The Association between Serum Adiponectin Levels and the Severity of Coronary Artery Disease

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Abstract
Coronary artery disease (CAD) is the leading cause of death worldwide, and it is expected that the rate of CAD will accelerate in the next decade. In human patients, serum adiponectin and CRP levels are negatively correlated. Thus adiponectin appear to play an anti-inflammatory role in atherosclerosis.

Objectives: Evaluation of the association between serum adiponectin levels and the severity of CAD as assessed by coronary angiography.

Study design: The study included 65 patients (56 males, 9 females; mean age 54.9 years) with angiographically documented significant CAD (50% stenosis). The patients were divided into three groups according to the number of vessels affected; 19 had single-vessel, 22 had two-vessel, and 24 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 25 subjects (7 males, 18 females; mean age 54.5 years) who were found to have normal coronary arteries on angiography.

Results: The number of male patients and the number of smokers were significantly higher in the CAD group than in control group (p-value <0.001). There was no significant difference between the both groups as regard to mean age, prevalence of hypertension, and BMI. Patients with CAD exhibited significantly lower serum levels of adiponectin compared to the control group (3.98±1.3ug/dL vs. 13.6±5.7u g/dL; p-value<0.001), on the other hand patients with CAD exhibited significantly higher serum levels of hs-CRP compared to the control group (5.60±3.10mg/L vs. 2.98±2.37mg/L; p-value <0.001). Serum adiponectin levels in patients with multivessels disease were significantly lower than in patients with two vessels disease and much lower than in patients with single vessels disease. There were strong negative correlation between serum adiponectin levels and the modified Gensini score (7=0.715; p-value <0.001) and hs-CRP (7=0.682; p-value <0.001).

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 in risk stratification.

Key Words: Adiponectin — Gensini score — Coronary artery disease.

Introduction
CORONARY artery disease (CAD) is the leading cause of death worldwide, and it is expected that the rate of CAD will accelerate in the next decade. The global burden of CAD carries with it a heavy financial cost.

Recently, adipose tissue has shed its label as a sedentary storage depot of excess energy, and has emerged as a metabolically active participant in mediating vascular complications, serving as an active endocrine and paracrine organ secreting an ever increasing number of mediators, known as adipokines, which participate in diverse metabolic processes [ii. Although most adipokines such as leptin, TNF-a, plasminogen activator inhibitor-1 appear to promote vascular disease, but among these adipokines is adiponectin which seems to possess antiatherogenic and anti-inflammatory effects and may be protective against cardiovascular disease development [2].

Currently, atherosclerosis is largely considered an inflammatory disease and individuals at high risk of developing atherosclerosis have high levels of circulating inflammatory markers such as CRP. In human patients, serum adiponectin and CRP levels are negatively correlated. Thus adiponectin appear to play an anti-inflammatory role in atherosclerosis [3].

Clinically, hypoadiponectemia has been observed in patients with obesity, diabetes mellitus, and coronary artery disease, these findings indicate that adiponectin acts as an endogenous antiatherogenic factor, therefore understanding the clinical significance of adiponectin may be helpful in preventing the development of atherosclerotic vascular diseases [4].
In this study, we assessed serum adiponectin levels of those diagnosed with CAD angiographically in different patient groups and investigated the association between serum adiponectin levels and the severity of coronary atherosclerosis.

**Patients and Methods**

The study included 65 patients (56 males, 9 females) who underwent coronary angiograms in Ain Shams university hospital and Air Force Military Hospital in the period between August 2010 and March 2011 and who were detected to have severe lesions (50% stenosis) in the coronary arteries. On the other hand, the control group consisted of 25 subjects (7 males, 18 females) with completely normal coronary arteries.

Prior to coronary angiography, informed consent was obtained from all subjects then a detailed medical history was obtained from every subject and risk factors of CAD were established. Subjects were also evaluated by complete physical examination and 12-lead electrocardiography. Obese patients, those with DM 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. Obesity was defined as body mass index (BMI) of 30kg/m2.

Estimation of serum levels of total adiponectin and high sensitivity C-reactive protein were performed to all subjects before angiography using 10-m L of 12-hour fasting venous blood samples. Blood samples were collected using a serum separator tubes and then the samples were allowed to clot for 30 minutes before centrifuged for 15 minutes at 3000 rpm then the serum were removed. The serum samples were stored at —20°C in the laboratory and levels of serum total adiponectin levels and high sensitivity CRP concentrations were measured using commercial enzyme linked immunosorbent assay kits (Human Total Adiponectin (Acrp 30) ELISA kit and Human C-reactive protein ELISA Kit respectively), manufactured by R&D systems, Inc. 614 McKinley Place NE Minneapolis, MN55413 United States of America.

Selective coronary angiography by standard Judkins technique was performed on all subjects with the right femoral approach. Evaluation of all coronary angiograms was made by two observers who were blinded to the clinical and laboratory data. Patients who were found to have severe coronary stenosis were divided into three subgroups according to the number of vessels affected: Single-vessel lesion (n=19: 15 males, 4 females), two-vessel lesions (n=22: 18 males, 4 females) and multi (3) vessel lesion (n=24: 23 males, 1 female).

The severity of coronary lesions was assessed using the modified Gensini score [16]. 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 the 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.

Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t-test (unpaired), Chi-square, Linear Correlation Coefficient, Receiver Operating Characteristic curve analysis (ROC curve) and Analysis of variance [ANOVA] tests by statistical package SPSS V18 (Self-Propelled Semi—Submersible version 18). p<0.05 was considered to be statistically significant.

**Results**

Table (1) shows comparison of the basic characteristics of patients and the control group. The number of male patients and smokers were significantly higher in patient group than the controls (p-value <0.001). There was no significant difference between the both groups as regard to mean age, prevalence of hypertension, and BMI. Serum adiponectin levels were found to be significantly lower in the patient group (3.985±1.307gg/dL) compared to the control group (13.600±5.755gg/dL) (p-value <0.001). On the other hand, serum hs-CRP levels were found to be significantly higher in patient group (5.602±3.108mg/L) compared to the control group (2.984±2.375mg/L) (p-value <0.001). The mean Gensini score which indicates prevalence of coronary lesions in the patient group was found to be 3.96±1.44.

There was no significant difference between the three subgroups as regard to mean age, sex, smoking, prevalence of hypertension, and BMI.

There was highly statistically significant difference between the three patient subgroups as regard adiponectin level (p-value <0.001). While there was no statistically significant difference between subgroup A and subgroup B (p-value >0.05), there was highly statistically significant difference between subgroup A and subgroup C.
(p-value <0.001) and there was statistically significant difference between subgroup B and subgroup C (p-value <0.05) as regard serum adiponectin level (pg/ml) (Fig. 1).

There was statistically significant difference between the three subgroups and between subgroup A and subgroup C as regard hs CRP (p-value <0.05), while there was no statistically significant difference between subgroup A and subgroup B and between subgroup B and subgroup C (p-value >0.05).

There was strong negative correlation between modified Gensini Score and serum adiponectin levels (1_g/m1) with p-value <0.001 (Fig. 2).

Also, there was strong negative correlation between hs-CRP (mg/L) and serum adiponectin levels (1_g/m1) with p-value <0.001 (Fig. 3).

Receiver-operating characteristics (ROC) curve showed that cut off point of adiponectin level for predicting CAD is 7.21_tg/m1 with sensitivity 100% and specificity 92% (Fig. 4).

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<th>Table (1): Baseline characteristics of patients and control groups.</th>
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Fig. (1): Comparison between the three subgroups according to serum adiponectin level.

Fig. (2): Correlation between serum adiponectin levels and modified Gensini score.

Fig. (3): Correlation between serum adiponectin levels and hs-CRP.

Fig. (4): Receiver-operating characteristics (ROC) curve for predicting CAD.
Discussion

In addition to major risk factors for CAD 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 [5].

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 [6] and that adiponectin levels is inversely associated with obesity, insulin resistance, type II diabetes and cardiovascular disease [7].

In our study, serum adiponectin levels were measured in ninety patients (0''/ 9 = 63/27) who underwent coronary angiograms in Ain Shams University Hospital and Air Force Military Hospital in the period between August 2010 and March 2011, the severity of coronary atherosclerosis was defined by modified Gensini score system.

Serum adiponectin levels were found to be significantly lower in the patient group compared to the control group. Also, serum adiponectin levels were found to be significantly different between the three patient subgroups, as serum adiponectin levels in patients with multiple-vessel disease are lower than in patients with two-vessel disease and much lower than in patients with single-vessel disease.

Initial observations from Ouchi et al., showed that plasma adiponectin concentrations were lower in patients with CAD than in age- and BMI-matched controls [8].

Zoccali et al., reported that decreased plasma adiponectin levels were shown to be related to future cardiovascular events in patients with end-stage renal failure, suggesting that hypoadiponectinemia may have a causative role in atherogenesis [9].

Kumada et al., studied 225 male patients who underwent coronary angiography and concluded that male patients with hypoadiponectinemia (<4.0 pg/mL) had a significant 2-fold increase in CAD prevalence, independent of well-known CAD risk factors [10].

A significantly lower plasma adiponectin concentration in patients with CAD than in the control group was reported in the study carried on 123 patients with coronary artery disease [11].

Similarly, Cesari et al., studied 400 nondiabetic patients undergoing coronary angiography reported that plasma adiponectin levels were inversely related to the CAD score and predicted the coronary atherosclerotic burden independent of other cardiovascular risk factors [12].

Seleuk et al., reported that patients with significant CAD had lower plasma adiponectin concentrations than those without CAD in a study performed on 167 patients with metabolic syndrome undergoing coronary angiography [13].

Liang et al., 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 [14].

There was a strong negative correlation detected between serum adiponectin level and modified Gensini score which indicates the extent (prevalence) of the coronary lesions, meaning that more severe and prevalent coronary lesions are observed in patients with lower levels of serum adiponectin. This might be attributed to the loss of protective functions of adiponectin on the vascular endothelium that may allow vascular inflammatory events to occur more rapidly.

Also, there was a strong negative correlation between serum adiponectin levels and serum levels of high sensitivity CRP which is an indicator of micro inflammation, thus adiponectin appear to play an anti-inflammatory role in atherosclerosis.

Goksoy et al., found that, serum adiponectin levels were significantly lower in patients with angiographically diagnosed CAD compared to the controls [15]. 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 multivessel lesions. This disagrees with the present study in which, there was a significant difference in serum adiponectin levels in patients with single-vessel lesions compared to the control group. We suggest that, this may be due to that the study performed by Goksoy et al., had included subjects with diabetes mellitus which proved to decrease the adiponectin level and we excluded diabetic patients in our study.

Limitations:

- Only total form of adiponectin was measured while High Molecular Weigh (HMW) HMW adiponectin alone may be a clinically useful marker of CAD than total form.
Although no significant association with adiponectin was found for gender variation, it should be noted that serum concentrations of adiponectin were measured with solid phase ELISA. This assay cannot distinguish between the lower weight trimer forms of adiponectin and the high molecular weight complexes, one of the factors associated with sex difference.

**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 in risk stratification and management as encouraging the use of agents that increase serum adiponectin level like PPAR γ agonists (Thiazolidinediones), ACE inhibitor, or angiotensin II receptor blockers (candesartan), Rimonabant: A selective cannabinoid-1 receptor blocker.

**References**