

Serum salusin- β levels as predictors of coronary artery disease in obese Egyptian women

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Background

Obesity is a growing health concern that has become an epidemic all over the world. Obesity is associated with coronary artery disease (CAD). Salusin- β is an endogenous bioactive peptide that accelerates inflammatory responses in vascular endothelial cells and increases oxidative stress. The objective of this study was to explore the potential roles of salusin- β in endothelial dysfunction in CAD. Also, we aimed to evaluate the association between salusin- β with severity of CAD in obese Egyptian women.

Patients and methods

This cross-sectional study enrolled 95 obese women who were classified into two groups: 58 patients without CAD and 37 patients with CAD. All patients were investigated using a 12-lead standard ECG, echocardiography, and coronary arteriography. Salusin- β levels were measured by enzyme-linked immunosorbent assay.

Results

Salusin- β levels were significantly higher in obese patients with CAD compared with patients without CAD. Salusin- β levels were positively correlated with cardiometabolic risks and severity of coronary occlusion. Serum salusin- β levels, high-sensitivity C-reactive protein, and BMI were independently correlated with CAD and BMI. Homeostatic model assessment of insulin resistance, high-sensitivity C-reactive protein, and uric acid were the main associated variables of serum salusin- β levels among other clinical and laboratory biomarkers. The diagnostic power of serum salusin- β levels in differentiating CAD from obese patients without CAD was highly sensitive (97.2%) and the specificity was 98.3%.

Conclusion

The higher levels of salusin- β levels in obesity, as well as CAD, were positively correlated with cardiometabolic risk factors and severity of coronary occlusion. Therefore, salusin- β levels seem to be a noninvasive biomarker of CAD.

Keywords:

coronary artery disease, endothelial dysfunction, obesity, oxidative stress, salusin- β

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Introduction

Despite attempts to increase awareness of the deleterious health consequences associated with obesity, there continues to be a significant increase in the obese population worldwide. A preponderance of evidence suggests that cardiovascular disease represents the most important complication associated with obesity. The development of endothelial dysfunction combined with vascular remodeling are the earliest manifestations of an altered vascular homeostasis, involved in the initiation, evolution, and complications of cardiovascular disorders [1].

Endothelial dysfunction, which is an early manifestation of altered vascular homeostasis due to exposure to cardiovascular risk factors, is a predictive index of cardiovascular events in high-risk patients.

Indeed; endothelial dysfunction is generally characterized by an increased level of vascular wall oxidative stress, supported mainly by the reactive oxygen species [2].

Salusin- β is an endogenous bioactive peptide with 20 amino acid residues [3]. It stimulates the proliferation, migration of vascular smooth muscle cells, and foam cell formation [4,5]. Salusin- β blockade ameliorates endothelial inflammation to improve pulmonary arterial hypertension [6] and pulmonary vascular

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remodeling [7]. Substantial evidence implicates the high salusin- β levels with hyperglycemia [8].

Obesity reflects a generalized proinflammatory state with high risk for metabolic comorbidities, such as coronary artery disease (CAD). Endothelial dysfunction is a systemic manifestation and is associated with CAD and mortality. Effective preventive strategies for high-risk patients with severe endothelial dysfunction are important to improve the prognosis. Thus, the objective of this study was to explore the potential roles of salusin- β in endothelial dysfunction in CAD. Also, we aimed to evaluate the association between salusin- β with severity of CAD in obese Egyptian women.

Patients and methods

Patients

This study included 95 obese women, having BMI more than 30 who were recruited from the Diabetes and Endocrinology outpatient clinic of Internal Medicine Department, Zagazig University Hospitals. They were classified into two groups: 58 patients without CAD and 37 patients with CAD. The diagnosis of CAD was based on the combination of clinical presentation and ECG. Patients with diabetes, decompensated liver disease, rheumatic valvular heart diseases, decompensated heart failure, previous myocardial infarction, or recent cerebrovascular events (such as brain infarction or hemorrhage) within the prior 6 months were excluded from the study. All patients were subjected to thorough history taking and full clinical assessment including blood pressure and anthropometric variables. BMI was calculated as weight (kg)/height (m²). The patients underwent elective coronary angiography for disease in the Cardiology Department of Zagazig University Hospitals. All patients were investigated using a 12-lead standard ECG, echocardiography. Coronary arteriography was performed to all patients by the Judkins technique for assessment of lesions' distribution and description. Severity of atherosclerotic CAD was assessed by using SYNTAX score which is based on the baseline diagnostic angiogram. The total SYNTAX score was calculated from the summation of the individual scorings for each separate lesion by using a SYNTAX score algorithm available on the SYNTAX website (<http://www.syntaxscore.com>). CAD was considered significant if there was at least a 0% diameter stenosis in at least one coronary artery.

The ethics committee of the Faculty of Medicine, Zagazig University approved our study protocol, and

all participants signed a written informed consent to participate in the study.

Collection of blood and biochemical analysis

Venous blood samples were collected from patients after an overnight fasting for the determination of total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and triglyceride (TG). Also, fasting plasma glucose (FPG) level and fasting serum insulin (FSI) levels were determined by high-sensitivity enzyme-linked immunosorbent assay kit provided by Biosource Europe S.A. (Nivelles, Belgium). Homeostasis model assessment of insulin resistance (HOMA-IR) were calculated. Serum TC, HDL cholesterol, and TG concentrations were determined calorimetrically by kits purchased from Stanbio Laboratory (Boerne, Texas, USA). Serum low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula [9]. C-reactive protein was measured using immunoturbidimetric assay on Roche/Hitachi Cobas system (c501) autoanalyzer (Roche Diagnostics, Mannheim, Germany). Serum salusin- β levels were measured by commercial enzyme-linked immunosorbent assay kits (Uscn Life Science, Houston, Texas, USA).

Statistical analysis

Categorical variables were presented as frequencies and percentages and compared using the χ^2 -test. Shapiro-Wilk's testing was conducted to determine the normal distribution of quantitative variables. Variables with normal distribution were compared using Student's *t*-test. Non-normally distributed variables were tested using the Mann-Whitney *U*-test. Correlations between continuous variables were determined by Pearson's correlation test. Logistic regression was conducted to evaluate the association between salusin- β levels and other correlated variables. Linear regression analysis tested the influence of the main independent variables against salusin- β . A receiver operating characteristic (ROC) curve was generated for serum levels of salusin- β . A *P*-value of less than 0.05 was considered statistically significant.

Results

Clinical, anthropometric, and laboratory characteristics of the studied patients

Among the obese groups, patients with CAD (*n*=37) had significantly higher values of systolic blood pressure, MI, waist/hip ratio as well as lipid profile (TG, TC and LDL) compared with women without CAD. Furthermore, there were significantly higher values of FPG, FSI, and HOMA-IR in obese

Table 1 Clinical, anthropometric, and laboratory characteristics of obese groups

	Without CAD (mean±SD) (n=58)	With CAD (mean±SD) (N=37)	P-value
Age (years)	30.5±6.7	28.8±6.2	0.212
Family history of CAD	10	22	<0.001*
Systolic blood pressure (mmHg)	127.3±12.08	133.78±13.9	0.019
Diastolic blood pressure (mmHg)	88.5±7.86	89.2±9.19	0.682
BMI (kg/m^2)	34.07±3.84	36.09±5.48	0.038
Waist/hip ratio	1.31±0.16	1.42±0.24	0.010
Ejection fraction (%)	46.66±6.1	43.17±6.41	<0.001*
Fasting plasma glucose (mg/dl)	97.62±32.4	172.5±33.16	<0.001*
Fasting serum insulin (IU/ml)	8.34±3.615	16.9±10.427	<0.001*
HOMA-IR	2.21±2.013	7.4±5.06	<0.001*
HDL-C (mg/dl)	35.66±6.10	35.2±5.889	0.725
LDL-C (mg/dl)	91.6±43.9	137.1±31.2	<0.001*
Total cholesterol (mg/dl)	158.84±51.85	189.2±9.16	<0.001*
Triglycerides (mg/dl)	165.3±33.9	179.4±26.36	0.035
Uric acid (mg/dl)	5.33±2.19	5.8±2.004	0.217
hs-CRP ($\mu\text{g}/\text{ml}$)	2.75±2.2	3.01±1.84	0.560
Cardiac medication			
β -Blocker	9	36	<0.001*
ACEI/ARB	15	37	
Statin	8	27	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol. * $P<0.05$.

patients with CAD compared with obese women without CAD. In addition, nontraditional risk factors such as serum uric acid and high-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in obese group patients with CAD compared with women without CAD ($P<0.001$) (Table 1).

Comparison of salusin- β levels in different studied groups

Our results showed statistically significant higher values of salusin- β levels in obese patients with CAD (418.4 ± 79.35) compared with obese women without CAD (250.9 ± 61.46) ($P<0.001$) (Fig. 1a).

Salusin- β levels in obese women with coronary artery disease stratified according to the number of coronary arteries occlusion

Among patients with CAD ($n=37$), patients with multivessel occlusion ($n=12$) had statistically significant higher values of salusin- β levels (626.2 ± 134.5) compared with patients with two-vessel occlusion ($n=15$, 451.5 ± 84.4) and patients with single-vessel occlusion ($n=10$, 349.1 ± 23.7) ($P<0.001$) (Fig. 1b).

The severity of coronary artery disease using the SYNTAX score

We estimated the severity of CAD according to coronary angiography findings and we used the SYNTAX score. The mean value of SYNTAX

score in CAD patients was 30.12 ± 5.365 , whereas in women without CAD it was 11.12 ± 4.365 ($P<0.001$) (Fig. 1c).

Correlation between salusin- β levels and severity of coronary artery disease using the SYNTAX score

In the CAD subgroup ($n=37$), there were significant positive correlations between salusin- β levels and Syntax score ($P<0.05$) (Fig. 2a).

Correlation between BMI and severity of coronary artery disease using the SYNTAX score

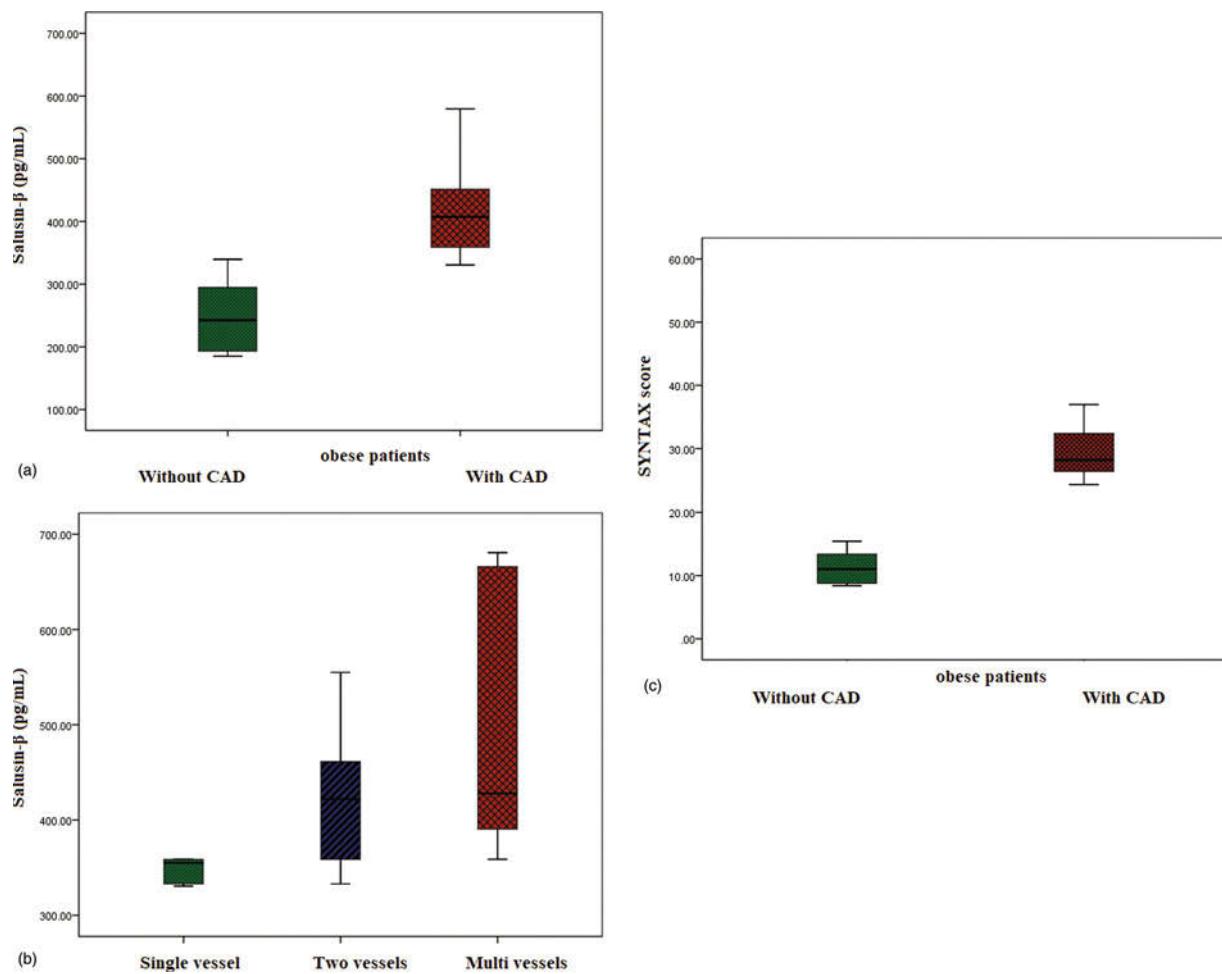
There were significant positive correlations between BMI and SYNTAX score ($P<0.05$) (Fig. 2c).

Pearson's correlation between salusin- β levels with clinical and laboratory parameters among type 2 diabetes mellitus patients

Our results showed that there were significant positive correlations between salusin- β levels and SBP, BMI (Fig. 2b), TC, TG, LDL, FSI, FPG, HOMA-IR, hs-CRP, and uric acid. In contrast, salusin- β levels were significantly negatively correlated with ejection fraction ($P<0.05$) (Table 2).

Linear regression analysis in obese groups

Our results found that BMI, HOMA-IR, hs-CRP, and uric acid were the main associated variables with salusin- β levels among other clinical and laboratory biomarkers ($P<0.05$) (Table 3).

Figure 1

(a) Comparison of salusin- β (pg/ml) levels in obese groups. (b) Comparison of salusin- β (pg/ml) levels in the coronary artery disease group. (c) Comparison of SYNTAX score in different obese groups. CAD, coronary artery disease.

Logistic regression analysis test was used to evaluate the association of salusin- β , with the severity of coronary artery disease among obese groups

Our study showed that the only variables associated with severity of CAD among obese patients were salusin- β [odds ratio=1.054, 95% confidence interval (CI)=1.022–1.086], hs-CRP (odds ratio=0.184, 95% CI=0.046–0.727), and BMI (odds ratio=1.303, 95% CI=1.014–1.674) ($P<0.001$) (Table 4).

The accuracy of circulating salusin- β levels in the diagnosis of coronary artery disease by receiver operating characteristic analysis

The power of salusin- β level to diagnose CAD among the studied patients was evaluated using the ROC analysis. The area under the curve was 0.982 (95% CI=0.953–1.000) with a sensitivity of 97.2%, specificity of 98.3%, and the cutoff values was found to be 345.3 (Fig. 3).

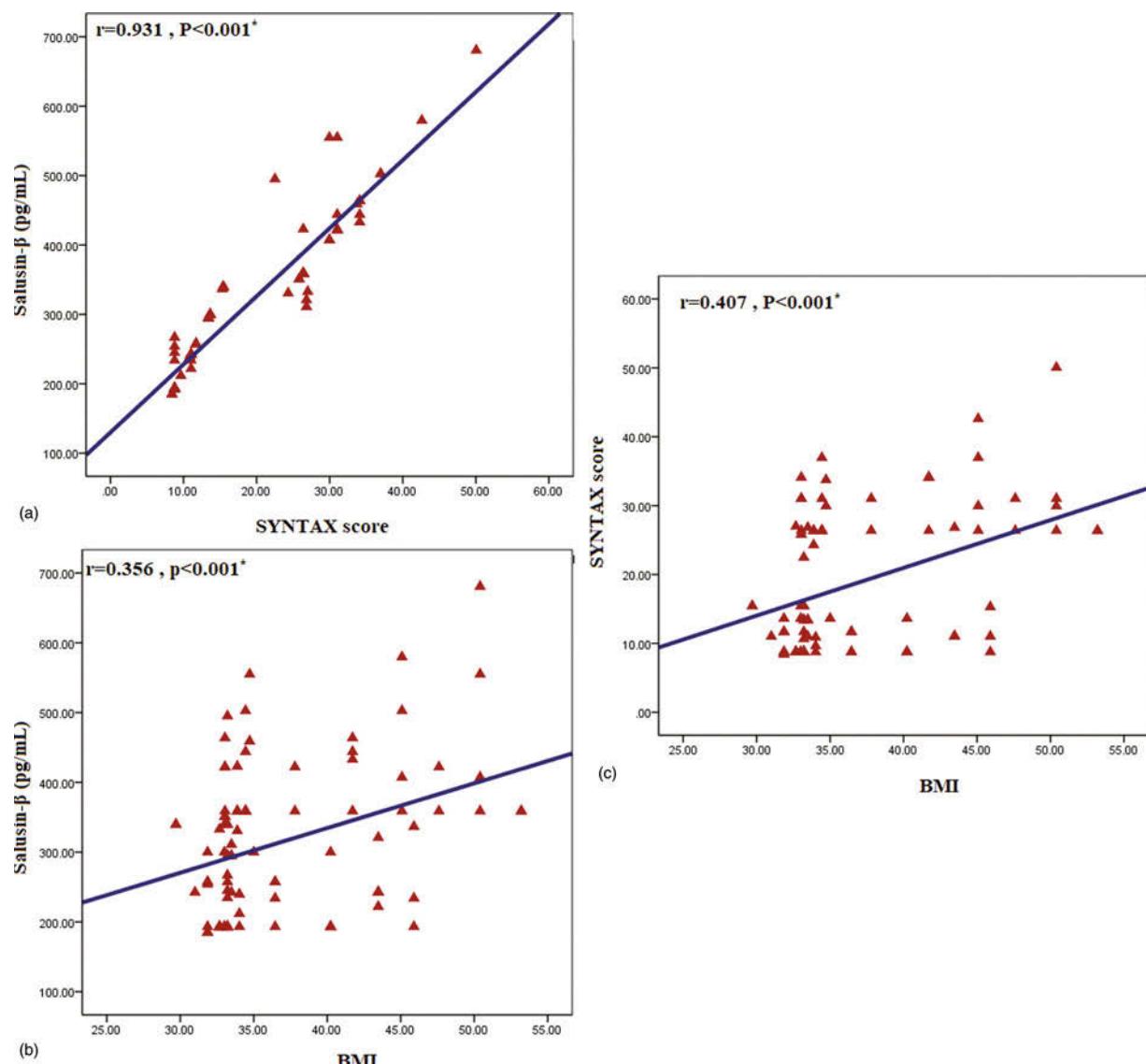
Discussion

Obesity is a challenge for global public health, particularly with regard for its effects on several

comorbid diseases including CAD [10]. Many recent studies proposed that obesity is associated with endothelial dysfunction [11]. Extensive data support a major role of perivascular adipose tissue on vascular tone through the secretion of a variety of proinflammatory cytokines that lead to oxidative stress and endothelial dysfunction [12,13].

Mounting evidence indicates that salusin- β levels are higher in patients with diabetes than healthy controls [7]. Even more importantly, it has been observed that the inhibition of salusin- β improves oxidative stress, inflammation, and cardiac dysfunction [14].

Conflicting data have been reported regarding the association between body weight and cardiovascular risk factors. Obesity is associated with advanced cardiovascular disease and a higher mortality rate [15]. Weight loss has been associated with improvement in preexisting cardiovascular risk

Figure 2

(a) Correlation between salusin- β (pg/ml) levels and SYNTAX. (b) Correlation between salusin- β (pg/ml) levels and BMI. (c) Correlation between SYNTAX values and BMI.

factors including hypertension, diabetes, and dyslipidemia and mortality [16]. Therefore, we aimed to explore the potential roles of salusin- β in endothelial dysfunction in CAD. Also, we aimed to evaluate the association between salusin- β with severity of CAD in obese Egyptian women.

As expected, our finding adds to the growing body of evidence implicating that obesity is associated with cardiometabolic disease [17,18]. According to our cross-sectional study, about 37 (38.9%) women had CAD documented by the result of coronary angiography. Obese patients with CAD had significantly higher cardiovascular risk factors. Interestingly, there were significant positive correlations between BMI and severity of coronary artery occlusion by the SYNTAX score.

Similar results were observed in the study by Flegal *et al.* [15]; the researchers observed a high-mortality rate in obese patients with CAD than lean patients with CAD.

In contrast, a study by Niraj *et al.* [19] did not find a correlation between obesity and severity of CAD after adjustment for confounders suggesting that younger age may influence the obesity paradox. Also, in contrast to our findings, a study by Parsa and Jahanshahi [20] reported an inverse relationship between BMI and severity of CAD in a cross-sectional, prospective study of 414 patients with suspected CAD.

Previous studies have indeed demonstrated a clear association between salusin peptides as endogenous modulators of atherogenesis [8] and atherosclerosis

[21]. Moreover, emerging data have demonstrated that atherosclerosis is a complex and multifactorial disease whose pathogenesis is associated with inflammatory responses [22,23].

Accumulating studies have reported that the endogenous salusin- β excessively produced in vascular lesions could contribute to the development of atherosclerosis [24]. In this respect, salusin- β is released from human monocytes/macrophage, suggesting a possible autocrine/paracrine role in the development and progression of atherosclerosis [25].

The results presented here are innovative, as this study was the first Egyptian study that investigated the serum levels of salusin- β in the obese group as well as patients with CAD. Our results showed statistically significant

higher values of salusin- β levels in the obese group in particular obese patients with CAD.

In agreement with our results, a study conducted by Kołakowska *et al.* [26] found higher salusin- β plasma levels in obese children than lean ones.

Similar to our result, a study conducted by Sato *et al.* [25] found circulating salusin- β levels increased in patients with CAD.

Our findings are in concordance with Liu *et al.* [27] who detected that serum salusin- β levels were significantly higher in patients undergoing coronary artery graft than those in healthy controls. Among patients undergoing coronary artery graft, patients with CAD had significantly higher serum salusin- β levels compared with patients without CAD [27].

Our results showed that there were significant positive correlations between serum salusin- β levels and SBP, BMI, TG, LDL, HOMA-IR, FSI, FPG, hs-CRP, and uric acid. In addition, serum salusin- β levels, hs-CRP, and BMI were independently correlated with CAD after adjusting other cofactors and BMI, HOMA-IR, hs-CRP, and uric acid were the main associated variables of serum salusin- β levels among other clinical and laboratory biomarkers.

Similarly, Liu *et al.* [27] detected that there was positive correlation between serum salusin- β levels and coronary atherosclerosis index score. Salusin- β acts as a potential proatherogenic factor via promoting macrophage foam cell formation [28].

In agreement with our results, a study conducted by Kołakowska *et al.* [26] derived a positive correlation between serum salusin- β level and the TG/HDL ratio.

Table 2 Correlation between salusin- β levels with cardiometabolic risk factors among obese patients

Variables	Obese patients (n=95)	
	r	P
Systolic blood pressure (mmHg)	0.342	<0.001*
Diastolic blood pressure (mmHg)	0.109	0.297
BMI (kg/m ²)	0.356	<0.001*
Waist/hip ratio	0.270	<0.001*
Ejection fraction (%)	-0.239	<0.001*
TC (mg/dl)	0.432	<0.001*
TG (mg/dl)	0.322	<0.001*
LDL-C (mg/dl)	0.479	<0.001*
HDL-C (mg/dl)	-0.070	0.503
Fasting plasma glucose (mg/dl)	0.703	<0.001*
Fasting serum insulin (IU/ml)	0.548	<0.001*
HOMA-IR	0.597	<0.001*
hs-CRP (μ g/ml)	0.342	<0.001*
Uric acid (mg/dl)	0.449	<0.001*

HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. *P<0.05.

Table 3 Linear regression analysis test used to explore the influence of the main independent variables against salusin- β (dependent variable) in obese patients

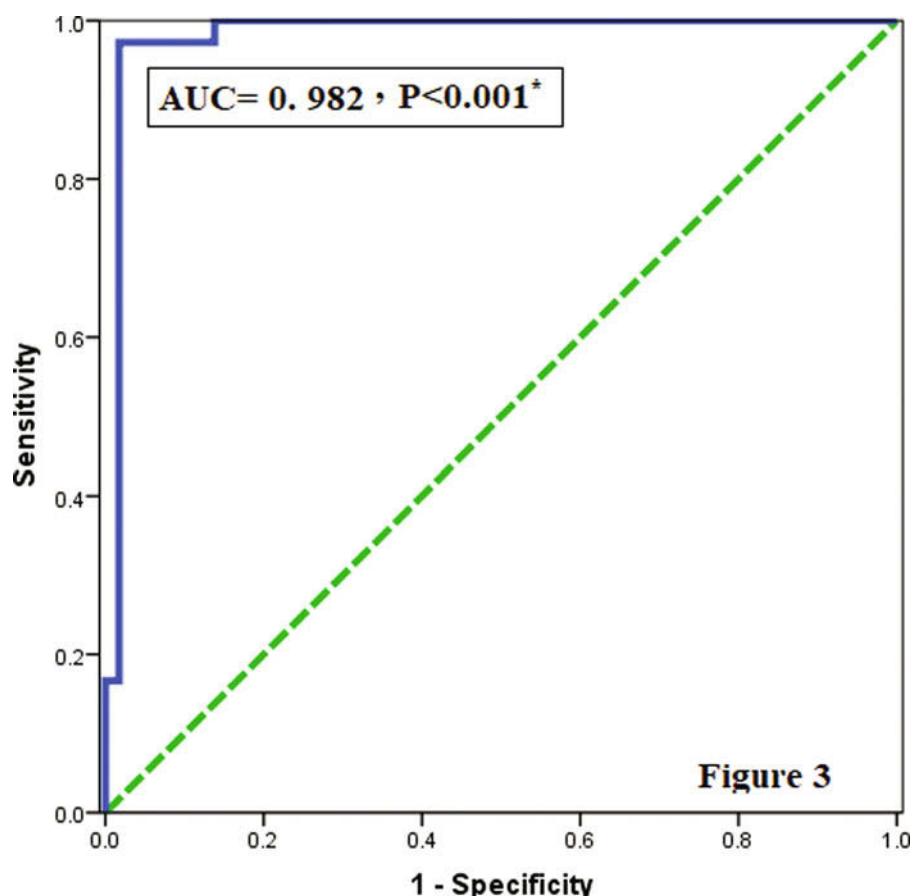
Model	Unstandardized coefficients		β	t	P	95% CI	
	B	SE				Lower bound	Upper bound
1							
Constant	26.290	92.007	–	0.286	0.776	-156.5	209.163
Ejection fraction (%)	0.549	1.965	0.033	0.279	0.781	-3.35	4.453
HDL-C	-1.551	2.051	-0.087	-0.756	0.452	-5.626	2.525
BMI	3.947	1.464	0.220	2.695	<0.001*	1.036	6.857
HOMA-IR	12.585	2.225	0.490	5.657	<0.001*	8.163	17.007
hs-CRP	-25.130	10.028	-0.489	-2.506	<0.001*	-45.06	-5.198
Uric acid	34.979	9.963	0.692	3.511	<0.001*	15.176	54.783

CI, confidence interval; HDL-C, high-density lipoprotein C; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein. *P<0.05.

Table 4 Logistic regression analysis test used to evaluate the association of salusin- β with severity of coronary artery disease among obese patients

	B	SE	t	P-value	Odds ratio	95% CI	
						Lower	Upper
Salusin	0.052	0.016	11.367	<0.001*	1.054	1.022	1.086
hs-CRP	-1.695	0.702	5.832	<0.001*	0.184	0.046	0.727
HOMA-IR	0.544	0.514	1.121	0.290	1.724	0.629	4.721
BMI	0.264	0.128	4.277	<0.05*	1.303	1.014	1.674
HDL-C	-0.004	0.109	0.001	0.969	0.996	0.805	1.232
Constant	-23.774	8.404	8.002	<0.001*	0.000	—	—

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein. *P<0.05.

Figure 3

Receiver operating characteristic curve for salusin- β , as diagnostic biomarkers for the diagnosis of coronary artery disease among obese women. AUC, area under the curve.

To better elucidate the diagnostic power of serum salusin- β , we tested our findings by using an ROC test which revealed that the diagnostic power of serum salusin- β level in differentiating CAD from obese patients without CAD was highly sensitive (97.2%) and the specificity was 98.3%.

Conclusion

Our results showed statistically significant higher values of serum salusin- β levels in the obese patients with CAD than those without CAD. The

higher levels of serum salusin- β levels were strongly correlated with cardiometabolic risk factors and severity of coronary occlusion. Therefore, serum salusin- β might be considered to be a noninvasive biomarker of CAD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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