Original Article

Association of Obesity and C-Reactive Protein with Coronary Artery Disease

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Abstract:

Background: Obesity is now becoming a global epidemic. It is most of the times associated with hypertension, diabetes mellitus (DM), metabolic syndrome and dyslipidemia which are known risk factors for coronary artery disease (CAD). Coronary arteriosclerosis comprises a series of inflammatory responses at cellular and molecular level, whose reactions are stronger in obese patients. The objective of this study was to observe the association of obesity and raised inflammatory markers with CAD.

Method: This cross-sectional study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh, involving 668 patients of ischemic heart disease who underwent coronary angiography (CAG) from January 2017 to December 2017. Obesity was defined as body-mass index (BMI) ≥30.0 kg/m^2. C-reactive protein (CRP) was measured as the inflammatory marker, and was considered as high if >10 mg/L. CAD was classified on the basis of CAG findings: insignificant if stenosis is <50% and significant if stenosis is ≥50%; and single-vessel, double-vessel, triple-vessel disease and normal coronaries according to number of vessels involved. Chi square test was used to analyze the categorical variables, and Pearson's correlation coefficient was used to test the relationship between CRP and BMI in CAD patients. p values of <0.05 were considered as statistically significant.

Results: Demographic characteristics like age, sex and educational status did not differ significantly between obese and non-obese patients. Risk factors for CAD were similar between obese and non-obese, as well as, between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in obese and high-CRP groups than in non-obese and non-high CRP groups. Raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04). Significant positive correlation was found between CRP and BMI (r=0.228; p=0.001). Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04), whereas normal coronaries were more common in non-obese than in obese counterpart. Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis.

Conclusion: Obesity is associated with raised inflammatory marker in patients with CAD, and a significant positive association exists between obesity and inflammation and CAD. Future studies are needed to explore the impact of type of obesity and inflammation on CAD.

Keywords: *Obesity, Body Mass Index, Inflammation, C-Reactive Protein, Coronary Artery Disease.*

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Introduction:

Ischaemic heart disease (IHD) or coronary artery disease (CAD) is an important cause of mortality and morbidity of Mankind, and is the leading cause of death over decades.[1,2] IHD affects around 126 million individuals (1,655 per 100,000), which is approximately 1.72% of the world's population. The current prevalence rate of IHD has been estimated to be 1,655 per 100,000 population is expected to exceed 1,845 by the year 2030.[1] Nine million deaths are caused by IHD globally.[1] On the other hand, IHD is the biggest killer, and accounts for 16% of the world's total deaths.[3] Since 2000, the largest increase in deaths has been for this disease, rising by more than 2 million to 8.9 million deaths in 2019.[3] A number of risk factors are now known to be associated with IHD, including diabetes mellitus (DM), hypertension, smoking, hyperlipidemia, obesity, homocystinuria, and psychosocial stress.[4] Among these, obesity is common, an important public health issue, and is currently considered as a global epidemic.[5] Its magnitude is on the rise. According to a systematic review of prevalence of overweight and obesity in children and adults during 1980-2013, the situation has worsened significantly in adults, as well as, in children, in developed, as well as, in developing countries.[6] Worldwide, the proportion of adults with a body-mass index (BMI) of ≥25 kg/m2 increased between 1980 and 2013 from 28·8% to 36·9% in men, and from 29·8% to 38·0% in women. Prevalence has increased substantially in children and adolescents in developed countries; 23·8% of boys and 22·6% of girls were overweight or obese in 2013. The prevalence of overweight and obesity has also increased in children and adolescents in developing countries, from 8·1% to 12·9% in 2013 for boys and from 8·4% to 13·4% in girls.

Obesity is now considered an independent risk factor of CAD.[7] The interplay between obesity, inflammation and CAD is complex, but important in the pathophysiology of CAD. Adipose tissue was traditionally thought to be metabolically inert, however, it is now known that fat, specially the abdominal fat is a highly active endocrine and paracrine organ It also secrets a number of biological molecules including the inflammatory mediators.[8] The proinflammatory cytokines released from the visceral fat of obese persons, e.g., tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), leptin and visfatin have a potential of causing atherosclerosis.[9] In obese individuals, macrophages first accumulate within the adipose tissue, leading to local inflammation. As the obesity increases, proinflammatory factors, including IL-1, IL-6 and TNF-±, are produced in the adipose tissue. Macrophage accumulation and the subsequent local inflammation result in systemic inflammation. Endothelial dysfunction occurs during the early stages of atherosclerosis and is responsible for the pathophysiological changes in subclinical atherosclerosis, which include changes in a variety of mediators, surface proteins, and in autacoids that are involved in vasomotion, coagulation and inflammation.[10-2] Obesity also can increase systemic oxidative stress independently of blood glucose and diabetes.[11] The association between obesity and clinically significant CAD is blatant in the Framingham Heart Study[13] and the Nurses' Health Study[14]. Each unit of change in BMI was associated with 9% increase in ischemic cardiac events in the Asia Pacific Cohort Studies Collaboration.[15]

C-reactive protein (CRP) is an acute-phase reactant, and also is one of the strongest markers of chronic inflammation. Besides diagnostic potential, it appears to have significant role in the aetiopathogenesis of coronary atherosclerosis.[16] More than 20 prospective epidemiologic studies have demonstrated that high-sensitivity CRP is an independent predictor of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death, even in apparently healthy individuals[17,18] On the other hand, CRP mRNA has been shown to be expressed in human adipose tissue, indicating that adipose tissue may be an important source of circulating CRP.[19] Two recent studies have demonstrated that exercise training in conjunction with weight reduction significantly affected the CRP levels, body composition, and human left ventricular growth.[20,21]

Both CAD and obesity are common public health issues in Bangladesh. Like other South Asians, Bangladeshis appear unduly prone to develop CAD, which is often premature in onset, follows a rapidly progressive course and angiographically more severe.[22] On the other hand, according to the 2011 Bangladesh Demographic and Health Survey, the prevalence of overweight and obesity in adults aged 35–70 years was 18.9% (male 17.4% and female 18.4%) and 4.6% (male 3.0% and female 6.0%) respectively.[23] Like many other aspects, the relationship between obesity, inflammation and CAD in Bangladeshi ethnicity has not been adequately studied.

Methods:

This cross-sectional study was carried out in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, Bangladesh, involving 668 patients of ischemic heart disease who underwent coronary angiography (CAG) from January 2017 to December 2017. Patients with infections, connective tissue disease and trauma were excluded. Also, patients with secondary

obesity like hypothyroidism were excluded. The patients' demographic variables, such as age, sex, waist and hip circumferences were recorded, and body-mass index (BMI) was calculated. BMI of ≥30.0 kg/m^2 was considered as obese.[24] Blood samples were collected for investigation before CAG. In this study, CRP was measured to assess inflammatory activity. CRP was assayed by turbidimetric assay using Beckman Coulter, model AU480 (250 S. Kraemer Blvd. Brea, CA 92821, USA). CRP values were divided into normal (<6 mg/L), borderline (6-10 mg/L) and high (>10 mg/L).[25] CAG was done as per institutional protocol, and CAG was analyzed by 2 independent interventional cardiologists. CAD was classified on the basis of CAG findings: insignificant if stenosis is <50% and significant if stenosis is ≥50%; and single-vessel, double-vessel, triple-vessel disease and normal coronaries according to number of vessels involved.

Categorical variables were expressed as proportions (percentages) and numerical data were expressed as mean (standard deviation) and range. Chi square test was used to analyze the categorical variables, and Pearson's correlation coefficient was used to test the relationship between CRP and BMI in CAD patients. Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows was used to analyze the data. p values <0.05 were considered as statistically significant.

The study was approved by the Ethical Review Board of Dhaka Medical College. Written informed consent was provided by the participants. Data were collected and analyzed by the investigators.

Results:

In the present cross-sectional study, almost 2/3rds (65.0%) of the patients belonged to age group 41-60 years. The mean age was 51.4±10.7 years, ranging from 25-85 years. Majority (82.3%) of the study patients were male. Among the risk factors, hypertension was the commonest (40.0%), followed by DM (31.3%), smoking (30.5%), history of IHD (28.3%) and dyslipidemia (22.6%). Demographic characteristics like age, sex and educational status did not differ significantly between obese and non-obese patients. (Table I) Risk factors for CAD were similar between obese and non-obese, however, DM, hypertension and dyslipidaemia were significantly more common in obese group than in non-obese group. (Table 2). In the present study, raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04), (Table 3) and a significant positive correlation was found between CRP and BMI (r=0.228; p=0.001) (Figure 1). Again, risk factors for CAD were similar between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in high-CRP group than in non-high CRP group. (Table 4) Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04). (Figure 2) Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis (Table V).

Most (65.0%) of the patients belonged to age 41-60 years. The mean age was found 51.4±10.7 years with range

Table-I

Association between obesity and demographic characteristics (N=668)

Demographic characteristics	Obesity		p value
	Yes (n=58)n (%)	No (n=610) n (%)	
Mean age (years)	49.8±12.0	51.5±10.6	0.249^{ns}
Range (min-max)	28-76	25-85	
Sex			
Male	45 (77.6)	505 (82.8)	0.321^{ns}
Female	13 (22.4)	105 (17.2)	
Educational status			
Illiterate	39 (67.2)	351 (57.5)	
Primary	7 (12.1)	103 (16.9)	
Secondary	5 (8.6)	106 (17.4)	0.261^{ns}
Higher	4 (6.9)	33 (5.4)	
Graduate and above	3 (5.2)	17 (2.8)	

Data were analyzed by chi-square test and unpaired t-test, ns= not significant

from 25-85 years. Majority (82.3%) patients were male and 390 (58.4%) patients were illiterate. In risk factors, highest 267 (40.0%) patients had hypertension followed by 209 (31.3%) diabetes mellitus, 204 (30.5%) smoker, 189 (28.3%) H/O ischemic heart disease, 151 (22.6%) dyslipidemia and 58 (8.7%) obesity. Mean age was little bit lower in obese group than non obese (49.8±12.0 vs 51.5±10.6 years), female patients were higher in obese group than non obese (22.4% vs 17.2%) but these results were not statistically significant (p>0.05) (Table I). Among the risk factors, diabetes mellitus, hypertension and dyslipidemia were found significantly higher in obese group than non obese (Table I). High CRP was found higher in obese than non obese (56.9% vs 47.9%) (Table III). Positive correlation (r= 0.228; p=0.001) was found between CRP and BMI (Figure 1). Among the risk factors, diabetes mellitus, hypertension and dyslipidemia were found significantly higher in high CRP group than normal and borderline group (Table IV). Triple vessel CAD was found significantly higher in obese group than non obese (29.3% vs 24.4%) and normal CAD was found significantly higher in non obese group than obese (Figure 2). Multi variable logistic regression was found high HbA1c, high CRP, diabetes mellitus and obesity were statistically significant (p<0.05) in severe CAD (Double and triple vessel) patient (Table V).

Table-II

Association between obesity with clinical risk factors (n=668)

Risk factor	Obesity		p value
	Yes (n=58)n (%)	No (n=610) n (%)	
Diabetes mellitus	41 (70.7)	168 (27.5)	0.001^{s}
Hypertension	32 (55.2)	235 (34.5)	0.013^{s}
Dyslipidemia	20 (34.5)	131 (21.5)	0.024^{s}
Smoking	22 (37.9)	182 (29.8)	0.200^{ns}
Smokeless tobacco	12 (20.7)	85 (13.9)	0.163^{ns}
Alcohol	1 (1.7)	1 (0.2)	0.166^{ns}
Family history of CAD	5 (8.6)	26 (4.3)	0.121^{ns}
H/o ischemic heart disease	19 (32.8)	170 (27.9)	0.429^{ns}
Previous PTCA	2 (3.4)	9 (1.5)	0.246^{ns}
Previous CABG	1 (1.7)	9 (1.5)	0.599^{ns}

Data were analyzed by chi-square test, s= significant, ns= not significant

Table-III

Association between obesity and CRP of the study population (N=668)

CRP	Obesity		p value
	Yes (n=58) n (%)	No (n=610) n (%)	
Normal (<6 mg/L)	0 (0.0)	56 (9.2)	
Borderline (6-10 mg/L)	25 (43.1)	262 (43.0)	0.045^{s}
High (>10 mg/L)	33 (56.9)	292 (47.9)	

Data were analyzed by chi-square test, s= significant

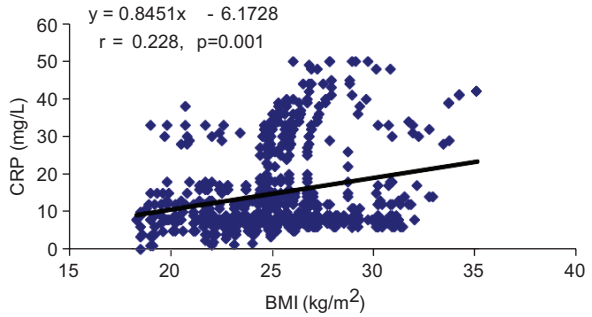

Fig.-1: *Scatter diagram showing correlation between CRP and BMI.*

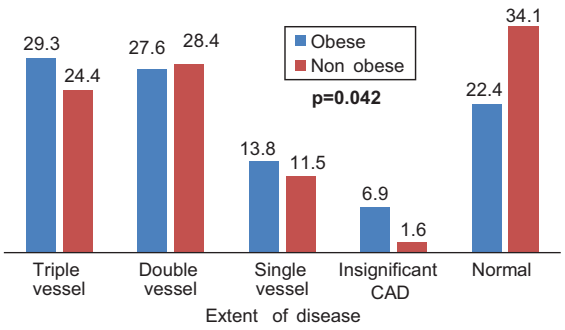

Fig.-2: *Bar diagram showing obesity and extent of coronary artery disease of the study population*

Table-IV

Association between CRP and clinical risk factors (N=668)

Risk factor	CRP		p value
	High (>10 mg/L) (n=325)n (%)	Not high (≤10 mg/L) (n=343)n (%)	
Diabetes mellitus	149 (45.8)	60 (17.5)	0.001^{s}
Hypertension	146 (51.1)	121 (29.4)	0.011^{s}
Dyslipidemia	88 (27.1)	63 (18.4)	0.048^{s}
Smoking	101 (31.1)	103 (30.0)	0.769^{ns}
Smokeless tobacco	50 (15.4)	47 (13.7)	0.537^{ns}
Alcohol	1 (0.3)	1 (0.3)	0.737^{ns}
Family history of CAD	16 (4.9)	15 (4.4)	0.736^{ns}
H/o ischemic heart disease	99 (30.5)	90 (26.2)	0.226^{ns}
Previous PTCA	6 (1.8)	5 (1.5)	0.693^{ns}
Previous CABG	6 (1.8)	4 (1.2)	0.343^{ns}

Data were analyzed by chi-square test, s= significant, ns= not significant

Table-V

Multivariable logistic regression analysis for severe CAD

	Adjusted	95% CI		P
	OR	Lower	Upper	Value
HbA1c (≥6.5)	0.261	0.025	0.882	0.023^{s}
CRP (>10 mg/L)	30.222	8.874	99.389	0.001^{s}
Diabetes mellitus	0.103	0.011	0.953	0.045^{s}
Obesity	0.396	0.195	0.967	0.048^{s}
Hypertension	1.059	0.268	4.181	0.935^{ns}
Dyslipidemia	0.698	0.146	3.346	0.653^{ns}
Smoking	0.547	0.143	2.092	0.378^{ns}
Constant	0.007	-	-	0.001^{s}

Data were analyzed by multivariable logistic regression, s= significant, ns= not significant, CAD= Coronary artery disease

Discussion:

In the present cross-sectional study, almost 2/3rds (65.0%) of the patients belonged to age group 41-60 years. The mean age was 51.4±10.7 years, ranging from 25-85 years. Majority (82.3%) of the study patients were male. Among the risk factors, hypertension was the commonest (40.0%), followed by DM (31.3%), smoking (30.5%), history of IHD (28.3%) and

dyslipidemia (22.6%). In the present study, 58 out of 668 patients were obese, hence the prevalence of obesity was 9.51%, which is higher than the national prevalence of 4.6%.[23] This disparity is presumably due to the patients having clustering of CAD risk factors included in the study. Similar observation was found by Khan et al.[26] Risk factors for CAD were similar between obese and non-obese, however, DM, hypertension and dyslipidaemia were significantly more common in obese group than in non-obese group. This is logical because risk factors of CAD tend to cluster together.

In the present study, raised CRP was significantly more common in obese than in non-obese patients (56.9% vs. 47.9%, p=0.04), and a significant positive correlation was found between CRP and BMI (r=0.228; p=0.001). A systematic review and meta-analysis involving various populations, obesity was associated with elevated levels of CRP and the association is stronger in women and North Americans/Europeans.[27] Another meta-analysis found significant correlation between CRP and obesity in Chinese adults and children.[28] Previously, in the study by Kao et al., higher BMI, as well as, central obesity were independently associated with higher levels of CRP.[29] Also, in a Mediterranean population, CRP concentrations increased significantly with increasing cardiovascular risk factors. Men and women with metabolic syndrome showed significantly higher levels of CRP than their counterparts, even after adjustment for BMI and age.[30] Again, risk factors for CAD were similar between high-CRP (>10 mg/L) and non-high CRP (≤10 mg/L) groups, however, DM, hypertension and dyslipidaemia were significantly more common in high-CRP group than in non-high CRP group. In an international multicentre study of 13,874 patients, among underweight, normal weight, overweight, and obese individuals, there was increasing prevalence of diabetes (7 vs.10% vs. 12 vs. 19%), hypertension (37 vs. 40% vs. 46 vs. 59%), and hyperlipidaemia (48 vs. 52% vs. 56 vs. 56%; P < 0.001 for trend).[31] Other studies demonstrated positive association between DM and metabolic syndrome with CRP.[32,33] Triple-vessel CAD was found significantly more commonly in obese group than in non-obese group (29.3% vs 24.4%, p=0.04). These findings correlate well with those of Khan et al. depicting higher presence of triple-vessel disease in obese patients compared to the non-obese counterparts.[26] In the present study, Obesity, high CRP (>10 mg/L), DM, and high HbA1c (≥6.5%) were found significant predictors of severe CAD (p <0.5) in multivariate logistic regression analysis. In the study by Labounty et al., higher BMI was independently associated with increased risk of myocardial infarction (hazards ratio: 1.28 per +5 kg/m(2), 95% CI: 1.12-1.45, P < 0.001).[31]

The study has got some limitations. This was a single-centre study. No distinction was made between generalized and visceral obesity. Only CRP was evaluated as a marker of inflammation. Also, CAD severity in CAG was determined by visual assessment, hence, intar- and inter-observer variability could not be ruled out.

Conclusion:

Obesity is associated with raised CRP in patients with CAD, and a significant positive association exists between obesity and inflammation and CAD. Future studies are needed to explore the impact of type of obesity and inflammation on CAD. Also, role of lifestyle modification and pharmacological management in reducing obesity and inflammation in the context of CAD may be evaluated.

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