Elective percutaneous coronary intervention leads to significant changes in serum resistin, leptin, and adiponectin levels regardless of periprocedural myocardial injury: an observational study

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Abstract

Objective: Bioactive roles of adipokines in coronary atherosclerosis and acute coronary syndromes have been demonstrated previously. However, there is a lack of data regarding the relationship between serum adipokines and periprocedural myocardial injury (PMI) following elective percutaneous coronary intervention (PCI). Therefore, we aimed to investigate the association between serum adipokines and PMI related to elective PCI.

Methods: In total, 153 consecutive patients (aged 60.6±8.2 years, 98 men) with stable angina pectoris undergoing elective PCI were enrolled in this observational cross-sectional study. Serum resistin, leptin, adiponectin, and high-sensitive Troponin T (hscTnT) levels were measured immediately before PCI and after 12-h PCI. The no-injury, PMI, and type 4a myocardial infarction (type 4a MI) groups were defined as groups consisting patients with post-procedural hscTnT concentrations <14 ng/L, between 14–70 ng/L, and >70 ng/L, respectively.

Results: Serum hscTnT, resistin, and leptin concentrations significantly ($p<0.001$) increased while serum adiponectin levels decreased ($p<0.001$) after 12-h elective PCI. However, no correlation was found between post-procedural hscTnT concentrations and resistin, leptin, and adiponectin levels. The no-injury group consisted of 65 patients (42.4%), whereas PMI and type 4a MI were observed in 70 (45.8%) and 18 (11.8%) patients, respectively. The average pre-procedural and post-procedural resistin, leptin, and adiponectin levels did not show any significant difference in the no-injury, PMI, and type 4a MI groups.

Conclusion: There is no correlation between serum adipokine levels and post-procedural troponin elevations reflecting PMI or type 4a MI. However, serum resistin and leptin levels increase, whereas adiponectin levels decrease significantly after elective PCI.

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Keywords: resistin, leptin, adiponectin, coronary

Introduction

Percutaneous coronary intervention (PCI) has become the predominant revascularization strategy in patients with atherosclerotic coronary artery disease. Although PCI is safe in majority of the cases, iatrogenic plaque rupture generated by balloon angioplasty and stent implantation may lead to periprocedural myocardial injury (PMI) even in successful and uneventful procedures (1–3). PMI has prognostic importance since significant cardiac biomarker elevation following PCI is associated with an increased risk of adverse cardiovascular events in short- and long-term follow up (4, 5). Therefore, clinical and procedural factors that may lead to PMI have been investigated to improve clinical outcomes in patients undergoing elective PCI. Although periprocedural side branch occlusion, coronary dissection, distal embolization, and no-reflow during stenting are well known factors to be related to PMI, actual data also indicate that metabolic status of the patient such as admission dyslipidemia, abnormal glucose levels, and albuminuria are associated with PMI in patients undergoing elective PCI (6–9).

The present study aimed to investigate the relationship between circulating adipokines and PMI in patients with stabil angina pectoris. Adipokines are bioactive serum proteins secreted by adipocytes, which regulate metabolism, insulin

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resistance, vascular inflammation, and endothelial functions (10). Alterations in serum concentrations of adipokines such as resistin, leptin, and adiponectin have been demonstrated to be linked with coronary artery disease progression, atherosclerosis severity (10–12), and in-stent restenosis (13–15), besides their prognostic roles in predicting major adverse cardiovascular events including death and myocardial infarction (16–19). Furthermore, several clinical trials have also represented adipokines as markers of myocardial necrosis because of the observed significant changes in their serum concentrations during acute coronary syndromes (20, 21).

However, there is a lack of data in the literature regarding the impact of admission serum adipokines on PMI following elective PCI in patients with stable coronary artery disease. Moreover, to the best of our knowledge, changes in serum concentrations of resistin in response to elective PCI in stable atherosclerotic coronary artery disease have not been evaluated before. Therefore, we aimed to evaluate serum resistin, leptin, and adiponectin levels together with high-sensitive cardiac troponin T (hscTnT) concentrations before and after elective PCI procedures and assess the correlation between circulating adipokines and post-procedural hscTnT concentrations reflecting PMI. In addition, the change in serum resistin concentrations after elective PCI was evaluated for the first time together with serum leptin and adiponectin levels in patients with stable angina pectoris in the present study.

Methods

Study protocol and population

In total, 153 consecutive patients at Acıbadem Kadıköy Hospital and Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Hospital, Departments of Cardiology with stable angina pectoris undergoing elective PCI procedures with objective signs of coronary ischemia detected by non-invasive modalities such as exercise stress test or myocardial perfusion scintigraphy were enrolled in this observational cross-sectional study. Exclusion criteria included acute or subacute myocardial infarction, unstable angina, heart failure, chronic renal failure, and chronic inflammation. The study was conducted according to the principles of Helsinki Declaration and approved by the Ethics Committee of Acıbadem University School of Medicine. A written informed consent was taken from each participant.

Coronary lesion morphology classification and PCI procedure

Coronary angiographies were performed with a cine-angiographic equipment (Siemens Artis Zee system, Forchheim, Germany). Quantitative coronary angiography (QCA) software with digital calibration was used to determine coronary lesion severity in terms of percent diameter stenosis (%). QCA measurement indicating a ≥70% diameter narrowing or 40%–70% diameter narrowing with a fractional flow reserve ≤0.80 in a coronary artery was defined as significant stenosis. Coronary lesion classification was defined according to the Society for Cardiac Angiography and Interventions (SCAI) lesion classification system (22), which uses type C lesion characteristics (23) as the key determinant of the lesion complexity. Accordingly, we defined four different lesion types (SCAI type 1–4) based on SCAI classification system. Standard PCI techniques were performed via femoral or radial approaches by two experienced interventional cardiologists who had already evaluated QCA and determined target coronary lesions. Twenty angiograms were randomly selected and measurements were repeated for assessment of intra- and inter-observer variability. The intra- and inter-observer variabilities for coronary artery stenosis measurements were <4% and <6%, respectively. All the cases were preloaded with 300 mg aspirin and 600 mg clopidogrel before the procedure. Intravenous heparin (70–100 IU/kg) was administered before PCI with subsequent bolus doses to maintain an activating clotting time between 250–300 s.

Determination of serum hscTnT, resistin, leptin, and adiponectin concentrations

Peripheral venous blood samples were collected just before PCI and 12 h after the procedure. Serum supernatant was separated and stored frozen at –80°C until analysis. Serum troponin T concentration was measured by a high-sensitive troponin T assay (Elecsys Troponin T- High Sensitive Immunoassay, Roche Diagnostics, Rotkreuz, Switzerland) with an analytical measurement range of 3–1000 ng/L. The assay coefficient of variation was <10% at this limit.

Serum resistin, leptin, and adiponectin concentrations were assayed by ELISA using commercially available assay kits (Boster Biological Technology, Co. Ltd. Pleasanton, Ca, USA).

Determination of PCI-related myocardial injury and infarction

The value for the upper reference limit (URL) of serum hscTnT was determined as 14 ng/L consistent with the normal value accepted for healthy population at the 99th percentile (24). Type 4a MI was defined as elevation of hscTnT values greater than five times the 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of hscTnT values >20% if the baseline values are elevated and are stable or falling in addition to clinical and/or laboratory findings indicative of myocardial ischemia (25). PMI was defined as previously described (2, 7–9). Accordingly, after exclusion of patients with elevated baseline troponin values, we categorized the participants into three groups based on post-procedural serum hscTnT concentrations:

1. No-injury group (patients with serum post-procedural hscTnT concentrations ≤14 ng/L) (24)
2. PMI group (patients with >14–<70 ng/L of post-procedural hscTnT concentrations)
3. Type 4a MI group (patients with ≥70 ng/L of post-procedural hscTnT concentrations with any symptoms suggestive of myocardial ischemia or new ischemic ECG changes or new segmentary wall motion abnormality detected by echocardiography).

Statistical analysis

All analyses were performed by using Sigma Plot 11.0 statistical software (Systat Software Inc., San Jose, California). Continuous variables were reported as mean (±standard error) unless otherwise stated. Two independent means were compared by using t-test. Pre-procedural and post-procedural serum hscTnT, resistin, leptin and adiponectin concentrations were compared by using paired t-test. For comparison between the three groups, one way analysis of variance (ANOVA) with the posthoc Tukey test was used. Non-normally distributed variables were presented as median (25^{th}–75^{th} percentile), and for comparison between groups either the Kruskal–Wallis (between 3 groups) or the Mann–Whitney U tests (between two groups) were used. For categorical data, chi-square or Fisher exact tests were used where appropriate. Correlations between serum hscTnT and adipokine (resistin, adiponectin, and leptin) concentrations were analyzed by using the Pearson Product Moment Correlation analysis. Multiple regression analysis was performed to identify the predictors of the elevation in serum hscTnT concentrations. Serum hscTnT, resistin, leptin, and adiponectin concentrations were adjusted for clinical and procedural characteristics of patients by using the weighted least square regression analysis. A probability value of <0.05, with ≥ 0.80 statistical power, was considered significant.

Results

Patient characteristics

The study group consisted of 153 patients; 55 women and 98 men with a mean age of 60.6±8.2 years. The average body mass index of the study group was 27.6±4.2 kg/m^2. Pre-procedural functional capacity evaluation indicated that only 19% of the study population has low functional capacity (<4 metabolic equivalents). Table 1 demonstrates demographic and clinical characteristics of the patients.

Procedural data

SCAI type 1 (47.7%) and type 2 (47.1%) coronary lesion characteristics existed in majority of the patients. Transfemoral access was used in 128 (83.7%) participants. Multivessel PCI and overlapping stenting were performed in 20 (13.1%) and 11 (7.2%) objectives, respectively. The mean total procedure time was 49±23 min. All of the procedures were completed successfully without any periprocedural complications such as no-reflow, side branch occlusion, coronary dissection or perforation, and no deaths occurred during the in-hospital follow up. Table 2 demonstrates procedural data of the patients.

Serum hscTnT, resistin, leptin, and adiponectin concentrations before and after PCI

The median values of the pre-PCI serum concentrations of hscTnT, resistin, leptin, and adiponectin were 8.6 ng/L, 7.0 μg/L, 13.1 μg/L, 19.0 mg/L, respectively. Serum hscTnT, resistin, and leptin concentrations significantly ($p<0.001$, paired t-test) elevated to 19.7 ng/L, 8.2 μg/L, and 15.0 μg/L 12-h after PCI, respectively, while serum adiponectin concentrations decreased ($p<0.001$; paired t-test) to 16.1 mg/L 12 h after PCI (Table 3).

Serum pre-procedural and post-procedural hscTnT, resistin and adiponectin concentrations were similar in men or women, smokers, in statin/beta-blocker/angiotensin converting enzyme/angiotensin receptor blocker users, in patients with diabetes mellitus (DM), hypertension, prior MI, prior PCI or prior CABG groups. However, serum pre-procedural leptin concentrations in women were higher than the observed values in men (29.0 μg/L vs. 8.7 μg/L, $p<0.001$) and increased after 12-h PCI from their baseline values in both men (8.7 μg/L vs. 11.1 μg/L, $p<0.001$) and women groups (29.0 μg/L vs. 32.4 μg/L, $p<0.001$) although other clinical factors did not point out any difference for serum pre- and post-procedural leptin levels.

Serum pre-procedural and post-procedural hscTnT, resistin, leptin and adiponectin concentrations were similar in patients with transradial or transfemoral PCI, with different lesion types (SCAI type 1–4), and DES or BMS implantations. However, the median value for serum post-procedural hscTnT concentration in patients undergoing multivessel PCI was significantly (26.0

Table 1. Demographic and clinical characteristics of patients

Age, years (mean±SD)	60.6±8.2
BMI, kg/m^2 (mean±SD)	27.6±4.2
Men, n (%)	98 (64.1%)
Women, n (%)	55 (35.9%)
Smoking, n (%)	32 (21%)
Diabetes mellitus, n (%)	67 (43.8%)
Hypertension, n (%)	109 (71.2%)
Previous MI, n (%)	18 (11.8%)
Previous PCI, n (%)	69 (45.1%)
Previous CABG, n (%)	29 (9.5%)
Creatinin, mg/dL (mean±SD)	0.9±0.2
TC, mg/dL (mean±SD)	180.7±28.2
TG, mg/dL (mean±SD)	131.7±58.4
LDL-C, mg/dL (mean±SD)	109.3±28.6
HDL-C, mg/dL (mean±SD)	41.5±13.8
LVEF, % (mean±SD)	67.3±3.5
Statin user, n (%)	79 (52%)
Beta-blocker user, n (%)	36 (23.5%)
ACEI-ARB user, n (%)	19 (12.5%)
Beta-blocker + ACEI-ARB user	79 (58.8%)

ACEI/ARB - angiotensin converting enzyme inhibitors/angiotensin receptor blockers; BMI - body mass index; CABG - coronary artery bypass grafting; HDL-C - high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol; LVEF (%) - left ventricular ejection fraction (%); MI - myocardial infarction; PCI - percutaneous coronary intervention; TC - total cholesterol; TG - triglyceride; SD- standard deviation

Table 2. Procedural characteristics of patients

SCAI Type 1 lesion, n (%)	73 (47.7%)
SCAI Type 2 lesion, n (%)	72 (47.1%)
SCAI Type 3-4 lesion, n (%)	8 (5.2%)
Transfemoral access n (%)	128 (83.7%)
Transradial access, n (%)	25 (16.3%)
Single vessel PCI, n (%)	133 (86.9%)
Multivessel PCI, n (%)	20 (13.1%)
Predilatation, n (%)	105 (68.6%)
Postdilatation, n (%)	24 (15.7%)
Direct stenting, n (%)	48 (31.4%)
Single stent, n (%)	122 (79.7%)
Overlapping stent, n (%)	11 (7.2%)
Stent length, mm (mean±SD)	25.4±12.3
Stent diameter, mm(mean±SD)	3.0±0.4
DES, n (%)	66 (43.1%)
BMS, n (%)	87 (56.9%)

BMS - bare metal stent; DES - drug eluting stent; PCI - percutaneous coronary intervention; SCAI - Society for Cardiac Angiography and Interventions; Data are number of patients (percentage). # indicates values reported as mean±standard deviation

Table 3. Pre-procedural and post-procedural serum concentrations of high-sensitive cardiac troponin T, resistin, leptin, and adiponectin in the study population

	Pre-procedural	Post-procedural	*P*
hscTnT, ng/L	8.6 (6.2–11.6)	19.7 (11.9–41.7)	*P*<0.001*
Resistin, µg/L	7.0 (4.2–9.3)	8.2 (5.0–11.3)	*P*<0.001*
Leptin, µg/L	13.1 (6.4–25.9)	15.0 (8.2–27.5)	*P*<0.001*
Adiponectin, mg/L	19.0 (13.5–25.9)	16.1 (10.7–21.4)	*P*<0.001*

Data are given as median with the interquartile ranges (in parenthesis). *Significantly (*P*<0.05–0.001) different from the respective pre-procedural values (paired test on ranks)

ng/L vs. 19.2 ng/L, p<0.01) higher than the median value observed in patients undergoing single vessel PCI, although resistin, leptin, and adiponectin levels were similar in multivessel and single vessel PCI groups.

Correlations between serum adipokins and hscTnT concentrations

Pre-procedural hscTnT concentrations were correlated with serum pre-procedural resistin (r=0.215; p<0.01) and post-procedural resistin (r=0.231; p<0.01) concentrations. However, correlation analysis did not show any correlation between post-procedural hscTnT levels and resistin concentrations before or after PCI. In addition, no correlation was found between serum leptin or adiponectin levels and hscTnT concentrations before and after PCI.

Adjusting of pre-PCI and post-PCI concentrations of resistin for clinical and procedural characteristics of patients revealed that pre-procedural hscTnT, prior PCI and prior CABG were the influencing factors for serum pre-procedural and post-procedural resistin concentrations. Regression analysis also showed that serum pre-PCI and post-PCI leptin levels were strongly associated with gender. None of other clinical and procedural factors were affecting serum pre-PCI and post-PCI leptin concentrations. In addition, serum pre-PCI and post-PCI adiponectin levels were not associated with any of the clinical and procedural factors.

Table 4. Serum pre-PCI and post-PCI concentrations of resistin, leptin, and adiponectin in patients from no-injury, PMI, and type 4a MI groups

Serum analyses	No-injury n=65	PMI n=70	Type 4a MI n=18
Resistin			
Pre-PCI resistin, µg/L	6.4 (3.3–9.2)	7.6 (4.6–9.6)	6.4 (4.0–7.3)
Post-PCI resistin, µg/L	7.3 (4.0–11.6)*	8.1 (5.0–11.4)*	8.4 (6.1–10.4)*
Difference, µg/L	1.9±0.7	1.7±0.8	2.5±0.9
Leptin			
Pre-PCI leptin, µg/L	18.1 (8.2–28.5)	12.0 (6.4–28.9)	10.4 (5.9–26.0)
Post-PCI leptin, µg/L	18.9 (9.3–31.2)*	14.5 (8.2–27.0)*	12.9 (7.1–34.4)*
Difference, µg/L	2.0±0.8	1.3±0.8	3.2±1.6
Adiponectin			
Pre-PCI adiponectin, mg/L	19.0 (11.9–28.9)	19.0 (14.0–23.7)	20.3 (16.1–24.7)
Post-PCI adiponectin, mg/L	16.3 (10.0–23.8)*	16.2 (10.6–20.7)*	15.3 (12.8–20.7)*
Difference, mg/L	-3.8±1.2	-3.0±0.6	-4.3±1.5

No-injury-patients with serum post-procedural hscTnT concentration ≤14 ng/L); PMI group=patients with >14–<70 ng/L of post-procedural hscTnT concentrations; Type 4a MI group (patients with ≥70 ng/L of post-procedural hscTnT concentrations.
Pre-PCI and Post PCI serum resistin, leptin and adiponectin values were gives as median (25%–75%). "Difference" indicates the difference between pre-PCI and post-PCI values of serum adipokins, and given as mean±SEM. *Significantly (*P*<0.05–0.001) different from the respective pre-PCI values (paired test on ranks).

Serum resistin, leptin, and adiponectin concentrations in no-injury, PMI, and type 4a MI groups

No-injury group consisted of 65 patients (42.4%) in the study population while PMI and type 4a MI were observed in 70 (45.8%) and 18 (11.8%) patients, respectively. One way ANOVA analyses revealed that post-procedural serum resistin [F (2,136)=0.07, p=0.928], leptin [F (2,136)=0.149, p=0.861], and adiponectin [F (2,136)=0.263, p=0.769] concentrations were not significantly different between no-injury, PMI, and type 4a MI groups. Pre-procedural serum resistin, leptin and adiponectin levels were also similar among no-injury, PMI, and type 4a MI groups (Table 4).

Discussion

These data clearly show that pre-procedural serum resistin, leptin, and adiponectin levels are not associated with PCI-related myocardial injury or type 4a MI in patients with stable angina pectoris. However, our observations indicate that resistin and leptin levels increase while adiponectin levels decrease significantly following elective PCI regardless of the presence of PMI or type 4a MI.

Adipokines regulate vascular inflammation and endothelial functions in humans, which may result in several forms of coronary artery disease including acute coronary syndromes (10–12). We have limited data regarding the relationship between adipokines and PMI as there is only one study in the literature, which has demonstrated that adipocytokine resistin correlates with oxidative stress and myocardial injury in patients undergoing on pump coronary by-pass surgery (26). This correlation was explained by the hypothesis that resistin may trigger reperfusion induced injury by binding specific receptors (26). To our knowledge, there is no published data regarding the relation between serum adipokines and PMI following elective PCI. However, the present study has found no correlation between serum adipokines and PCI induced PMI although significant alterations in serum levels of adipokines in response to PCI were observed.

The present study is the first to demonstrate the elevation of serum resistin levels after elective PCI in stable coronary artery disease. The observed association between pre-procedural serum concentrations of resistin and hscTnT in accordance with the previous studies show that resistin has a pathological role in the development and progression of atherosclerosis (27), and serum resistin increases in the course of acute coronary syndromes (16, 20). In the present study, serum concentrations of resistin and hscTnT are both increased significantly following PCI. However, we observed that neither pre-procedural nor post-procedural serum resistin concentrations are associated significantly with the post-procedural serum hscTnT concentrations. Furthermore, the post-procedural serum resistin concentrations and the increase in serum resistin concentrations 12 h after PCI were similar in the non-injury, PMI and the type 4a MI patient groups. Taken together, these data indicate that pre-procedural serum resistin concentration is not a useful marker to predict the magnitude of increase in serum concentrations of hscTnT reflecting PMI following PCI. On the other hand, the rise of serum resistin levels in response to elective PCI in both non-injury and PMI groups may be a result of iatrogenic plaque rupture formed by angioplasty and stenting. As resistin has been shown to be concentrated in atherosclerotic plaques and its secretion is predominantly stimulated by a pro-inflammatory state, rupture of an atherosclerotic plaque inducing an inflammation response may explain subsequent resistin elevation following PCI even in patients presenting with stable angina (27–30). We have also demonstrated that circulating resistin concentrations were influenced by pre-procedural hscTnT, prior PCI, and prior CABG history, which reflect the atherosclerotic plaque burden in combination with increased pro-inflammatory state of the individuals.

Leptin is the first discovered adipokine, which has regulating effects on vascular tone, platelet aggregation, and endothelial functions (31–33). The present study has demonstrated that serum leptin levels significantly increase after elective PCI consistent with a previous study including forty-eight non-diabetic patients (34). Increased leptin induced by circulating inflammatory cytokines (35, 36) acts on specific endothelium receptors and exerts its vascular effects leading to endothelial dysfunction (37). Therefore, increased inflammatory cytokines in response to iatrogenic plaque rupture may lead to increased release of leptin from the adipocytes in addition to local release of binded-leptin from endothelium at the site of balloon dilatation. However, the exact mechanism of leptin rise should be particularly investigated in experimental models and humans. Our observations indicating the absence of a significant association between pre-procedural serum leptin concentrations and PMI rule out the possibility that circulating leptin is an important determinant for PCI-related myocardial injury and/or infarction. Baseline leptin concentrations were higher in women than in men in the present study, which is consistent with the previous data; this has been explained by different abdominal fat distribution and increased subcutaneous fat compared with men (38).

Previously published data indicate a strong relation between decreased serum adiponectin and coronary atherosclerosis (39, 40). Adiponectin displays anti-inflammatory and anti-atherogenic effects by increasing NO production, reducing of the adhesion molecules in endothelial cells, inhibiting cytokine production from macrophages, and suppressing the formation of foam cell (41, 42). Clinical trials have revealed that low plasma adiponectin levels are associated with future cardiovascular events in patients presenting with acute coronary syndromes (43). The present study revealed that there is no association between pre-procedural adiponectin levels and PCI-related myocardial injury. However, we observed a decrease in serum adiponectin levels 12 h after elective PCI consistent with the findings of two clinical studies, which have explained this decline because of the inflammatory response triggered by PCI (14, 34). It has been shown that adiponectin binds to the catheter-injured vessels and concentrates in the non-intact endothelium and subendothelial space with macrophages by using immuno-histochemical analyses (44). These observations suggest that the decline in adiponectin levels may be the consequence of plaque rupture that impairs endothelial integrity leading to adiponectin accumulation in subendothelial space in response to PCI.

Study limitations

First of all, the main limitation of this study lies in its observational cross-sectional design. Second, patients taking several drug therapies which have the potential of affecting the metabolic status may be randomized to observe whether these drugs

have impact on serum levels of adipokines or not. Third, the new definition of type 4a MI includes patients revealing an increase in hscTnT values >20% if the baseline values are elevated and are stable or falling in addition to clinical and/or laboratory findings indicative of myocardial ischemia (25). As the present study excluded patients presenting with MI, the association between serum adipokines and PCI-related myocardial infarction and serum adipokine alterations in this specific sub-group of patients may be evaluated in a different study. The absence of serum high sensitive CRP levels measurements is another limitation which could provide more information regarding the inflammatory status of the individuals.

Conclusion

The present study demonstrates as an original finding that serum resistin and leptin levels increase and adiponectin levels decrease significantly following elective PCI in patients with stable angina pectoris. However, there is no correlation between serum adipokine levels and post-procedural troponin elevations reflecting PMI or type 4a MI. Our data clearly indicates that iatrogenic plaque rupture generated by PCI leads to significant alterations in serum levels of adipokines which could enlighten the future researches evaluating the close relation between vascular inflammation and metabolic status of the patients.

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