# Sensitivity of Biomarker: Leptin, Adiponectin or High Sensitivity C-reactive protein in diagnosis of Coronary Heart Disease

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## ABSTRACT

***Background:*** *Adipose tissue is known to produce and release numerous bioactive substances, known as adipokines (such as leptin and adiponectin), which have been found to be involved in various physiological processes, including the regulation of arterial tone. Also, high sensitivity C-reactive protein (hs-CRP) is related to cardiovascular risk factors and adipokines.* ***Methods:*** *Forty patients with established coronary heart disease (CHD) defined as old myocardial infarction & angina pectoris classified as CHD group and ten normal healthy subjects classified as the control group participated in the present study. All patients and controls were subjected to complete clinical history taking, clinical examination including 12 lead electrocardiogram (ECG), diagnostic coronary angiography (CA) and the measurement of serum levels of triacylglycerols (TGs), total cholesterol (total-C), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), leptin, adiponectin and hs-CRP.* ***Results:*** *Serum levels of leptin, hs-CRP, LDL-C and total-C showed highly significant ($p < 0.0001$) increase, while, adiponectin levels showed highly significant ($p < 0.0001$) decrease in the group of patients when compared to the levels of the control group. The levels of HDL-C in the group of patients were significantly ($p < 0.05$) lower than in the control group. There was no significant difference between the levels of TGs in the patients versus the controls. Leptin was weakly correlated positively with hs-CRP, while, non-significantly correlated negatively with adiponectin. Hs-CRP was moderately correlated negatively with total-C. The overall positive rates obtained from Receiver operating characteristic (ROC) curve for evolution of sensitivity and specificity of the different biomarkers is obtained. The sensitivity was 100% for both leptin and adiponectin, but, it was 75% for hs-CRP. ROC curve results revealed that the specificity for leptin, adiponectin and hs-CRP were 100%, 90% and 80%, respectively.* ***Conclusion:*** *The results obtained in the present study reveals that serum leptin, adiponectin and hs-CRP might play an important role in the pathogenesis of CHD and the circulating levels of leptin and adiponectin provide highly sensitive and specific biomarkers for CHD more than hs-CRP.*

***Key Indexing Terms:*** *ADIPONECTIN – LEPTIN – CRP –CORONARY HEART DISEASE*

## INTRODUCTION

White adipose tissue stores excess energy in the form of triglycerides, while brown adipose tissue is actively involved in the regulation of body temperature[1]. Recent studies have shown that adipose tissue is an active endocrine and paracrine organ secreting several mediators called adipokines.

Adipokines include hormones, inflammatory cytokines and other proteins[2]. These adipokines include hormones as leptin and adiponectin, inflammatory cytokines as tumor necrosis factor α, interleukin-6 and other proteins as plasminogen activator inhibitor-1, angiotensinogen and resistin[3].

Furthermore, adipose tissue is known to release an unidentified adipocyte-derived relaxing factor[4], which relaxes several arteries. Leptin is an ob gene-expressed protein mainly secreted by adipose tissues, with a primary role of inhibiting food intake, modulating weight balance and promoting energy metabolism[5].

Previous researches have revealed that leptin is a stress mediator after injuries, and it proceeds to maintain homeostasis by accelerating oxidation of glucose and fatty acids, alleviating reactive oxygen species-induced apoptosis, and ameliorating post-septic multiple organ dysfunction[6,7].

Several experimental studies have shown that increased leptin level may directly or indirectly exert multiple actions at the cardiovascular level[8], where leptin receptors have been identified in various peripheral tissues, including the cardiovascular system and in human coronaries; it seems to have both vasodilatory and vasoconstrictory actions on vascular endothelium[9].

Furthermore, leptin is involved in a number of diverse physiological processes, such as regulation of endocrine functions, inflammation, immune response, reproduction and angiogenesis[10]. Several studies have found a significant association between circulating plasma leptin with insulin resistance and inflammatory markers, suggesting leptin as a risk factor for cardiovascular disease[11].

Adiponectin is a protein hormone secreted by adipocytes; it binds to two different seven transmembrane domain receptors called AdipoR1 and AdipoR2. AdipoR1 is predominantly expressed in skeletal muscles, whereas AdipoR2 is predominantly expressed in liver and throughout the brain[12]. Many other cells have adiponectin receptors as macrophages, osteoblasts, adipocytes, endothelial and muscular cells of the vascular wall, pancreatic cells and central nervous system[13].

Adiponectin has been considered an anti-inflammatory and antioxidative adipokine that protects against cardiovascular disease[14]. Plasma adiponectin has been correlated with endothelium-dependent vasorelaxation in humans[15]. These results were confirmed by other studies that have shown an increase in NO production as well as NO-mediated and potassium channel-mediated (that is,

voltage-dependent) vasorelaxation in rats by adiponectin[16, 17, 18]. Increased NO production inhibits platelet aggregation, leucocyte adhesion to endothelial cells and vascular smooth muscle cell proliferation. Furthermore, it reduces oxidative stress by decreasing ROS production in endothelial cells. All of these effects protect the vascular system against endothelial dysfunction[14].

C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP) are recognized as valuable inflammatory biomarkers, but a growing body of evidence supports the active role of CRP in the devolvement of vascular damage[19]. There are, however, significant sex-related differences in the location of the adipose tissue, the number of fat cells and fat cell size, plasma levels of CRP and adipokines[20]. The associations between adipokines and markers of inflammation have been previously demonstrated in cohorts of healthy subjects, patients with diabetes, and patients with coronary artery disease[21].

The objective of the present study is to establish the role of leptin, adiponectin and hs-CRP in the occurrence of coronary heart disease and compare the sensitivity and specificity of the circulating levels of the three biomarkers in the clinical diagnosis of CHD.

## MATERIALS & METHODS

**Patients and study protocol:** The criteria for the diagnosis of CHD include myocardial infarction and angina pectoris based on the clinical history, ECG and diagnostic coronary angiography (CA) was carried out on forty consecutive patients with age ranging between 50-65 years with mean ±SD of 59.175±3.112 years (24 males and 16 females) who were selected from the cardiology outpatients' clinic of Al Minia university hospitals to participate in the current study, the duration between the onset of disease and the time of performing the assay of the biomarkers was ranging between 90-270 days with mean ±SD of 136.48±4.96 day. The control group included 10 normal healthy subjects with age ranging between 54-61 years with mean ±SD of 57.200±2.573 years (7 males and 3 females) with no history of myocardial infarction and angina pectoris having normal ECG and normal (CA). A written informed consent was obtained from each participant. All patients and the control groups were subjected to diagnostic coronary angiography (CA) in Cath-Lab of Cardiology Department and the biochemical analyses were carried out in the Medical Biochemistry Department, Faculty of Medicine, Al Minia University.

**Diagnostic coronary angiography** (CA): It was done for all participants using a flat-panel imaging system. All subjects were in the fasting sedated state. It was performed from the arterial femoral approach after local groin infiltration of 10-20 ml xylocaine 2% using modified seldinger's technique after injection of 5000 IU of Heparin, 6F JL then JR coronary catheters were used to engage the corresponding arteries. The study was conducted with a

General Electric Innova 2000 angiographic unit (GE medical system Milwaukee, WI, USA). The selection criteria of the patients were presence of more than 50% of coronary lesions in their angiographic projections and normal (CA) to be used as a control group.

**Laboratory measurements**: Blood samples were drawn after an overnight fast from each patient of the test group and each healthy subject of the control group. Each blood sample was centrifuged to collect serum which was stored at -20ºC till the time of analysis. Total-C, HDL-C and TGs were measured by enzymatic colorimetric methods as described by ***Richmond*[22], *Gordon et al.*[23] *and Jacobs & Vandemark*[24]**, respectively, using reagents from (Human Gesellschaft fur Biochemica Diagnostica GmbH, Germany). LDL-C was calculated by Friedewald' s formula[25]. Leptin, adiponectin and high sensitive C-reactive protein (hs-C- reactive protein) were measured using a Human Leptin ELISA kit (SRL, Tokyo), a Human Adiponectin ELISA kit (Otsuka Pharmaceutical Inc., Tokyo) and Auto LIA CRP MX type (Nippon Seiyaku, Japan) as described by ***Engvall et al.*[26].**

**Statistical analysis:**

All data were analyzed using SPSS (Statistical Program for Social Sciences version 14 for windows, 2006, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and discrete variables were presented as frequencies and percentages. Continuous variables were compared between the two groups using the unpaired Student's t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. The relationships between the variables (laboratory parameters) were analyzed using Pearson correlation coefficient (r). A P value less than to .05 was considered statistically significant. ROC curve analysis was done using MedCalc software for evolution of sensitivity and specificity of the different biomarkers.

## RESULTS

The biochemical parameters of the patients' group versus the control group are presented in Table 1, in the form of mean±SD. The results showed highly significant ($p< 0.0001$) increase in the levels of leptin, hs-CRP, LDL-C and total-C of the CHD group versus the control group, also, there was highly significant ($p< 0.0001$) decrease in the levels of adiponectin of patients when compared to the controls. HDL-C values revealed a significant ($p< 0.05$) decrease for CHD group in respect to the control group, while, the values of TGs showed insignificant difference ($p=0.0871$).

In CHD group, the obtained results showed that there was a positive correlation between leptin and hs-CRP ($r=0.371$, $p<0.018$), a non-significant negative correlation with adiponectin ($r=-.087$, $p=.592$), a moderate negative correlation between hs-CRP and total-C ($r=-.501$, $p=0.001$) and a non-significant negative correlation between hs-CRP and adiponectin ($r = -.010$, $p = 0.953$) (Figure 1).

Table 2 shows the area under the ROC curves for leptin, adiponectin and hs-CRP in (1.00, 0.00 and 0.882 for the three parameters, respectively). Also, figures 2, 3, 4 and 5 show that the optimal cutoff value of leptin (27.7 ng/ml) (sensitivity 100% and specificity 100%) (Fig. 2), of adiponectin (7.6µg/dl) (sensitivity 100% and specificity 90%) (Fig. 3) and 0.26 mg/dl for hs-CRP (sensitivity 75% and specificity 80%) (Fig. 4)

**Table 1. Baseline biochemical parameters of CHD and control groups**

| Parameter | CHD group (n=40) | Control group (n=10) |
|---|---|---|
| Leptin (ng/ml)[a] | 28.168±4.007* | 12.73±1.347 |
| Adiponectin (µg/dl)[a] | 7.5295±.7769* | 12.08±.91869 |
| hs-CRP (mg/dl)[a] | .2515±.04693* | .1880±.02700 |
| TGs (mg/dl)[a] | 301.562±32.4515** | 240.952±8.46132 |
| LDL-C (mg/dl)[a] | 148.562±6.4195* | 104.622±4.70598 |
| HDL-C (mg/dl)[a] | 33.1500±3.0884*** | 39.6100±2.47766 |
| Total-C (mg/dl)[a] | 286.852±26.17549* | 190.372±2٠.802 |

[a] *Values were expressed as mean ± standard deviation (SD), *=P<0.0001is highly significant, **=P>0.05is insignificant and ***=P<0,05is significant when compared with the values of the control group.*

**Figure 1.** Correlations between some of the biochemical parameters of the study (CHD) group

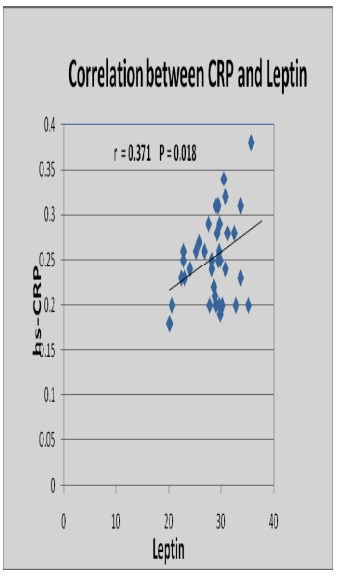


**Figure 2.** ROC curve for leptin

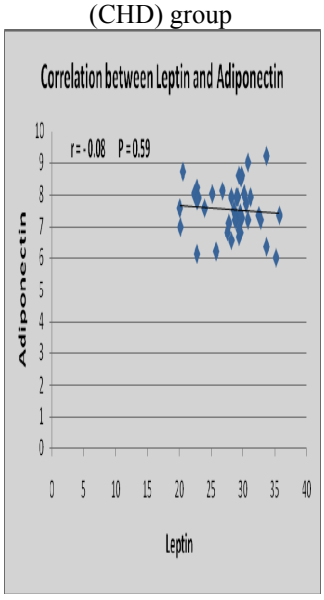


**Figure 3.** ROC curve for adiponectin

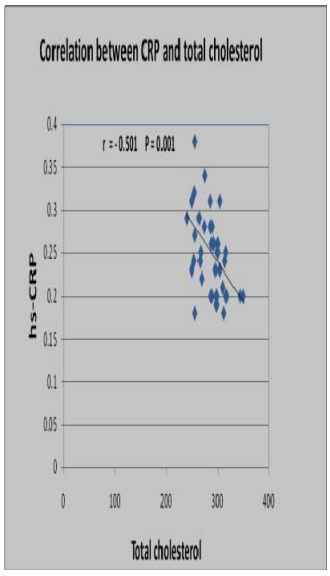


**Figure 4**. ROC curve for hs-CRP

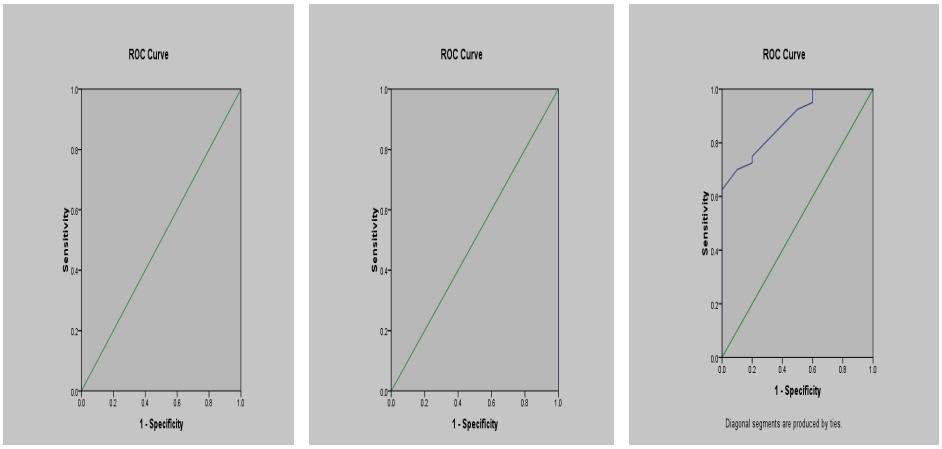


**Table 2.Area under the (ROC) curves for the three parameters**

| Test Result Variable(s) | Area | Asymptotic 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| Leptin | 1.000 | 1.000 | 1.000 |
| Adiponectin | .000 | .000 | .000 |
| Hs-CRP | .882 | .784 | .981 |

## DISCUSSION

Leptin and adiponectin differ from almost all other adipocytokines in being secreted exclusively by adipocytes, the details of all the factors regulating their synthesis, secretion and clearance remain incomplete[27].

Adiponectin is a 244 amino acid protein[28]; it has been shown to have several beneficial effects in the cardiovascular system including an essential role in the maintenance of heart architecture, as the cytokine may attenuate angiotensin II-induced cardiac hypertrophy[29]. Also, it represses atherosclerotic lesions in a mouse model of atherosclerosis and adiponectin-deficient mice exhibit an accelerated vascular remodeling response to injury[30].

In addition, adiponectin stimulates nitric oxide production in endothelial cells through AMPK-dependent and AMPK-independent phosphorylation of endothelial nitric oxide synthase (eNOS)[31] and hypoadiponectinemia is associated with the progression of left ventricular hypertrophy (LVH), which is accompanied by diastolic dysfunction[32].

Although whether low levels of adiponectin predict hypertension remains controversial[33] and whether adiponectin levels in hypertension are decreased[34], low adiponectin

levels might contribute to the pathogenesis of obesity-related hypertension.

This study confirms the previous reports that plasma adiponectin levels are lower in patients with CHD. Studies in experimental animals have shown that adiponectin has the potential to inhibit neointimal formation[35], which is supported by the report of [36] who stated that adiponectin-deficient mice have severe neointimal thickening and increased proliferation of vascular smooth muscle cells in mechanically injured arteries that can be attenuated by adenovirus-mediated adiponectin administration[37]. Our findings show that the levels of adiponectin are correlated positively and negatively with the values of HDL-C and LDL-C values, respectively, in CHD group which is in agreement with the results obtained by ***Yutaka et al.***[38]**.**

Adiponectin suppresses lipid accumulation in macrophages, resulting in markedly decreased uptake of oxidized LDL and inhibition of foam cell formation which provides vasculoprotection through improvement of lipid metabolism[39], which is supporting the results obtained in present study. The group of patients showed increase in the levels of total cholesterol, LDL-C and triacylglycerols, while, the levels of HDL-C are decreased with the decrease in the levels of adiponectin, the mechanism by which adiponectin influences lipid metabolism suggests that the positive effects of adiponectin on HDL levels might result from the significant positive relationship with lipoprotein lipase activity[40]. Furthermore discussion about the mechanism of adiponectin in atherosclerosis is inappropriate because of a lack of direct data regarding this issue. Nevertheless, these reported findings, with the present results, indicate that lower levels of adiponectin may provide certain information for predicting CHD[38]**.**

Leptin is a 26 kDa[40], almost exclusively secreted by white and brown adipocytes[41], its expression and secretion are also regulated by a variety of other factors; for example, leptin is increased by insulin, glucocorticoids, TNF-α, and estrogen[40]. Under normal conditions; leptin contributes to blood pressure homeostasis by its vasorelaxing and vasocontractile effects[42]. While the contractile effect of leptin is attributed to sympathetic nervous system activation [43]. Various mechanisms seem to be responsible for leptin-induced vasorelaxation. This latter effect can be endothelium-dependent, either through the release of NO[44] or by other mechanisms[45]. The vascular effects in an isolated preparation are independent of any neutrally mediated actions of leptin. They are consistent with several previous demonstrating leptin-induced vasodilatation of coronary artery in humans and activation of endothelial nitric oxide production in human aortic endothelial cells[44].

In the present study, the mean value of serum leptin levels of CHD group were higher when compared to the control group and inversely correlated to the levels of serum adiponectin. Our findings are in agreement with the reported results

of ***Yutaka et al.***[38], also, leptin levels show positive insignificant correlations with values of HDL-C and LDL-C. Chronic elevation of blood CRP and hs-CRP levels has been observed in individuals with cardiovascular risk factors such as diabetes, smoking, obesity, hypertension, and dyslipidemia[46, 47].

The results obtained in the present study show that there is a statistically significant increase in the serum level of hs-CRP in the patients group versus the control group. In previously published reports, it has been shown that the difference between the levels of hs-CRP was insignificant in coronary heart disease patients when compared to the non- coronary heart disease subjects[38]. The disagreement between our findings and the results obtained by[38] may be due to the existence of any other inflammatory conditions that can result in increase in the levels of hs-CRP. Several reports have demonstrated that there is an inverse relationship between plasma adiponectin and CRP[21, 48].

From the results of Receiver operating characteristic (ROC) curve for the studied parameters, it is shown that sensitivity of leptin and adiponectin as biomarkers for CHD are higher than hs-CRP, also, leptin is more specific than the other two parameters. A previous report showed that leptin levels were the most sensitive marker for predicting the accumulation cardiovascular risk factors in the general population of elementary school children[49]. ***Nakatani et al.***[50], reported that serum leptin was a useful biomarker of metabolic abnormalities than high molecular weight adiponectin in general male adolescents.

## CONCLUSION

Serum leptin, adiponectin and hs-CRP are biomarkers for and correlated to CHD and the most sensitive &specific parameter is leptin. The limitation to the present study is the relatively small patients' number included in the study.

The future plan will be directed towards leptin receptor gene polymorphisms and their effects on the circulating levels of leptin and the signaling capacity of leptin.

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## تقييم حساسية الدلالات الكيميائية (ليبتن، اديبونكتن والبروتين المتفاعل سى عالى الحساسية) كدلالات لتشخيص أمراض القلب التاجية

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**خلفية**:

من المعروف أن الأنسجة الدهنية تفرز مجموعة من المواد النشطة حيويا تسمى أديبوكاينزمثل الليبتن والأديبونكتن والتى تقوم بوظائف فسيولوجية عديدة متضمنة وظيفة البروتين المتفاعل سى عالى الحساسية والمرتبط بالعديد من العوامل الخطرة المؤدية لأمراض الشرايين التاجية ومجموعة الأديبوكاينز.

**الهدف**: تحديد دور الليبتن والأديبونكتن وكذلك البروتين المتفاعل سى عالى الحساسية فى مرض القلب التاجى وكذلك المقارنة بين بين مستويات الثلاثة دلالات واكثرهم حساسية كدلالة كيميائية تشخيصية.

**الطرق**:

أجريت الدراسة على ٤٠ مريض سبق اصابتهم بأمراض الشرايين التاجية تم تشخيصهم أعتمادا على التاريخ الأكلينيكى وتخطيط القلب الكهربائى ونتائج القسطرة القلبية لهم وشملت الدراسة ١٠ اشخاص كمجموعة ضابطة من الاصحاء ليس لهم تاريخ مرضى سابق فيما يخص متلازمة الشريان التاجى ولا توجد لديهم أية إصابات في شرايين القلب. جميع الحالات التى شملتها الدراسة خضعت لأخذ التاريخ المرضى والفحص السريرى وتخطيط القلب الكهربائى والقسطرة التشخيصية ثم تم

قياس مستويلت دهون الدم ومستوى الليبتن و الأديبونكتن والبروتين المتفاعل سى عالى الحساسية.

**النتائج**:

جاءت كل القياسات الكيميائية مفيدة إحصائيا عند مقارنتها بنفس القياسات فى المجموعة الضابطة ماعدا كوليسترول البروتينات الدهنية ذات الكثافة العالية. كذلك اثبتت النتائج أن مستويات الليبتن ارتبطت ارتباطا ايجابيا مع البروتين المتفاعل سى عالى الحساسية وكذا ترتبط ارتباطا سلبيا غير مفيد مع مستويات الأديبونكتن. كما أرتبط سلبيا مع الكولسترول الكلى. دراسة منحنى الحساسية الخاص بالثلاثة دلالات اثبتت أن درجة حساسية كل من الليبتن والأديبونكتن كانت أعلى من درجة حساسية البروتين المتفاعل سى عالى الحساسية أما درجة التخصصية فكانت أعلى فى جانب الليبتن اكثر من الأديبونكتن وكذلك اعلى من البروتين المتفاعل سى عالى الحساسية.

**الإستنتاج**:

تلعب الدلالات الثلاثة دورا هاما فى حدوث متلازمة أمراض شرايين القلب التاجية وكذا تمثل مستويات الليبتن والأديبونكتن أكثر دلالات التشخيص الكيميائي حساسية ودقة من البروتين المتفاعل سى عالى الحساسية من حيث اسخدامهما كدلالات حيوية لتشخيص أمراض تصلب الشرايين التاجية.