The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1322-1327

# Role of Leptin as A Risk Factor and Prognostic Marker in Patients with Acute Coronary Syndrome

**Sameh Attia, Bandar Abdulla, Khaled Saeed**
Department of Cardiology, Faculty of Medicine, Ain Shams University, Egypt
***Corresponding author:** Sameh Attia, **Mobile:** (+20) 01141991996, **E-Mail:** drsamehattia201@hotmail.co.uk

## ABSTRACT

**Background:** Leptin is a bioactive substance secreted by adipose tissue and exerts pleiotropic actions on glucose metabolism. It may promote atherosclerosis and increase cardiovascular events.

**Objective:** The aim of this study was to determine the role of leptin as a risk factor in non-obese patients presented with acute coronary syndrome and its relation to midterm prognosis.

**Patients and Methods:** The study included 60 non-obese patients who were presented to Coronary Care Unit (CCU) of Ain Shams University Hospital with acute coronary syndrome (ACS). Patients were classified into 3 Groups. Group A was composed of 30 patients presented with ST-segment elevation myocardial infarction (STEMI), Group B included 15 patients presented with non-ST segment elevation myocardial infarction (NSTEMI) and Group C included 15 patients presented with unstable angina. The study also included control group composed of 20 healthy non-obese subjects who gave no history of chest pain or symptoms suggestive of coronary artery disease (CAD).

**Results:** Mean serum leptin level in all patients was significantly higher compared to control group. As regards complications; mean serum leptin level was higher in patients with adverse outcome compared to other patients.

**Conclusion:** The concentration of leptin is positively correlated with ACS. The mean value of serum leptin in all patients was significantly higher compared to control. The study suggests that leptin is a significant cardiovascular risk factor for ACS independent of traditional cardiovascular risk factors. Serum leptin may be a useful marker in risk stratification of ACS.

**Keywords:** Acute coronary syndrome, Adipocytokines, Atherosclerosis, Leptin.

## INTRODUCTION

Acute coronary syndrome (ACS) comprises a set of life-threatening health conditions affecting the heart. This encompasses myocardial infarction and unstable angina (UA) [(1)]. ACS can be caused by a variety of risk factors, including a family history of heart attack or unstable angina, cigarette smoking, hyperlipidemia, hypertension, diabetes mellitus, obesity, a sedentary lifestyle, stress, and several non-traditional factors particularly inflammatory markers and markers of atherosclerotic burden, which have recently emerged as a result of advances made in the understanding of atherosclerosis pathophysiology [(2)].

Now, it is well-established that adipose tissue appears to be a hormonally active endocrine organ that produces several biologically active substances that regulate and correlate with insulin sensitivity, vascular function, and atherosclerotic disease, collectively known as the "adipocytokines" [(3)]. Two major adipocytokines, leptin and adiponectin are assumed to play important roles in the regulation of metabolic homeostasis and the development of atherosclerotic diseases [(4)].

Leptin shows angiogenic activity, increases oxidative stress in endothelial cells, promotes vascular smooth muscle cell migration and proliferation, stimulates platelet aggregation and atherothrombosis, decreases arterial distensibility, and contributes to obesity-associated hypertension. These factors correlate negatively with vascular health and are strongly involved in the pathophysiology of atherosclerosis and the development of ACS [(5)].

The aim of this study was to determine the role of leptin as a risk factor in non-obese patients presented with acute coronary syndrome and its relation to midterm prognosis.

## PATIENTS AND METHODS

Our study included 60 non-obese patients (based on body mass index (BMI) < 30 kg/m$^2$ and waist circumference (WC) <102 cm) who were admitted to coronary care unit because of acute coronary syndrome excluding obese patients (based on BMI ≥ 30 kg/m$^2$ and WC > 102 cm).

Patients with a history of acute myocardial infarction in the previous six months and those with atrial fibrillation and previous coronary artery bypass graft also were excluded from the study in addition to those with a history of malignancies or renal failure.

**Patients were divided into 3 groups: Group A:** Included 30 patients presented with STEMI, **Group B:** Included 15 patients presented with NSTEMI, and **Group C:** Included 15 patients presented with unstable angina. The study also included a control group composed of twenty healthy non-obese volunteers who gave no history of chest pain or symptoms suggestive of CAD.

All patients were subjected to full history taking including determination of risk factors of CAD as a history of diabetes mellitus, hyperlipidemia, systemic hypertension, and cigarette smoking.

BMI was calculated using the formula: body weight divided by height squared (weight/height$^2$ (kg/m$^2$)). Weight was measured (in Kilogram) using a



Received: 13/10/2021
Accepted: 11/12/2021

standardized weighing balance and height was measured from the vertex to the heel using a portable stadiometer. Waist circumference was used to exclude abdominal obesity and was measured at the horizontal circumference midway between the lowest rib margin and the uppermost lateral border of the right iliac crest.

Investigations were done to all patients including 12 leads resting ECG that was performed on admission and recorded daily during the hospital stay. Routine laboratory investigations were done including complete blood count, fasting blood glucose, renal function tests, and total lipid profile including total cholesterol level (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides level (TG). Cardiac biomarkers including serum troponins and creatine kinase-MB (CK-MB) were measured on admission and daily till discharge from the coronary care unit.

Blood samples were collected from all patients on admission and healthy volunteers after 12 hours of overnight fast to measure serum leptin levels. This was done by venipuncture allowing the sample to clot, and separate serum by centrifugation at 3000 r/min at room temperature. Specimens were capped and stored for up to 24 hours at 2-8 ºC before quantitative assaying using ELISA kits.

All patients were followed up in the hospital and after 3 months for complications including heart failure, ventricular arrhythmia, re-infarction, and death.

**Ethical approval:**

**The design of the study was approved by the Ethical Committee of the Cardiology Department, Faculty of Medicine, Ain Shams University, and it was following the 1975 Helsinki declaration. All patients included in our study have given written informed consent after explaining the procedures and before participation in the study.**

***Statistical analysis***

All data were entered in a Microsoft Access database table using the Predictive Analytics Software (PASW Statistics 18). Descriptive statistics were done using mean and standard deviation for numerical data and frequency and percentage for non-numerical data. Categorical variables were compared using the Chi-square test. For normally distributed numerical data comparison between two independent populations was done using independent t-test while F-test (ANOVA) was used for comparison between the subgroups; and if the difference was significant then Tukey´S test was used for multiple comparison. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the p-value < 0.05.

**RESULTS**

**The difference in baseline characteristics between study groups:**

There was no significant difference between patients and control as well as between different patients' subgroups regarding baseline characteristics (Table 1).

**Distribution of risk factors of CAD in different patients subgroups:**

No significant difference was observed in distribution of risk factors of CAD between the 3 patients' subgroups including smoking, hypertension and diabetes mellitus (Table 1).

**Table (1): Difference in basic characteristics and risk factors of CAD between patients' groups**

| | **Group A STEMI** | **Group B NSTEMI** | **Group C Unstable Angina** | **p-value** |
|---|---|---|---|---|
| | **Number = 30** | **Number = 15** | **Number = 15** | |
| **Age ( years )** Mean±SD | 56.733 ± 9.333 | 58.400 ± 11.63 | 54.933±11.151 | 0.661 |
| **Gender (Males)** | 21(70% ) | 10(66.67%) | 11 ( 73.33% ) | 0.924 |
| **Smoking** | 14 ( 46.67% ) | 9 (60.00% ) | 8 ( 53.33% ) | 0.693 |
| **Hypertension** | 23 ( 76.67% ) | 10 ( 66.67% ) | 9 ( 60.00% ) | 0.490 |
| **Diabetes mellitus** | 11 ( 36.67% ) | 7 ( 46.67% ) | 6 ( 40.00% ) | 0.812 |

SD: Standard deviation

**Differences in serum lipids between study groups:**

Regarding lipid profile the mean value of serum LDL-c in all patients was (130.133 mg/dl). The mean value of serum LDL-c was found to be statistically significantly higher in all patients and in different patients subgroups compared to the control group (Tables 2 and 3).

**Table (2):** Comparison between patients' subgroups and control according to LDL

| Subgroups | LDL (mg/dL) | P-value |
|---|---|---|
| | Mean±SD | |
| **Group A** | 142.667±4.467 | 0.018* |
| **Group B** | 113.667±5.938 | |
| **Group C** | 121.533±5.569 | |
| **Control** | 107.600±3.712 | |
| **TUKEY´S test** | | |
| **Group A and Control** | **Group B and Control** | **Group C and Control** |
| 0.019* | 0.972 | 0.745 |

*: Statistically significant, SD: Standard deviation

The mean value of serum triglycerides in all patients was (176.383 mg/dl), in group A was (196.733 mg/dl), group B was (146.267mg/dl), group C was (165.800 mg/dl) whereas the control subjects had a mean serum triglycerides level of (95.450 mg/dl). This yielded a statistically significantly higher value of serum triglycerides in different patients subgroups compared to the control group ($p<0.001$*).

The mean value of serum HDL-c in all patients was (55.217 mg/dl), in group A was (57.400 mg/dl), group B was (53.267 mg/dl), group C was (52.800 mg/dl) and in the control group it was (55.800 mg/dl). No statistically significant difference was found between patients and control as well as between different patients' subgroups regarding serum HDL-c levels.

**Serum leptin in different study groups:**

Serum leptin in all patients' subgroups was significantly higher compared to the control group (Table 3 and 4).

**Table (3): Comparison between the patients and control group according to serum Leptin level and LDL**

| | Groups | | P-value |
|---|---|---|---|
| | **Patients** Mean ± SD | **Control** Mean ± SD | |
| **Leptin (ng/L)** | 46.675 ± 9.452 | 3.920 ± 0.151 | < 0.001* |
| **LDL (mg/dL)** | 130.133±4.736 | 107.600±3.712 | 0.039* |

*: Statistically significant, SD: Standard deviation

**Table (4): Comparison between the patients' subgroups and control group according to serum leptin level**

| Subgroups | Leptin (ng/L) | P-value |
|---|---|---|
| | Mean ± SD | |
| **Group A (STEMI)** | 67.567 ± 6.949 | < 0.001* |
| **Group B (NSTEMI)** | 33.667 ± 1.215 | |
| **Group C (UA)** | 17.900 ± 3.566 | |
| **Control** | 3.920 ± 0.151 | |
| **STEMI and Control** | **NSTEMI and Control** | **Unstable angina and Control** |
| < 0.001* | < 0.001* | 0.022* |

*: Statistically significant, SD: Standard deviation, UA: Unstable angina

**Relation between serum leptin and risk factors of CAD in different patients subgroups:**

The mean level of serum leptin showed no statistically significant correlation in diabetic compared to non-diabetic patients, the same in hypertensive compared to normotensive patients as well as between smokers and non-smokers (Table 5).

**Table (5): Relation between serum leptin level and risk factors of CAD in different patients' groups**

| | | Leptin (ng/L) | | p-value |
|---|---|---|---|---|
| | | N | Mean±SD | |
| **Diabetes mellitus** | No | 36 | 42.347±7.127 | 0.165 |
| | Yes | 24 | 53.167±3.126 | |
| **Hypertension** | No | 18 | 37.27827.947 | 0.106 |
| | Yes | 42 | 50.702±9.479 | |
| **Smoking** | No | 29 | 48.431±3.629 | 0.659 |
| | Yes | 31 | 45.032±8.716 | |

SD: Standard deviation

**Correlation between serum leptin and serum lipids in different patients groups:**
A significant positive correlation was detected between mean serum leptin level and LDL-c (Table 6).

**Table (6): Correlation between serum leptin and serum Lipids in different patients groups**

| | Leptin (ng/L) | |
|---|---|---|
| | **r** | **P-value** |
| **LDL (mg/dL)** | 0.282 | 0.029***** |
| **HDL (mg/dL)** | 0.140 | 0.285 |
| **TG (mg/dL)** | 0.118 | 0.368 |

r: Pearson coefficient factor *: Statistically significant

**Relation between serum leptin and adverse outcomes:**

Incidence of adverse outcomes including heart failure, ventricular arrhythmia, re-infarction, and death during the hospital stay and 3 months after discharge was 38% in all studied groups. There was no statistically significant difference among the ACS groups as regard incidence of adverse outcomes (Table 7).

**Table (7): Incidence of Adverse outcomes in different patients' subgroups**

| Follow up | Subgroups | | | | | | | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | Group A STEMI | | Group B NSTEMI | | Group C Unstable angina | | Total | | |
| | N | % | N | % | N | % | N | % | |
| **No** | 16 | 53.33 | 9 | 60.00 | 12 | 80.00 | 37 | 61.67 | 0.220 |
| **Yes** | 14 | 46.67 | 6 | 40.00 | 3 | 20.00 | 23 | 38.33 | |
| **Total** | 30 | 100.00 | 15 | 100.00 | 15 | 100.00 | 60 | 100.00 | |

N: Number %: Percentage

The incidence of complications was significantly higher in ACS patients with higher mean serum leptin level where the mean level of serum leptin was found to be significantly higher in patients with adverse outcomes compared to other patients (Table 8).

**Table (8): Relation between serum leptin level and incidence of adverse outcome in patients' groups**

| Incidence of adverse outcome | Leptin (ng/L) | | p-value |
|---|---|---|---|
| | N | Mean±SD | |
| **No** | 37 | 37.243±2.986 | 0.001* |
| **Yes** | 23 | 61.848±3.838 | |

*: statistically significant, N: Number, SD: Standard deviation.

## DISCUSSION

Adipose tissue produces and secretes inflammatory factors (adipocytokines or adipokines) that are known to play important roles in the atherosclerotic process. Most adipocytokines are pro-inflammatory such as leptin, which is secreted by adipose tissue in direct proportion to the amount of body fat [6].

In the current study, we were aiming to study the role of serum leptin as a risk factor only in non-obese patients presented with acute coronary syndrome compared to the control subject and its relation to midterm prognosis. We studied the role of leptin in 60 patients presented with ACS (30 STEMI patients, 15 NSTEMI patients, and 15 UA patients).

**Associations of leptin level with baseline characteristics:**

**Changes in leptin with age:**

In the current study, there was no significant correlation between serum **leptin** level and age in all studied groups. The results of the current study are concordant with **Piestrzeniewicz *et al.*** [7] who reported that no significant correlation existed between leptin levels and age. On the other hand, the results of our study differ from those done by **Ostlund *et al.*** [8] where they found that there was a weak inverse relationship between leptin levels and age independently of body fat. These results could suggest a possible decrease in adipose tissue leptin production in the elderly.

**Changes in leptin with gender:**

The results of the current study suggested that a relationship between increased serum **leptin** level and female gender could exist but not statistically significant. This observation is supported by the study of **Isidori *et al.*** [9] and others [10,11]. This gender-related difference could be explained by the presence of more abundant subcutaneous fat in women.

**Relation between acute coronary syndrome, traditional risk factors, and serum leptin level:**

**Diabetes mellitus (DM):**

In the current study, there was no significant correlation between DM and different subgroups of ACS. Similar results were presented by **Meier-Ewert and Nesto** [12]. In our study, the mean serum leptin level was higher in diabetic than in non-diabetic patients in all subgroups (A, B, C) but, not statistically significant. These results are concordant with **Krasnodebski *et al.*** [13].

**Hypertension:**

The current study showed no significant correlation between hypertension and all studied group. These results are matching with **Xavier *et al.*** [14] that failed to show a significant correlation between hypertension and any subgroup of ACS.

Also, no significant correlation could be observed between hypertension and serum leptin in all studied groups. The results of the current study are different from a study by **Thomopoulos *et al.*** [15] that showed increased leptin levels in non-obese normoglycemic subjects with masked hypertension.

**Cigarette smoking:**

In our study, no statistically significant difference was found regarding the prevalence of smoking between various subgroups. The mean level of serum leptin was higher in non-smokers compared to smokers but did not reach a statistically significant value. These results are consistent with findings of a study conducted by **Hodge *et al.*** [16] who showed that serum leptin was lower in smokers compared to non-smokers, as smoking may modify the sensitivity of hypothalamic leptin receptors and consequently, modulate the synthesis and reduce body weight. On the other hand, a study done by **Larsson and Ahrén** [17] showed no difference between smokers and non-smokers regarding circulating serum leptin levels.

**Dyslipidemia:**

The mean LDL-c was higher in different patient subgroups compared to control subjects and there was a positive correlation between mean serum leptin level and mean LDL-c in the current study. The results of our study are concordant with **Piestrzeniewicz *et al.*** [7] that showed that mean LDL-c was higher in ACS patients and correlated with serum leptin levels.

**Correlation between serum leptin levels and ACS:**

In the current study, the mean serum leptin level in different patients' subgroups was higher than the control group. Similar results were presented by the **Wallace *et al.*** [18]. In this study, plasma leptin levels were measured at baseline in 377 men who then experienced a coronary event, and in 783 men (controls) who shared the same characteristics with cases concerning age and smoking history and did not experience any event during the 5-year follow-up period of the study. This study demonstrated that higher plasma leptin levels predicted a higher risk of a future coronary event and they interpreted this finding based on the known relationships between leptin and several facts of the metabolic syndrome. So, leptin moderately but independently increases the relative risk of CAD [18].

**Wolk *et al.*** [19] demonstrated the positive relationship between leptin and cardiac events. This relation was independent of other recognized cardiovascular risk factors, including lipid levels and C-reactive protein (CRP). Leptin (both unadjusted and adjusted for body mass) had a significant association with the combined endpoint of cardiac death, myocardial infarction, cerebrovascular accident, or revascularization.

**Correlation between serum leptin levels and prognosis:**

In the current study, serum leptin was a significant and independent predictor of recurrent cardiovascular events, which is matching with the results of the **Soderberg *et al.*** [20]**,** which comprised 9014 ACS patients aged 31–75 years, in whom serum leptin was a significant and independent predictor of recurrent cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and stroke) in men with earlier acute coronary syndromes and correlated with BMI and triglyceride levels.

**Study limitations:**

The results were obtained from a single medical center and further studies with a larger number of patients are needed to confirm our findings. Our study showed the association between elevated leptin with CAD but does not differentiate whether it was a cause or consequence of ACS.

**CONCLUSION**

The concentration of serum leptin is positively correlated with ACS. The mean value of serum leptin in all patients (STEMI, NSTEMI, and unstable angina) was significantly higher compared to control subjects. The results of our study suggest that leptin may be a significant cardiovascular risk factor for ACS independent of traditional cardiovascular risk factors. Also, serum leptin may be a useful marker in risk stratification of ACS where the incidence of complications was significantly higher in ACS patients with higher mean serum leptin levels.

**Financial support and sponsorship:** Nil.
**Conflict of interest:** Nil.

## REFERENCES

1. **Hani J, Jeffrey L, Adams C *et al.* (2012):** UA/NSTEMI Guideline: 2012 Update Incorporated. J Am Coll Cardiol., 60(7):645-81.
2. **Greenland P, Alpert J, Beller G *et al.* (2010):** 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the ACC /AHA on Practice Guidelines. J Am Coll Cardiol., 56: 50–103.
3. **Mallika V, Goswami B, Rajappa M (2007):** Atherosclerosis pathophysiology and the role of novel risk factors. Angiology, 58:513–22.
4. **Sugiura K, Tamakoshi K, Yatsuya H *et al.* (2008):** Contribution of adipocytokines to low-grade inflammatory state. International Journal of Cardiology, 130: 159– 64.
5. **Singhal A (2002):** Influence of leptin on arterial distensibility: A novel link between obesity and cardiovascular disease? Circulation, 106(15):1919-1924.
6. **Ouchi N, Ohashi K, Shibata R *et al.* (2012):** Adipocytokines and obesity-linked disorders. Nagoya J Med Sci., 74(1-2):19-30.
7. **Piestrzeniewicz K, Luczak K, Komorowski J *et al.* (2007):** The relationship between leptin and obesity and cardiovascular risk factors in men with acute myocardial infarction. Cardiol J., 14(3):252–59.
8. **Ostlund R, Yang J, Klein S *et al.* (1996):** Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. J Clin Endocrinol Metab, 81: 3909-13.
9. **Isidori A, Strollo F, Morè M *et al.* (2000):** Leptin and aging: correlation with endocrine changes in healthy adult populations of different body weights. J Clin Endocrinol Metab., 85: 1954-62.
10. **Baumgartner R, Walters D, Morley E *et al.* (1999):** Age-related changes in sex hormones affect the sex difference in serum leptin independently of changes in body fat. Metabolism, 48: 378-84.
11. **Al-Harthy R (2004):** Relationship of leptin concentration to gender, body mass index, and age in Saudi adults. Saudi Med J., 25: 1086-90.
12. **Meier-Ewert H, Nesto R (2002):** targeting the use of glycoprotein IIb/IIIa antagonists – the diabetic patient. Rev Cardiovasc Med., 3 (1): 20-27.
13. **Krasnodebski P, Bak M, Opolski G *et al.* (2010):** Leptin in acute myocardial infarction and period of convalescence in patients with type 2 diabetes mellitus. Kardiol Pol., 68(6):648–53.
14. **Xavier D, Pais P, Devereaux P *et al.* (2008):** Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. Lancet, 371: 1435-42.
15. **Thomopoulos C, Papadopoulos D, Papazachou O *et al.* (2009):** Free leptin is associated with masked hypertension in nonobese subjects: a cross-sectional study. Hypertension, 53(6):965-72
16. **Hodge A, Westerman R, De Courten G *et al.* (1997):** Is leptin sensitivity the link between smoking cessation and weight gain? Int Jou Obes., 21:50–3.
17. **Larsson H, Ahrén B (1999):** Smoking habits and circulating leptin in postmenopausal non-obese women. Diabetes Obes Metab., 1:57–59.
18. **Wallace A, McMahon A, Packard C *et al.* (2001):** Plasma leptin and the risk of CVD in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation, 104: 3052– 56.
19. **Wolk R, Berger P, Lennon R *et al.* (2004):** Plasma leptin and prognosis in patients with established coronary atherosclerosis. J Am Coll Cardiol., 44:1819–24.
20. **Soderberg S, Colquhoun D, Keech A *et al.* (2009):** Leptin, but not adiponectin, is a predictor of recurrent cardiovascular events in men: results from the LIPID study. International Journal of Obesity, 33: 123–30.