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# Serum Leptin and Adiponectin Levels and the Coronary Artery Disease in Patients Undergoing Angiography

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## Abstract

***Background:*** *It has been shown the adipokines, including leptin and adiponectin, have a prominent role in the pathogenesis of coronary artery disease (CAD). Nevertheless, conflicting results have been reported. The aim of the current study was to clarify the association of the leptin, adiponectin, and leptin to adiponectin (L/R) ratio with the severity of coronary atherosclerosis in an Iranian patient with CAD undergoing angiography.*

***Methods:*** *We evaluated leptin, adiponectin, and leptin/ adiponectin (L/A) ratio as predictors of CAD severity in 179 Iranian patients based on the severity of CAD. Participants were divided into four groups. Statistical analyses were performed using SPSS22 software, and significance was defined as P-value<0.05.*

***Results:*** *Among participants 78 persons (43.6%) were female. The mean (SD) age, BMI, serum leptin, adiponectin levels were 58.99 (10.07), 28.26 (4.11), and 1.55 (0.40), 8.48 (2.40) respectively. The angiographic evaluations of patients showed that 52 (29%) of participants had only one involved vessel, 29 (16%) had two involved vessels, 26 (15%) had three involved vessels, and 72 (40%) had mild vessel involved.*

***Conclusions:*** *Our analysis found no significant link between L/A ratio and CAD severity.*

**Keywords:** Leptin, Adiponectin, Leptin/Adiponectin ratio, Coronary artery disease.
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## Introduction

In spite of the widespread occurrence of Coronary artery disease (CAD), there is no consensus on the precise processes of the onset of atherosclerosis[1]. The total crude prevalence of CVD reached 607.64 million cases in 2020, making a 29.01% rise from 2010[2]. The excessive levels of adipokines, such as leptin and adiponectin have been reported to be responsible for the occurrence and progress of CAD[3]. Leptin and adiponectin are produced by white adipose tissue, that is one of the most potent lipid regulators[4, 5]. These are known to be involved in a wide range of physiological processes[6]. Leptin that is a product of adipose tissue according to the amount of body fat stores are involved in the regulation of food intake, neuroendocrine function, reproduction, angiogenesis, and blood pressure, among others[7, 8]. Circulating leptin levels correspond closely with the total amount of body fat being, therefore, increased in overweight individuals[9]. Many studies confirm the involvement of leptin in the pathogenesis of CAD. In the prospective West of Scotland Coronary Prevention Study, a moderate association was revealed between increased leptin concentration and increased risk of CAD[10]. Another study showed plasma leptin concentration as an independent predictor of cardiovascular disease circumstances in patients with established coronary atherosclerosis[11]. Paradoxically, some researchers consider leptin as a reducing factor in atherosclerosis[12]. On the other hand, adiponectin because of its cardioprotective functions, has a protective role against insulin resistance and excessive hepatic lipid accumulation, while at the same time exerts anti-inflammatory effects[13]. Plasma adiponectin concentration is decreased in patients with CAD[14, 15] (Figure 1), while the circulating adiponectin levels are increased by routine drugs used for treating cardiovascular disease[16, 17]. Different studies have shown inconsistent results about adiponectin and severity of CAD. For example, Lim et al. found no significant relation between serum adiponectin and the extent or severity of coronary atherosclerosis[18].

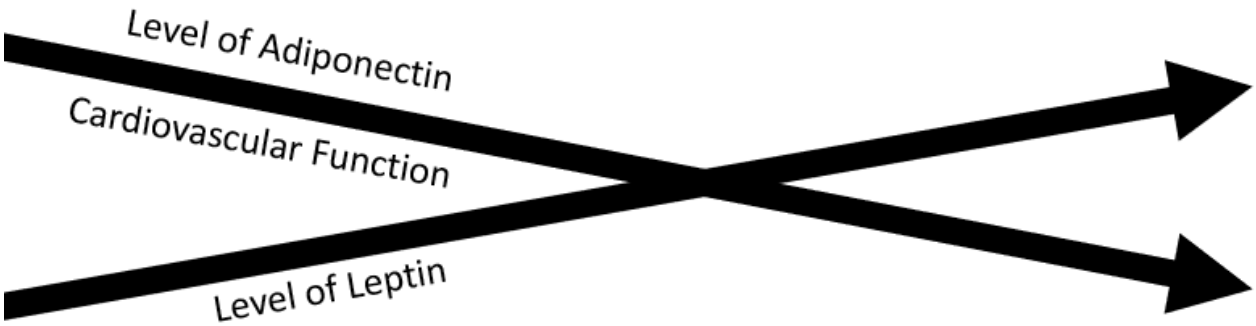


**Figure 1. Leptin/Adiponectin and cardiovascular function according to literature**

To sum up, leptin promotes inflammation[19], while adiponectin has anti-inflammatory effects, making their ratio a potential CAD marker. Furthermore, carotid intima-media thickness (CIMT) is used as a measure to assess the severity of carotid atherosclerotic vascular conditions and the prior literature has reported the plasma L/A ratio as a more appropriate predictor of CIMT alterations and the risk of CAD in comparison with the leptin or adiponectin serum level alone[20]. To address these gaps, we conducted an observational study analyzing biomarkers linked to CAD severity.

## Materials and Methods

This was an analytical observational study in which a sample of 179 patients with a degree of CAD participated in the cardiology ward at Shahid Beheshti Hospital in Qom, a city in the central region of Iran, between October 2018 and March 2018. The samples to be included in the study, should meet the criteria of a history of myocardial infarction, angiographic evidence of at least 50% stenosis by area in at least 1 coronary artery, evidence of exercise-induced ischemia, or history of coronary revascularization. On the other hand, the exclusion criteria were having a history of myocardial infarction within 1 month, and symptomatic active malignant diseases, any autoimmune diseases or hematological disorders. Moreover, patients with acute coronary syndromes or chronic inflammation were excluded. The study population filled up a questionnaire of demographic parameters, including age, gender, marital status, diabetes mellitus, and their BMI were calculated. Coronary angiography was carried out and the results were collected by two cardiologists based on the severity of atherosclerosis; the patients were divided into 4 categories according to the number of involved vessels; patients with mild coronary artery involvement, patients with involvement of 1 coronary artery, patients with involvement of 2 coronary arteries, and patients with involvement of 3 coronary arteries. After fasting for 10 hours, blood samples were taken and stored in certain sterilized containers. The serum samples collection was also done, during which a centrifuge system with 4000 rounds per min (rpm) for 5 min at -4° C was used. The samples were stored in the refrigerator at -80° C. to measure adiponectin and leptin serum levels, the researchers used an enzyme-linked immunosorbent assay (ELISA) assessment with a human kit. To be leveled with the kit structure, special pits were used containing 100 mL of the samples. They were covered with human anti-adiponectin monoclonal immunoglobulin G, and to detect adiponectin, anti-adiponectin antibody conjugated horseradish peroxidase was added. Then, a washout procedure was performed to eradicate the unattached enzymes. Finally, the chromogen solution was added and the dye solution was spectrophotometrically read at 450 nm using a microplate reader. The manufacturer's protocol was observed during Adiponectin (mg/ml) and leptin (ng/ml) concentrations. Lipid profiles and plasma Hba1c were measured using routine laboratory techniques.

We used statistical models to test biomarker links to CAD severity. Descriptive analyses of the data included the expression of the mean ± standard deviation. Moreover, Pearson Correlation analysis was used for the correlations between variables. To perform all statistical analyses were, SPSS22 software was used. Statistical significance was defined as P-value<0.05.

## Results

This study included 179 participants who were all married, 78 persons (43.6%) were female and 60 participants (33.5%) had diabetes mellitus. Their mean (SD) age, BMI, serum leptin, and adiponectin levels were 58.99 (10.07), 28.26 (4.11), 1.55 (3.50), and 8.48 (21.23) respectively. Among them 148 persons (82.6%) had less than a diploma, 17 persons (9.5.6%) had a diploma, and 14 persons (7.8%) had a university degree. The angiographic evaluations of patients showed that 52 (29%) of participants had only one involved vessel, 29 (16%) had two involved vessels, 26 (15%) had three involved vessels and 72 (40%) had mild vessel involved. Having established demographic trends, we now analyze biomarker correlations. Statistical analysis using the one- way ANOVA indicates that no significant relationship was observed between leptin (F=1.48, P-value=0.22), adiponectin (F=1.11, P-value=0.34) levels, and L/A ratio (F=0.43, P-value=0.72) variables (Table 1).

Multiple logistic regression found no significant association between leptin/adiponectin levels, L/A ratio, and CAD severity (Table 2).

**Table 1. The results of One Way ANOVA Test among variables**

| | | N | Mean | Std. Deviation | 95% CI | F | P |
|---|---|---|---|---|---|---|---|
| | Mild | 72 | 56.42 | 10.520 | 53.94-58.89 | | |
| | 1VD* | 52 | 59.77 | 9.757 | 57.05-62.49 | | |
| **Age** | 2VD* | 29 | 61.72 | 10.670 | 57.67-65.78 | 3.04 | 0.03* |
| | 3VD* | 26 | 61.54 | 7.123 | 58.66-64.42 | | |
| | Total | 179 | 58.99 | 10.074 | 57.51-60.48 | | |
| | Mild | 72 | 162.63 | 7.865 | 160.78-164.48 | | |
| | 1VD | 52 | 164.46 | 8.658 | 162.05-166.87 | | |
| **Height** | 2VD | 29 | 167.10 | 8.993 | 163.68-170.52 | 2.08 | 0.11 |
| | 3VD | 26 | 164.92 | 8.555 | 161.47-168.38 | | |
| | Total | 179 | 164.22 | 8.463 | 162.97-165.47 | | |
| | Mild | 72 | 75.99 | 11.155 | 73.37-78.61 | | |
| | 1VD | 52 | 75.70 | 14.441 | 71.68-79.72 | | |
| **Weight** | 2VD | 29 | 78.78 | 10.023 | 74.97-82.60 | 0.48 | 0.70 |
| | 3VD | 26 | 75.48 | 13.824 | 69.90-81.06 | | |
| | Total | 179 | 76.28 | 12.380 | 74.46-78.11 | | |
| | Mild | 72 | 28.7503 | 3.99615 | 27.81-29.69 | | |
| | 1VD | 52 | 27.9445 | 4.83518 | 26.60-29.29 | | |
| **BMI** | 2VD | 29 | 28.2594 | 3.37323 | 26.98-29.54 | 0.69 | 0.56 |
| | 3VD | 26 | 27.5639 | 3.59228 | 26.11-29.01 | | |
| | Total | 179 | 28.2644 | 4.10702 | 27.66-28.87 | | |
| | Mild | 72 | 2.1915 | 4.41862 | 1.15-3.24 | | |
| | 1VD | 52 | 0.8882 | 2.03525 | 0.3158-1.4607 | | |
| **Leptin** | 2VD | 29 | 1.3586 | 3.67108 | -0.0378-2.7550 | 1.48 | 0.22 |
| | 3VD | 26 | 1.3192 | 2.48468 | 0.3156-2.3228 | | |
| | Total | 179 | 1.5514 | 3.50284 | 1.031-2.07 | | |
| | Mild | 72 | 11.30 | 25.733 | 5.21-17.39 | | |
| | 1VD | 52 | 4.36 | 9.619 | 1.68-7.04 | | |
| **Adiponectin** | 2VD | 29 | 7.82 | 22.498 | -0.74-16.37 | 1.11 | 0.35 |
| | 3VD | 26 | 9.76 | 22.848 | 0.53-18.99 | | |
| | Total | 179 | 8.48 | 21.233 | 5.34-11.62 | | |
| | Mild | 72 | 0.3064 | 0.53750 | 0.1792-0.4336 | | |
| | 1VD | 52 | 0.2857 | 0.55915 | 0.1285-0.4430 | | |
| **L/A Ratio** | 2VD | 29 | 0.2039 | 0.17051 | 0.1390-0.2687 | 0.44 | 0.73 |
| | 3VD | 26 | 0.2258 | 0.17730 | 0.1542-0.2974 | | |
| | Total | 179 | 0.2718 | 0.46306 | 0.2031-0.3405 | | |

**1VD*. 1-vessel disease; 2VD*. 2-vessel disease; 3VD*. 3-vessel disease**

**Table 2. Association of independent variables with leptin, adiponectin levels and L/A in patients with CAD**

| Variables | Odds Ratio | SE | P-value | 95% CI |
|---|---|---|---|---|
| **Leptin** | 0.95 | 0.04 | 0.25 | 0.86-1.04 |
| **Sex** | 3.41 | 1.14 | 0.000 | 1.80-6.55 |
| **DM** | 2.30 | 0.73 | 0.008 | 1.24-4.30 |
| **1VD** | 0.12 | 0.31 | | -0.49-0.73 |
| **2VD** | 1.50 | 0.33 | | 0.82-2.12 |
| **3VD** | 2.50 | 0.36 | | 1.77-3.20 |
| **Adiponectin** | 0.996 | 0.008 | 0.60 | 0.98-1.01 |
| **Sex** | 3.45 | 1.15 | 0.000 | 1.79-6.63 |
| **DM** | 2.30 | 0.72 | 0.008 | 1.24-4.24 |
| **1VD** | 0.16 | 0.31 | | -0.45-0.77 |
| **2VD** | 1.53 | 0.33 | | 0.87-2.20 |
| **3VD** | 2.54 | 0.37 | | 1.82-3.25 |
| **L/A Ratio** | 0.77 | 0.24 | 0.40 | 0.42-1.41 |
| **Sex** | 3.43 | 1.14 | 0.000 | 1.80-6.57 |
| **DM** | 2.21 | 0.70 | 0.01 | 1.19-4.10 |
| **1VD** | 0.10 | 0.32 | | -0.52-0.73 |
| **2VD** | 1.50 | 0.33 | | 0.79-2.12 |
| **3VD** | 2.47 | 0.37 | | 1.74-3.20 |

**1VD*. 1-vessel disease; 2VD*. 2-vessel disease; 3VD*. 3-vessel disease**

## Discussion

Due to conflicting prior results, we evaluated biomarker links to CAD severity. The study showed that serum leptin and adiponectin levels and L/A ratio had no significant relationship with the severity of coronary atherosclerosis in patients with CAD. This was contrary to several studies reporting an association between leptin[21-24], adiponectin[21, 25-28] and also L/A ratio levels with CAD[21]. Most of the studies showed a direct association between leptin serum level and CAD, while adiponectin serum level was inversely associated with CAD, in the same way L/A ratio was higher in cases with CAD. However, not all findings are consistent. Welsh et al. found that leptin was not associated with the risk of CVD[29]. Brennan et al. in a prospective cohort study, cannot found a significant association between leptin and either cardiovascular morbidity and/or mortality in women with type 2 diabetes[30].

Regarding CAD, it has been observed that the incidence of CAD increases with advancing age[31]. The processes associated with oxidative stress and mitochondrial activity, genomic integrity and epigenetic modifications, lipid metabolism, extracellular matrix, coagulation/hemostasis, inflammation, and endothelial balance are all believed to be significant contributors to vascular aging[32, 33].

Moreover, prospective study results suggest that leptinemia does not appear to be an independent risk factor for the development of ischemic heart disease in men[34]. Sattar and colleagues in their prospective study and systematic review to determine the link between leptin and coronary heart disease (CHD) argued that previous studies appear to have overestimated associations of leptin and CHD risk[35]. Also, Lawlor et al. in a prospective study of women found no strong statistical evidence that leptin is associated with CHD risk in older British women[36]. Leptin may serve as a significant biomarker for osteoporosis in postmenopausal women, making it a potentially valuable screening tool for the clinical monitoring of these patients[37].

On the other hand, the antiatherogenic effects of adiponectin in atherosclerotic patients have been challenged. Lim et al. found no significant relation between serum adiponectin and the extent or severity of coronary atherosclerosis[18].

Lee et al. found in a meta-analysis study that there was no association between adiponectin levels and CHD events[38]. Moreover, the true association between adiponectin levels and CAD was challenged by Tragante and Asselbergs[39].

A limitation for this study is that findings may not apply to non-Iranian populations due to genetic or environmental differences. Another limitation is the cross-sectional nature of the study that could be compensated by longitudinal cohort studies.

In conclusion, according to our findings, future studies are needed to explore multi-biomarker panels for CAD risk stratification.

## Ethical Considerations

Researchers took into account the ethical considerations including institutional and national standards as well as the 1964 Helsinki declaration and its later amendments. Every patient received a full explanation of the procedures and was requested to fill up an informed consent form. In every stage of the research, patients were allowed to withdraw if they wished. This study was approved by the Qom University of Medical Sciences Ethics Committee (IR.MUQ.REC.1395.8).

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## Conflict of Interest

The authors declare that they have no competing interests.

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