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Original Article

Serum Leptin Level and Its Correlation with Angiographic Severity of Coronary Artery Disease

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Abstract

Introduction: In India, coronary artery disease (CAD) manifests almost a decade earlier than in Western countries. This is a study to discuss the distribution of coronary angiograms among the patients admitted to the Cardiology Department, Stanley Medical College.

Aim: This study aimed to determine the relationship between leptin and angiographic severity of CAD.

Materials and Methods: This is a cross-sectional analysis study, included 122 adult patients undergoing diagnostic coronary angiography.

Results: Among 122 patients, 55 (45.08%) patients had comorbid diseases, mean age of the patients was 49.87 ± 9.13 years. There is a significant difference between the relationship of leptin score and level of coronary angiography.

Conclusion: Our results revealed that the leptin level was markedly elevated in significant obstructive coronary disease.

Key words: Cardiovascular events, Coronary artery disease, Leptin

INTRODUCTION

Cardiovascular diseases have come as the largest cause of death in the world.[1] The South Asian region, one of the world's most densely populated regions, comprises about 20% of the world's population, with a total of more than 1.4 billion residents. India is the largest country in South Asia and it is densely populated. In India, over 30 million people are living with coronary heart disease (CHD).[2] At present, about 30% of all inhabitants in this region live in an urban setting, a number that is expected to reach 43% by 2025. In 2000, the prevalence of CHD has increased to 10.5%. Various studies showed that rural/urban protection no longer exists. About 52% of death due to cardiovascular disease occurs in younger people resulting in a considerable burden from coronary artery disease (CAD) on working age citizens.[3]

Coronary atherosclerosis is the most important cause of CHD. Atherosclerosis is the leading cause of morbidity and mortality throughout the globe. Acute CAD is mostly due to coronary thrombosis. Non-atherogenic forms of CAD are less common. During the natural evolution of atherosclerotic plaques, especially lipid-laden plaques, an abrupt and catastrophic transition can occur, characterized by plaque disruption. During the last couple of years, there is a change in the field of atherosclerosis both in understanding and treatment.[4,5]

We can assess the components of atherosclerosis, that is, coronary angiography and CT angiography, angioscopy to assess the lumen of the vessels, vascular MRI, intravascular ultrasound (IVUS), OCT, inflammation for plaque morphology, intravascular thermography, FDG, PET imaging, and biochemical markers for the assessment of inflammation.[6]

However, a prominent role for inflammation in the pathogenesis of atherosclerosis has been established, the

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concept that inflammation governs atherosclerosis and its complication has provided a new unifying hypothesis of the link between risk factors and the cellular and molecular alterations that underlie this disease.[7,8] The hallmark of atherosclerotic lesions is the formation of foam cells.[9] Foam cell formation leads to macrophage death which further can lead to lesional necrosis, the release of cellular proteases, inflammatory cytokines, adipokines, and prothrombotic molecules. These could contribute to plaque instability, plaque rupture, and acute thrombotic vascular occlusion. One such adipokine, that is, leptin which has come under increasing examination over the past 10 years or genetics and in particular, the genes involved in the regulation of leptin within the body. Hence, the present study aimed on the role of leptin and its association with cardiovascular disease.

MATERIALS AND METHODS

This cross-sectional analysis study was designed to enroll the 122 adult patients undergoing diagnostic coronary angiography. For the patient enrolled in the study, blood sample was taken for fasting serum leptin level in the morning, when the diagnostic coronary angiography was performed. Blood for fasting glucose and lipid profile was also collected at the same time. The patient's medical history and medication usage were recorded. Clinical examination of the patient was done before angiography.

The variables in the study are the demographic variables, body mass index (BMI), blood pressure level, fasting blood sugar, lipid profile, serum leptin, and coronary angiography. The severity of CAD was measured with standardized coronary angiographic technique (QUA) – Gensini score.

Leptin was quantitatively determined in patients' serum by enzyme immunoassay method. As for all clinical assays, each laboratory should collect data and establish its range of expected normal values.

Two-dimensional and M-mode measurements were obtained with patients in the left lateral position using an Aloka SSD 4000 phased array system equipped with tissue Doppler and harmonic imaging technology with Doppler frequency of 2.5–3.8 MHZ. With the measurement of LV end-diastolic dimension in diastole and LV end-systolic dimension in systole, LV ejection fraction was measured.

A coronary angiogram was done in the Siemens mobile unit cath lab in our hospital. Coronary angiography was performed by the radial approach or by the femoral approach. Coronary angiograms were done through radial or femoral approach using modified Seldinger technique after getting patients and patient's relative consent and included at least four views of the left coronary artery and two views of the right coronary artery. A low osmolar non-ionic contrast agent was used. Coronary artery stenosis was evaluated by use of multiple projections quantitative analysis was done with a medical imaging system CMS analysis software.

Following coronary angiogram, the degree of narrowing was assessed by taking into account the maximum narrowing of each stenotic lesion in at least two orthogonal views. The severity of CAD was evaluated by the 0–3 vessel disease score, Gensini, and ACC/AHA scores. In the clinical 0–3 vessel disease scoring system, arteries were as being involved if more than 50% luminal diameter narrowing occurred, and the patients were defined as having 0-, 1-, 2-, 3-vessel disease according to the number of vessels involved.

Descriptive (frequencies, percentages, mean, and standard deviation) and inferential statistics were used to analyze the data. Continuous variables are presented as mean + standard deviation and categorical variables are presented as the percent. The comparison of continuous variables was performed by the Student's t-test and the ANOVA test was appropriate. Linear regression analysis and multiple linear regressions were used to identify the correlation. All *P*-values were two tailed, the significance level was considered to be 0.05. Statistical analysis was performed with the help of Widows SPSS software Version 16.0.

RESULTS

The analysis and interpretations of data were collected from 122 family members of cardiac patients to assess the information needed in the study. Data collected from 103 normal persons without coronary angiogram from medical camps were used as controls for comparison of leptin levels only.

The mean age of the patients was 49.87 ± 9.13 years (male = 50.14 ± 9.00 and female = 48.57 ± 9.84). Most patients (n = 46) were in the age group of 51–60 years. The youngest patient was 23 years old and the oldest was 67 years. There is no significant difference which was found between male and female age. The mean score of males, females, and the total was 23.71 ± 3.63, 25.55 ± 3.15, and 24.02 ± 3.61. The difference between BMI scores of males and females is significant ($P < 0.04$).

Distribution of BMI of study subjects revealed that majority of them 52 (42.62%) have normal BMI, 6 (4.92%) have underweight, 2 (1.64%) had morbid obese, 31 (25.41%) had overweight, and 31 (25.41%) were obese.

The mean waist of the sample was 36.41 ± 3.66 and the mean waist not differed between gender. Males had 36.53 ± 3.58 and females had 35.75 ± 4.08. There is no statistical significance. The mean hip score has significantly differed between males (37.95 ± 3.11) and females (39.80 ± 3.97) ($P < 0.02$.). There is statistical significance in hip measurements. The mean SBP of the sample was 135.08 ± 22.94. The mean SBP score not differed significantly between males and females. The mean DBP was found to be 89.90±16.48 but did not differ significantly between males (90.29 ± 14.72) and females (91.90 ± 15.04).

The association between level of laboratory score and gender of the patient, the mean score on fasting blood sugar – mean of the male was 149.90 ± 63.79 and female was 219.86 ± 106.58. There is a significant difference between the FBS of the patients ($P < 0.001$). Females had a mean cholesterol level of 223.70 ±64.37, which was higher than the men' mean cholesterol level of 221.84 ±59.61. There is no significant difference between the sex of the patient and cholesterol level.

The mean score of triglycerides (mg/dl) in male is 169.57 ± 69.58 and female is 161.05 ± 50.01. The males had a higher score than females but the difference is not statistically significant. The mean score of LDL in females is 145.45 ± 50.75 and male is 143.32 ± 47.25. Females had a little high score than males but the difference is not statistically significant. Females had a mean level of HDL of 42.20 ± 11.31 which is more than that of the male's mean HDL score of 41.93 ± 8.80. There is no significant difference between the sex of the patient and cholesterol level. The mean score on VLDL male is 32.91 ± 13.14 and female is 32.15 ± 9.68. The difference is not statistically significant.

Subgroups of Study Patients

A total of 122 CAD samples were used for this study. Males comprised 101 (82.79%) and females 21 (17.21%) of the total. Sixty-four (52.46 %) of the sample had CAD and 58 (47.54 %) had acute myocardial infarction (AMI). The distribution between the sex of the CAD and AMI was statistically significantly different $P = 0.02$ [Table 1].

CAD: Unstable Angina, Non-ST Elevation Myocardial Infarction, Chronic Stable Angina, Old Myocardial Infarction

Acute myocardial infarction

Among 122 patients, 57 (56.40%) patients had no comorbid diseases, 9 (8.90%) patients had diabetes mellitus, 9 (8.90%) patients had hypertension, 23 (22.80%) patients had previous infarction, and both DM/HT/previous myocardial infarction 3 (3%) patients. Sixty-four (52.46%) of the sample had CAD and 58 (47.54%) had AMI. The distribution of diseases in this group was statistically significant ($P < 0.001$).

The mean leptin score in normal BMI (18.5–22.99) was 27.58 ± 8.22, overweight 28.52 ± 10.03, obese 34.40 ± 10.57, morbid obese 47.85 ± 16.61, and underweight 26.97 ± 8.25. It is statistically significant. The F value reveals that there is a significant difference between the relationship of leptin score and level of BMI [Table 2].

Results of Coronary Angiogram

The distribution of coronary artery system among 122 patients is 9.8% (12 patients) which are codominant system, 15.5% (19 patients) are left dominant system, and 74.59% (91 patients) are right dominant system. Sixty-three patients are thrombolysed.

Among the patients, 36 (29.75%) had double vessel disease; 34 (28.10%) had single vessel disease; 30 (24.79%) had triple vessel disease; and 21 (17.36%) had normal vessels. The Chi-square value reveals that there is no significant association between coronary disease status and gender.

The association between gender and Gensini and ACC/AHA score. The females had a mean level of Gensini score of 36.43 ± 31.82 which is more than the male's Gensini score of 25.67 ± 22.99. There is no significant difference between the gender and Gensini score of the patient. The mean score on ACC/AHA of the male is 6.41 ± 4.89 and female is 6.67 ± 5.51. The difference is not statistically significant [Table 3].

The Gensini score in normal vessel is 0.70 (0), in single vessel disease is 19.81+16.01, double vessel disease is 36.67 ± 23, and triple vessel disease is 44.15 ± 25.36. There is a significant difference in the F ($F = 23.22$) and p ($P < 0.001$) value. It is statistically significant.

The relationship between Gensini score and BMI, there is a difference between the BMI groups. However, there is no statistically significant difference.

A statistically significant difference between a normal coronary artery and significant obstructive CAD was observed.

Leptin score in normal, single vessel disease, double vessel disease, and triple vessel disease was 22.53 ± 7.40, 23.98 ± 5.05, 30.29 ± 6.45, 42.16 ± 8.92, and 30.11 ± 10.23, respectively. The F value reveals that there is a significant difference between the relationship of leptin score and level of coronary angiography [Table 4].

There is a significant difference in leptin value between normal and abnormal coronary vessels but it is not statistically significant.

Table 1: Subgroups of study patients

Group	Total (%)	Male, *n*=101 (%)	Female, *n*=21 (%)	*P*-value
Coronary artery disease	64 (52.46)	48 (47.52)	16 (76.19)	0.02
Acute myocardial infarction	58 (47.54)	53 (52.48)	5 (23.81)	

Table 2: List of the values of BMI and leptin in the study group (CVD) and control group (non-CVD)

Class	BMI (kg/m^2)	Leptin (ng/ml)
Normal weight		
Non-CVD (21)	21.5629±1.32228	15.29± 8.616
CVD (52)	20.0673±1.13373	27.58 ± 8.22
P-value	0.03	0.007
Overweight		
Non-CVD (45)	24.7096±1.24606	18.85± 12.219
CVD (31)	26.0700±1.38817	28.52 ± 10.03
P-value	0.033	0.0001
Obese		
Non-CVD (36)	31.6586±3.47939	27.06± 12.430
CVD (33)	29.4408±1.4798	34.40 ± 10.57
P-value	0.005	0.002

Table 3: Gensini score versus significant obstructive coronary artery

Characteristics	Normal Mean±SD	Significant obstructive coronary artery Mean±SD	Total Mean±SD	*P*-value
Gensini score	0.70±2.70	3318±23.81	27.53±24.94	0.001

Table 4: Leptin versus coronary angiography

Variables	Coronary angiography	Mean±SD	*P*-value
Leptin (ng/dl)	Normal vessel	22.53±7.4	0.001
	Single vessel disease	23.98±5.05	
	Double vessel disease	30.29±6.45	
	Triple vessel disease	42.16±8.92	
	Total	30.11±10.23	

The leptin level in the study group along with Gensini and ACC/AHA score, the r-value was 0.35 which shows a significant positive correlation between leptin level and Gensini score. The r-value was 0.49 which shows a significant positive correlation between leptin level and ACC/AHA score ($P < 0.01$) [Figure 1].

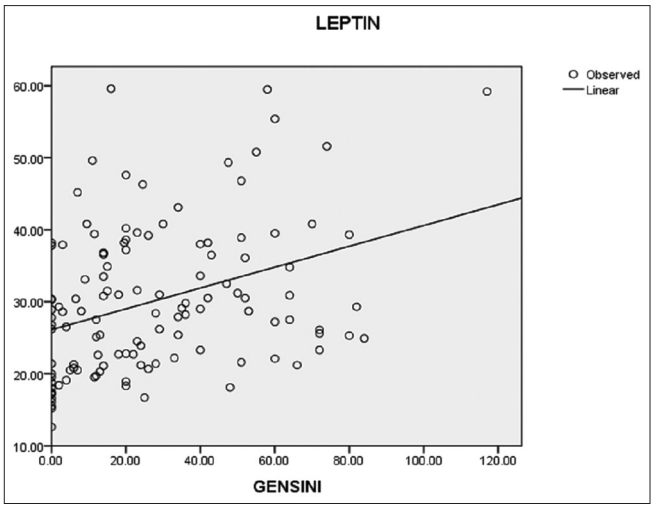

Figure 1: Correlation between serum leptin level and Gensini score

DISCUSSION

Leptin is one of the factors that play a pivotal role in connecting common forms of obesity and cardiovascular disease.[10] Comparison between BMI and serum leptin level in both control group and study group shows a positive correlation. A notable finding is that serum leptin level increases with the increase in BMI. In the case of the control group, there is an increase in leptin values as a function of BMI. This is similar to the study done by Martin *et al.* and Enriori *et al.*, in which they have said that most of the obese individuals are hyperleptinemic and this was due to leptin resistance and this resistance was due to defective hypothalamic regulation food intake in obese persons.[11,12]

The values obtained for leptin are interestingly found to be higher in the CVD group when compared to the control group in all categories of BMI.

Leptin values are expected to be higher in thin subjects and lesser in obese subjects since it is known to correlate with energy expenditure. However, the computed values of leptin are much higher in obese subjects and less in thin subjects. This could be indicative of leptin resistance where circulating leptin might be higher when compared to bound leptin. Thus, the amount of circulating leptin might be higher in obese subjects when compared to thin subjects and leptin might play a paracrine role in addition to the endocrine role played in humans. The increase in leptin values in CVD subjects when compared to that of normal subjects suggests that leptin acts as a pro-inflammatory cytokine.

Higher serum leptin level was associated with more severe coronary atherosclerosis which is confirmed by angiographic measurement with Gensini score and ACC/AHA score.

The cardiovascular consequences of inflammation are well established and many studies have correlated increased levels of pro-inflammatory cytokines with adverse outcomes. In particular, inflammatory factors produced by cells of the myocardium (cardiomyocytes, endothelial cells, fibroblasts, and smooth muscle cells) and by infiltrating leukocytes, platelets, and macrophages can impact the

structure and function of the myocardium, and systemic inflammation also impacts vascular function.[13,14]

Various studies showed that there is both a positive and negative correlation between serum leptin and clinical atherosclerosis.[9] Soderberg *et al.*, 1999, found a positive association between plasma leptin level and first myocardial infarction. Jose *et al.*, 2005, suggested that serum leptin level is elevated in patients with first AMI.[15] Wolk *et al.* have said that leptin level in angiographically proven CAD patients had prognostic significance.[16] Tamer *et al.* found that leptin levels were higher in myocardial infarction patients.[17] However, plasma leptin levels were not associated with cardiovascular disease in the Quebec cardiovascular study cohort.[18]

In our study, there is a significantly high serum leptin level present in CAD. There is a positive correlation between significant obstructive CAD predicted by Gensini score, ACC/AHA score, and the number of coronary vessel involvement and serum leptin level. Between the AMI (complete occlusive disease) and unstable angina, chronic stable angina (partial obstructive disease), the leptin level is higher in AMI patients. This shows that leptin is a pro-inflammatory activity. We also found that higher serum leptin level was associated with dyslipidemia, blood pressure, and angiographic severity of CAD. These findings are likely due to multiple factors such as increased sympathetic activity, enhanced platelet aggregation, increased oxidative stress, or endothelial dysfunction effects.

CONCLUSION

Serum leptin level was found to be increased in the persons with increased BMI both in the study group and the control group. When the study group was compared with the control group with the same BMI, leptin level was increased more in the study group. In the study group, the leptin level was markedly increased in those who have a significant obstructive coronary disease (Gensini, ACC, and AHA score). Further study is needed, in the future with a large group of patients to find the facts between leptin level and significant coronary obstructive disease.

Limitation of the Study

Despite the significant results of this study, this study examined a small number of patients. Large cohorts are required in local settings to assess the relationship of leptin levels with the severity of coronary atherosclerosis in local settings. The concentrations of serum leptin levels vary according to different measuring times.

The coronary angiographic assessment is based on luminal assessment and lacks plaque visualization. IVUS-based assessment of coronary atherosclerotic burden in correlation with serum leptin levels may be an area of interest for future investigation.

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