Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 9 (4): 214-218
15th May, 2009

Leptin, Insulin and Glucose Levels in Menopause Women During Acute Myocardial Infarction

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The purpose of this study was to measure leptin, glucose and insulin concentration in the blood of patients during ST elevation acute myocardial infarction and to compare them with values obtained from normal subjects. Leptin concentration was measured in 31 menopause Jordanian women patients (50-72 years of age) with acute myocardial infarction and 19 normal menopause women (49-64 years of age). Leptin concentration were measured using two sites immunoradiometric assay (IRMA) principle. In normal (N = 19) leptin concentration was 15.5±5.4 ng mL^{-1} (Mean±SD). While, in patients with acute myocardial infarction was 22.9±5.7 ng mL^{-1} (Mean±SD). Data showed significant difference in both groups (p = 0.000). In addition insulin concentrations were significantly increased in patients with acute myocardial infarction (74.2±10.8 vs. 38.8±14.5 pmol L^{-1}, p = 0.000) compared to the control group. Glucose concentrations were lower in patients with acute myocardial infarction (107.5±7.2 vs. 166.9±11.7 mg dL^{-1}, p = 0.000) compared to the normal group. Also, both total cholesterol and triglyceride were significantly higher in patients with acute myocardial infarction compared to the control group. It was comcluded that leptin, insulin, cholesterol and triglyceride concentrations were significantly higher and glucose level was significantly lower in patients with acute ST elevation myocardial infarction compared to normal group.

Key words: Menopause women, leptin, insulin, myocardial infarction

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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INTRODUCTION

Leptin is a 16 KDa protein produced by obesity gene, first implicated in the regulation of metabolism and food intake (Zhang *et al*., 1994). Circulating leptin concentrations are proportional to the degree of obesity which is a risk factor for cardiovascular diseases such as hypertension and atherosclerosis (Soderberg *et al*., 1999; Considine *et al*., 1996; Wallace *et al*., 2001). Leptin is also produced in addition to the adipose tissue by heart, vascular smooth muscle, placental tissue, digestive epithelia and gastric mucosa (Purdham *et al*., 2004; Zeidan *et al*., 2005; Masuzaki *et al*., 1997; Sobani *et al*., 2000). Vascular function of leptin is controversial; some studies indicate that leptin is a Nitric Oxide (NO) dependent vasodilator in various non coronary vascular beds (Kimura *et al*., 2000; Lembo *et al*., 2000; Jaffar *et al*., 2005; Mohammed *et al*., 2007) where as others showed that it exerts NO-independent vasodilatation (Nakagawa *et al*., 2002). Other studies have shown that leptin decreases arterial distensibility (Singhal *et al*., 2002). Leptin is also involved in many atherogenic process common to pathogenesis of cardiovascular disease, including platelate aggregation and thrombosis (Corsonello *et al*., 2003; Konstantinides *et al*., 2001a,b). In addition leptin cause cardiac hypertrophic effect (Karmazyn *et al*., 2007; Chris and Pemberton, 2008).

Atherosclerosis is one of the known high risks in cardiovascular disease and mortality. Peelmana *et al*. (2004) identified high expression levels of leptin receptors in atherosclerosis lesions. Leptin induces direct endothelial cell migration (Park *et al*., 2001; Matsuda *et al*., 2003) and since atherosclerosis is caused by abnormalities in endothelial function, this action of leptin could explain it's proatherogenic effect.

Knudson *et al*. (2005) found leptin receptors in coronary arteries and concluded that hyperleptinemia was responsible for significant coronary endothelial dysfunction. In addition hyperleptinemia was found to be a strong predictor of acute myocardial infarction (Soderberg *et al*., 1999). Other studies documented that the plasma leptin concentration elevated during acute myocardial infarction (Soderberg *et al*., 1999; Jose *et al*., 2005). Many others reported hyperglycemia as an important predictor of adverse outcomes associated with acute myocardial infarction (Yydkin and Oswald, 1987; Bellodi *et al*., 1989; O'Sullivan *et al*., 1991; Wong *et al*., 2004b; Hadjadi *et al*., 2004; Ceriello, 2005).

With all these findings regarding the different effects of leptin on cardiovascular system, mainly on development of coronary artery disease and the consequence of hyperglycemia during acute myocardial infarction. This study was planned to examine leptin hormone, glucose and insulin concentrations during acute myocardial infarction in menopause women. Also, we looked at the level of serum Total Cholesterol (TC) and Triglyceride (TG). All these values were compared with the values obtained from control group without coronary arteries disease.

MATERIALS AND METHODS

This study was done in Department of Physiology, Jordan University of Science and Technology, Irbid, Jordan, Department of Medicine, Princess Basma Teaching Hospital, Irbid, Jordan and Department of Cardiology, King Hussain Medical Center, Amman, Jordan. The study was carried out from January 2006 to March 2007.

The study group consisted of thirty one female patients aged from 50 to 72 (mean, 58.5 SD+5.5) years with acute ST Elevation Myocardial Infarction (STEMI) and with elevated serum creatin kinase who were admitted to the Department of Cardiology, Coronary Care Unit in Queen Alia Heart institute and Princes Basma teaching Hospital. Patients with valvular heart disease, congenital heart disease, diabetes mellitus, hypertension and congestive heart disease were excluded from the study. Also, patients with hepatic, renal and thyroid diseases were also excluded from the study.

Nineteen normal volunteer female subjects aged from 49 to 64 (Mean, 56.9; SD±4.5) years without history of chest pain, coronary artery disease (CAD), ECG changes, hypertension, or diabetes were included in this study and this group was designated as normal control group.

Informed consents were obtained from all patients and volunteers who participated in this study The base line characteristics of patients such as age, blood pressure and Body Mass Index (BMI) were recorded.

Analysis of blood samples: Blood samples were withdrawn after 14 h of fasting from all patients with STEMI within 24 h from the time of admission to the coronary care unit. Also, blood samples from normal volunteer subjects taken after 14 h fasting. Blood samples for determination of leptin and insulin were frozen at -70°C until analysis.

Leptin concentrations were measured using two sites immunoradiometric assay (IRMA) principle. All kits were purchased from.

The insulin concentration was measured using electrochemiluminescence immunoassay (ECLIA).

Statistical analysis: All results are shown as Mean±SD. Statistical analysis of the data was carried out using one-

way ANOVA and unpaired student t-test for inter-groups analyses. p-values less than 0.05 were taken as being significant.

RESULTS AND DISCUSSION

General characteristics of all participants in this study are shown in Table 1. There are no significant differences between age, BMI and systolic and diastolic blood pressure. Table 1 shows that menopausal women had significant higher level of plasma total cholesterol ($p<0.005$) and triglyceride ($p<0.05$). Also, patient group had significant higher level of serum leptin, glucose and insulin ($p<0.0005$).

We studied the relationship between serum level of leptin, glucose, insulin, total cholesterol and triglyceride in female patients with acute myocardial infarction and compared them with their levels in normal subjects. During AMI there were significant increases in serum levels of leptin, glucose, total cholesterol and triglyceride compared with normal subjects, but insuline level in AMI was less than in normal group. No significant differences were detected in age, SBP, DBP and BMI with AMI and normal subjects (Table 1). Increased level of leptin in patients with AMI was reported by many other studies (Jose *et al*., 2005; Soderberg *et al*., 1999; Yydkin and Oswald, 1987; Meisel *et al*., 2001; Tamer *et al*., 2002; Taneli, 2006). Also, the increased level of glucose in AMI patients was shown by other study (Yydkin and Oswald, 1987; Bollodi *et al*., 1989; O'Sullivan *et al*., 1991; Wong *et al*., 2004a; Hadjadj *et al*., 2004; Ceriello, 2005). An evidence suggests hat myocardial infarction is associated with local and systemic inflammation (Mulvihill and Foley, 2002). This inflammatory effect could contribute to increase C-reactive protein from the liver which is also reported by Wong *et al*. (2004a) and C-reactive protein may act directly on fat cells to increase leptin secretion in patients with acute myocardial infarction (Grunfeld *et al*., 1996; Kirchgessner *et al*., 1997; Janik *et al*., 1997). Hyperliptenemia increases stimulation of the sympathetic system to increase catecholamine (Haynes *et al*., 1997).

Table 1: Clinical and demographic data of normal subjects and patients

Parameters	Control (n = 19)	PT AMI n (31)	p-value
Age (year)	56.9+4.5	58.5+5.5	NS
BMI (kg m^{-2})	30.4+2.2	30.2+1.7	NS
SBP (mmHg)	130.5+9.9	126.3+11.8	NS
DBP (mmHg)	78.4+7.3	79.7+7.4	NS
Total cholesterol (mg dL^{-1})	208+20.7	226.8+24.5	0.003
Triglyceride (mg dL^{-1})	194.1+16.9	206.8+15.9	0.010
Leptin (ng mL^{-1})	15.5+5.4	22.9+5.7	0.0001
Glucose (mg dL^{-1})	107.5+7.2	166.9+11.7	0.0001
Insulin (pmol L^{-1})	74.2+10.8	38.8+14.5	0.0001

NS: Non significant, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, All values are expressed as Mean±SD

Several factors can explain leptin ability to increase the cardiovascular risk; leptin stimulates vascular smooth cell proliferation (Oda *et al*., 2001), accelerates vascular calcification (Parhami *et al*., 2001), induces oxidative stress in endothelial cells that may contribute to atherogenesis (Yamagishi *et al*., 2001) and promotes coagulation by increasing platelet adhesiveness (Konstantindes *et al*., 2001a).

Hyperglycemia often occurs in the acute phase of myocardial infarction but there is a controversy about the meaning of this hyperglycemia whether it is a temporary manifestation or precipitation of latent diabetes. This hyperglycemia that developed during acute myocardial infarction could be due to elevated serum catecholamines from hyperleptinemia during AMI as explained above and/or the effect of stress during AMI result of sympathetic stimulation which could develop by the effect of fear and pain, hypoxia and hypotension or local cardiac damage at the infarcting myocardium. It is reported by Matsumura *et al*. (2000) that intracerebroventricular leptin infusion acts in the central nervous system and activates sysmpathoadrenal outflow, resulting in increases in arterial pressure and plasma glucose levels in conscious rabbit. In addition catecholamines inhibit insulin secretion from cells of pancreas and hence there is decreased peripheral utilization of plasma glucose by muscle and adipose tissue (Sundaram and Moses, 1995). Goyal *et al*. (2006) reported that higher plasma glucose levels after acute myocardial infarction predicted higher mortality in non diabetic patients, which is not surprising as glucose is pro-inflammatory and insulin has anti-inflammatory actions. In addition to its pro-inflammatory effects, it may also directly contribute to the pathogenesis of AMI by promoting thrombosis (Goyal *et al*., 2006).

Comparing total cholesterol and trigyleceride in AMI patients with those of normal subjects, results showed significant difference between patients and normal subjects as shown in Table 1. These high serum level of cholesterol and high triglyceride are well known atherogentic risk factors for development of myocardial ischemia and myocardial infarction.

CONCLUSION

Our observations strongly indicate that serum leptin and glucose levels in menopause women are elevated in acute ST elevation myocardial infarction, while insulin is decreased during AMI in menopause patients. These changes could develop because of the effect of high level of catecholeamine during acute myocardial infarction and also due to increased C-reactive protein which is increases by the inflammatory process that develops

during acute myocardial infarction. Also, during AMI total cholesetrol and triglyceride were significantly higher than in normal women and this could explain the significance of these lipids changes in the development of atherosclerosis in menopause women.

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