was also significantly different between the three groups (P=0.008); the diabetics with coronary artery complications had the lowest serum levels of adiponectin. When compared two diabetic groups with each other in the case of adiponectin, diabetics with coronary artery complications were significantly lower than the normal diabetics (P=0.002).

Regarding the result from Table 4, we identified HDL as a confounding variable (P=0.008). It revealed that when HDL rises in diabetic subjects, the serum level of adiponectin will also rise (P=0.043).

The results of the univariate logistic model and modulation of the effect of confounders are shown in Table 5. By modulating the BMI effect, adiponectin was significantly correlated with HDL and other coronary artery-related factors (P=0.039). According to the odds ratio, we can predict if adiponectin decreases by one unit, the likelihood of coronary artery complication will increase by 38% in diabetic patients.

In another survey, when we compared the serum levels of adiponectin in diabetic patients who are taking anticoagulant medications with those who are not receiving such drugs, we found that the group of diabetics who are taking anticoagulants have significantly higher serum levels of adiponectin (P=0.039).

Table 2. Comparison of demographic indices between the three groups

	Control	DM without CAD	DM with CAD	Result	Result
		Mean±SD Median (IQR)			Diabetic v.s. CAD
Age	45.6±6.2	54.5±8.5	57.6±8.5	F=18.34, *P*<0.001	0.163
Waist circumference	88.6±6.4	99.5±7.2	104.7±9.7	F=31.91, *P*<0.001	0.024
Duration of disease	--	8.9±9.4 6 (7.5)	9.3±6.9 8 (11.0)	--	0.828
BMI	27.2±3.6 26 (5.2)	29.1±2.5 29 (4.0)	28.6±3.6 28 (5.0)	X^2=6.64, *P*=0.036	0.432
SBP	118.6±7.3 120 (10.0)	122.8±10.4 120 (10.0)	125.5±16.8 122.5 (30.0)	X^2=3.30, *P*=0.191	0.368
DBP	73.3±6.6 70 (10.0)	76.5±7.3 80 (10.0)	77.9±8.3 80 (15.0)	X^2=5.30, *P*=0.070	0.649

DM: diabetes mellitus

Table 3. Comparison of Laboratory tests between the Study Groups

	Control	DM without CAD	DM with CAD	Result	Result
		Mean±SD Median (IQR)			Diabetic v.s. CAD
Adiponectin	4.4±1.8	5.2±1.7	3.8±1.5	F=5.15, *P*=0.008	0.002
Triglyceride	120.4±44.7	69.2±12.6	142.0±67.7	F=3.67, *P*=0.030	0.228
Hpp_2	106.6±19.7	217.7±71.9	252.0±57.2	F=43.55, *P*<0.001	0.087
LDL	119.5±31.7	99.6±22.4	86.7±27.2	F=10.88, *P*<0.001	0.051
Insulin	9.6±5.1 9.4 (7.4)	13.81±8.9 11.0 (8.7)	12.15±11.4 8.7 (9.5)	X^2=4.61, *P*=0.100	0.125
HOMA-ir	1.9±1.1 1.8 (1.5)	5.3±3.9 3.8 (3.0)	5.1±4.7 4.0 (2.6)	X^2=30.44, *P*<0.001	0.876
Creatinine	1.1±0.12 1.1 (0.2)	1.14±0.15 1.1 (0.2)	1.17±0.22 1.2 (0.3)	X^2=4.01, *P*=0.135	0.549
Microalbumin	11.6±11.8 7.0 (10.9)	36.1±54.9 21.0 (23.8)	51.4±95.2 15.9 (25.6)	X^2=8.62, *P*=0.013	0.517
FBS	80.7±9.5 79.5 (14.2)	150.8±36.5 145.5(41.5)	176.7±57.9 167.0(106.7)	X^2=58.62, *P*<0.001	0.107
HBA_1C	4.5±0.28 5.4 (0.5)	7.02±1.5 6.9 (1.0)	5.4±1.04 7.7 (1.5)	X^2=58.54, *P*<0.001	0.033
HDL	44.5±6.5 44.0 (9.0)	45.4±10.14 44.0(10.25)	36.9±9.6 34.0 (10.0)	X^2=18.66, *P*<0.001	<0.001

Table 4. The relationship between the quantitative variables and adiponectin

	Diabetics		all		
	R	***P***	**R**	***P***	**SIG**
Age	-0.112	0.405	-0.141	0.202	--
BMI	0.130	0.343	0.196	0.076	--
SBP	0.122	0.366	0.073	0.504	--
DBP	0.222	0.096	0.185	0.091	--
Duration of diabetes	-0.118	0.383	-0.141	0.297	--
Weight	0.121	0.481	0.199	0.114	--
Waist Circumference	0.003	0.980	0.052	0.638	--
Hpp2	0.052	0.741	-0.026	0.841	--
Microalbumin	0.127	0.365	0.078	0.493	--
TG	0.052	0.700	0.018	0.870	--
Creatinine	0.120	0.372	0.100	0.365	--
LDL	0.079	0.557	0.062	0.574	--
HDL	0.348**	0.008	0.220*	0.043	Significant
FBS	-0.187	0.164	-0.097	0.378	--
HBA_1C	-0.065	0.632	0.001	0.996	--
HOMA-ir	-0.063	0.647	-0.036	0.743	--
Insulin	0.074	0.586	0.040	0.717	--

Table 5. Results of logistic regression analysis for the relationship between adiponectin and coronary artery complications in single and multivariates

						95% C.I. for EXP	
	B	S.E.	Wald	Sig.	Exp	Lower	Upper
Anti-Coagulant Medications	1.530	.767	3.986	.046	4.620	1.028	20.753
SBP	0.018	0.025	0.492	0.483	1.018	0.969	1.070
LDL	-0.011	0.015	0.515	0.473	0.989	0.961	1.018
HDL	-0.036	0.040	0.784	0.376	0.965	0.892	1.044
BMI	-0.018	0.121	0.022	0.883	0.982	0.775	1.246
Adiponectin	-0.468	0.226	4.279	0.039	0.627	0.402	0.976

Discussion

In the present study, we aimed to survey the role of adiponectin on the development of coronary artery complications in diabetic patients.

When compared three groups with each other, in case of age, waist circumference, and BMI, we had seen a significant difference (P<0.001, P<0.001, and P=0.036 respectively), but when we compared the diabetic groups with each other, only waist circumference was significantly different between them (P=0.024). These results can suggest the role of obesity, especially in the regions of waist and hip, as the risk factor for diabetes followed by coronary artery complications.

Adiponectin levels were lower in diabetics with coronary artery complications when compared to normal diabetics (P=0.002), which shows the reverse effect of adiponectin in the development of a coronary artery complication. Eva *et al*., had also shown the same results where they showed that the adiponectin has a protective role against atherosclerotic changes, and its reduced levels might be associated with the development of coronary artery complications due to atherosclerotic lesions (13). In another study, Kamada *et al*., (14), Hotta *et al*., (15), and Kazemi *et al.,* (15) also showed that the lower serum levels of adiponectin might be connected with increased risk of coronary artery complications. Our study also revealed that the serum levels of adiponectin in normal diabetic patients were higher than what we have measured in the control group. None of the studies that we controlled were reported this finding, while all of them reported that levels of adiponectin would decrease in diabetic patients (6,8,16,17). In a study ran by Osei *et al*., they have shown that the plasma levels of adiponectin are significantly lower in patients who have insulin resistance, even before they proceed to catch IGT and type to diabetes (18). In another study, Li *et al*., have shown that the higher serum levels of adiponectin are correlated with a lower risk of catching type 2 diabetes (16).

In the present study, the results of the univariate logistic model by modulating the BMI effect show a significant correlation of the serum levels of adiponectin with HDL and other cardiovascular-related factors (P=0.039). According to the odds ratio, the present study suggests if the serum levels of adiponectin decrease by one unit, the likelihood of coronary artery complication will increase by 38% in diabetic patients.

The present study revealed that the lower serum levels of adiponectin are correlated with an increased risk of coronary artery events in patients who have type 2 diabetes mellitus. According to our result, we found a relation between adiponectin and the likelihood of coronary artery events development in diabetics where reduction of adiponectin serum level by one unit causes a 38% increase in coronary artery complications.

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