Original Article

Adiponectin, central obesity and carotid intima media thickness in coronary artery disease patients

Rajesh Jain, MD, DM*; Shridhar Dwivedi, MD†; Amitesh Aggarwal, MD§

* DM resident IPGME &R Kolkata DM (Resident) in Endocrinology at Institute of Post Graduate Medical Education And Research, Kolkata

† Retired Professor and Head, Department of Medicine, Division of Endocrinology, University College of Medical Sciences (University of Delhi) and GTB Hospital, Delhi – 95, India.

§ Assistant Professor, Department of Medicine, Division of Endocrinology, University College of Medical Sciences (University of Delhi) and GTB Hospital, Delhi – 95, India.

Abstract

Background: Atherosclerosis related coronary artery disease has emerged as a principal cause of death all over the world. One of the clinical syndromes which often lead to coronary artery disease (CAD) is metabolic syndrome. Adiponectin is diminished both in metabolic syndrome and CAD. Carotid intima media thickness (CIMT), a surrogate marker of subclinical atherosclerosis has been found to be increased in CAD and has inverse relationship with adiponectin. In view of the paucity of Indian studies available addressing the interrelationship between adiponectin, waist circumference, CAD and CIMT; we aimed to examine the interrelationship between adiponectin, central obesity and CIMT in patients suffering from CAD.

Methods: We studied the levels of adiponectin, measured CIMT and obesity profile of CAD patients (n = 50) ≤60 years admitted in CCU of GTB Hospital and compared it with apparently healthy controls (n = 50). Increased waist circumference, considered as central obesity was defined as WC >90 cm in males, ≥80 cm in females and obesity was considered as body mass index ≥25 kg/m^2.

Results: The mean age in CAD cases (43.7 ± 8.2 years) and controls (43.6 ± 9.2 years) were similar. Smoking was found to be 36(72%) in CAD cases and 23(46%) in control subjects. Increased waist circumference was found to be 24(48%) in CAD cases and 12(24%) in control subjects and raised BMI was found in 42% cases as compared to 22% in healthy controls. Mean adiponectin levels in CAD patients was 8.14 ± 3.86 µg/ml as compared to 9.4 ± 3.9 µg/ml in healthy controls. Values though higher in CAD group was statistically insignificant. Mean CIMT was higher in CAD cases as compared to healthy controls (0.68 ± 0.10 vs. 0.60 ± 0.11mm). The mean adiponectin levels were higher in non-obese as compared to obese individuals (9.2 vs. 6.9 µg/ml) and those without central obesity as compared to those with central obesity (9.3 vs. 7.2 µg/ml) in CAD patients. Adiponectin had a negative correlation with CIMT in CAD patients [Pearson's correlation = –0.198 (p = 0.220)].

Conclusion: Our findings indicate evidence of low adiponectin, increased CIMT and increased prevalence of central obesity in CAD patients.

Key Words

- Coronary artery disease
- Adiponectin
- CIMT (Carotid intima media thickness)
- Hypertension
- Obesity

Introduction

Coronary artery disease (CAD) is a modern epidemic, closely competing infectious diseases in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015[1] and this figure will jump to 60% by 2020.[2] The most disturbing fact is its rising incidence, varying between

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4–10% among young people ≤35 years of age.[3] CHD among Indians has been found to be more severe, manifesting at a younger age and following a malignant course.[4]

Important factors for CAD among Indian subjects are: smoking, dyslipidemia, central obesity, hypertension, diabetes mellitus, family history of premature CAD, psychosocial stress and genetic factors. Epidemiological studies have recorded a high prevalence of metabolic syndrome and cardiovascular mortality in India.[5,6]

Asian Indian men and women have a higher incidence and mortality rate from cardiovascular diseases (CVD) than Caucasian men and women, yet the pathology behind this increased susceptibility is not fully understood.[7] Within India there has been a drastic increase in the incidence of CVD as a result of improving social and economic conditions.[8] Even immigrants within the same environment, when compared to Europeans or Caucasians, have a 1.5–4.0 times higher mortality rate from CVD and this risk increases with duration of residence.[9]

One of the clinical syndromes which often lead to CAD is metabolic syndrome which consists of diabetes mellitus; hyperlipidemia, especially hypertriglyceridemia; hypertension and central obesity. In association with CVD, obesity is an important and easily assessed risk marker. At the population level the metabolic syndrome is closely linked to lifestyle factors. The epidemic of obesity and a sedentary lifestyle provide fertile soil for the syndrome. A moderate grade of physical activity reduces the likelihood of the development of the metabolic syndrome.

Both increased BMI and increased WHR (Waist Hip Ratio) are risk factors for CAD.[10] Obesity is an emerging major public health problem throughout the world and adolescence is one of the critical periods in the development of obesity. A study conducted in East Delhi indicated that the prevalence of obesity among affluent adolescent girls in India is approaching that of their counterparts in developed countries.[11] A 5% increase in weight is associated with 20–30% increased risk of developing hypertension and future CAD.[12] Some trials have shown that waist/hip ratio shows a graded and higher significant association with myocardial infarction risk worldwide.[13]

One of the important biomarker which is currently used to study CAD, obesity, type 2 DM and metabolic syndrome is adiponectin. Serum adiponectin levels have been shown to be reduced in the presence of obesity, insulin resistance (IR), and cardiovascular disease.[14,15] It would, therefore, be worthwhile to study this biomarker in Indian patients suffering from CAD.

As regards imaging markers are concerned coronary heart disease has been linked with changes in carotid intima media thickness (CIMT). It is said that 0.1 mm increase in IMT increases the likelihood of acute MI by 11%. IMT measurement of ≥1.00 mm are generally accepted as abnormal with the progression rate of IMT estimated at between 0.02 mm and 0.003 mm per year in the population based Kuopio Ischemic Heart Disease Risk Factors Study.[16]

Taking all above points in consideration like importance of adiponectin, and CIMT in the risk evaluation of CAD; this study was planned to evaluate adiponectin, and carotid intima media thickness in CAD patients.

Materials and methods

The study was conducted in the Coronary Care Unit (CCU) of UCMS & GTB Hospital, Delhi. It included 50 CAD patients ≤60 years (Group 1), presenting first time with acute chest pain due to myocardial infarction (MI)/acute coronary syndrome (ACS), unstable angina pectoris documented by classical history, raised cardiac injury enzymes (CPK-MB/Troponin-T), ECG and/or echocardiographic findings. Another 50 age and sex matched healthy controls were taken for evaluation and comparison (Group 2).

Patients already suffering from MI/ACS, history of coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, overt congestive heart failure, cardiomyopathies, advanced heart failure, rheumatic fever, acute illness, renal disease, hypothyroidism and hepatic dysfunction were excluded from the study. Informed consent was taken from all individuals.

Clinical work-up including proper history, complete cardiovascular system and physical examination of all the subjects was done. Diagnosis of MI/ACS was made on the basis of classical history, cardiac enzymes (CPK-MB/Troponin-T) and ECG changes.[17] Samples of fasting/postprandial blood sugar, lipids, and adiponectin were taken in the fasting state with minimum 8 hours of fasting. The blood sugar fasting, postprandial and lipids were estimated within 24 hours of the MI/ACS. Serum from the samples for adiponectin were taken and preserved at –70°C in the deep freezer, which were later estimated when adequate samples were collected. CIMT was done during the patient's stay in the hospital. Adiponectin levels were estimated in 80 subjects of which 40 were of group 1 and 40 were of group 2.

Dyslipidemia was defined as either raised TG levels ≥150 mg/dl, low HDL-cholesterol <40 mg/dl for men and <50 mg/dl in women, or specific treatment for previously detected hypertriglyceridaemia and/or reduced HDL-cholesterol.[18]

Serum adiponectin

Adiponectin levels were measured by ELISA method using standard kit (Biovender GmbH, Germany).[19]

Carotid intima media thickness (CIMT) measurement

The intima media thickness of the carotid artery was determined by a high resolution B mode USG System (HDI 1500) having an electronic linear, high frequency broadband transducer for superficial scanning with a mid-frequency of 7.5 MHz.[20] It was measured at several areas along the vessel wall including (1) the posterior aspect of the common carotid artery, (2) common carotid artery bifurcation, (3) anterior wall of internal carotid artery.

Statistical analysis

Unpaired t-test was applied to study the difference between cases and controls for adiponectin, blood sugar (fasting and postprandial), body mass index, total cholesterol, HDL-C, LDL-C, TG and mean CIMT.

Correlation between adiponectin and mean CIMT was obtained and their relationship was studied using regression analysis.

Results

The mean age in group 1 (43.7 years) was not different from the mean age of controls in group 2 (43.6 years). Of group 1 patients 36(72%) were smokers and in group 2 smoking was found in 23(46%) study subjects. The mean height, weight and waist circumference was not significantly different in both the study groups. But the BMI in group 1 (24.2 kg/m^2) was significantly higher ($p< 0.01$) than BMI of group 2 subjects (22.4 kg/m^2) (See Table 1).

The fasting blood sugar was higher in group 1 than group 2 (107.5 vs. 98.2) and was significant ($p = 0.03$). The postprandial sugar was also higher in group 1 than group 2 (152.7 vs.124.2) and was significant ($p = 0.001$) (Table 1).

The adiponectin levels were found to be decreased in CAD cases than healthy controls but the difference was statistically insignificant ($p >0.05$). Mean adiponectin levels in CAD patients were 8.14 µg/ml as compared to 9.4 µg/ml in healthy controls (Table 1).

Table 1: Demographic and biochemical parameters of study subjects

Variable	Group 1	Group 2	p-value
Mean age (yrs)	43.7 ± 8.2	43.6 ± 9.2	0.945
Male:Female	7.3 : 1	2.8 : 1	–
Height (cms)	164.1 ± 6.9	164.3 ± 8.8	0.890
Weight (kg)	65.2 ± 11.6	60.6 ± 11.7	0.55
BMI (kg/m^2)	24.2 ± 3.8	22.4 ± 3.6	**0.014**
Waist circumference (cms)	85.9 ± 11.6	82.2 ± 8.4	0.72
Smokers	36(72%)	23(46%)	–
FBS (mg/dl)	107.5 ± 26.9	98.2 ± 17.0	**0.03**
PPBS (mg/dl)	152.7 ± 48.4	124.2 ± 30.5	**0.001**
Adiponectin (µg/ml)	8.14 ± 3.86	9.4 ± 3.9	0.130
Total Cholesterol (mg/dl)	173.0 ± 52.3	150.8 ± 39.9	**0.019**
HDL-Cholesterol (mg/dl)	35.6 ± 8.1	36.6 ± 8.7	0.562
LDL-Cholesterol (mg/dl)	107.2 ± 47.3	95.5 ± 27.6	0.132
Triglycerides (mg/dl)	129.9 ± 60.3	117.3 ± 57.8	0.286

The CIMT measurements right, left and mean CIMT was higher in cases than controls and was found to be highly significant (p-value of 0.001 for right and left and <0.001 for mean CIMT) as shown in Table 2 . Three patients had a plaque in group 1, whereas plaque was found in one of the controls. Two of our patients showing plaque were ≤40 years of age (one was 38-years-old and other 40-years-old), third was 45 years of age. One of the controls who had plaque was 46 years of age.

Table 2: CIMT values in the study groups

Variable	Group 1	Group 2	p-value
CIMT (Rt) (mm)	0.68 ± 0.10	0.60 ± 0.12	**0.001**
CIMT (Lt) (mm)	0.69 ± 0.13	0.61 ± 0.12	**0.001**
Mean CIMT (mm)	0.68 ± 0.10	0.60 ± 0.11	**<0.001**
Plaque (no. & side)	3 (Right)	1 (Left)	–

Table 3: Incidence of obesity in the study groups

Variable	Group 1	Group 2
Total centrally obese	24 (48%)	12 (24%)
Male (WC ≥90 cms)	19 (43.1%)	6 (16.2%)
Female (WC ≥80 cms)	5 (83.3%)	6 (46.15%)
Total obese BMI ≥25 kg/m^2	21 (42%)	11 (22%)

Table 4: Correlation in cases (Pearson's correlation)

Parameters	Adiponectin	TC	HDL-C	LDL-C	TG
Adiponectin	1	–0.067	0.211	–0.111	–0.047
TC	–0.067	1	**0.429**	**0.923**	**0.321**
HDL-C	0.211	**0.429**	1	**0.280**	0.060
LDL-C	–0.111	**0.923**	**0.280**	1	0.161
TG	–0.047	**0.321**	0.060	0.161	1

TC – Total Cholesterol, HDL-C – High Density Lipoprotein Cholesterol, LDL-C – Low Density Lipoprotein Cholesterol, TG – Triglycerides.

Obesity (both central and total) was found in higher number of patients in group 1 as compared to group 2 (Table 3).

The mean adiponectin levels were higher in non-obese patients than obese patients in both the cases (9.2 vs. 6.9 µg/ml) and controls (10.1 vs. 7.4 µg/ml) and reached statistical significance at 6%.

The mean adiponectin levels were higher in non-centrally obese patients than centrally obese in cases (9.3 vs. 7.2 µg/ml) and controls (9.7 vs. 8.4 µg/ml). It approached statistical significance at 8% in group 1 but not in group 2.

Adiponectin had a negative correlation with mean CIMT (–0.198); though it did not reach statistical significance. But in controls, adiponectin had a positive correlation with mean CIMT and it also did not attain statistical significance.

Adiponectin had a positive correlation with HDL-C (0.211) and negative correlation with TC – Total cholesterol (–0.067), LDL-C (–0.111) and TG (–0.047) but none of it was significant (Table 4).

All the lipid components had a positive correlation with each other though the strongest correlation was seen between TC and LDL-C (0.923). The correlation between HDL-C and LDL-C was also positive and significant (0.280).

Adiponectin had a positive correlation with HDL-C (0.117) and TG (0.090) and negative correlation with TC (–0.214), LDL-C (–0.0.036) as shown in Table 5 , but none of it was statistically significant. TC had a positive correlation with LDL-C (0.619) and TG (0.421) which was found to be highly significant and positive correlation with HDL-C which was not statistically significant (0.106). HDL-C had a positive correlation with TC and LDL-C (0.115) and negative correlation with TG (–0.014) none of which was statistically significant. LDL-C had a strong positive correlation with TC (0.619) and also positive correlation with HDL-C (0.115) and also with TG (0.264) which were not statistically significant.

Discussion

There was higher number of males in both the groups. The BMI was significantly higher in cases as compared to controls pointing to the purported role of obesity in CAD.[10] The waist circumference was also higher in cases as compared to controls. There was significant dyslipidemia in cases as compared to controls and also higher blood sugar levels both fasting and postprandial in cases as compared to controls. Higher number of dyslipidemia, hyperglycemia and obesity in CAD group again support the hypothesis of metabolic syndrome in the causation of CAD.[4]

The adiponectin in CAD patients was found to be lower compared to controls in our study. These findings are supported by other studies done in CAD subsets of subjects.

Table 5: Correlation in controls (Pearson's correlation)

Parameters	Adiponectin	TC	HDL-C	LDL-C	TG
Adiponectin	1	–0.214	0.117	–0.036	0.090
TC	–0.214	1	0.106	**0.619**	**0.421**
HDL-C	0.117	0.106	1	0.115	–0.014
LDL-C	–0.036	**0.619**	0.115	1	0.264
TG	0.090	**0.421**	–0.014	0.264	1

TC – Total Cholesterol, HDL-C – High Density Lipoprotein Cholesterol, LDL-C – Low Density Lipoprotein Cholesterol, TG – Triglycerides.

In the present study, we found that adiponectin levels were higher in non-obese individuals (9.2 µg/ml; BMI <25) as compared to obese individuals (6.9 µg/ml; BMI ≥25). This is in agreement with the other studies (See Table 6) conducted by Weiss et al. (2003)[25] and Vikram et al. (2004).[26]

Table 6: Adiponectin levels in various studies in CAD

Author (year)	No. and type of cases	Mean adiponectin
Stejskal et al. (2003)[21]	No signs of CAD	5.9±2.7 mg/l
	Stable angina pectoris	4.9±1.2 mg/l
	ACS (NSTEMI) >48 hours	5.2±4.1 mg/l
	STEMI first 4 hours	4.6±2.7 mg/l
Yaturu et al. (2006)[22]	34 with CAD	5.02±0.82 µg/ml
	55 without CAD	9.94±1.02 µg/ml
Sattar et al. (2006)[23]	589 with CHD	10.22 µg/ml
	1231 controls	10.75 µg/ml
Pilz et al. (2006)[24]	273 controls	8.56 µg/ml
	367 with silent CAD	8.60 µg/ml
	608 stable angina	7.22 µg/ml
	378 unstable angina	6.72 µg/ml
Present study (2008)	CAD cases (n=40)	8.14±3.86 µg/ml
	Controls (n=40)	9.4±3.9 µg/ml

Increased CIMT is conventionally considered to be a marker of subclinical atherosclerosis. In the present study, we found that mean CIMT was higher in CAD patients as compared to controls. This is in accordance with the previous studies as shown in Table 7. Interestingly plaque was demonstrated in 3 of our CAD subjects and 1 apparently healthy control. All were in the 31–50 years age group. This reflects that premature atherosclerosis is very much a reality in our patient population. The present study also shows a negative correlation of adiponectin with CIMT. This is supported by the observation of other workers.[27,28]

Potential of adiponectin as a therapeutic tool needs to be explored and various studies have shown that adiponectin may be used as a therapeutic target.

Whitehead et al. (2006) have shown the beneficial effect of the adipokine in animal studies, there is exciting potential for adiponectin replacement therapy in insulin resistance and related disorders.[35]

Sakamoto et al. (2006) did a pilot study in Japanese patients with CAD and hypercholesterolemia and found that six months of treatment with pravastatin 10–20 mg/day was associated with significant increase in serum adiponectin concentrations.[36]

Table 7: CIMT findings in various studies

Author (year)	No. and type of cases	Mean CIMT
Baldassarre et al (2000)[29]	CAD patients (n=133)	1.08±0.49 mm
	Controls (n=266)	0.94±0.38 mm
Frauchiger et al (2001)[30]	CAD patients (n=157)	0.78±0.16 mm
	Controls (n=13)	0.55±0.07 mm
Rosa et al (2003)[31]	CAD patients (n=29)	0.81±0.25 mm
	Controls (n=29)	0.62±0.18 mm
Hansa et al (2003)[32]	CAD patients (n=101)	0.82 mm
	Controls (n=140)	0.67 mm
Tewari et al (2004)[33]	CAD patients (n=185)	0.84±0.16 mm
	Controls (n=135)	0.65±0.15 mm
Kasliwal et al (2004)[34]	CAD patients (n=64)	0.842±0.12 mm
	Controls (n=84)	0.657±0.05 mm
Present study (2008)	CAD patients (n=50)	0.68±0.10 mm
	Controls (n=50)	0.60±0.10 mm

Han et al. (2007) have shown that the effects of lifestyle modifications and cardiovascular drugs on adiponectins and insulin resistance suggest plausible mechanisms that may be important for treating atherosclerosis and coronary heart disease.[37]

Naruszewicz et al. (2007) have found significant increase in adiponectin levels and reduction in systolic and diastolic blood pressure and shown that chokeberry flavonoids reduce the severity of inflammation, regardless of statins, and can be used clinically for secondary prevention of ischemic heart disease.[38]

Ohashi et al. have suggested that hypoadiponectinemia contributes to the development of obesity-related hypertension, at least in part, directly, in addition to its effect via insulin resistance, and that adiponectin therapy can be potentially useful for hypertension in patients with the metabolic syndrome.[39]

Conclusion

Coronary artery disease is a modern epidemic. Its rising incidence among young people in India is a matter of grave concern. Early detection of atherosclerosis employing appropriate biomarkers and imaging technique is the need of the hour. This study was undertaken with the aim to have an insight into the link between the adiponectin, CIMT and obesity with CAD. Findings suggested an evidence of low adiponectin, increased CIMT and prevalence of central obesity in CAD patients.

This needs to be further explored in a larger sample size. As derangements in adiponectin and CIMT starts early and progresses at faster rate in the presence of hereditary factors, smoking and central obesity, healthy individuals

should be given counseling regarding smoking cessation and optimal waist length.

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Address for correspondence
Dr. Rajesh Jain: Email: docrajeshjain@gmail.com