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C-PEPTIDE AND CARDIOVASCULAR DISEASES

Biochemistry

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ABSTRACT

Introduction: Cardiovascular diseases (CVD) are a major cause of death and disability throughout the world. This group of disorders is preceded by atherosclerosis which is usually the underlying pathology and develops many years earlier to the time the symptoms occur. Although many molecules have been considered, C-peptide has been shown to play a major role in atherogenesis.
Aim: The present study was thus planned to study the role of C-peptide in various cardiac disorders.
Material and Methods: The study comprised of 100 patients of various cardiac disorders and 100 apparently healthy normal individuals served as controls. All the subjects were investigated for baseline parameters i.e. Fasting plasma glucose, Glycated hemoglobin, Lipid profile and C-peptide. Body Mass Index was also calculated.
Results: Body Mass Index increased significantly in male patients as compared to controls ($p<0.05$). Both Fasting plasma glucose and Glycated hemoglobin along with Total cholesterol, Triglycerides, Low Density Lipoprotein-Cholesterol, Very Low Density Lipoprotein-Cholesterol increased significantly ($p<0.05$) in both male and female patients as compared to controls whereas High Density Lipoprotein-Cholesterol decreased highly significantly ($p<0.001$) in female patients as compared to controls whereas change in male patients was significant ($p<0.05$). The HDL-C: LDL-C ratio was atherogenic in these individuals. Levels of C-peptide also increased significantly ($p<0.001$) in patients with cardiac disorders as compared to normal individuals.
Conclusion: C-peptide once deposited in the sub endothelial space may promote inflammation and lower High Density Lipoprotein-Cholesterol levels, thus it can be postulated that increased levels of C-peptide are associated with cardiac disorders.

KEYWORDS

Lipid profile, Atherosclerosis, C-peptide

INTRODUCTION:

Cardiovascular diseases are a major cause of disability and premature death throughout the world. In the year 2015, 17.9 million deaths occurred in a year, a number which is expected to grow more than 23.6 million by the year 2030 [1]. The underlying pathology of cardiac disorders is atherosclerosis which develops over the years and at the time the symptoms occur, it is usually advanced [2].

Studies have reported significant increase in levels of C-peptide in patients with myocardial infarction thus indicating the stimulation of β cells in hemodynamic impairment [3]. The levels of c-peptide in these patients is inversely related to left ventricular ejaculation fraction, which can be an adaptive mechanism to stress as in other acute conditions like trauma, post surgery or critical illness. In acute coronary syndrome C-peptide is a predictor of disturbance of glucose metabolism and is related to adverse outcome in these patients [4,5].

C-peptide is associated with the incidence of myocardial infarction and coronary artery disease in general population. It can be an early predictor of coronary events than impaired fasting glucose [6].

The various factors which may contribute to the development of cardiovascular diseases includes modifiable risk factors like unhealthy diet and life style along with various alternations in the biochemical parameters including lipid profile, lipoproteins etc. In addition to these, C-peptide has been found to play an important role as pro-inflammatory molecule in the development of cardiovascular diseases. Previous studies report that the endothelial dysfunction in patients with insulin resistance stimulates the deposition of C-peptide molecule in the vascular wall intima where this deposition favors accumulation of monocytes which trigger the process of atherosclerosis. C-peptide also plays a role in enhancing the process of atherosclerosis by promoting differentiation of macrophages into foam cells and proliferation of smooth muscle cells. It also increases the expression of CD36, an important scavenger receptor for macrophage uptake of oxidized low density lipoprotein in atherosclerotic lesion [7]. C-peptide induces infiltration of macrophages and CD4+ lymphocytes leading to release of kinases, Rho GTPases thereby increasing the accumulation of polymerized actin at the leading edge of cells [8]. In addition to this,high levels of C-peptide induce proliferation of smooth cells by 40% and phosphorylation of protein tyrosine kinase [9]. The proliferated smooth muscle cells migrate into the developing atheroma and recruit inflammatory cells leading to the loss of arterial elasticity, reduce arterial compliance and may subsequently leads to the coronary artery disease[9].

Basal C-peptide levels are also being significantly correlated with the intima media thickness of the carotid artery in type 2 diabetic patients, suggesting that it could be a surrogate marker of sub clinical atherosclerosis [10]. It is emerging as a molecule displaying potential beneficial effects on C-peptide mediated vascular injury. Thus, keeping in view the role of C-peptide in inflammation in various cardiac disorders the present study was planned to study the levels of C-peptide in the patients of various cardiac disorders and to find an association of C-peptide with other base line parameters in these patients.

MATERIALAND METHODS

The present study was conducted in the Department of Biochemistry, Government Medical College, Amritsar in collaboration with the Department of Medicine, Guru Nanak Dev Hospital, Amritsar for a period of one year from January 2018 to December 2018. The study comprised of 200 subjects in which 100 subjects were suffering from various cardiac disorders which were taken either from the emergency wards or admitted in the medicine wards of Guru Nanak Dev Hospital, Amritsar. One hundred age and sex matched apparently healthy asymptomatic individuals who accompanied the patients were enrolled to serve as controls. Both the controls and patients belonged to the age group of 30-65 years. A detailed history was taken and every case was thoroughly interviewed. Written informed consent was taken from all individuals. The study was conducted after taking approval from Institutional Ethics Committee, Government Medical College, Amritsar.

Inclusion criteria

The patients of various cardiac disorders who presented in the medicine outdoor and emergency wards were included in the present study.

Exclusion Criteria

Patients with thyroid disorders, acute renal complications, hepatic disorders, rheumatoid arthritis, rheumatic fever, acute infections, diabetes, pulmonary diseases and drug addicts were excluded from the present study.

All the subjects were investigated for Fasting Plasma Glucose by

GOD-POD Method as explained by Trinder [11] (1969), Glycosylated Hemoglobin by Ion Exchange Resin Method as described by Trivelli [12] (1971), Total Cholesterol based on Trinder's Method [13], Triglycerides by GPO Method, as described by Trinder [14] (1969), HDL-Cholesterol by Phosphotungstic Acid Method, as described by Burstein et al[15], LDL-Cholesterol [16] and VLDL-Cholesterol [17] were calculated by Frieldward formula. All these baseline parameters were done on ERBA EM 360 fully automated analyzer using system packs. Prior to performing the investigations, the machine was standardized using erba norm and erba path. C-peptide in serum was estimated by method based on direct solid phase enzyme immunoassay as described by Kuzuya H in 1977 [18] by using Lisa scan EM.

The data thus generated was analyzed statistically using student't' test for comparison of two groups and Pearson's correlation for finding the correlation between the levels of C-peptide and other parameters.

Observations:

All the individuals were classified according to their age and sex as Group 1 having individuals of 30-45 years, Group 2 including individuals of >45-60 years and Group 3 including individuals of >60 years. It was observed that maximum number of individuals belonged to the age group of >45-60 years which included both males and females. The number of male patients were more than the female patients in both cases and controls except for the age group of >60 years in controls where the number of females were more than males.

The Body Mass Index, Fasting plasma glucose and Glycosylated hemoglobin was compared amongst patients and controls. It was observed that Body Mass Index was increased significantly in male ($p<0.05$) patients as compared to controls. Fasting plasma glucose was increased significantly($p<0.001$) in patients of cardiac disorders as compared to controls. The levels of Glycosylated hemoglobin were significantly more ($p<0.001$) as compared to age and sex matched controls thus indicating that levels of fasting plasma glucose and glycosylated hemoglobin are in correlation with each other and though not significant, had a positive correlation ($r=0.38$, $p=0.76$) with Body Mass Index. Similarly, levels of lipid profile i.e. Total Cholesterol, Triglycerides, HDL-C, LDL-C and VLDL-C were segregated depending upon the gender of the patient. It was observed that except for HDL-C in controls, there was an insignificant variation in lipid profile in relation to gender of individuals. HDL-C was significantly increased in control females as compared to control males thus indicating that females have a protective effect of HDL-C as compared to males and reduction in the levels of HDL-C can be one probable parameter for the development of cardiac disorders (Table 1)

Table 1. Comparison of Baseline parameters of the patients and controls, both males and females.

S. No.	Group	Sex	BMI (Kg/m^2)	Fasting Plasma Glucose (mg/dl) (Mean ± SD)	Glycosylated Hemoglobin (%) (Mean ± SD)	Total Cholesterol (mg/dl) (Mean ± SD)	Triglycerides (mg/dl) (Mean ± SD)	High density lipoprotein (mg/dl) (Mean ± SD)	Low density lipoprotein (mg/dl) (Mean ± SD)	Very low density lipoprotein (mg/dl) (Mean ± SD)	Total Cholesterol :high density lipoprotein ratio	Low density lipoprotein : high density lipoprotein ratio
1.	Patients	Male	22 ± 3.2*	124 ± 44*	5.9 ± 1.5*	231 ± 15*	171 ± 12*	40 ± 5.2*	157 ± 17.6*	34 ± 2.4*	5.7*	3.9*
		Female	18.5 ± 3.7	129.6 ± 54.3*	6.4 ± 1.8*	232 ± 14*	174 ± 10*	38.3 ± 5.1**	159 ± 16*	34.8 ± 2.1*	6.1*	4.1*
2.	Controls	Male	20.9 ± 2.7	91.5 ± 10	4.8 ± 0.35	161.4 ± 5.2	131.3 ± 12.3	45.2 ± 2.8	89.9 ± 6.4	26.2 ± 2.4	3.5	1.9
		Female	18.2 ± 2.1	87 ± 8.7	4.6 ± 0.3	163 ± 7.2	128 ± 11	54.1 ± 3.0	83.6 ± 9	25.7 ± 2.3	3.0	1.5

*($p < 0.05$)when patients and controls were compared with each other
** ($p<0.001$) when patients and controls were compared with each other (using student t test)

Table 2. Comparison of C-peptide in the patients and controls.

S.No.	Group	C-peptide (ng/ml) (Mean ± SD)
1.	Patients	2.5 ± 2.1*
2.	Controls	0.92 ± 0.5

*($p<0.001$) when patients and controls were compared with each other. (Student t test)
Co-efficient of correlation (r) = + 0.42, $p<0.001$(Pearson's correlation)

C-peptide, a by-product of insulin molecule, secreted in equimolar quantities as insulin was estimated both in patients and controls. It was observed that the mean levels of C-peptide were significantly more in patients suffering from cardiac disorders as compared to controls. The difference in the mean values in patients and controls was statistically highly significant ($p<0.001$) thus indicating that insulin is being synthesized and secreted more in patients with cardiac disorders and the patients may have insulin resistance as well.

All the patients (n=100) suffering from cardiac disorders were classified according to their diagnosis on admission to Guru Nanak Dev Hospital, Amritsar. It was observed that maximum number of patients (32%) had Coronary Artery Disease (CAD) followed by Myocardial Infarction (MI) (28%), Angina Pectoris (15%), Acute Coronary Syndrome (ACS) (13%) and Heart Arrhythmias (12%).

Table 3. Comparison of C-peptide in patients of various cardiac disorders with controls.

S.No.	Cardiac Disorders	C-peptide (ng/ml) (Normal range 0.8-3.1 ng/ml) (Mean ± SD)	p value as compared to controls
1.	Coronary Artery Disease(CAD)	3.43 ± 1.72*	p<0.001
	Myocardial Infarction (MI)	2.67 ± 1.75*	p<0.001
	Heart Arrythmia	2.37 ± 0.55*	p<0.001
	Acute Coronary Syndrome (ACS)	2.27 ± 1.07*	p<0.001
	Angina Pectoris	0.59 ± 0.55	
2.	Controls	0.92 ± 0.5	

The levels of C-peptide were compared using student t test amongst the patients suffering from different cardiac disorders and it was observed that except for Angina Pectoris, the levels of C-peptide were significantly increased as compared to controls. The highest levels were observed in CAD followed by MI, Heart Arrhythmias and ACS thus indicating that C-peptide may have a role to play in the development of cardiac disorders. The base line parameters of the patients suffering from various cardiac disorders indicated significantly increased levels of LDL-C and VLDL-Cas compared to control subjects. The Total cholesterol to HDL-C ratio was significantly increased as compared to controls. Variations in BMI, glycemic status was not significant when compared amongst various cardiac disorders. Levels of total cholesterol and triglycerides though increased when compared to controls did not show any significant variations amongst various cardiac disorders. Levels of HDL-C were decreased significantly as compared to controls.

DISCUSSION

During the 2nd half of the century the prevalence of cardiac disorders has increased in India, particularly in the urban population. Though males are more prone to coronary artery disease, post menopausal females need special attention as they belong to high risk group. Indians have four times higher risk of coronary artery disease while Americans 6 times more than Chinese and 20 times more than Japanese. Indians are being affected about 1-5 years earlier than other communities. It is reported that in the age group of 45-60 years 25-40% Indians suffer from Coronary artery disease [19,20]. Similar results have been obtained in our study where the number of male patients in the age group of 45-60 years was maximum as compared to female patients in the same age group.

The ongoing urbanization of rural India has increased the risk factors important one being BMI which is associated with sedentary life style, increased consumption of calories, saturated fats, salt, tobacco and alcohol. All these factors contribute to obesity, dyslipidemia and hypertension. Central obesity depicted by waist hip ratio[21] is an independent risk factor for CAD and even the modest increase will lead to increased risk. Although the levels of fasting plasma glucose were increased in the patients as compared to controls, the levels are indicative of impaired fasting plasma glucose (as per American Diabetes Association), which is again a grey zone as is depicted by atherogenic changes leading to cardiac disorders. The prevalence of

diabetes mellitus in patients with CAD is about 20% in middle age and additional 20% may have impaired glucose. Even moderate elevation of glucose in Indians is associated with increased risk of CAD which also hold true for the present study.The levels of total cholesterol were increased significantly in patients as compared to controls. Even though the levels were within the defined normal range i.e. 140-250 mg% for the individuals for a given method, still Indians are at a higher risk of CAD because of genetic predisposition which leads to increased levels of lipoproteins-a which has been considered as independent risk factor for cardiac disorders. In Indian patients, high levels of triglycerides are found more often than high cholesterol levels [22] which are also depicted in the present study where triglycerides were significantly more in patients as compared to controls. Triglycerides bring about a change in LDL particle size, density, distribution and composition reducing them to smaller, denser and more atherogenic particles[23]. Estimation of triglyceride levels gives an indirect measure of particle size. An increase in levels from 90-180 mg% leads to double incidence of cardiac disorders [24]. A triad of high triglycerides with increased LDL-Cholesterol and low HDL-Cholesterol constitutes the deadly risk factor which was also observed in the present study. Ratio of Total Cholesterol to HDL-Cholesterol depicts the atherogenicity of lipid profile. In the present studythis ratio was found to be highly atherogenic as compared to normal individuals (5.86 versus 3.31). Usually Total Cholesterol to HDL-C and LDL-C to HDL-C ratio is used to predict ischemic/cardiac heart risk. The superiority of these two indices is not known, however the results of prospective studies[25,26] have shown that HDL-C to LDL-C ratio combined with hypertriglyceridemia is associated with highest risk of cardiac disorders. This lipidemic state has been described as atherogenic Dyslipidemia [27].

C-peptide is synthesized and secreted in equimolar concentration as insulin. It has proximate half-life of 30 minutes and is an accurate marker of insulin secretion and indicator of insulin resistance [28-30]. In individuals with increased c-peptide, increased BMR, hyperlipidemia, increased Total Cholesterol to HDL-C ratio has been reported as atherogenic metabolic disturbance which was also observed in the present study. It is thus proposed that ratio of Total Cholesterol to HDL-C along with parameters of insulin resistance i.e. insulin or c-peptide be taken into consideration in patients of cardiac disorders in addition to established conventional risk factors. In the last few decades, C-peptide has emerged as an active peptide which leads to induction of local inflammation. The deposition increases macrophage and CD4+ lymphocyte infiltration thus inducing chemotaxis [31,32]. In our study, elevated levels of C-peptide were observed in patients suffering from various cardiac disorders as compared to controls thus indicating its pro-inflammatory effects via various pathways mentioned above. The NHANES study clearly indicated that increased levels of C-peptide have 3.2-fold increased risk of deaths from cardiovascular disease. In our study, levels of C-peptide have a highly significant positive correlation ($r= +0.42$, $p< 0.001$) with fasting plasma glucose whereas there was no significant correlation with BMI. HDL-C had a significant negative correlation ($r= -0.060$, $p<0.05$) thus indicating that C-peptide levels are inversely correlated with HDL-C, thus depicting that increased levels of C-peptide decrease the cardio-protection offered by circulating HDL levels. This observation has been reported in some previous studies[33,34]. The presence of insulin resistance in patients of various cardiac disorders is an observation that the levels of C-peptide should be taken into consideration while monitoring these patients.

All the 100 patients included in the present study were classified according to their signs and symptoms into various cardiac disorders. It was observed that maximum number of patients have CAD, followed by MI, Angina, ACS and Heart Arrhythmia in our population. Baseline parameters indicated that BMI had a non-significant negative correlation with triglycerides and VLDL-C ($r= -0.028$, $r= -0.46$) respectively. It can be postulated that BMI has a correlation with development of disorders as has been postulated in various other studies[35]. An associated increase in levels of fasting plasma glucose was observed in patients of MI and CAD. BMI is associated with obesity which is an important modifiable risk factor rapidly becoming a major health problem. In our study, no correlation was observed in BMI and fasting plasma glucose however some previous studies have reported a positive correlation. Total lipid Profile was indicated by increased total cholesterol, triglycerides, LDL-C and VLDL-C as compared to controls with significantly reduced levels of HDL-C. The ratio of Total Cholesterol to HDL-C and LDL-C to HDL-C ratio was atherogenic. The highest atherogenicity was seen in patients with Heart arrhythmia, followed by CAD, MI, Angina pectoris and ACS. Evidence based on clinical, epidemiological and experimental studies have shown that increased levels of c-peptide are associated with cluster of cardiovascular risk factors such as hypertension, obesity, elevated triglycerides and reduced HDL-C levels [36]. It may also promote atherogenesis but the effect of serum C-peptide on HDL-C concentration is unclear. In the present study, the levels of C-peptide were increased in patients suffering from various cardiac disorders and there was a significant negative correlation between C-peptide and HDL-C.

Studies suggest that administration of C-peptide increases blood flow in several tissues improving endothelial dysfunction. This action may be mediated by nitrous oxide- sensitive vascular mechanism thereby maintaining the endothelial function[37, 38]. Under physiological conditions, excess nitrous oxide combines with superoxide anion to form peroxynitrite which rapidly reacts with tyrosine residue of the protein to form nitro-tyrosine which can induce the production of oxidized HDL thereby negating its antioxidative effect.

Experimental data suggests that C-peptide may play a role in the pathophysiology of atherosclerosis as it co-localizes monocytes, macrophages and T-cell in early atherosclerotic lesions. It induces cell migration thus suggesting C-peptide once deposited in the sub endothelial space may promote infiltration of inflammatory cells into the vessel walls thus contributing to early atherogenesis[39,40]. Thus, keeping in view the various studies and postulated mechanism of C-peptide in lowering HDL-C it can be hypothesized that increased levels of C-peptide are associated with cardiac disorders.

CONCLUSION:

The urbanization of rural India has increased the risk factor for CAD important one being change in Body Mass Index associated with sedentary life style, increased consumption of calories, saturated fats, salt, tobacco and alcohol. Along with obesity, these factors contribute to dyslipidemia and hypertension. Impaired fasting glucose along with the disturbance in the ratio of the lipoproteins and total cholesterol are used to predict the ischemic/cardiac heart risk combined with hypertriglyceridemia. This lipidemic state is known as atherogenic dyslipidemia. On association with this the increased levels of C-peptide which is indicative of Insulin resistance along with the role in pathophysiology of atherosclerosis becomes a marker for the atherogenesis. Once deposited in the sub-endothelial space it promotes the infiltration of inflammatory cells into the vessel wall. This contributes to early atherogenesis. Also, it has a negative correlation with HDL-C. It is hereby suggested that patients with IFG along with C-peptide so as to negate the development of atherosclerosis and other cardiac disorders.

Limitations of the study:

The author proposed that a longer sample size should be studied so the role of C-peptide can be authenticated in the development of cardiac disorders.

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