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ORIGINAL ARTICLE

Relationship between serum levels of Fibronectin, Leptin and hs-CRP with extension of Coronary Artery Disease

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ABSTRACT
Endothelial dysfunction ,obesity and inflamation are cooperative event involved in atherosclerosis development.In the present study the serum levels of Fibronectin, Leptin, hs-CRP and lipid profile were investigated in patients of Coronary Artery Disease with control group. In This study we messured serum leveles of Fibronectin, Leptin and hs-CRP on 180 person include 160 patient with CAD and 20 individaul as control group ,also patient with malignancy, renal and liver disease and other disease were exclude from the study. The seum levels of Fibronectin, Leptin and hs-CRP were increased significantly as compared to control group (p=<0.05 in all cases).There was strong(+)correlation between Fibronectin, Leptin and hs-CRP. It was concluded that endothelial dysfunction ,obesity and inflamation are cooperative event involved in atherosclerosis development.
***Key words**: Coronary artery disease, Fibronectin, leptin, hs-CRP*

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INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in developed countries [1] which results 7.2 million deaths per year in human society in the world (2). The disease is affected by factors like age, gender [3], diabetes, lipid profile, body mass index (BMI), oxidative stress, homeostasis disorder, metabolic syndrome, smoking and heredity [4].

Blood platelets, coagulation factors, endothelial cells, and fibrinolytic system play an important role in homeostasis [5], which its disruption makes body susceptible to CAD. Also, it is interesting to know that changing in endothelial cells phenotype and fibrinolytic system is more common than the other factor in atherosclerosis. [6,7]. Alteration in fibrinolytic systems, gene expression, response to growth factors, and size of Golgi apparatus and rough endothelium reticulum increase changes of endothelial cells phenotype [7,8]. Endothelial cells are the main source of Fibronectin [6]. Fibronectin is a high molecular weight glycoprotein presenting in body fluids and tissue`s extracellular matrix in soluble and insoluble forms respectively [8, 9]. It acts as a bridge between cells and collagen network and also involves in various processes such as cell growth, adhesion, migration and wound healing process [9].Increased expression of Fibronectin makes changes of muscle cell forms in intimae layer of atherosclerotic lesions [7].

Metabolic syndrome is one of the most important public health issues and its prevalence increases with diabetes and obesity [10]. Obesity is associated with adipose tissue inflammation and its progress stimulates adipose tissue to secrete Adipokines like Leptin, Adiponektin, and Resistin (11). obesity gene (ob) expresses Leptin as a 160 KD hydrophobic protein in adipose tissue [10]. Leptin receptor (OB-R) is belonged to thr first class of cytokine receptors and expressed by diabetes gene (12). It act through JAK/STATand AMPK signaling pathway [13]. OB-R is present in the surface of cells such as monocytes, atherosclerosis plaques, platelets, endothelial cells, neointima cells, and vascular smooth muscle cells (12,14). Leptin secretion is motivated by insulin and its concentratin is assosiated with obesity, BMI, and

Food intake. Leptin plays an important role in angiogenesis, osteogenesis, immune system, and pregnancy [15, 16]. It's majore roles in immune system includes macrophage differentiation and phagositosis, neutrophil chemotaxis, free radicals releasing by monocytes, activating NK cells, and MCP-1 production [12,13,17]. Leptin increases mitochondrial superoxidedismutase products, fatty acid oxidation, protein kinase A, and reactive oxygen species (ROS) (18). Increased ROS more than antioxidant capacity cause oxidative stress involving in CAD by damaging biomolecules likes lipids, proteins, and nucleic acids(19,20). ROS increases hs-CRP in endothelial cells by activating ERK 1/2 [21].

hs-CRP is a marker of CAD (22), increase susceptibility to atherosclerosis by 3 mechanisms:

1- Activating complement system and platelets by inducing cytokines in monocytes and ROS releasing .
2- Increasing vascular cell adhesion molecule-1 (VCAM-1), intra cellular adhesion molecule-1 (ICAM-1), and Monocyte chemoattractant protein-1 (MCP-1) expression.
3- Formation of foam cells (23).

This article discusses associatation betwen serum levels of Fibronectin, leptin, and hs-CRP with CAD that investigated in patients.

MATERIALS AND METHODS

Study population

The study investigated on 180 person by analytical descriptive method. The patients divided to 4 groups based on angiography results, first group with3 clogged arteries (n=40), second group with 2 clogged arteries (n=40), third group with 1 clogged arteries (n=40) and the forth group as patientswithout clogged arteries (n=40) (normal patient). The control group was healthy people with no sign of CAD, diabetes, hypertension, and hyperlipidemia (n=20). All of the volunteers were checked for the presence of disease such as, advanced liver disease, renal failure, autoimmune diseases, and other infectional diseases.

Data collection

After project description and satiafaction of volunteers ,10 mL venous blood was collected at 10 am after one night rest and fasting. Blood pressure was measured after 5 minutes in the prone position.

Normal and hypertensive subjects were divided into two groups based on blood pressure greater or less than 90/140 mmHg. Weight and height measured based on Kg and meter unite respectively.BMI was calculated by weight/height^2.

Laboratory method

Venous blood samples were centrifuged at speed of 2000 RPM for 10 minutes and then freeze at-80 until testing. Serum leptin and Fibronectin were measured by ELISA method using kits from German Imediagnostic and Chinese Crystal Day companies respectively. Moreover, hs-CRP measured by Immunoturbidimetry method using Spanish Biosystem kit. Fasting blood sugar, cholesterol, and TG, measured by enzymatic methods, and LDL and HDL, by sedimentary methods, using Pars Azmoon kits running on Hitachi/912.

Analytical methods

Conventional methods were used for the Calculation of means, standard errors of the mean and standard deviation. The significance of difference between variables of the patient and control group was determined by the student-t test, Anova/Tukey test. For correlation analysis, Pearson correlations were used. P- Values equal to or less than 0.05 were considered significant.

RESULTS

Table 1 show profile of study population. There was no significant different in the mean age and sex between the control and patients group. Also there was significant different in the Family History between the control and patients group.

Table 1: Baseline characteristics of subject with CAD and control group.

Characteristic	Control	Normal	1VD	2VD	3VD	P.value
Number	20	40	40	40	40	
Age Mean ± SD Range	57±5	59±1	59±1	60±2	60.5±2	0.7
Gender Male Female	 17 3	 19 21	 25 15	 29 11	 28 12	 0.1*
HT%	0	64.1	62.5	59	34.2	0.00*
FH%	0	20.5	34.3	30	26.31	0.05*
Smoker	0	19	20	24	16	0.02*

*P<0.05; HT= hypertension, FH = Family history1VD=1 Vessel disease, 2VD=double vessels disease, 3VD=3 vessels disease.

The results of serum Fibronectin analysis are shown in Table 2. As the table shows,mean serum Fibronectin levels in patients were significantly higher than the control group (p< 0.05).In patient`s groups, patients with 3-clogged arteries and mean serum levels of Fibronectin significantly higher than the normal, 1-clogged artery, and 2-clogged artery groups. As the table shows, the difference of mean levels among 1-clogged vessels and 2- clogged and also between 2- clogged and 3-clogged Arteries are significant (p<0.05).

Table 2: Serum Fibronectin Level in patient with Coronary Artery Disease and control Group

Group	N	Fibronectin (mg/mL) (X ±SD)
Control	20	259.03±27.07**+
Normal	40	268.85±24.65*
1 VD	40	257.54±33.36**
2 VD	40	275±22.33**
3 VD	40	303.93±27.27**
All patients	160	276.33±26.90 +

*P=0.00; (3 VD-control, normal, 1VD), According to Anova/Tukey test; **p=<0.01; (1VD -2VD) ;(3VD-2VD); According to Anova/Tukey test; + p=<0.05; (All patient-control); According to student t test.1VD=1 Vessel disease, 2VD=double vessels disease, 3VD=3 vessels disease.

Table 3 indicates the results of leptin and hs-CRP serum levels and BMI among patients and control gropups. Mean levels of serum leptin in CAD patients is significantly higher than healthy people as control group (p<0.05). As the table shows, there is significant difference between serum levels of leptin in patients who have 3-clogged arteries and other patients (p=0.00). In the other side, the table shows that this difference is not significant among patients with 2-clogged and 1-clogged vessels. Also, there is no significant difference of BMI between all of the patient`s and control groups.
Mean hs-CRP levels between serum of patients and control groups are significantly different, as shown in table 3 (p<0.05). In patients groups, levels of serum hs-CRP in 2-clogged artery group is higher than the others (p<0.05). The table 3 also shows that there is significant difference between normal and other patients groups, in terms of hs-CRP levels in serum (p=0.00), whereas there is no significant difference between groups with three-clogged and one-clogged arteries.

Table 3: Serum Leptin, BMI, hs-CRP Levels in patient with Coronary Artery Disease and control Group

Group	N	Leptin(ng/mL)(X±SD)	Hs-CRP (mg/mL)(X±SD)	Body Mass Index(kg/mL)(X±SD)
Control	20	2.57±0.067*+	2.85±0.47** #	24.50±0.74
Normal	40	4.86±2.26*	2.28±1.94 **	23.60±1.09
1 VD	40	5.60±1.92 *	5.41±0.80 **	23.35±1.67
2 VD	40	7.17±1.43 *	8.37±1.66 **	24.04±1.87
3VD	40	17.45±2.49 *	5.21±1.20 **	23.40± 1.95
All patients	160	8.7±2 +	5.31 ± 2.79 #	23.59± 1.64

*P=0.00; (3VD-control, Normal , 1VD , 2VD), according to Anova/Tukey test; + p=<0.05; (All patient-control) According to student t test ;** p=0.00; (normal-1VD, 2VD , 3VD); (1VD – 2VDl, control); (2VD-control, 3VD); According to Anova/Tukey test; # p=<0.05 ; (All patient-control) According to student t test; 1VD=1 Vessel disease ,2VD=double vessels disease, 3VD=3 vessels disease.

Table 4 shows the levels of serum cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol in control and patients groups. As the table indicates, Mean serum levels of triglycerides in the patient groups is significantly higher than the control group (p<0.05).

Table 4. Serum Total Cholesterol, Triglyceride, HDL and LDL Cholesterol Levels in Patients with Coronary Artery Disease and Control Group

Group	N	Total Cholesterol (mg/dL)(X±SD)	Triglyceride (mg/dL)(X±SD)	HDL_C (mg/dL)(X±SD)	LDL_C (mg/dL)(X±SD)
Control	20	183.5±10.7	132±14.5*	37±1.1**	120±11.5
N vessel	40	177.5± 8.5	174±12.5	34±1.2	109±7.5
1 VD	40	203±8.5	203.5±11.2	34±1.1	128±7.7
2 VD	40	188.5±11	177±14.5	32±1.5	122±8.6
3 VD	40	199.5±12	175±14.5	34±1.4	127±10.7
All patients	160	191.5±5.2	181.5±6.7*	33.5±0.6**	122.5±4.5

*p=0.01; (All patients-Control);**p=0.04; (All patients-Control); According to Student t test; p=0.01; (1VD-Control); According to Anova/Tukey test;
HDL: high-density lipoprotein; LDL: low-density lipoprotein.
1VD=1 Vessel disease ,2VD=double vessels disease, 3VD=3 vessels disease.

Table 5 shows serum levels of Fibronectin, Leptin and hs-CRP in smoker/non smokers and hypertensive /non hypertensive patient. The average Fibronectin level in smoker is higher than non smoker but there were no statically significant difference (P>0.05). Also, there were no significant difference in serum level of Fibronectin, Leptin and hs-CRP between hypertensive and no hypertensive patient.

Table -5 Serum Fibronectin, Leptin and hs-CRP levels in Hypertensive/No hypertensive and Smokers/Non smoker's patient.

Group	N	Fibronectin (mg/mL)(X±SD)	Leptin (ng/mL)(X±SD)	Hs-CRP (mg/mL)(X±SD)
Hypertension(+)	76	276.90±31.8	10.07±7.2	5.71±6.68
Hypertension(-)	104	278.03±41.45	8.46±7.6	5.81±6.11
Smoker	72	281.38±4.35	7.84±5.02	6.23±0.65
Non Smoker	108	274.46±30.60	10.23±8.7	5.38±0.62

Table 6 indicates the Pearson correlation results of Fibronectin, Leptin, hs-CRP, BMI and lipid profile .It found positive significant correlation between BMI and hs-CRP (P=<0.05) .This correlation is strongly significant (+) between BMI and Leptin (P=0.00) and on the other hand, there was strong (+) correlation between Leptin and Fibronectin (P=0.00)

Table -6: Pearson correlation Results in patient with Coronary Artery Disease

	CHOL	TG	HDL	LDL	Leptin	BMI	Hs-CRP	Fibronectin
CHOL	1	.782*	-.604*	.981*	.158	-.041	-.031	-.034
TG		1	-.552*	.663*	.044	-.145	.016	-.081
HDL			1	-.645*	-.082	.016	.051	.143
LDL				1	.175	-.010	-.043	-.035
Leptin					1	.377*	.219**	.380*
BMI						1	.265**	.121
Hs-CRP							1	.037
Fibronectin								1

*p=<0.001, **p=<0.05
HDL: high-density lipoprotein; LDL: low-density lipoprotein.

DISCUSSION

Coronary artery disease (CAD) is one of the biggest causes of death worldwide [24]. It is believed that the disease is an ongoing and continuing process which causes tissue damage and heart failure [25]. The Heart Disease risk factors include lipid profile, obesity, changes in homeostasis, oxidative stress, and etc [16]. Fibronectin (FN) gene expression is distinctly associated with vascular smooth muscle cell and Leptin affected the expression by ERK1/2. ERK ½ is a MAP kinase with 42 up to 44 KD molecular weight which its activation is one of the major pathways in regulating proliferation of the vascular smooth muscle cells. FN participates in the processes which changes form of vascular smooth muscle cells during atherosclerosis and cause accumulation of cells [8, 14, and 26]. FN with fibrinogen/fibrin can contribute to the growth and sustainability of thrombosis. Cross connection of FN to fibrin is established by FXIII which increase platelet adhesion and thrombus development as well as atherosclerosis [26]. Several studies found a positive association between the expression of Fibronectin and atherosclerosis. Hakan Ekmeci et al showed that the mean plasma Fibronectin levels in patients with atherosclerosis was significantly higher than healthy people [27]. Another study by Wanger revealed that reduction of plasma Fibronectin delays extension of thrombosis in arterial trauma [28]. This study approved the positive assossiation between FN level in serum and atherosclerosis progression and moreover showed FN level in serum increased by developing of atherosclerosis. As the table 2 Shows, serum levels of FN in CAD patients are higher than control group. In addition, in patients with 3 clogged arteries FN levels in serum is higher than the other patients groups. Taken together, these data indicate that FN expression is closely associated with development of CAD.

Obesity and high BMI is one of the biggest risk factors for heart disease. Adipose tissue secrets different adipokines which understanding their influence on development of CAD could help us to control the disease.

Leptin is an Adipokine with 167 amino acid residues that it`s gene is obesity (ob) gene in adipose tissue. Leptin secretion affects hypothalamus to reduce food intake and also modulates carbohydrate and lipid metabolism to increase energy consumption [29]. Serum levels of Leptin are highly related to BMI, diabetes, and genetic disorders which is variable by dietary changes [13, 14]. Based on the data obtained from animal and human studies, hyperleptinemia is associated with increased mortality in CAD. Increased serum leptin levels in humans are associated with atherosclerosis, obesity, myocardial infarction, insulin resistance, inflammation, and homeostasis disruption. Leptin increases the production of MCP-1 and SOD products in aorta endothelial cells. Therefore, it plays an important role in the recruitment of macrophages, the formation and development of atherosclerotic plaque [13]. According to recent reports, Leptin play a major role in the development of atherosclerotic lesions .SelcukGormez et al reported that leptin gene expression in subcutaneous, Epicardial, and pericardial adipose tissue in CAD disease is significantly higher than other people [10]. Maureen and colleagues stated in their study that high leptin levels could help identify SLE disease associated with atherosclerosis. They reported significant high serum leptin levels in patients with both SLE and CAD componet to whith CAD patients alone [30]. In the USA, Virend et al reported that MI patients have high serum level of Leptin compared to control group [31]. Wolfgang Koenig [32], Hakan Emekci [27], Robert Wolk [33], and Johan than [34] reported Leptin as CAD development novel marker. As the table 3 Shows, serum levels of leptin in CAD patients are higher than control group. In addition, in patients with three clogged arteries leptin levels in serum is higher than other patients groups. According to this data, two hypotheses can be concluded; first, there is a positive association between CAD disease and serum levels of Leptin, and second, serum levels of Leptin increases with development of atherosclerosis.

Hs-CRP gene expression increases by Leptin secretion [21]. CRP is an acute phase protein and a risk factor of CAD [35]. CRP is a major mediator in the development of atherosclerosis because of its localization and roles in complement system activation, cell adhesion, and thrombosis. Several reports describe causal role of hs-CRP in atherosclerosis [35]. Prof. S. B. Sharma during his study in India, observed a positive relationship between hs-CRP and CAD disease among young people [20]. Virend K. Somers achieved two important results during his studies; first, leptin increases expression of CRP in vascular endothelial cells, and second, apparent increase in hs-CRP expression occurs when Leptin concentrations is greater than 30ng/ml. Also, he stated that leptin increases CRP production with enhancement of ROS production and ERK ½ phosphorylation [21]. Shamsuzzaman [36] and Ble A [37] reported positive correlation between serum levels of leptin and CRP. As our results indicates in table 3, hs-CRP increases in CAD patients in compare with healthy people and this increase associated positively with development of CAD. Therefore, it can be concluded that hs-CRP level increase in serum could be a marker of disease development.

CONCLUSION

It was concluded that endothelial dysfunction ,obesity and inflamation are cooperative event involved in atherosclerosis development.Fibronectine, Leptin and hs-CRP have become greatly importatnt in pathogenesis of Coronary Artery Disease and association between Fibronectin, Leptin, inflamation marker and lipid profile sugest that their involvement in atherosclerosis development.

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