



# Relationship of Adiponectin and High-Sensitivity C-Reactive Protein with Left Ventricular Dysfunction among Patients Undergoing Coronary Angiography

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## ABSTRACT

**Background:** Decreased levels of adiponectin (APN) and elevated levels of high-sensitivity C-reactive protein (hs-CRP) have been found as predictors of left ventricular dysfunction and cardiovascular events. Therefore, this study aimed to assess the relationship of APN and hs-CRP with the severity of left ventricular dysfunction among Egyptian patients undergoing coronary angiography (CAG).

**Methods:** A cross-sectional study was conducted among 100 Egyptian patients who underwent clinically indicated CAG at Suez Canal University Hospital in Ismailia - Egypt, from May 2009 to December 2010. The left ventricular ejection fraction (LVEF) scoring system was used to assess left ventricular function based on echocardiographic findings. Pearson correlation was used to determine the relationship of APN and hs-CRP levels with echocardiographic LVEF score, and analysis of variance (ANOVA) was used to compare clinical and biochemical parameters among patients according to left ventricular function at  $P$ -value  $<0.05$ .

**Results:** The mean hs-CRP level had a significant weak negative correlation with the mean HDL-cholesterol level ( $r = -0.222$ ;  $P = 0.048$ ), while the mean APN level had a significant weak negative correlation with BMI ( $r = -0.269$ ;  $P = 0.007$ ) but a significant weak positive correlation with the mean hs-CRP level ( $r = 0.215$ ;  $P = 0.031$ ) and a significant moderate positive correlation with the mean HDL-cholesterol level ( $r = 0.302$ ;  $P = 0.002$ ). Left ventricular function in patients undergoing CAG was normal in 34 (34%), mildly impaired in 41 (41%) patients and moderately impaired in 25 (25%), with significantly different mean hs-CRP levels among the three groups ( $P = 0.025$ ) that increased from normal to moderately impaired left ventricular function. However, there was no statistically significant difference in left ventricular function according to the mean level of APN.



**Conclusion:** The hs-CRP level is negatively correlated with HDL-cholesterol, while APN is negatively correlated with BMI and hs-CRP but positively correlated with HDL-cholesterol in Egyptian patients undergoing CAG. The hs-CRP level correlates with the severity of left ventricular dysfunction. However, left ventricular function does not appear to correlate with APN levels.

**Keywords:** Adiponectin ▪ C-reactive protein ▪ Left ventricular ejection fraction ▪ Coronary angiography ▪ Egypt

## 1. Introduction

Left ventricular ejection fraction (LVEF) is the volume of blood pumped from the left ventricle of the heart with each contraction.<sup>(1)</sup> LVEF is the most commonly used parameter to assess patients with heart failure.<sup>(2)</sup> It is expressed as a percentage, and healthy individuals have LVEF  $\geq 60\%$ .<sup>(3)</sup> It is commonly known that patients with impaired LVEF are more susceptible to cardiac outcomes, such as coronary artery disease (CAD), than those with normal LVEF.<sup>(4)</sup>

Proinflammatory cytokines can lead to left ventricular dysfunction,<sup>(5)</sup> which can correlate with the severity of clinical manifestations associated with CAD.<sup>(6)</sup> In healthy individuals, adipocytes in white adipose tissues secrete large quantities of adiponectin (APN), an adipokine that regulates various metabolic processes.<sup>(7)</sup> Decreased levels of APN have been associated with many pathological conditions, including CAD, diabetes mellitus and hypertension.<sup>(8-9)</sup> The normal range of APN in human plasma is between 3 and 30  $\mu\text{g/ml}$ ; however, as body mass increases, its level decreases.<sup>(10)</sup> The larger adipocytes in obese subjects usually produce lower levels of APN but higher levels of pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and high-sensitivity C-reactive protein (hs-CRP).<sup>(11)</sup> This acute-phase reactant is a strong independent predictor of CVDs.<sup>(12, 13)</sup> Therefore, this study aimed to assess the correlation of APN and hs-CRP levels with left ventricular dysfunction among Egyptian patients undergoing coronary angiography (CAG). In addition, clinical and biochemical parameters were compared according to

the risk groups associated with APN levels and the left ventricular functions of those patients.

## 2. Methods

### 2.1. Study design, patients and setting

A cross-sectional study was conducted among Egyptian patients who underwent clinically indicated CAG at Suez Canal University Hospital in Ismailia city - Egypt, from May 2009 to December 2010. One hundred patients (70 males and 30 females) aged between 43 and 66 years who consented to participate voluntarily during the study period were enrolled.

### 2.2. Data and sample collection

A pre-designed data collection sheet was used to collect data about the gender and age of patients. The height and weight of patients were also measured to calculate the body mass index (BMI).

Venous blood samples were taken from patients into sterile EDTA and plain tubes under aseptic conditions after overnight fasting. Plasma and serum specimens were obtained by centrifugation of whole blood at 2500 x g for 15 min. These specimens were then used to measure the levels of APN, hs-CRP, glucose, cholesterol and triglycerides. Patients were categorized into three risk groups according to APN levels: low-risk group ( $>6.0 \mu\text{g/ml}$ ), moderate-risk group (3.5–6.0  $\mu\text{g/ml}$ ), and high-risk group ( $\leq 3.49 \mu\text{g/ml}$ ).



### 2.3. Biochemical measurements

The levels of fasting blood glucose, total cholesterol, triglycerides and high-density lipoprotein (HDL)-cholesterol were measured using manual enzymatic colorimetric assays by kits (Analyticon® Biotechnologies AG, Muhlenberg, Germany). Low-density lipoprotein (LDL)-cholesterol and very low-density lipoprotein (VLDL)-cholesterol were calculated according to the Friedewald formula.<sup>(14)</sup> The levels of plasma APN and hs-CRP were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Human Total Adiponectin/Acrp30 Quantikine® ELISA, R&D Systems, Minneapolis, USA, and C-Reactive Protein HS ELISA, DRG International Inc., Springfield, USA, respectively).

### 2.4. Assessment of left ventricular function

The LVEF scoring system was used to assess the left ventricular function of patients based on echocardiographic findings.<sup>(3)</sup> The ventricular function was considered normal at LVEF  $\geq 60\%$ , mildly impaired at LVEF  $\geq 45-59\%$ , moderately impaired at LVEF  $\geq 30-44\%$ , and severely impaired at LVEF  $< 30\%$ .<sup>(3)</sup>

### 2.5. Statistical analysis

Data were analyzed using the Statistical Packages for the Social Sciences (SPSS) software, version 15.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as mean  $\pm$  standard deviation (SD). Pearson correlation was used to test the relationship of APN and hs-CRP levels with echocardiographic LVEF score. Differences in LVEF scores were compared according to clinical and biochemical parameters using analysis of variance (ANOVA). Statistical significance was considered at  $P$ -value  $< 0.05$ .

## 3. Results

### 3.1. Characteristics of patients

The mean age of patients undergoing CAG was  $55.1 \pm 6.3$  years (range: 43–66), and the mean BMI was  $31.8 \pm 4.2$  kg/m<sup>2</sup>. On the other hand, the mean levels of fasting blood glucose, triglycerides, LDL-cholesterol, HDL-cholesterol and VLDL-cholesterol in mg/dl were  $126.1 \pm 56$ ,  $208.9 \pm 77.2$ ,  $135.6 \pm 56.1$ ,  $40.6 \pm 11.6$  and  $40.8 \pm 14.8$ , respectively. On the other hand, the mean levels of hs-CRP (mg/dl) and APN ( $\mu$ g/ml) were  $7.6 \pm 3.1$  and  $4.3 \pm 1.3$ , respectively (Table 1).

**Table 1:** Characteristics and biochemical parameters of patients enrolled in the study (N =100; 70 males and 30 females)

Variable	Mean (SD)
Age (years)	55.1 $\pm$ 6.3
BMI (kg/m <sup>2</sup> )	31.8 $\pm$ 4.2
Fasting blood glucose (mg/dl)	126.1 $\pm$ 56.0
Triglycerides (mg/dl)	208.9 $\pm$ 77.2
LDL-cholesterol (mg/dl)	135.6 $\pm$ 56.1
HDL-cholesterol (mg/dl)	40.6 $\pm$ 11.6
VLDL-cholesterol (mg/dl)	40.8 $\pm$ 14.8
hs-CRP (mg/dl)	7.6 $\pm$ 3.1
APN ( $\mu$ g/ml)	4.3 $\pm$ 1.3

SD, standard deviation; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; APN, adiponectin.

### 3.2. Correlation of hs-CRP and APN with, BMI, metabolic parameters and LVEF

The mean level of hs-CRP showed a significant weak negative correlation with the mean level of HDL-cholesterol ( $r = -0.222$ ;  $P = 0.048$ ). On the other hand, the mean level of APN showed a significant weak negative correlation with mean BMI ( $r = -0.269$ ;  $P = 0.007$ ). However, it showed a significant weak positive correlation with the mean hs-CRP level ( $r = 0.215$ ;  $P = 0.031$ ) and a significant moderate positive correlation with the mean HDL-cholesterol level ( $r = 0.302$ ;  $P = 0.002$ ) (Table 2).



**Table 2:** Correlation of serum hs-CRP and APN levels with BMI, metabolic parameters and LVEF among patients undergoing CAG at Suez Canal University Hospital, Ismailia, Egypt

Parameter	hs-CRP		APN	
	r	P value	r	P value
BMI (kg/m <sup>2</sup> )	0.043	0.672	-0.269	0.007
Fasting blood glucose (mg/dl)	0.122	0.228	0.132	0.189
Triglycerides (mg/dl)	0.018	0.856	-0.025	0.803
Total cholesterol (mg/dl)	-0.090	0.371	-0.128	0.203
LDL-cholesterol (mg/dl)	-0.058	0.568	0.070	0.487
VLDL-cholesterol (mg/dl)	0.055	0.585	0.011	0.912
HDL-cholesterol (mg/dl)	-0.222	0.048	0.302	0.002
hs-CRP (mg/dl)			-0.215	0.031
LVEF (%)	0.151	0.134	0.072	0.474

CAG, coronary angiography; hs-CRP, high-sensitivity C-reactive protein; APN, adiponectin; LVEF, left ventricle ejection fraction; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; r, Pearson correlation coefficient.

### 3.3. Adiponectin risk groups

According to serum APN levels, 11 (11%) patients were classified as low risk, 56 (56%) as moderate risk, and 33 (33%) as high risk. There was a statistically significant difference among the three groups in the mean BMI values ( $P = 0.001$ ) and mean hs-CRP levels ( $P = 0.032$ ), with an increasing trend in these two

parameters from the low-risk to the high-risk groups. On the other hand, there was a significant difference among the three groups in the mean HDL-cholesterol levels ( $P = 0.012$ ), with decreasing HDL levels from the low-risk to the high-risk groups. There was also a statistically significant difference among the three risk groups in the mean fasting blood glucose levels ( $P = 0.036$ ) (Table 3).

**Table 3:** Comparison of clinical and laboratory parameters among APN risk groups among patients undergoing CAG at Suez Canal University Hospital, Ismailia, Egypt

Parameter	APN risk groups			P value
	Low risk (>6 µg/ml) n = 11 (11%)	Moderate risk (3.5-6 µg/ml) n = 56 (56%)	High risk (<3 µg/ml) n = 33 (33%)	
Age (years)	55.4±4.3	55.1±6.3	55±7.1	0.984
BMI (kg/m <sup>2</sup> )	28.2±4.7	31.3±3.7	33.3±4.1	0.001
Fasting blood glucose (mg/dl)	98±25.1	138.4±66.2	114.8±40.6	0.036
Triglycerides (mg/dl)	188.3±69.6	210.1±83.9	213.8±68.1	0.633
Total cholesterol (mg/dl)	231.7±59.9	218.3±64	201.7±56.4	0.289
LDL-cholesterol (mg/dl)	141.7±64.2	139.3±58.6	127.2±49.3	0.580
VLDL-cholesterol (mg/dl)	37.3±14.1	41.6±11.8	41.7±12.6	0.686
HDL-cholesterol (mg/dl)	47.4±10.2	41.6±11.8	36.4±10.1	0.012
hs-CRP (mg/dl)	5.3±2.6	7.7±3.3	8.2±2.7	0.032
LVEF (%)	53.8±10.2	53.3±10.6	56.5±11.9	0.417

APN, adiponectin; CAG, coronary angiography; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; LVEF, left ventricular ejection fraction.

### 3.4. Left ventricular function

Based on the LVEF scoring system, the left ventricular function in patients undergoing CAG was normal in 34 (34%), mildly impaired in 41 (41%) patients and moderately impaired in 25 (25%) patients. There was a statistically significant difference in the mean levels of glucose ( $P = 0.014$ ) and triglycerides ( $P = 0.011$ ) among

the three groups. On the other hand, the mean level of hs-CRP was significantly different among the three groups ( $P = 0.025$ ), with an increasing trend from normal to moderately impaired left ventricular function. However, there was no statistically significant difference in left ventricular function according to the mean level of APN.



**Table 4:** Comparison of clinical and laboratory parameters among patients undergoing CAG at Suez Canal University Hospital, Ismailia, Egypt according to left ventricular function (N = 100)

Parameter	Left ventricular function			P value
	Normal (LVEF >60%) n = 34 (34%)	Mildly impaired (LVEF ≥45-59%) n = 41 (41%)	Moderately impaired (LVEF ≥30-44%) n = 25 (25%)	
Age (years)	53.9±5.4	55.6±7.1	56.1±6.2	0.367
BMI (kg/m <sup>2</sup> )	31.7±3.8	31.1±4.2	32.5±4.4	0.417
Fasting blood glucose (mg/dl)	104.1±43.6	108.1±26.8	138.7±46.2	0.014
Triglycerides (mg/dl)	199.7±62.7	193.3±67.2	246.9±81	0.011
Total cholesterol (mg/dl)	223.1±64.5	199.6±54.4	226.5±65.8	0.133
LDL-cholesterol (mg/dl)	147.9±59.6	126±55.7	134.3±50.5	0.242
VLDL-cholesterol (mg/dl)	39.7±12.6	38.8±13.4	46.1±18.7	0.127
HDL-cholesterol (mg/dl)	37.6±9.6	41.6±11.7	42.8±13.1	0.164
hs-CRP (mg/dl)	6.3±3.2	7.2±3.1	8.5±2.9	0.025
APN (µg/ml)	4.3±1.3	4.3±1.2	4.2±1.4	0.716

CAG, coronary angiography; LVEF, left ventricular ejection fraction; BMI, body mass index; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; APN, adiponectin.

## 4. Discussion

In the present study, hs-CRP showed a significant negative correlation with HDL-cholesterol levels, while APN showed a significant negative correlation with BMI and hs-CRP but a significant positive correlation with HDL-cholesterol among Egyptian patients undergoing CAG. However, neither hs-CRP nor APN was correlated with the LVEF percentage. The findings of the present study are in agreement with previous studies.<sup>(8, 15, 16)</sup> Circulating APN levels were found to be inversely associated with adiposity, triglycerides and CRP and positively associated with HDL-cholesterol among British patients.<sup>(16)</sup>

It is noteworthy that APN has been found to be positively correlated with left ventricular dysfunction,<sup>(17)</sup> and patients with severe angiographic CAD tend to have lower levels of APN.<sup>(10)</sup> A significant relationship has been reported between hs-CRP and left ventricular dysfunction assessed by echocardiography in patients with cardiovascular risk factors,<sup>(18, 19)</sup> but was not found to be associated with the severity of CAD.<sup>(19)</sup> Moreover, patients with severe CAD may have normal LVEF.<sup>(20)</sup>

In agreement with the findings of the present study, a case-control study found a significant association between APN and HDL-cholesterol.<sup>(21)</sup>

There is in vitro evidence that APN acts as a protective agent against atherosclerosis in endothelial cells, macrophages, and aortic smooth muscle cells.<sup>(14)</sup> However, the results of prospective studies investigating the association between APN and chronic heart disease in humans have been inconsistent.<sup>(22, 23)</sup> Furthermore, the causal relationship between APN and atherosclerosis in humans remains to be elucidated.<sup>(24)</sup>

In the present study, hs-CRP significantly increased in patients with moderately impaired left ventricular function compared to those with normal or mildly impaired function. However, there was no statistically significant difference in left ventricular function according to APN. The relationship of hs-CRP with the severity of CAD and the extent of atherosclerosis is controversial.<sup>(25)</sup> Zebrack et al.<sup>(12)</sup> found a weak correlation between CRP and the extent of CAD using a CAD score. The lack of significant correlation between APN levels and LVEF score in the present study is consistent with that reported by Fukuta et al.,<sup>(26)</sup> who found that APN level did not significantly correlate with ejection fraction in either men or women.

The present study is limited by being conducted in a single hospital and the small sample size due to logistic constraints. Therefore, its findings may not be



generalizable to patients undergoing CAG in the country. Further large-scale, multicenter studies are recommended, preferably adopting case-control or cohort designs.

## 5. Conclusion

The hs-CRP level is negatively correlated with HDL-cholesterol, while APN is negatively correlated with BMI and hs-CRP but positively correlated with HDL-cholesterol in Egyptian patients undergoing CAG. The hs-CRP level correlates with the severity of left ventricular dysfunction. However, left ventricular function does not appear to correlate with APN levels.

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## Ethical approval and consent

The protocol of this study was reviewed and approved by the Research Ethics Committee of the Faculty of Pharmacy, Suez Canal University, Egypt. Written Informed consent was obtained from patients after explaining to them its purpose. The privacy of patients and confidentiality of data were ensured. Patients were also informed that they had all the right to withdraw from the study without giving a reason.

## Conflict of Interest

The author declares no conflicts of interest.

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None.

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