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A New Aprroach for the Assesment of Coronary Artery Disease Risk

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Abstract: Coronary artery disease (CAD) represents a major cause of death worldwide and atherosclerosis is considered as the main cause of the disease. The whole spectrum of coronary artery disease evolves through various events leading to the formation and progression of atherosclerotic plaque and finally its complications. Atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at every step. Adiponectin is an adipocytokine that appears to have significant antiatherogenic and antiinflammatory properties in the process of atherosclerosis. Objective: to investigate whether circulating concentrations of adiponectin may constitute a significant coronary risk factor and the relation between plasma concentrations of adiponectin and various groups of CAD patients including stable angina pectoris (SAP) and acute coronary syndrome (ACS) patients. Subjects and methods: This study included 80 subjects; 20 apparently healthy subjects as a control group and 60 patients diagnosed as CAD (20 patients with SAP and 40 patients with ACS [27 patients with UA/NSTEMI and 13 patients with STEMI]. All subjects (patients and controls) were subjected to clinical evaluation, ECG examination, laboratory tests namely; Troponin I, CK, CK-MB, LDH, Specific laboratory tests included Lipid profile, Fasting blood glucose, and adiponectin and Coronary angiography when indicated Results: Serum concentrations of adiponectin differed significantly among patients with CAD versus control group, STEMI versus SAP and control groups, UA/NSTEMI versus SAP and control groups, ACS (AMI and UA/NSTEMI) versus SAP and control groups. While no statistical difference was observed in adiponectin concentration when comparing SAP versus control group, or UA/NSTEMI versus STEMI. There was negative correlation between adiponectin versus fasting glucose, triglyceride, and LDH. Serum adiponectin levels differed significantly between diabetic and non- diabetic patients with CAD. Angiographic data of number of vessels involved with atherosclerosis did not correlate significantly with serum concentrations of adiponectin. Conclusion: Adiponectin as a marker of atherosclerosis can be used to assess patients at risk of development of CAD and it can be used for risk stratification of patients with myocardial ischemia.

Key words: Adiponectin- Coronary artery disease-(CAD), acute coronary syndrome (ACS)

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death worldwide. It is expected that the rate of CAD will accelerate in the next decade, contributed to increased incidence of aging, obesity, DM, and metabolic syndrome. Risk factors for CAD includes modifiable factors including DM, hypertension, Dyslipidemias, tobacco smoking, physical activity, and obesity and nonmodifiable factors including age, gender, family history, and metabolic syndrome. CAD include many subdivisions that is to say stable angina pectoris (SAP), unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI), and ST segment elevation myocardial infarction (STEMI), the last two categories are included under the title of acute coronary syndrome (ACS) those subdivisions can be differentiated by careful history taking, physical examination, many laboratory tests, ECG examination, imaging techniques, and coronary angiography (*Bonow et al., 2002).*

Atherosclerosis is considered as the main cause of CAD. The whole spectrum of coronary artery disease evolves through various events leading to the formation and progression of atherosclerotic plaque and finally its complications. It has been suggested that atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at every step and all the risk factors contribute to its pathogenesis by aggravating the underlying inflammatory process employing immune cells and lipoprotein fractions (*Mallika et al., 2007).*

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Kershaw and Flier, 2004 suggested that adipose tissue may play an important role in mediating the chronic inflammatory process and, subsequently, cardiovascular disease risk. Increasing evidence supports that the adipose tissue may have an active endocrine function producing several hormones and substances known as adipocytokines.

Adiponectin is an adipocytokine that is believed to have significant antiatherogenic and anti-inflammatory properties *(Wolk et al., 2007)*. It appears to be a clinically important protein in the process of atherosclerosis (*Von Eynatten et al., 2006)* Physiologic levels of adiponectin are necessary to maintain the normal, noninflammatory state of the vascular wall *(Ouedraogo et al., 2007)* through acting as an endogenous modulator of both macrophage to foam cell transformation and endothelial inflammatory response (*Nakamura et al., 2004)*.

Low adiponectin has been linked to the presence of CAD and has been shown to be a risk factor for cardiovascular events .Adiponectin serum levels can be considered as an interesting tool in the risk stratification of CAD and to identify at an early stage subjects in whom preventive strategies should be more aggressive *(Tarquini et al, 2007)*.

Commercially available ELISA assays and RIA-based assays have been used for measuring adiponectin concentrations. The enzyme immunometric assay is an easily implementable tool for measuring adiponectin concentrations on a standard platform in clinical laboratory research (S*uominen 2004).*

MATERIALS AND METHODS

The present study was conducted in Kasr Al Aini Hospital, Cairo University. 80 subjects participated in our study and were divided into 2 groups namely control group (Group I), 20 apparently healthy subjects and study group (Group II), 60 patients suffering from CAD based on patient history, symptoms, ECG findings, stress myocardial perfusion imaging, or coronary angiographic studies, and CK test. Group II was subdivided into 3 subgroups: Group II (A) 20 patients with Stable Angina Pectoris group (SAP), Group II (B) 27 patients with unstable angina versus Non ST- Elevation Myocardial Infarction group (UA/NSTEMI) and Group II (C) 13 patients with ST Elevation Myocardial Infarction group (STEMI). Group II (B) & II (C) included collectively 40 patients with Acute Coronary Syndrome (ACS).

All subjects (patients and controls) were subjected to: Complete clinical evaluation, Electrocardiogram (ECG) for patients, Coronary angiography when indicated, diagnostic laboratory tests including: TroponinI, Creatine kinase (CK),Creatine kinase MB (CK-MB), Lactate dehydrogenase (LDH), and Specific laboratory tests after overnight fasting for 12-14 hours including Lipid profile (including total cholesterol, HDL- C, LDL-C and triglycerides), Fasting blood Glucose, and Serum Adiponectin.

Sampling:

7ml of venous blood were withdrawn from each subject after 12-14 hours fasting & divided into 2 tubes one to which Na fluoride was assessed for glucose assay, the second was collected on dry vacutainer, centrifuged and serum was divided into 2 aliquots one for analysis of cardiac enzymes and lipid profile while The second aliquot was immediately frozen at -70ºC for analysis of adiponectin.

Methods of Determination:

Routine tests including fasting blood glucose, cardiac enzymes and lipid profile were done in the Chemical Pathology unit, Kasr Al Ainy Hospital on the chemistry auto analyzer Hitachi 917 using Roche Diagnostics kits. LDL-C was calculated according to Freidwald formula**.** CK-MB isoenzyme was assayed using Immunoinhibition UV assay. Troponin-I was done using a rapid, qualitative, membrane based chromatographic immunoassay for detection of cTnI. It was supplied by ACON laboratories.

Determination of Adiponectin Level in Serum using Enzyme-Linked Immunosorbent Assay:

Detection of adiponectin level in serum was done by Orgenium Laboratories' human Adiponectin ELISA kit. This test is a solid-phase ELISA assay designed to measure the quantitative amount of total human Adiponectin in serum and plasma. This assay employs an antibody specific for human adiponectin coated on a 96-well plate. Standards, samples and biotinylated anti-human Adiponectin are pipetted into the wells and Adiponectin present in a sample is captured by the antibody immobilized to the wells and by the biotinylated Adiponectin specific detection antibody. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin is pipetted to the wells. The wells are again washed. Following this second wash step, TMB substrate solution is added to the wells, resulting in color development proportional to the amount of

Adiponectin bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color is measured at 450 nm.

Statistical Analysis:

The data were collected, tabulated and statistically analyzed using SPSS program. Student t-test was used for 2 group quantitative variables. P-value > 0.05 was used to determine significance and r-values was used to assess the correlation.

Results:

Comparison of the individual data of CAD patient subgroups and the control group is presented in **Table 1** showing the number of subjects, age, sex & incidence of hypertension and diabetes within the groups

Table 1: Characteristics of patient subsets and control group.

	Control	SAP	UAP /NSTEMI	STEMI
Number	20	20	27	13
Age (years) (± SD)	51(7)	57(11)	56(8)	57(10)
Sex (%)				
Male	60	60	66.7	46.2
Female	40	40	33.3	53.8
Hypertension (%)				
Hypertensive	0	75	55.6	61.5
Non - Hypertensive	100	25	44.4	38.5
Diabetes Mellitus (%)				
Diabetic	0	25	48	62
Non – Diabetic	100	75	52	38

Comparison of the laboratory parameters including Adiponectin, fasting glucose, lipid profile & cardiac enzymes between CAD patients and the control group are presented in **Table 2.** Significant differences were encountered when comparing Adiponectin, fasting glucose, HDL-C, and cardiac enzymes between CAD patients and the control group (P<0.05).No significant difference was observed during comparison of the previous groups regarding Total cholesterol, LDL-C, and Triglycerides (P>0.05).

Table 2: Comparison of studied laboratory parameters in patients and controls.

	Controls (n=20) Mean ± SD	CAD Patients (n=60) Mean ± SD	p value
Adiponectin (ug/ml)	27.2 (4.7)	23.9 (5.8)	0.003
Fasting Glucose (mg/dl)	89.9 (9.3)	150.5 (85.6)	0.001
Total Cholesterol (mg/dl)	202.4 (40.4)	201 (51)	0.674
HDL- Cholesterol (mg/dl)	45.7 (10.2)	38.9 (6.7)	0.001
LDL- Cholesterol (mg/dl)	133.5 (41.1)	131 (48.5)	0.833
Triglycerides (mg/dl)	132.4 (74.7)	175.9 (144.3)	0.572
LDH (U/L)	293.4(48)	536.3 (272.2)	0.001
CK (U/L)	66.7(25.4)	267.4 (581.8)	0.001
CK- MB (U/L)	5.6(2.4)	44.5 (125.6)	0.001
Troponin (%)			
Negative	100%	82%	0.019
Positive	0%	18%	

As shown in **Table 3** Significant differences between CAD patient subgroups and the control group were encountered in Adiponectin, fasting glucose, HDL-C, cardiac enzymes and Troponin (p<0.05). Other parameters including Total cholesterol, LDL-C, triglycerides showed no statistical differences (p>0.05).

Plasma Concentrations of Adiponectin in Patients with CAD:

As presented in **Tables 4 and 5** plasma concentrations of adiponectin in patients with STEMI were significantly lower than those in patients with SAP and control group (p<0.05). In addition, plasma concentrations of adiponectin in patients with UA/NSTEMI were significantly lower than those in patients with SAP and control group (p<0.05). Although, plasma concentrations of adiponectin were lower in patients with SAP than in the control group, however this difference was statistically nonsignificant. Similarly, plasma concentrations of adiponectin were lower in patients with STEMI than in patients with UA/NSTEMI, however this difference was statistically nonsignificant. Collectively, all parameters compared with each other in all groups and subgroups, adiponectin levels in all groups except in the comparison between SAP versus control and UA/NSTEMI versus STEMI groups.

Table 3: Comparison of studied laboratory parameters in CAD patients (SAP, UA/NSTEMI, and STEMI) and controls.

	Controls Mean ± SD	SAP Mean ± SD	UA/NSTEMI Mean ± SD	STEMI Mean ± SD	p value
Adiponectin (ug/ml)	27.2 (4.7)	26 (6.7)	22.9 (5)	20.8 (4.5)	0.003
Fasting Glucose (mg/dl)	89.9 (9.3)	135.8 (79.3)	153 (88.8)	168 (91.1)	0.001
Total Cholesterol (mg/dl)	202.4 (40.4)	201.2 (47.4)	205.6 (57.7)	191.1 (42.7)	0.674
HDL- Cholesterol (mg/dl)	45.7 (10.2)	40.7 (7)	39.6 (5.7)	34.5 (7)	0.001
LDL-Cholesterol (mg/dl)	133.5(41.2)	129.7 (39.7)	134.2 (57.7)	125.8 (40.2)	0.833
Triglycerides(mg/dl)	132.4 (74.7)	190.6 (220.4)	167 (85.8)	171.7 (94.7)	0.572
LDH (U/L)	293.4 (48.1)	418.5 (118.3)	499.1 (185.7)	794.9 (410.8)	0.001
CK (U/L)	66.7 (25.4)	87.4 (31.5)	103.8 (93.1)	884.1 (1057.2)	0.001
CK- MB (U/L)	5.6 (2.4)	6.4 (3.6)	17.9 (12.9)	158.4 (243.1)	0.001
Troponin (%)					
Negative	100	100	93	31	0.019
Positive	0	0	7	69	

Table 4: Comparative study of patient characteristics, metabolic parameters and investigations between CAD subsets (SAP, UA/NSTEMI & STEMI) versus control group

	Control Vs SAP p value	Control Vs UA/NSTEMI p value	Control Vs STEMI p value
Age	0.037	0.043	0.039
Adiponectin (ug/ml)	0.493	0.008	0.002
Fasting Glucose (mg/dl)	0.019	0.001	0.001
Total Cholesterol (mg/dl)	0.94	0.822	0.333
HDL- Cholesterol (mg/dl)	0.038	0.008	0.001
LDL- Cholesterol (mg/dl)	0.802	0.958	0.427
Triglycerides (mg/dl)	0.171	0.38	0.381
LDH (U/L)	0.001	0.001	0.001
CK (U/L)	0.026	0.039	0.001
CK- MB (U/L)	0.46	0.001	0.001
Troponin	0.958	0.145	0.001

Table 5: Comparative study of patient characteristics, metabolic parameters and investigations between UA/NSTEMI & STEMI versus SAP.

	SAP Vs UA/STEMI p value	SAP Vs STEMI p value	UA/NSTEMI Vs STEMI p value
Age	0.829	0.794	0.647
Adiponectin (ug/ml)	0.049	0.01	0.274
Fasting Glucose (mg/dl)	0.111	0.008	0.186
Total Cholesterol (mg/dl)	0.76	0.366	0.227
HDL- Cholesterol (mg/dl)	0.636	0.017	0.033
LDL- Cholesterol (mg/dl)	0.75	0.571	0.381
Triglycerides (mg/dl)	0.551	0.752	0.861
LDH (U/L)	0.135	0.001	0.022
CK (U/L)	0.838	0.001	0.001
CK- MB (U/L)	0.001	0.001	0.001
Troponin	0.145	0.001	0.001

Correlation Between Plasma Concentrations of Adiponectin and Patient Characteristics, Metabolic Parameters and Investigations Done:

As shown in **table 6** there was negative correlation between serum concentrations of adiponectin and fasting glucose, total cholesterol, triglycerides, and cardiac enzymes while other parameters did not correlate.

Significant correlation was encountered between Adiponectin and fasting glucose, triglycerides and LDH ($p<0.05$). With no significant correlation observed for the other parameters when compared to adiponectin. Interestingly, there was a significant difference between adiponectin concentrations in diabetic and non-diabetic patients with CAD ($p=0.004$). There was no significant difference observed between adiponectin concentrations in men and women with ($p = 0.6$).

Table 7 showed no statistical significance was observed comparing adiponectin concentrations and angiographic data ($p>0.05$).

Discussion:

Coronary artery disease (CAD) has been recognized as the leading cause of morbidity and mortality. Atherosclerosis is considered as the main cause of CAD. It has been suggested that atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at every step (*Mallika et al., 2007).*

Table 6: Correlation between Adiponectin and studied laboratory parameters and angiographic findings among the patients & control group.

Variable correlated with Adiponectin	r value	p value
Age	0.026	0.817
Fasting Glucose (mg/dl)	-0.236	0.035
Total Cholesterol (mg/dl)	-0.058	0.608
HDL- Cholesterol (mg/dl)	0.199	0.077
LDL- Cholesterol (mg/dl)	0.051	0.661
Triglycerides (mg/dl)	-0.269	0.016
LDH (U/L)	-0.336	0.002
CK (U/L)	-0.197	0.080
CK- MB (U/L)	-0.173	0.124
Vessel Disease	0.119	0.471

Table 7: Correlation between Adiponectin and Angiographic data of vessels involved with atherosclerosis.

Vessels involved	Adiponectin Mean ± SD	p value
1V	21.9 (6)	P=0.401
2V	20.1 (6.4)	
3V	25.2 (4)	
LMT (Left Main Trunk)	21.9 (7.2)	

Kershaw and Flier, 2004 and *Rothenbacher et al., 2005* suggested that the adipose tissue by producing several cytokines (e.g. Il-6 & TNF-α) and adiponectin may play an important role in mediating the chronic inflammatory process and, subsequently, cardiovascular disease risk. Adiponectin appears to be a clinically important protein in the process of atherosclerosis. Its Physiologic levels are necessary to maintain the normal, noninflammatory state of the vascular wall (*Ouedraogo et al., 2007).*

Ouchi et al., 1999 reported that plasma concentrations of adiponectin are reduced in CAD patients. Subsequent studies suggested that hypoadiponectinemia may be a novel and important risk factor for CAD and that high plasma adiponectin concentration is associated with lower risk of AMI (*Kumada et al., 2004)* and (*Hara et al., 2007)*

In our study, the results showed a significant difference in adiponectin levels between patients with CAD versus control group, STEMI and UA/NSTEMI versus SAP and control groups, STEMI versus SAP and control groups, UA/NSTEMI versus SAP and control groups (P>0.05).

Additionally, considering STEMI and UA/NSTEMI together as ACS adiponectin levels were significantly lower in patients with ACS than in those with SAP and control groups (P>0.05).

On the other hand, there was no statistical difference in adiponectin level when comparing SAP versus control group, and UA/NSTEMI versus STEMI. There was a negative correlation between serum LDH concentrations and serum concentrations of adiponectin. LDH is one of the cardiac enzymes that increase in cases of cardiac muscle necrosis. However CK, CK-MB & Troponin did not correlate with serum adiponectin levels.

Results of our study are in agreement with those reported by *Nakamura et al., 2004* who studied the same subgroups of CAD (including SAP, UAP & AMI groups). They reported that there was statistically significant difference when comparing adiponectin levels between all previous groups. *Von Eynatten et al., 2006 and Hara et al., 2007* further augmented that plasma concentrations of adiponectin were significantly lower in patients with CAD than those without. In support with our findings *Rothenbacher et al., 2005* reported that adiponectin serum concentrations were lower in angiographically confirmed stable CAD patients than in age- and gender-matched controls, both in men and in women. *Zoccali et al., 2002* have shown the same results in their studies that involved patients with end stage renal disease. *Dzielinska et al., 2003* concluded the same data when studies were done on hypertensive patients with coronary artery disease.

In contrast to these data and the present findings are those reported by *Sattar etal., 2006* although they found lower adiponectin levels in patients with ACS when compared to healthy individuals and persons with SAP, yet the differences were not statistically significant. This may be due to the contribution of other CAD disease risk factors such as obesity.

In our study, plasma fasting glucose concentrations correlated negatively with plasma concentrations of adiponectin in patients with CAD. There was a significant difference between adiponectin concentrations in diabetic and non-diabetic patients with CAD (p>0.05).Recent studies suggest that low plasma adiponectin may contribute to the pathogenesis of insulin resistance and diabetes mellitus *(Hotta et al., 2001). Schulze et al., 2005* concluded that plasma levels of adiponectin in diabetic individuals with coronary artery disease were found to be lower than those in diabetic patients without coronary artery disease in a 5-year follow up study. *Furuhashi et al., 2004* concluded that impaired utilization of adiponectin in the coronary artery and/or the heart, may promote the development of atherosclerosis.

In terms of the lipid parameters, our study revealed that serum triglyceride levels were correlated negatively with adiponectin level, while total cholesterol concentrations, HDL-C and LDL-C concentrations did not correlate with plasma concentrations of adiponectin. Our data were in agreement with those reported by *Sattar et al., 2006* and *Nakamura et al., 2004*.

Angiographic data of number of vessels involved with atherosclerosis did not correlate significantly with serum concentrations of adiponectin ($p<0.05$). Our findings agreed with those of *Lim et al., 2005*. In contrast to our findings *Von Eynatten et al., 2006* demonstrated that serum adiponectin levels showed a significant correlation to the extent of CAD in men.

Conclusion:

Our preliminary results showed that Adiponectin as a marker of atherosclerosis can be used to assess patients at risk of development of CAD and it can be used for risk stratification of patients with myocardial ischemia.

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