Research Article

Association between serum leptin level and acute myocardial infarction

Adeeb Jader Hussein, FICMS ; Dhyaa Jabbar Kadhim, M.Sc.

Date Submitted:8-10-2012

Date Accepted:5-4-2013

Address for Correspondence:
Adeeb Jader Hussein
Al-yarmouk teaching hospital , Baghdad, Iraq.

Abstract

Objective: To assess the relationship between serum leptin level and acute myocardial infarction in patients who received thrombolytic therapy.

Methods: Fifty patients with acute myocardial infarction (mean age:58.16±11.73 years)at first 12 hours of admission and thirty four normal control group (mean age: 53.98±15.46 years) matched for age ,sex and other risk factors were enrolled in this study, serum level of cardiac troponin I was measured in patients and control group(mainly for diagnostic purpose),two readings were obtained for the patients(one at admission and 6-9 hours later).The patients were followed up clinically during entire hospitalization period to assess patients response to thrombolytic therapy as well as for the development of any complication, Serum level of leptin also measured in the first 12hour in both groups.

Results: The study showed that serum leptin level in patients with acute myocardial infarction(mean 10.03ng /ml) was significantly higher than that of control group (mean 6.97ng/ml), p value <0.0001.

Conclusion: The present study showed that higher serum level of leptin was associated with occurrence of myocardial infarction as etiological factor or sequel.

Keywords: leptin, acute myocardial infarction, risk factor

INTRODUCTION

Leptin, an adipose tissue-derived hormone that is involved in body weight regulation and insulin homeostasis, has been implicated in contributing to a raised risk of myocardial infarction (MI) and stroke in patients with and without known coronary artery disease.[1-5] The major action of leptin was on hypothalamus to control body weight and fat deposition through its effect on hypothalamic receptor which leads to appetite inhibition as well as stimulation of metabolic rate and thermogenesis.[6,7] Thus increase leptin level would be expected to decrease weight ,more recently leptin has been shown to have a variety of central and peripheral action to regulate energy balance ,fertility and bone metabolism.[8,9]

High levels of leptin are believed to be associated with lower arterial distensibility and involved in pathogensis of atherosclerotic process through mechanism other than vascular relaxation,[10] it promote angiogenesis ,regulate osteoblastic differentiation , enhance calcification of vascular cells and potentiate the pro thrombotic platelet aggregation.[11,12,13]

An association between serum leptin concentration and various cardiovascular manifestations including stroke,[14] chronic heart failure,[15,16] acute myocardail infarction,[17] coronary heart disease,[18] and left ventricular hypertrophy [19] has been observed. Several mechanisms has been proposed about leptin role in inducing cardiovascular disorders, one of these mechanisms related to effect of leptin on endothelial cells, it impairs nitric oxide

dependent vasorelaxation induced by acetylcholine both in vitro and in vivo[20] These novel findings suggest hyperleptinemia as a potential mechanism by which obesity and metabolic syndrome leads to significant coronary dysfunction and potentially coronary heart disease. Other mechanism related to pro inflammatory effects of leptin. Leptin potentiates secretion of tumor necrosis factor and interleukin 2 and 6,[21] increase generation and accumulation of reactive oxygen species.[22] Physiological concentration of leptin stimulate expression of C-reactive protein in primary human hepatocyte.[23] Thus, the ability of leptin to promote pro inflammatory signaling through cytokines and growth factors may contribute to endothelial dysfunction and atherosclerosis in hyperleptinemic states.

PATIENTS AND METHODS

The present study was carried out at Al-Yarmouk teaching hospital from December 2011 until June 2012.This case control study was conducted on fifty patients who were treated for acute myocardial infarction with the following inclusion criteria

1) First experience of acute M.I. 2) A maximum of 12hr between onset of symptoms and initiation of thrombolytic therapy (alteplase). The diagnosis of myocardial infarction was made on the basis of detection of a rise and /or fall of cardiac biomarker values {preferably cardiac troponin (cTc) and at least one of the following: 1) symptoms of ischemia, 2) New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block, 3) Development of pathological Q waves in the ECG.

All patients in the study were treated by standard therapy for acute MI. 34 subjects were selected as a control group compared to cases regarding age, sex, and other coronary heart disease risk factors such as hypertension, diabetes mellitus, body mass index, smoking and renal function.

Sample collection and preparation

Blood samples were collected from all patients by venipuncture (5ml) to measure study parameters which include lipid profile, uric acid, blood urea, serum creatinine, cardiac Troponin and serum leptin. The sample was transferred into clean plain tube, left at room temperature for at least 30 minutes for clotting, centrifuged, then serum separated and stored to be used for measuring the studied parameters. Serum leptin level was determined by using a ready-made kit for this purpose. The RaY Bio R human leptin Elisa kit (USA) is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human leptin in serum, plasma, cell culture supernatants and urine.

Statistical analysis

Statistical analysis was performed by SPSS (VERSION 11; SPSS, Inc, Chicago, IL). Nominal variables are compared using chi-square test .Continuous variables were summarized as mean±standard deviation (SD). Continuous variable are tested for normality using Shapiro Wilk test. Normally distributed variables are compared using t-test. Non-normally distributed variables are compared using Mann-Whitney U test. Pearsons correlations were performed to evaluate the relationship between leptin and other selected clinical variables among patients with acute MI.

RESULTS

Demographic, clinical characteristics and baseline laboratory variables of the study groups show significant difference regarding smoking and diabetes mellitus with no significant difference regarding BMI, hypertension and other laboratory variables.

Table 1: Demographic, clinical characteristics and baseline laboratory variables of the study groups.

	patients	control	P* value
Number of patients	50	34	
Male/female	41/9	25/9	0.35a
Age (year)	58.16±11.2	53.98±15.46	0.16b
BMI(kg/m^2)	28.05±4.27	27.89±3.50	0.96c
Diabetes	15	4	0.049a
Hypertension	18	12	0.96a
Smokign	26	8	0.009a
S.uric acid mg	4.94±1.32	5.12±1.24	0.37c
S.creatinine(mg/dl)	0.91±0.31	0.85±0.28	0.37c
S.urea (mg/dl)	39.12±11.16	37.20±8.06	0.67 c
s. Total cholesterol (mg/dl)	199.62±41.09	189.26±28.35	0.09c
S.HDL-c (mg/dl)	41.03±4.79	43.17±10.56	0.36c

BMI: body mass index, S.HDL-c; serum high density lipoprotein cholesterols, a: chi-squared test, b: t. test, c: Mann-Whitney U test. (p* value < 0.05 considered significant).

Results presented in table 2 showed that serum leptin level in patients with acute MI on admission were significantly higher than those in the control group (10.03±1.08ng/ml vs 6.97±0.86ng/ml respectively) p<0.0001.

Table2: Serum leptin level in acute MI patients compared to control

	Patients n=50	Control n=34	P value
Serum leptin ng/ml	10.03±1.08	6.97±0.86	P<0.0001 **

Values are presented as mean±SD, n=number of patient. ** Highly significant difference (p<0.0001)

Studying the association between admission serum leptin level and selected clinical variables among patients with acute MI (diabetes, hypertension, sex, etc...) revealed no significant differences.

Table 3 admission serum leptin and selected clinical variables

mean+SD	Leptin level(ng/ml Cut off level		P*value
	Yes	No	
Diabetes	9.82±1.o5(n=15)	10.13±1.09(n=35)	0.35
Hypertension	9.95±0.96(n=18)	10.08±1.14(n=32)	0.77
Male gender	10.03±1.13(n=41male)	10.07±0.85(n=9fema	0.91
AnteriorMI	10.09±1.12(n=31)	9.94±1.02(n=19)	0.62
Development of HF	9.87±0.65(n=9)	10.07±1.15(n=41)	0.62
Development of AF	10.50±1.06(n=6)	10.04±1.04(n=44)	0.31
Development of VT or VF	10.28±1.02(n=5)	10.07±1.06(n=45)	0.68
Successful reperfusion	10.02±1.10(n=12)	10.04±1.08(n=38)	0.96

Values are presented as mean ±SD, n- number of patients, HF = heart failure, AF=atrial fibrillation, VT= ventricular tachycardia, VF=ventricular fibrillation* P value > 0. 05 considered significant.

Studying the correlation between admission serum leptin and selected demographic and laboratory variables (age, BMI, uric acid, s. creatinine etc...) revealed no significant correlation between leptin level and all these variables as shown in table 4.

Table 4: admission serum leptin and selected demographic and laboratory variables.

		Correlation coefficient Serum leptin ng/ml	P* value
1	Age	0.026	0.858
2	Body mass index	-0.011	0.938
3	S.Uric acid	-0.089	0.540
4	S.creatinine	0.137	0.341
5	S.urea	0.073	0.614
6	S.Total cholesterol	-0.003	0.982
7	S.HDL-c	0.012	0.935
8	S.cardiac TnI	-0.185	0.199

*P value>0.05 considered significant

DISCUSSION

The current study showed that serum leptin level was significantly increased in patients with acute myocardial infarction when compared with control, these results are in agreement with similar studies done on patients with acute MI,[27-29] in one of these studies , JOSE VJ et al tested 94 patient presented with acute MI and 46 control subjects. The serum leptin level in patients with acute MI, was (6.51ng/ml) versus (2.86 ng/ml) in control subjcts (28).In another study serum leptin level was measured in 40 patients with acute MI and 30 control subjects, serum leptin level was significantly higher in patients with acute STEMI compared to control group (8.22ng/ml) versus (6.37ng/ml) respectively.[30] Wallander M et al in a case control study demonstrated that compared with control subjects, patients of both genders had significantly higher leptin levels 2 days after myocardial infarction.[25]These levels were higher than those obtained at hospital discharge and at 3 month of follow-up. They also concluded that elevated circulating levels of leptin on first morning after an acute MI were associated with abnormal glucose tolerance at discharge and with poorer long-term prognosis. Elevated plasma leptin were shown in Wascops study to predict coronary event in men during 5-year follow up period.[19] Plasma leptin is also independent predictor of myocardial infarction in men and women especially with arterial hypertension.[24] Plasma level is higher in male patients who subsequently develop first-event myocardial infarction than in control group.[17] Several studies have shown that it is a predictor of myocardial infarction, coronary events and stroke independent of body mass index (BMI).[14,17,18,24,25] Regarding the association between admission serum leptin level and selected clinical variables among patients with acute MI, such as hypertension, diabetes mellitus, development of complications ,sex, location of MI , etc. The current study revealed no significant difference in all of these parameters. In agreement with the finding of current study, Basri et al found no significant difference in short-term adverse cardiovascular events among acute MI patients with low and high admission serum leptin level.[31] However, he found that high admission leptin level was associated with a lesser efficacy of thrombolytic therapy and increased needs for invasive therapeutic interventions after thrombolytic therapy. Regarding association between serum leptin level and selected demographic and laboratory variables among patients with acute MI, the current study revealed significant correlation between serum leptin with diabetes mellitus and smoking, this findings is compatible with Krasnodebski et al study that found plasma leptin level in diabetic and smoker are significantly elevated in acute stage of acute MI,[29] also the study show no significant correlation between the leptin levels and BMI, hypertension, uric acid etc.., this findings is compatible with Taneli et al study that found no significant correlation between the leptin levels and selected classical coronary

risk factors in patients with chronic stable angina pectoris and ST elevation myocardial infarction.[30]

So according to reported data in the study,one can conclude that:

1- Patients with acute MI have significantly higher admission serum leptin concentrations (similar to the increased serum cardiac troponinI) compared with controls,these findings suggest possible diagnostic value of leptin in acute MI.

2- No significant associations were found between admission serum troponin, Leptin levels with short –term outcome during hospitalization period especially response to thrombolytic therapy as well as development of complications.

REFERENCES

1. Wolk R et al (2004) Plasma leptin and prognosis in patients with established coronary atherosclerosis.J Am CollCardiol 44: 1819–1824.
2. Soderberg S et al (1999) Leptin is associated with increased risk of myocardial infarction. J Intern Med 246: 409–418
3. Soderberg S et al (2004) Leptin, but not adiponectin, predicts stroke in males. J Intern Med 256: 128–136
4. Wallace AM et al (2001) Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 104: 3052–3056
5. Sierra-Johnson J et al (2007) Relation of increased leptin concentrations to history of myocardial infarction and stroke in the US population. Am J Cardiol 100: 234–239
6. Misra A, Garg A. Leptin: its receptor and obesity. J Invest Med 1996;44:540–8.
7. Lonnqvist F. The obese (ob) gene and its product leptin: a new route towards obesity treatment in man? J Med 1996;89:327–32.
8. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J ObesRelatMetabDisord 2002;26:1407–33.
9. Seufert J. Leptin effects on pancreatic beta-cell gene expression and function. Diabetes 2004;53(suppl 1):S152–8.
10. Chu NF, Spiegelman D, Rifai N, Hotamisligil GS, Rimm EB. Glycemic status and soluble tumor necrosis factor receptor levels in relation to plasma leptin concentrations among normal weight and overweight US men. Int J Obes Relat MetabDisord 2000;24:1085–92.
11. Sierra-Honigmann MR, Nath AK, Murakami C, et al. Biological action of leptin as anangiogenic factor. Science 1998;281:1683–6.
12. Parhami F, Tintut Y, Ballard A, et al. Leptin enhances the calcification of vascular cells: artery wall as a target of leptin. Circ Res 2001;88:954–60. on arterial thrombosis following vascular injury in mice. JAMA 2002;287: 1706–9.
13. Chaldakov GN, Fiore M, Stankulov IS, et al. NGF, BDNF, leptin, and mast cells in human coronary atherosclerosis and metabolic syndrome. Arch Physiol Biochem 2001;109:357–60.
14. Ren J. Leptin and hyperleptinemia – from friend to foe for cardiovascular function. J Endocrinol 2004;181:1–10.
15. Soderberg S, Ahren B, Stegmayr B, et al. Leptin is a risk marker for first-ever hemorrhagic stroke in a population-based cohort. Stroke 1999;30:328–37.
16. Leyva F, Anker SD, Egerer K, Stevenson JC, Kox WJ, Coats AJ. Hyperleptinaemia in chronic heart failure. Relationships with insulin.Eur Heart J 1998;19:1547–51.
17. Schulze PC, Kratzsch J, Linke A, et al. Elevated serum levels of leptin and soluble leptin receptor in patients with advanced chronic heart failure. Eur J Heart Fail 2003;5:33–40.
18. Soderberg S, Ahren B, Jansson JH, et al. Leptin is associated with increased risk of myocardial infarction. J Intern Med 1999;246:409–18.
19. Wallace AM, McMahon AD, Packard CJ, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001;104:3052–6.
20. Knudson JD,DincerUD,ZhangC,etal.leptin receptors are expressed in coronary artreiesandhyperleptinemia causes significant coronary endothelial dysfunction. Am J Phsiol.2005:289:H48-H56
21. Loffreda S, Yang SQ, Lin HZ,etal.leptin regulates proinflammatory immune responses.FASEB J.1998:12:57-65
22. Yamagishi SI,Edelstein D ,Du XL,etal.leptin induces mitochondrial superoxide production andmonocytechemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinasea.JBiol Chem2001:276:25096-25100
23. Ke Chen, Fanglong Li, JiLi, etal. Induction of leptin resistance through direct interaction of C-reacptin.Nat Med.2006:12:425-432.
24. Li MD, Kane JK. Effect of nicotine on the expression of leptin and forebrain leptin receptors in the rat. Brain Res 2003;991:222–31.
25. Wallander M, Soderberg S, Norhammer A. Leptin—a predictor of abnormal glucose tolerance and prognosis in patientswithmyocardial infarction and without previously known Type 2 diabetes. Diabet Med 2008;25(8):949–55.

26. Makris TK, Hatzizacharias AN, Krespi PG, et al. Markers of risk in young offspring with paternal history of myocardial infarction. Int J Cardiol 2003;89:287–93.
27. Wallander M, sodeberg S, Norhammer A. Leptin - a predictor of abnormal glucose tolerance and prognosis in patients with myocardial infarction and without previously known type 2 diabetes. Diabt Med 2008,25[8]:949-55
28. Jose VJ,Mariappan P ,George PV,etal.serumleptin level in acute myocardial infaraction. ndian Heart J.2005Jan-Feb:57(1):39-43
29. Krasnodebski P,Bak MI,Opolski G,Karnafel W:Leptin in acute myocardial infarction and peroid of convalescence in patients with type 2 diabetes mellitus.Kardiol Pol.2010 JUN,68(6):648-653.
30. Taneli F ,Yegane S, UlmanC,etal.increased serum leptin concentrations in patients with chronic stable angina pectoris and ST-elevated myocardial infaraction.Angiology.2006May-June:57(3):267-72
31. Basri,KudretA,Sedat K,et al.Admission Plasma Leptin Level Strongly Correlates With Success of Thrombolytic Therapy in Patients With Acute Myocardial Infarction. Angiology 57:671-680,2006