Original Article

Role of Serum Adiponectin Levels and IL-10 as a Marker for Angiographic Stenosis in Coronary Artery Disease

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Abstract

Objectives: This study aimed to determine the association of interleukin (IL)-10 and adiponectin (Ad) levels with the angiographic severity of coronary artery disease (CAD). **Methods:** In this case–control study, the study population included 50 patients with angiographically proven CAD as the case group and 50 apparently healthy age and sex-matched adults as a control group. The severity of CAD was assessed by SYNTAX scores. Serum Ad levels and IL-10 were measured using ELISA-based kits. The levels of Ad and IL-10 were associated with angiographic severity of CAD. $P < 0.05$ was considered statistically significant. **Results:** Cases had significantly lower Ad level (1.89 ± 1.18 vs. 2.59 ± 1.48, $P = 0.0003$) and significantly higher IL-10 level (8.96 ± 6.84 vs. 3.5 ± 3.57, $P < 0.0001$) as compared to controls. There was a significant correlation between the levels of Ad and IL-10 ($r = 0.315$, $P = 0.026$). There was a significant negative correlation between the Ad and angiographic stenosis of CAD ($r = –0.939$, $P < 0.001$). Both Ad and IL-10 showed a significant association with the severity of CAD in terms of SYNTAX score. **Conclusion:** Patients with CAD had lower Ad levels and higher IL-10 levels. Ad levels showed a significant decrease with increasing coronary artery stenosis. Both the markers (Ad and IL-10) showed significant association with the severity of CAD, thereby signifying their role as a marker for CAD.

Keywords: Adiponectin, coronary artery disease, stenosis

Introduction

The term "coronary artery disease" (CAD) includes diseases caused due to the atheromatous changes in coronary vessels. CAD is "a condition in which there is an inadequate supply of blood and oxygen to the myocardium," which is due to the coronary arteries occlusion and leads to mismatch of demand-supply of oxygen. CADs have been gaining importance in India recently because of the increased incidence of the disease. It is a leading cause of morbidity and mortality in India.[1] The current prevalence is estimated to be 3%–4% in rural areas and 8%–10% in urban areas, according to population-based cross-sectional surveys.[2]

CAD mediated by atherosclerosis is initiated very early in human life and manifests itself clinically after a long latent phase of integrative and cumulative insults to the vessel wall by genetic, environmental, behavioral, and dietary risk factors. Identification of CAD in the early stages may help in reducing the complications arising out of it. Biochemical markers may play an important role, as depicted by their rise with increasing severity of CAD.[2]

Adiponectin (Ad) is one such marker which is a 30-kDa peptide hormone exclusively secreted by adipose tissue. It plays an important role in the regulation of lipid metabolism and glucose metabolism. Ad is an adipocyte-derived peptide which is also known as GBP 28, Acrp30, AdipoQ, and apM1.[3] It has been proven to have a role in the prevention of development

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of atherosclerosis by inhibiting vascular adhesion factors in endothelial cells,[4] inhibiting foam cell formation, and suppressing growth and function of macrophages.[5]

Ad also influences interleukin-10 (IL-10) levels, which is an anti-inflammatory cytokine. IL-10 protects against atherosclerosis by exerting an anti-apoptotic and anti-inflammatory action through downregulation of Th1 response, inhibiting matrix-degrading matrix metalloproteinases and tissue factor, thereby preventing plaque instability.[6]

Both these markers fluctuate with the increasing levels of coronary artery stenosis and thus their monitoring may be helpful in monitoring the increasing severity of the CAD.[7]

Hence, the study was conducted to evaluate the Ad levels and its correlation with the angiographic stenosis of CAD. We also aimed to study the association of serum Ad and IL-10 levels in patients with CAD.

Methods

This case-control study was conducted in the Department of Biochemistry and Department of Cardiothoracic and Vascular Surgery, New Delhi, over a period of 18 months from October 2016 to March 2018.

Ethical clearance was obtained from the Institutional Ethics Committee* before proceeding for the study (IEC/VMMC/SJH/Thesis/October/2016, dated 22.10.16).

Study population

Fifty patients with angiographically proven (>60% stenosis in one or more vessels) were included as cases. Fifty apparently healthy age- and sex-matched people were taken as controls. Individuals with obesity, diabetes mellitus (DM), hypertension, liver, kidney diseases, and chronic inflammatory disease and with history of intake of drugs such as peroxisome proliferator-activated receptor agonists, angiotensin-converting enzyme inhibitors, angiotensin receptor type 1 blockers, anticonvulsant, and glucocorticoids were excluded from the study. The case history was recorded duly on the pro forma, and a complete clinical examination was performed. The control group consisted of healthy people who underwent a routine checkup that consisted of an electrocardiography, chest X-ray, and serum analysis. They were classed as healthy because their physical examination was uneventful without any previous symptoms of chest pain or shortness of breath, and they had no personal or family history of, or reasons for suspecting CAD.

Informed written consent was obtained from each subject before enrolling them in the study. Height, weight, and body mass index (BMI) for all patients and controls were recorded.

Definition and extent of coronary artery disease

For investigating CAD, coronary angiography was done by an experienced independent observer. The significant CAD was defined as "≥50% stenosis in lumen diameter in any major epicardial coronary arteries including the left main coronary artery, left anterior descending artery, left circumflex artery, right coronary artery, or one of their major branches." Distribution of the CAD was categorized as one-vessel disease (one-VD; disease in one vessel), two-vessel disease (two-VD; disease in two vessels or left main trunk disease without right coronary artery stenosis), or three-vessel disease (three-VD; disease in three vessels or left main trunk disease with right coronary artery stenosis)."[8]

The severity of CAD was assessed by SYNTAX and Gensini scores. The SYNTAX score was assessed using the guidelines.[9] The calculation was performed with the Internet-based SYNTAX calculator version 2.10 from the web address: www.syntaxscore.com. SYNTAX scores were estimated by scoring all coronary lesions producing a ≥50% diameter stenosis in vessels ≥1.5 mm, by the use of the algorithm present at the website. The angiographic visual analysis was done by an interventional cardiologist for evaluating the SYNTAX score. SYNTAX scores were categorized into:

SYNTAX $score_{HIGH}$ ≥22

$SXscore_{LOW\text{-}INTERMEDIATE}$ <22

No significant CAD (reference category)[10]

Blood investigations: Interleukin-10 and adiponectin

Three milliliter venous blood was collected in (ethylene diamine tetraacetic acid) vial and 3 mL was collected in the plain vial for serum separation in a single prick. The blood samples were used for biochemical (lipid profile, liver functions tests, and renal function tests) and molecular analysis. Ad estimation was done using a commercially available ELISA kit by QAYEE-BIO. The serum was used to analyze biochemical parameters, including kidney function test (urea and creatinine), liver function tests (total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase (AST), and alkaline phosphatase [ALP]) and lipid profile. The remaining serum was stored at −70°C, which was later used to measure the levels of IL-10 and Ad.

IL-10 estimation was done using a commercially available kit by *Diaclone* following manufacturer's instructions. Serum Ad estimation was done using a commercially available kit by *QAYEE-BIO* following the manufacturer's instructions. The outcomes measures were the severity of CAD and its relation with IL-10 and Ad.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± standard deviation and median. Normality of data was tested by the Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used. Quantitative variables were compared using the Independent *t*-test/Mann–Whitney Test between the two groups and ANOVA/Kruskal–Wallis test was used for comparison between three groups. Qualitative variables were correlated using Chi-square test/

Fisher exact test. Odds ratio with a 95% confidence interval was calculated. Spearman rank correlation coefficient was used to assess the association of IL-10 and Ad. $P < 0.05$ was considered statistically significant.

Results

The mean age of cases was 52.74 ± 12.42 years and of controls was 48.42 ± 15.05 years ($P = 0.434$) [Table 1]. There were 86% males in cases and 74% males in the control group ($P = 0.134$) [Figure 1].

Table 2 shows the baseline parameters of cases and controls. It was observed that serum levels of AST, ALT, and urea were significantly higher in cases as compared to controls. On the other hand, levels of low-density lipoprotein, total cholesterol, and triglycerides were lesser in the cases as compared to controls. All other baseline parameters, such as height, weight, BMI, serum triglyceride, total bilirubin, ALP, and creatinine were comparable in the two groups.

As compared to control group, cases had significantly lower Ad level (1.89 ± 1.18 vs. 2.59 ± 1.48, $P = 0.0003$) and significantly higher IL-10 level (8.96 ± 6.84 vs. 3.5 ± 3.57, $P < .0001$) [Table 3]. There was a significant correlation between the levels of Ad and IL-10 ($r = 0.315$, $P = 0.026$) [Figure 2].

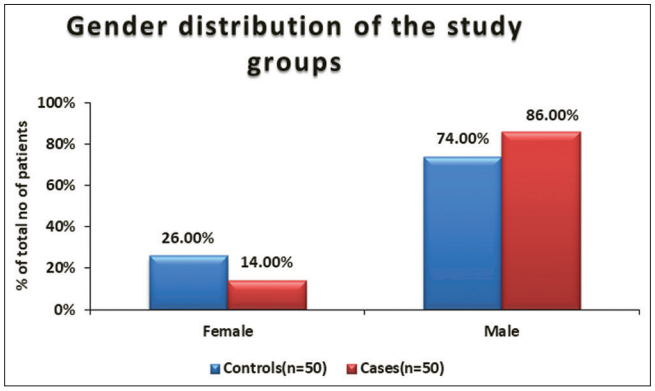

Figure 1: Gender distribution of study subjects

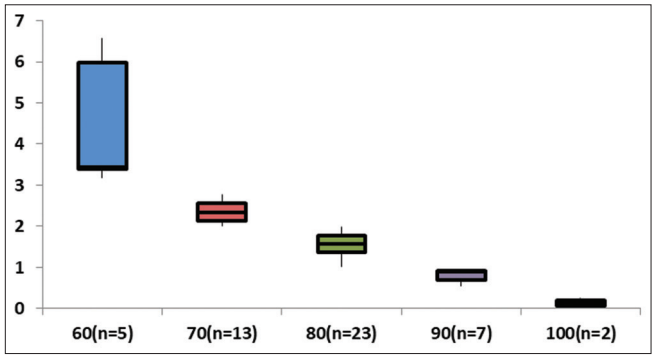

Figure 3: Comparison of adiponectin (μg/mL) between % of stenosis in one of the three highest stenotic vessels. (nonparametric variable, Box-whisker plot)

There were decreasing levels of Ad from 4.51 to 0.13 μg/mL, with increasing stenosis of coronary arteries from 60% to 100% [Table 4 and Figure 3]. A significantly negative correlation was seen between Ad levels and stenosis % in one of the highest stenotic coronaries ($r = –0.939$, $P < 0.001$) [Figure 4].

Compared to patients with SYNTAX score <22 ($n = 15$), patients with SYNTAX score ≥22 ($n = 35$) had significantly higher IL-10 (10.85 ± 4.56 vs. 7.76 ± 5.84, $P = 0.049$) and significantly lower Ad levels (1.16 ± 1.02 vs. 1.93 ± 1.29, $P = 0.0286$) [Table 5].

Discussion

One of the major risk factors for CAD is obesity, and adipose tissue forms a storehouse of fat. Among the various adipocytokines released by the adipose tissue, Ad is a specific marker that modulates the relationship of risk factors and stenosis of CAD. It plays an anti-atherogenic role along with IL-10 (anti-inflammatory) and can be considered as one of the prognostic markers for CAD.

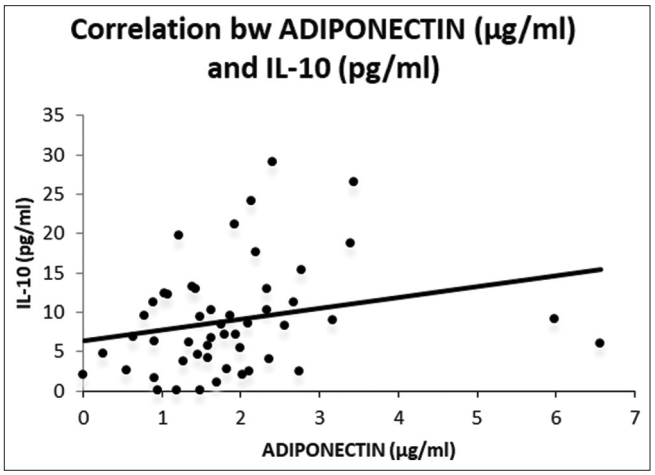

Figure 2: Correlation between interleukin-10 and adiponectin levels in coronary artery disease patients. (Correlation coefficient = 0.315, $P = 0.026$, statistically significant)

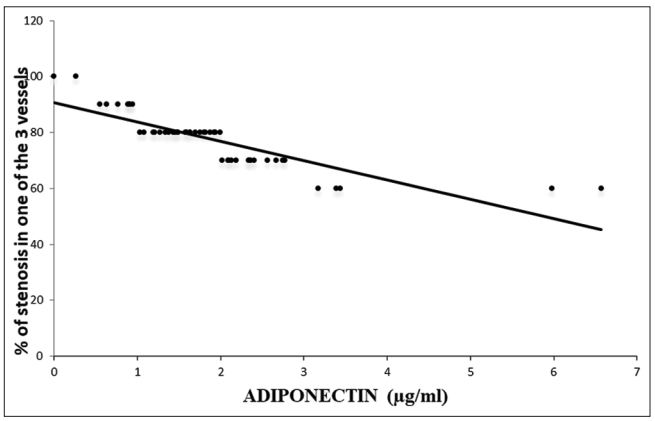

Figure 4: Correlation between ADIPONECTIN (μg/mL) and % of stenosis in one of the three highest stenotic vessels

Table 1: Age distribution of study subjects

Age distribution (years)	CAD		Total, *n* (%)	*P*
	Controls (*n*=50), *n* (%)	Cases (*n*=50), *n* (%)		
≤30	8 (16.00)	5 (10.00)	13 (13.00)	0.434
31-40	6 (12.00)	2 (4.00)	8 (8.00)	
41-50	11 (22.00)	11 (22.00)	22 (22.00)	
51-60	15 (30.00)	22 (44.00)	37 (37.00)	
61-70	5 (10.00)	7 (14.00)	12 (12.00)	
>70	5 (10.00)	3 (6.00)	8 (8.00)	
Mean ± SD	48.42 ± 15.05	52.74 ± 12.42	50.58 ± 13.80	

CAD: Coronary artery disease, SD: Standard deviation

Table 2: Baseline parameters of the study groups

Baseline characteristics	Control (*n*=50)		Case (*n*=50)		*P*
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Height (cm)	162.12 ± 5.61	160 (158-165)	162.66 ± 6.09	162 (158-166)	0.637
Weight (kg)	59.94 ± 6.09	60 (55-65)	60.92 ± 7.07	62 (55-65)	0.534
BMI (kg/m^2)	22.77 ± 1.64	22.7 (21.800-24.200)	23.01 ± 2.35	23 (21.300-24.500)	0.552
Serum triglyceride (mg/dL)	133.3 ± 97.11	101.5 (71-154)	130.26 ± 44.38	127 (94-152)	0.081
Serum cholesterol (mg/dL)	154.48 ± 39.11	149.5 (126-186)	127.94 ± 26.58	123.5 (109-148)	0.0001
LDL (mg/dL)	104.94 ± 36.8	97.5 (75-134)	84.94 ± 27.29	85.5 (62-101)	0.008
Total bilirubin (mg/dL)	0.57 ± 0.31	0.5 (0.400-0.600)	0.72 ± 0.42	0.6 (0.500-1)	0.065
SGOT/AST (U/L)	27.54 ± 15.12	25 (18-31)	56.66 ± 45.16	38.5 (26-68)	<0.0001
SGPT/ALT (U/L)	24.68 ± 22.53	16.5 (11-32)	42.94 ± 32.5	29.5 (19-57)	0.0001
ALP (U/L)	90.64 ± 28.9	81 (69-111)	87.3 ± 30.28	79.5 (65-106)	0.364
Blood urea (mg/dL)	24.96 ± 9.25	24.5 (19-28)	29.3 ± 12.48	27 (23-31)	0.036
Creatinine (mg/dL)	0.72 ± 0.21	0.7 (0.600-0.800)	0.75 ± 0.16	0.7 (0.600-0.900)	0.283

IQR: Interquartile range, SD: Standard deviation, BMI: Body mass index, LDL: Low-density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

Table 3: Comparison of adiponectin and interleukin-10

	Cases (*n*=50)		Control (*n*=50)		*P*
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Adiponectin (µg/mL)	1.89 ± 1.18	1.72 (1.210-2.340)	2.59 ± 1.48	2.6 (1.700-3.400)	0.0003
IL-10 (pg/mL)	8.96 ± 6.84	7.75 (4-12.300)	3.5 ± 3.57	2.15 (0.100-6.100)	<0.0001

IQR: Interquartile range, SD: Standard deviation, IL-10: Interleukin-10

Table 4: Comparison of adiponectin (µg/mL) between percentage of stenosis (60-100%) in one of the three highest stenotic vessels

Adiponectin (µg/mL)	60 (*n*=5)	70 (*n*=13)	80 (*n*=23)	90 (*n*=7)	100 (*n*=2)	Total	*P*	Test performed
Mean ± SD	4.51 ± 1.63	2.36 ± 0.26	1.55 ± 0.28	0.8 ± 0.15	0.13 ± 0.18	1.89 ± 1.18	<0.0001	Kruskal-Wallis test; χ^2=43.204
Median (IQR)	3.44 (3.39-5.98)	2.34 (2.13-2.56)	1.58 (1.36-1.775)	0.89 (0.7-0.905)	0.13 (0.065-0.195)	1.72 (1.225-2.302)		
Range	3.17-6.57	2.02-2.77	1.03-1.99	0.55-0.94	0-0.26	0-6.57		

IQR: Interquartile range, SD: Standard deviation

We found a significant negative correlation of Ad levels with increasing angiographic stenosis of CAD. Even, there was a significant association of Ad with IL-10 in CAD patients. Our findings were in line with various other studies showing a similar negative correlation of Ad with CAD.[7,11-14]

In a case-control study like ours, the comparability of the baseline characteristics such as age and gender ensures that the final outcome measures of Ad and IL-10 levels may be purely ascribed to the differences in the severity of CAD. We found cases to have significantly higher liver enzyme levels and lower cholesterol levels as compared to controls (though the levels were within the range). This may be due to higher ongoing vigilance and control of the diet and other factors among cases as compared to controls. The cases already knew

Table 5: Comparison of adiponectin and interleukin-10 between SYNTAX score <22 and ≥22

Parameters	SYNTAX				*P*
	<22 (*n*=15)		≥22 (*n*=35)		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
Adiponectin (µg/mL)	1.93±1.29	1.89 (1.27-2.58)	1.16±1.02	1.22 (1.110-2.108)	0.0286
IL-10 (pg/mL)	7.76±5.84	6.55 (3-9.5)	10.85±4.56	9.8 (6-13.4)	0.049

IQR: Interquartile range, SD: Standard deviation, IL-10: Interleukin-10

that they had an underlying CAD and they need to monitor and change their lifestyle habits.

We found that the median value of Ad in cases was significantly less than controls (1.72 vs. 2.6, $P = 0.0003$). Ad is an adipocytokine, which is secreted from the white adipose tissue. It is also synthesized by cardiomyocytes, osteoblasts as well as skeletal muscle. At increased levels, it has favorable antidiabetic and anti-atherogenic properties. Its levels vary according to gender, body fat distribution, as well as metabolic status.[15] The effect of Ad on CAD can be described by the effects of Ad on vascular structure and function, such as endothelial thickening inhibition, arterial vasodilatation induction, foam cell formation inhibition, and adhesion molecules suppression.[12]

Comparable to our study, Laughlin *et al*.[13] also reported that the level of Ad was lower in patients with prevalent CHD than individuals without CHD, but the difference was borderline statistically significant (11.0 vs. 11.9, $P = 0.056$). Kumada *et al*.[7] also reported similar results as the median Ad level in the CAD patients was 4.7 µg/mL and in control subjects was 5.9 µg/mL; thus, in the CAD patients, plasma Ad levels were significantly lower as compared to control subjects ($P < 0.0001$).

Moreover, we found a significant association of IL-10 and Ad with the severity of CAD in terms of SYNTAX score and coronary stenosis, with Ad levels being decreased and IL-10 levels being increased with increasing severity of the disease.

In a study by Otsuka *et al*.,[12] also, plasma Ad levels were found to be significantly lower in stable CAD patients with complex coronary lesions as compared to those with simple lesions (4.14 vs. 5.27 µg/mL, $P = 0.006$). Ji *et al*.[15] reported that Ad levels in patients with CAD, stable angina pain, unstable angina pain, and acute myocardial infarction were significantly lesser than controls (5.95 ± 3.13 vs. 6.74 ± 3.01 vs. 6.19 ± 3.14 vs. 4.92 ± 3.02 vs. 8.34 ± 3.06, $P < 0.05$). Similarly, Hascoet *et al*.[16] reported that Ad levels were significantly lower in CAD patients than controls (5.6 vs. 7.1).

On the other hand, the median value of IL-10 in cases was significantly higher than controls (7.75 vs. 2.15, $P < 0.0001$). In contrast to our study, Waehre *et al*.[17] reported that in the patients with unstable angina, in those with stable angina, and in the controls, there was no significant difference in IL-10 levels. While Smith *et al*.[18] in their study observed that there were reduced levels of IL-10 in unstable angina patients than stable angina patients.

In the pathophysiology of atherosclerotic events (like CAD), the role of inflammatory responses is confirmed by the growing evidences. CAD develops by the formation of plaque and its deposition in the arteries walls, which leads to disruption of blood flow; it is known as atherosclerosis. Cytokines are potent inflammatory factors, which regulate each stage of atherosclerosis and thus result in the development of CAD. IL-10 is an important anti-inflammatory cytokines; it serves as an anti-inflammatory agent by downregulation of the Th1 as well as suppression of pro-inflammatory cytokines, like IL-1, IL-6, IFN-γ, and TNF-α. It leads to atherosclerosis by inhibition of the metalloproteinase synthesis. In addition, stability of plaque is promoted by IL-10 by preserving the extracellular matrix and fibrous cap. Furthermore, the IL-10 gene consists of variable sites (polymorphisms and microsatellites) that influence the IL-10 expression level. Thus, it may be associated directly and indirectly with CAD development.[19]

We found a significant association between Ad and IL-10. An anti-inflammatory action of the v is the IL-10 induction. The Ad is sufficient to induce the expression of anti-inflammatory cytokines such as IL-10 and IL-1RA in many myeloid cell types, such as monocytes, a myeloid cell line (THP-1), primary human dendritic cells, and monocyte-derived macrophages. Ad is a significant adipose tissue-derived regulator of immunological processes, which is mainly mediated by the modulation of macrophage function.[20] Thus, it always seems appropriate to measure and assess both Ad and IL-10 levels to monitor the patients of CAD.

Limitations of the study

The study was a cross-sectional study, and thus, the patients were not followed up for risk assessment and outcomes of CAD. Furthermore, simultaneous assessment of other risk factors such as diabetes, hypertension and obesity was not done. Finally, the sample size was small, and thus, we recommend future multicentric studies to have a better sample size and long-term follow-up evaluation to determine the mortality and morbidity outcomes.

Conclusion

Patients with CAD had lower Ad level and higher IL-10 level as compared to controls. Ad levels showed a significant decrease with increasing severity of coronary artery stenosis.

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Conflicts of interest
There are no conflicts of interest.

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