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Serum Leptin in Coronary Heart Disease

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Abstract: *Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide. Apart from a number of biomarkers for diagnosis of coronary heart disease, leptin has recently been shown to be associated with the disease. Leptin is an adipose tissue derived protein. It helps in regulating energy balance by inhibiting hunger. Increased leptin levels has been suggested to be an independent risk factor for coronary artery disease. The aim of our study is to estimate serum leptin levels in patients suffering from coronary artery diseases and in normal healthy individual. A case-control study was conducted in the Department of Biochemistry in collaboration with Department of Medicine, RIMS, Imphal. 24 cases and 24 controls were selected randomly irrespective of sex and socio-economic status to form the study group. Serum leptin was estimated by leptin ELISA kit. The mean leptin level was higher in cases than in controls. It was seen that mean ± SD leptin levels were higher in females compared to males with 13.4±1.2 and 8.3±0.8 ng/ml respectively. This study confirm the association of high serum leptin with coronary heart disease. Thus, it can be concluded that estimation of serum leptin may be used as a biomarker for diagnosis of coronary heart disease and may provide a potential therapeutic modality in the treatment of coronary heart disease.*

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I. Introduction

Coronary artery disease (CAD) or ischemic heart disease (IHD) is a group of diseases that include: stable angina, unstable angina, myocardial infarction and sudden cardiac death.[1] Risk factors include: high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor diet, excessive alcohol and depression.The underlying mechanism involves reduction of blood flow and oxygen to the heart muscle due to atherosclerosis of the arteries of the heart.[2] A number of tests may help with diagnosis including: electrocardiogram, cardiac stress testing, coronary computed tomographic angiography and coronary angiogram, among others.[3] Myocardial infarction is responsible for almost one fourth of all deaths in the United States.[4] In 1990 the number of deaths due to CAD was 5.74 millions (12%) whereas in 2013 it has increased to 8.14 million (16.8%).[5] In 2003, the prevalence was estimated to be 3-4% in rural areas and 8-10% in urban areas according to population based cross sectional surveys.[6,7] In 2000, there were an estimated 29.8 million people with CHD in India out of a total estimated population of 1.03 billion, or a nearly 3% overall prevalence.[8,9] Typically, coronary artery disease occurs when part of the smooth, elastic lining inside a coronary artery (the arteries that supply blood to the heart muscle) develops atherosclerosis. With atherosclerosis, the artery's lining becomes hardened, stiffened and accumulates deposits of calcium, fatty lipids and abnormal inflammatory cells to form a plaque. Calcium phosphate (hydroxyapatite) deposits in the muscular layer of the blood vessels appear to play a significant role in stiffening the arteries and inducing the early phase of coronary arteriosclerosis. People with coronary artery disease might have just one or two plaques or might have dozens distributed throughout their coronary arteries. A more severe form is chronic total occlusion (CTO) when a coronary artery is completely obstructed for more than 3 months.[10] The diagnostic approach and the clinical management of the patients who present with a suspected acute coronary syndrome or cardiac dysfunction are challenging.[11] The manifestations of myocardial ischemia are varied and multiple, like chest pain, epigastric discomfort, breathlessness, nausea and vomiting. However, these symptoms may be subtle and they may not be easily recognized. Because of their varied presentations and as they are associated with high mortality, an early identification of the patients with acute myocardial infarction is very critical.[12] Assessment of the cardiac biomarker levels e.g. Myoglobin, Creatine Kinase-MB and Troponins is one of the most essential and effective ways for detecting myocardial damage. The current conventional cardiac biomarkers, CK-MB, Troponin I (Tn I) and T are sensitive and specific tests for the detection of myocardial necrosis, but they show a great rise approximately 3-6 hours after the onset of the myocardial cell injury and other diagnostic tools such as stress testing and echocardiology are not routinely available.[13]

Leptin is the 16,000 Dalton protein product of the obesity gene (ob).[14] It is a 167 amino acid hormone, with interleukin-6 homology, mainly produced by adipose tissue, circulates in blood in free form and bound to

proteins, that acts on a specific receptor located in the hypothalamus to decrease appetite and increase energy expenditure which has been hypothesized to be an "adiposity signal" for the long-term regulation of body weight by the brain. [15,16] It may also be produced by brown adipose tissue, placenta, ovaries, skeletal muscle, stomach, mammary epithelial cells, bone marrow and gastric chief cells.[17] In obesity, a decreased sensitivity to leptin occurs, resulting in an inability to detect satiety despite high energy stores.[18] The mechanisms leading to its impact on cardiovascular dysfunction are complex. Leptin enhances sympathetic nervous tone, which increases vascular tone and blood pressure, but this action is counter- balanced by its direct and indirect peripheral vaso-relaxation action.[19] Moreover, in vascular endothelial cells chronic hyperleptinemia induces intra-cellular signalling, which results in oxidative stress and may activate the atherogenic process.[20] Leptin was found to be an independent risk factor, after adjusting for conventional risk factor, for the development of CHD in a large prospective study.[21]

So far, there is no study on leptin in CAD in this region. The study is therefore planned to investigate the serum level of leptin in CAD and to assess if there is any association between leptin and CAD.

II. Material And Methods

The study population consisted of patients above 18 years of age suffering from coronary artery diseases either attending OPD or admitted in medicine wards which formed the study group. A group of normal healthy individual who were free from any systemic disease attending OPD for some minor ailments were included in the control group. The study was done after obtaining the approval from Research Ethics Board (REB), RIMS, Imphal.

Study Design: Case control study

Study Location: The study was carried out in the department of Biochemistry, Regional Institute of Medical Sciences (RIMS), Imphal in collaboration with department of Medicine, RIMS Imphal, Manipur.

Study duration: The study was carried out during a period of 24 months with effect from October 2016 to September 2018.

Sample size: 24 cases and 24 controls.

Inclusion criteria: Individuals whose age were 18 years and above, irrespective of sex, caste and creed, diagnosed case of coronary artery disease and who were willing to participate in the study were voluntarily included in the study. The control individuals also fulfilled the same criteria but were free of any coronary artery diseases.

Exclusion criteria: Patients who had concurrent illness which might influence serum leptin level independently were excluded while selecting study group like

1. Diabetes mellitus
2. Renal diseases

Procedure methodology: Voluntary consent was taken from each of the selected patients before starting the study. No patients were forced to participate in the study.

A detailed history including the patient's name, age, sex, duration of disease, age of onset of disease, cause of disease, presence of diabetes, hypertension, use of prescribed drugs for hypertension, diabetes, hypercholesterolemia. Personal history of smoking, consumption of alcohol, presence or absence of obesity and family history of diabetes, hypertension or coronary heart disease were recorded in the enclosed proforma.

Systolic and diastolic blood pressure, weight, height and body mass index (BMI) were measured once at the beginning of the study.

After a proper informed consent 5ml of blood was collected in plain vials from patients. Blood samples were allowed to stand for 30 minutes and centrifuged for 5 minutes and the serum thus separated was analysed for estimation of serum leptin. Serum leptin was measured by ELISA using DBC Leptin ELISA kit, Canada as described by Meier U and Gressner AM.[22]

Statistical analysis:

The collected data was analyzed using SPSS version 21 for windows. Descriptive statistics like mean, percentage and proportion was used. P value <0.05 was taken as significant.

III. Results

In this study 24 cases of coronary heart disease patients were taken as study group and 24 cases of normal healthy subjects as control group. Majority of the age groups in both the cases and controls were from >55 years. Although there were some differences, it was found to be statistically insignificant (p>0.05). So, both the groups were comparable with respect to age.

It is evident from Table 1, that the majority of coronary heart disease cases (50%) occurred in the age group of >55years, followed by 37.5% in the age group >45-55 years, 12.5% in the age group of 35-45 years. Of the normal controls, majority of the respondents were in the age group of >55 and >45-55 years of age which

constitutes 50%, followed by 29.2% in the age group of >45-55 years of age, 20.8% in the age group of 35-45 years. Although there were some differences, it was found to be statistically insignificant (p>0.05). So, both the groups were comparable with respect to age.

Table no 1: Age distribution of the respondents stratified by cases and controls

Age in years	Cases n (%)	Controls n (%)	Total N (%)	Chi-square test , p-value
35-45	3(12.5)	7(29.2)	10(20.8)	p>0.05
>45-55	9(37.5)	5(20.8)	14(29.2)	
>55	12(50)	12(50)	24(50)	
total	24(100)	24(100)	48(100)	

Table no 2: Shows female predominance in cases (79.2%) and also in controls (58.3%) whereas in males the percentage distribution in cases as 20.8% and in controls 41.7%. The findings observed was found to be statistically insignificant (p>0.05) and so there was no difference between the groups regarding sex. So, both the groups were comparable.

Table no 2: Distribution of the respondents by sex stratified by cases and controls

Sex	Cases n(%)	Controls n(%)	Total N(%)	Chi-square test , p-value
Female	19(79.2)	14(58.3)	33(68.7)	p>0.5
Male	5(20.8)	10(41.7)	15(31.3)	
Total	24(100)	24(100)	48(100)	

Table no 3: Obesity was more in cases than in controls as shown in table 3. Mean BMI was also significantly higher in cases (28.7 kg/m^2) than in control (25.5 kg/m^2). The majority of coronary heart disease cases (75%) occurred with BMI >30, followed by 12.5% with BMI 25-29.9 and 12.5% with BMI 18.5-24.9. Of the normal controls, majority of the respondents were having BMI 18.5-24.9 (45.8%) and >30 which constitutes 33.4%, followed by 20.8% in the BMI range of 25-29.9. Also the mean ±SD in cases was 28.7±4.0 and in control it was 25±4.3. Although there were some differences, it was found to be statistically insignificant (p>0.05). So, both the groups were comparable with respect to BMI.

Table no 3: Distribution of the respondents by BMI stratified by cases and controls

BMI	**Cases n(%)**	**Controls n(%)**	**Total N(%)**	**Chi-square test p-value**
<18.5	0(0.0)	0(0.0)	0(0.0)	p-0.00
18.5-24.9	3(12.5)	11(45.8)	14(29.2)	
25-29.9*	3(12.5)	5(20.8)	8(16.7)	
30 and above*	18(75)	8(33.4)	26(54.1)	
Total	24(100.0)	24(100.0)	48(100)	
Mean ±SD	28.7±4.0	25±4.3	-	p-0.000

Table no 4: This table shows the mean±SD in cases as 12.4±2.4 and 6.4±2.1 in controls. So, overall the mean leptin levels were higher in cases than in controls and the finding was found to be statistically significant with p-value = 0.000.

Table no 4: Association of the respondents by Leptin stratified by cases and controls

Leptin Cases Mean±SD	Leptin Control Mean±SD	t-test p-value
12.4±2.4	6.4±2.1	p-0.000

IV. Discussion

In the present study, 12.5% of the coronary heart disease patients are in the age group of 35-45 years, 37.5% in the age group of >45-55 years, followed by 50% in the age group above 55 years. Among the controls, 29.2% are in the age group of 35-45 years, followed by 20.8% in the age group of >45-55 years of age and 50% in the age group of more than 55 years. The importance of age on the prevalence of coronary heart disease cannot be underestimated. The majority of coronary artery disease patients globally are in the age group of more than 55 years and the most important demographic change to coronary heart disease prevalence across the world appears to be the increase in the proportion of people > 55 years of age.[23] The prevalence of coronary heart disease in our study is highest in the age group of more than 55 years of age. This may be due to the fact that coronary heart disease is common among older aged population. The high prevalence of coronary heart disease in the older aged population may also be due to acute ischaemic syndromes according to Reynon K and Bachmann K.[24]

The present study shows that number of males is 5(20.8%) and number of females is 19(79.2%) in coronary heart disease cases. Among the controls, 10(41.7%) and 14(58.3%) were males and females respectively. Many studies have reported the prevalence of coronary heart disease more in females than in males which are similar with our findings. A study by Towfighi A et al[25] reported that over the past two decades the prevalence of myocardial infarctions has increased in midlife (35 to 54 years) women while declining in similarly aged men.

The mean± SD BMI in kg/m^2 in controls and coronary heart disease cases are 25±4.3 and 28.7±4.0 respectively which is statistically significant. Almost similar findings were also observed by Flint AJ.[26]According to WHO recommendation a BMI of 18.5-22 is considered healthy for the Asian population.[27] In our study, half of the cases have BMI above the recommended range and the BMI in males and females are 21.4±3.4 and 27.9±2.3 respectively. This findings observed however closely resemble those found by Canoy D et al.[28]

Overall the mean leptin levels were significantly higher in cases than in controls. This is because leptin could induce the production of interleukin-6, CRP and other acute-phase reactants, thus contributing to the maintenance of chronic low-grade inflammation state involved in the progression of obesity and its associated comorbidities. This finding is consistent with the observation of Bullo M et al [29] who reported that mean leptin levels are raised in cardiovascular diseases and concluded that the relationship between peripheral inflammatory markers, plasma cytokines, and overall adipose tissue cytokine expression supports the dynamic role of adipose tissue in the etiology and maintenance of chronic inflammation associated with obesity, type 2 diabetes, and cardiovascular disease.Adipose tissue expression of leptin, shows a positive relationship with serum CRP levels and plasma IL-6. Several authors have attributed some pro-inflammatory properties to leptin. Therefore, it is possible that the relationship between TNF and adipocyte leptin production could be a mechanism through which TNF can modulate inflammation. Similar findings were described by Wolk R et al[30] where it was seen that in patients with established and angiographically confirmed atherosclerosis, plasma leptin could be a novel predictor of future cardiovascular events. One possible explaination relates to the association of leptin with left ventricular hypertrophy, although further studies are required. In a study by Akram S et al [31]leptin levels were higher in coronary heart disease patients as compared to controls but the difference was non-significant.This may be due to the potential confounding effect of treatment with aspirin and statins. Xia D et al[32] also verified hyperleptinemia in CHD patients.In a study by Wallace et al[21] leptin levels were 16% higher in cases than in controls and higher leptin concentrations were associated with higher risk of a future coronary events. Soderberg S et al[33] had also revealed that leptin levels were higher in patients with MI compared to controls. Schulze PC et al[34] observed that patients with congestive heart failure exhibit elevated plasma leptin levels

V. Conclusion

Coronary heart disease (CHD) is a leading cause of morbidity and mortality worldwide. Apart from a number of biomarkers for diagnosis of coronary heart disease, leptin has recently been shown to be associated with the disease. This study shows that serum leptin level is significantly raised in coronary heart disease patients as compared to normal controls. The results of this study confirm the association of high serum leptin with coronary heart disease. Thus it can be concluded that estimation of serum leptin may be used as a biomarker for diagnosis of coronary heart disease and may provide a potential therapeutic modality in the treatment of coronary heart disease.

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