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Evaluating the correlation of serum leptin levels with evidence of coronary artery disease on myocardial perfusion single-photon emission computed tomography in suspected coronary artery disease patients

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Background **Cardiovascular disease is currently the most common cause of death worldwide. Several risk factors have been identified for cardiovascular diseases, including hypertension, hyperlipidemia and diabetes. Leptin is a peptide hormone that acts as a proinflammatory cytokine and has a variety of effects in hemostasis and metabolism such as lipid metabolism, production of glucocorticoid, angiogenesis, etc. The aim of this study was to determine the relationship between the concentrations of leptin with evidence of coronary artery disease in the myocardial perfusion scan.**

Method **A one year retrospective cross-sectional study was conducted on patients who are suspected of coronary artery disease that referred to the nuclear medicine department for performing myocardial perfusion scan. The patients were classified based on the results of the myocardial perfusion scan. Serum leptin was measured with ELISA assay. The correlation of serum leptin with these parameters and also with different groups of age, sex and coronary artery disease risk factors was also compared.**

Results **The mean serum level of leptin was 290.44 ng/ml (82.9-1600 ng/ml). There is no meaningful relation between serum leptin and coronary artery disease risk factors, age and sex; also, none of the quantitative myocardial perfusion scan parameters have a significant correlation with serum leptin.**

Conclusion **Based on our findings, there was no significant correlation between myocardial perfusion scan parameters and leptin levels. Serum leptin and different groups of age, sex and coronary artery risk factors were not correlated as well.** *Nucl Med Commun* **43: 265–269**

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Keywords: coronary artery disease, leptin, myocardial perfusion single-photon emission computed tomography

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Introduction

Coronary artery disease (CAD) is considered as one of the major leading causes of morbidity and mortality; however, detection of risk factors and related mechanism and interactions involving different metabolic pathways is still challenging. Serum leptin level has been increasingly investigated and suggested as a prognostic and predictive factor in CAD.

Leptin acts as an adipocyte hormone to regulate adipose tissue mass and is expressed in adipocytes. Obesity is positively associated with higher leptin levels and leptin resistance in humans. Through hypothalamic activation, leptin plays a key role in food intake and energy hemostasis [1]. Although a potential role for leptin has been suggested in the pathogenesis and prognosis of CAD, there are still conflicting results in the literature. In some studies, serum leptin level has been shown to be remarkably higher in patients with known CAD than in normal control [2–6]. This relation is also highlighted in patients with stable angina because leptin level is higher in a multivessel CAD rather than in single-vessel disease and controls [7]; however, there are other research studies that showed no significant correlation between CAD and leptin [8–10]. It has also been suggested that leptin level is positively associated with an increased rate of cardiac events and a poorer prognosis [11,12]. A recent meta-analysis showed that increased leptin levels in women with CAD can be a predictor for cardiovascular death and nonfatal myocardial infarction but leptin does not predict secondary events in men [11]. In contrast, one study reveals that in obese patients with a history of coronary bypass graft, leptin level and BMI do not probably predict the prognosis of cardiovascular events among them [13]. Other studies, however, revealed a better prognosis with higher leptin levels in CAD patients [14,15]. Overall, although the extent of CAD might be

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determined by the plasma level of leptin, there are still controversial results regarding leptin's role in the development or prognosis of CAD [16]. Nonetheless, the role of leptin in the prediction of CAD and risk stratification of suspected CAD patients before noninvasive imaging has not been thoroughly investigated.

Modern modalities and technologies provide noninvasive imaging for not just diagnosis but also for selecting appropriate therapeutic choices and prognostic purposes in suspected CAD patients. Myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is widely used as an accepted noninvasive functional method for the evaluation of CAD in suspected patients [17,18]. The aim of this study is to assess the relationship between serum leptin level and evidence of CAD in MPI SPECT of suspected CAD patients.

Methods and materials

Study population

In a 1-year duration, patients with clinical suspicion to CAD, referred to the Nuclear Medicine Department for SPECT MPI, were prospectively evaluated before imaging. Patients who were at least 25 years old and suspected to CAD were included. However, patients with a history of previous cardiovascular disease (such as valvular heart disease, heart failure or previous cardiac surgeries or interventions including revascularization) or those with a history of any metabolic disease or other underlying chronic disease were excluded. For each patient who consented to participate in the study, detailed history including classical cardiac risk factors was taken and the blood sample was obtained for measurement of serum leptin level. This study is approved by the local ethics committee of the Shiraz University of Medical Sciences.

Serum leptin level measurement

Endocrine and Metabolism Research Center of the Shiraz University of Medical Sciences evaluated the serum level of leptin with informed consent; 5 cm^3 of blood was obtained from the patients before imaging. The samples were centrifuged to separate the serum component for leptin level determination. For this purpose, ELISA kit based on biotin double-antibody sandwich technology, designed for evaluation of human serum leptin, was used. In this method, samples, standards or controls are added to the wells of the ELISA kit which are precoated with leptin mAb and bind to the antibody. A sandwich is formed by the addition of the second antibody; then, a substrate solution is added that reacts with the enzyme-antibody-leptin complex to produce a measurable signal. The intensity of this signal is directly proportional to the concentration of leptin present in the original sample. Serum leptin levels are measured in nanograms per milliliter (ng/ml). The analytical sensitivity and assay range of this method are 1.02 and 2–1500 ng/ml, respectively.

Single-photon emission computed tomography myocardial perfusion imaging

A 2-day stress/rest SPECT MPI protocol was carried out by injection of 15-20 mCi ^{99m}Tc-sestamibi on each phase. For the stress phase of the study, patients might undergo either exercise or pharmacological stress based on appropriate indications. Imaging was performed with a dual-head cardiac-dedicated gamma camera for 45-60 min after injection, by covering a 180° arc from 45° left posterior oblique to 135° right anterior oblique in 32 steps (30 s for each projection) with a matrix size of 64 × 64. An ordered subset expectation maximization algorithm was used to reconstruct the images (order: 4; subset: 8; post-filter: Butterworth). All images were evaluated by a nuclear medicine specialist and those with suboptimal quality were excluded. Quantification of images was performed by QPS/QGS software and the quantitative and semiquantitative perfusion SPECT parameters were extracted for each patient based on a 17-segment model for left ventricle (LV): SSS (summed stress scores), SDS (summed difference scores), SRS (summed rest scores), TPD (total perfusion deficit) at stress (TPDs) and rest (TPDr) phase. The semiquantitative perfusion parameters (SSS, SRS and SDS) derived by the software were reevaluated by an expert nuclear medicine physician and modified if needed. The TPDs and TPDr values were recorded without changes; however, cases with significant variation from the interpretation of the nuclear medicine physician due to apparent artifacts (such as diaphragmatic and breast attenuation artifacts) were excluded. These parameters are well correlated with a visual scan interpretation and are recommended by the current guidelines as part of quantitative image processing for LV perfusion [19]; so, the patients were categorized based on the SSS (SSS < 4 vs. SSS ≥ 4) and TPDs (TPDs < 5 vs. TPDs ≥ 5) to normal and abnormal scan.

Statistical analyses

Symmetrically distributed variables are presented as mean values and SD. Discrete variables are described through relative and absolute frequencies. For comparison of leptin levels between the groups based on scan results or cardiac risk factors, independent *t*-test was used. Regression analysis was also utilized to evaluate the relationship of scan results and cardiac risk factors with serum leptin levels. Pearson's correlation coefficients were also calculated to identify the correlation of leptin level with quantitative scan parameters. All statistical analyses were performed by SPSS software for Windows. *P* values less than 0.05 were considered as the level of statistical significance.

Results

Finally, 172 patients were included with a female/male ratio of 115/57. The mean age of the total patient population was 57 ± 10 (28-78 years). Baseline features of patients are displayed in Table 1.

The mean serum leptin level in the total population was 340.5 ± 290.44 ng/ml. Comparison of serum leptin levels between the patients with normal and abnormal scan results based on SSS or TPDs parameter showed no statistically significant difference (Table 2).

Also, leptin revealed no significant difference between patients with or without different cardiac risk factors (Table 3). When regression analysis was utilized for the evaluation of any independent relationship between scan results or cardiac risk factors with serum leptin level, no variable was found to have any significant association.

Finally, correlation analyses with Pearson's correlation test did not also show any significant correlation between serum leptin levels with different quantitative perfusion parameters of SPECT MPI including SSS, SRS, SDS, TPDs and TPDr (Table 4).

Discussion

This study showed no significant relationship between quantitative perfusion abnormalities in SPECT MPI with serum leptin levels in suspected CAD patients. No significant correlation was also found between major cardiac risk factors and serum leptin levels in our patient population.

Although many studies have suggested a positive relationship between serum leptin level and risk of CAD, there are also studies that revealed controversial results. A study by Rahmani *et al.* reported that there was a direct relationship between serum levels of leptin and the number of involved vessels in patients that underwent coronary angiography compared to controls [18]. However, Sattar *et al.* [20] conducted a large prospective study in British men and revealed a moderate but NS correlation between serum leptin level and incident CAD. They indicated that this correlation might be overestimated in the previous studies. Another study by Ku *et al.* [21] also suggested a negative association between serum leptin level and risk of a cardiovascular event in patients with known CAD, regardless of BMI and sex. Our study also showed no significant relationship between leptin and evidence of CAD on SPECT MPI. It has been indicated that the mechanism of leptin in the pathogenesis of CAD is multifactorial and there might be different results according to the clinical background of the investigated population. For instance, Bickel *et al.* [11] found that there is significant role of leptin in the prediction of hard cardiac events in women with known CAD, whereas men showed a nonsignificant correlation. Several studies with computed tomography angiography (CTA), which is mostly used in the low to intermediate risk group as a noninvasive method, indicted a significant negative correlation of leptin with the presence of coronary plaque on CTA images. Al-Nimer *et al.* [22] found that high serum leptin levels exert a favorable effect upon the patients with ischemic heart disease, as it was associated with negative coronary CTA and improvement in left ventricular function. Another study by Caselli *et al.* [23] evaluated a group of patients with stable chest pain and intermediate probability for CAD, and suggested a significant correlation of low high-density lipoprotein (HDL) cholesterol, low leptin level and high interleukin-6 with high-risk coronary anatomy as illustrated by CTA. Likewise, in the current study, a specific patient population with unknown CAD has been selected to evaluate the predictive ability of leptin for CAD which consequently favored the

Table 1. Clinical characteristics of the patients

Clinical variable	Mean ± SD or number (%)
Age	57.8 ± 10.6
Sex (m/f)	57 (33.1%)/115 (66.9%)
Diabetes mellitus	45 (26.2%)
Hypertension	84 (48.8%)
Hyperlipidemia	73 (42.4%)
Smoking	37 (21.5%)
Family history	37 (21.5%)

Table 2. Comparison of leptin level between the normal and abnormal quantitative scan results

Grouping variable	Groups (*n*)	Leptin level (ng/ml)	*P* value
SSS	SSS < 4 (131)	299.84 ± 362.51	0.51
	SSS ≥ 4 (41)	260.42 ± 259.78	
TPDs	TPDs < 5 (118)	280.67 ± 326.34	0.58
	TPDs ≥ 5 (54)	311.69 ± 372.03	

SSS, summed stress scores; TPDs, total perfusion deficit at stress phase.

Table 3. Comparison of leptin level between the groups with and without cardiac risk factors

Grouping variable	Groups (*n*)	Leptin level (ng/ml)	*P* value
Age	Age < 60	299.84 ± 362.51	0.680
	Age ≥ 60	260.42 ± 259.78	
Sex	Male (118)	280.67 ± 326.34	0.070
	Female (54)	311.69 ± 372.03	
Diabetes mellitus	Yes	259.79 ± 314.33	0.484
	No	301.30 ± 349.90	
Hypertension	Yes	296.73 ± 367.990	0.814
	No	284.43 ± 314.24	
Hyperlipidemia	Yes	299.26 ± 371.77	0.771
	No	283.93 ± 317.36	
Smoking	Yes	271.94 ± 338.18	0.709
	No	295.51 ± 342.27	
Family history of CAD	Yes	322.47 ± 408.13	0.520
	No	281.66 ± 320.75	

CAD, cardiovascular disease.

Table 4. Correlation of semiquantitative perfusion parameters with serum leptin level

Parameter	Correlation coefficient	*P* value
SSS	−0.042	0.58
SRS	−0.071	0.35
TPDs	−0.010	0.90
TPDr	−0.032	0.67
SDS	−0.017	0.83

SRS, summed rest scores; SSS, summed stress scores; TPDr, total perfusion deficit at rest phase; TDPs, total perfusion deficit at stress phase.

poor correlation of leptin with CAD. This has been also reported in a recent meta-analysis and systematic review by Yang *et al*. [10] which found no significant correlation between leptin and risk of CAD and stroke.

Considering CAD as a chronic multifactorial disease, the relationship between serum leptin levels and classical CAD risk factors can also be helpful in further understanding the correlation between leptin and CAD. The study conducted by Bickel *et al*. [11], which was performed on patients who were referred for angiography with at least 30% stenosis in one major coronary artery, also showed significant influence of clinical variables of age, body weight and renal function on leptin concentration. Elevated leptin level has been shown to be related to insulin resistance, type 2 diabetes mellitus and subsequent increased cardiovascular risk [24,25]. Hypertension has also been widely investigated and revealed a positive association with serum leptin level [26]. However, our study showed no significant differences in mean serum leptin level between the diabetic and nondiabetic, and also hypertensive and nonhypertensive patients. Other cardiac risk factors in this study also showed no statistically significant correlation with leptin. These results of subgroup analysis, which could be partly explained by limited sample size, are in agreement with our main finding. Therefore, it can be indicated that the correlation of leptin and evidence of CAD might be associated with the rate and prevalence of other risk factors in the population.

Finally, it should be stated that perfusion abnormalities on the MPI SPECT mostly imply the functional and hemodynamic significance of anatomical coronary artery stenosis. Thus, an abnormal scan result could not be totally considered to be the same as angiographically proven CAD [27]. Consequently, our results should not be directly compared with those studies that used angiography as the diagnostic test. According to the purpose of our study, however, our result suggested that leptin is not beneficial enough to further stratify suspected patients noninvasively and is not correlated with the MPI SPECT result as an established method.

This study has also some limitations. Although the total sample size was acceptable, the subgroups of different cardiac risk factors in the two sexes were relatively small for analysis. In addition, MPI SPECT is not a gold standard in the diagnosis of CAD, and the possibility of interfering image artifact and subsequent misinterpretation is inevitable. Further research studies with larger samples and other modalities are required to evaluate the predictive role of leptin in suspected CAD patients.

Conclusion

According to our results, it seems that serum leptin level is not correlated with perfusion abnormalities on MPI SPECT and consequently CAD in suspected CAD patients. Although more dedicated prospective studies are still needed, this might be somewhat related to the prevalence of other cardiac risk factors that are influenced by leptin in their pathogenesis.

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Conflicts of interest

There are no conflicts of interest.

References

1 Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. *Cytokine* 2019; **121**:154735.
2 Raheem S, Siyar M, Khalid M, Israr M, Farhan Z, Jan M, *et al*. Relationship of serum leptin with coronary artery disease. *Journal of Bacha Khan Medical College*. 2017; **1**:3.
3 Gumanova NG, Gavrilova NE, Chernushevich OI, Kots AY, Metelskaya VA. Ratios of leptin to insulin and adiponectin to endothelin are sex-dependently associated with extent of coronary atherosclerosis. *Biomarkers* 2017; **22**:239–245.
4 Montazerifar F, Bolouri A, Paghalea RS, Mahani MK, Karajibani M. Obesity, serum resistin and leptin levels linked to coronary artery disease. *Arq Bras Cardiol* 2016; **107**:348–353.
5 Shanker J, Rao VS, Ravindran V, Dhanalakshmi B, Hebbagodi S, Kakkar VV. Relationship of adiponectin and leptin to coronary artery disease, classical cardiovascular risk factors and atherothrombotic biomarkers in the IARS cohort. *Thromb Haemost* 2012; **108**:769–780.
6 Taneli F, Yegane S, Ulman C, Tikiz H, Bilge AR, Ari Z, Uyanik BS. Increased serum leptin concentrations in patients with chronic stable angina pectoris and ST-elevated myocardial infarction. *Angiology* 2006;**57**:267–272.
7 Jerez-Valero M, Meliveo-García A, Jordán-Martínez L, Carrasco-Chinchilla F, Moreno-Santos I, Ordóñez A, *et al*. Role of serum leptin in the severity of coronary artery disease in patients with stable angina. *Medicina Clínica (English Edition)*. 2016; **147**:7–12.
8 Hoefle G, Saely CH, Risch L, Rein P, Koch L, Schmid F, *et al*. Leptin, leptin soluble receptor and coronary atherosclerosis. *Eur J Clin Invest* 2007; **37**:629–636.
9 Poulakou MV, Paraskevas KI, Wilson MR, Iliopoulos DC, Tsigris C, Mikhailidis DP, Perrea D. Apolipoprotein J and leptin levels in patients with coronary heart disease. *In Vivo* 2008; **22**:537–542.
10 Yang H, Guo W, Li J, Cao S, Zhang J, Pan J, *et al*. Leptin concentration and risk of coronary heart disease and stroke: a systematic review and meta-analysis. *PLoS One* 2017; **12**:e0166360.
11 Bickel C, Schnabel RB, Zeller T, Lackner KJ, Rupprecht HJ, Blankenberg S, *et al*. Predictors of leptin concentration and association with cardiovascular risk in patients with coronary artery disease: results from the AtheroGene study. *Biomarkers* 2017; **22**:210–218.
12 Puurunen VP, Kiviniemi A, Lepojärvi S, Piira OP, Hedberg P, Junttila J, *et al*. Leptin predicts short-term major adverse cardiac events in patients with coronary artery disease. *Ann Med* 2017; **49**:448–454.
13 Buschmann K, Wrobel J, Chaban R, Rösch R, Ghazy A, Hanf A, *et al*. Body mass index (BMI) and its influence on the cardiovascular and operative risk profile in coronary artery bypass grafting patients: impact of inflammation and leptin. *Oxid Med Cell Longev* 2020; **2020**:5724024.
14 Caselli C, Rocchiccioli S, Rosendael A, Buechel R, Teresinska A, Pizzi M, *et al*. P6167 Low leptin plasma levels are associated with progression of coronary atherosclerosis in patients with stable coronary artery disease from the SMARTool Study. *Euro Heart J*. 2019; **40**(Supplement_1):ehz746.0773.
15 Simiti LA, Todor I, Stoia MA, Goidescu CM, Anton FP, Farcas AD. Better prognosis in overweight/obese coronary heart disease patients with high plasma levels of leptin. *Clujul Med* 2016; **89**:65–71.

16 Rahmani A, Toloueitabar Y, Mohsenzadeh Y, Hemmati R, Sayehmiri K, Asadollahi K. Association between plasma leptin/adiponectin ratios with the extent and severity of coronary artery disease. *BMC Cardiovasc Disord* 2020; **20**:474.
17 Dorbala S, Ananthasubramaniam K, Armstrong IS, Chareonthaitawee P, DePuey EG, Einstein AJ, *et al*. Single Photon Emission Computed Tomography (SPECT) myocardial perfusion imaging guidelines: instrumentation, acquisition, processing, and interpretation. *J Nucl Cardiol* 2018; **25**:1784–1846.
18 Ghaedian T, Behbudnia T, Dehghani P. Comparison of quantitative perfusion and function parameters of Gated-SPECT myocardial perfusion imaging in patients with concordant and discordant left bundle-branch block. *Clin Nucl Med* 2020; **45**:7–10.
19 Tilkemeier PL, Bourque J, Doukky R, Sanghani R, Weinberg RL. ASNC imaging guidelines for nuclear cardiology procedures. *J Nucl Cardiol*. 2017; **24**:2064–2128.
20 Sattar N, Wannamethee G, Sarwar N, Chernova J, Lawlor DA, Kelly A, *et al*. Leptin and coronary heart disease: prospective study and systematic review. *J Am Coll Cardiol* 2009; **53**:167–175.
21 Ku IA, Farzaneh-Far R, Vittinghoff E, Zhang MH, Na B, Whooley MA. Association of low leptin with cardiovascular events and mortality in patients with stable coronary artery disease: the Heart and Soul Study. *Atherosclerosis* 2011; **217**:503–508.
22 Al-Nimer MS, Alhusseiny AH, Ibrahim AK. Assessment of serum adiponectin and leptin levels in patients with ischaemic heart disease: an association with the ejection fraction, coronary calcium score and coronary angiogram. *Folia Cardiologica*. 2018; **13**:204–209.
23 Caselli C, De Graaf MA, Lorenzoni V, Rovai D, Marinelli M, Del Ry S, *et al*. HDL cholesterol, leptin and interleukin-6 predict high risk coronary anatomy assessed by CT angiography in patients with stable chest pain. *Atherosclerosis* 2015; **241**:55–61.
24 Ambad R, Jha RK, Chandi DH, Hadke S. Association of leptin in diabetes mellitus and obesity. *Res J Pharm Technol*. 2020; **13**:6295–6299.
25 Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. *Acta Pharmacol Sin* 2018; **39**:1176–1188.
26 Ghaedian MM, Nazari Jaz A, Momeni M, Ghaedian T, Samiei N. Plasma leptin level is positively associated with blood pressure measures independent of gender and BMI. *Clin Exp Hypertens* 2020; **42**:31–35.
27 Nudi F, Iskandrian AE, Schillaci O, Peruzzi M, Frati G, Biondi-Zoccai G. Diagnostic accuracy of myocardial perfusion imaging with CZT technology: systemic review and meta-analysis of comparison with invasive coronary angiography. *JACC: Cardiovasc Imaging*. 2017; **10**:787–794.