Serum Visfatin Levels and Coronary Artery Disease

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ABSTRACT

Introduction: Adipose tissue is not only source of energy but also an active endocrine organ serving function by secreting bioactive molecules called adipokines. Visfatin is a recently discovered adipokine and is proposed to play role in inflammatory and atherosclerotic states. We aimed to investigate the association of visfatin with coronary artery disease (CAD).
Patients and Methods: Twenty patients undergoing coronary artery bypass grafting due to CAD were compared with 20 individuals without CAD angiographically. Gender, age, body mass index, and serum visfatin levels were compared between the two groups. Relationship of visfatin levels and severity of CAD, cross-clamp and cardiopulmonary bypass times were also investigated in the study group.
Results: Age, gender, BMI, and blood pressures were not significantly different between the groups. There was significant difference in serum visfatin levels between the two groups (47.31±33.03 ng/mL and 9.04±7.18 ng/mL, p=0.0001). A strong correlation between the Gensini score and pre-operative visfatin levels (r=0.81; p=0.0001) was observed for the study group. No correlation was detected between the visfatin level and cardiopulmonary bypass and cross clamp times.
Conclusion: Increased visfatin levels may be associated with inflammation and atherosclerotic cardiovascular diseases. Circulating visfatin level is increased in patients undergoing coronary artery bypass grafting. Further studies are warranted to determine the predictive value of serum visfatin as a biomarker and potential therapeutic target for metabolic and cardiovascular diseases.
Key Words: Adipose tissue; adipokine; visfatin; atherosclerosis; coronary artery disease

Serum Visfatin Seviyesi ve Koroner Arter Hastalığı

ÖZET

Giriş: Yağ dokusu yalnızca enerji kaynağı olmayıp aynı zamanda adipokin olarak adlandırılan biyoaktif maddeleri salgılayan bir endokrin organdır. Visfatin son dönemlerde keşfedilen, inflamasyon ve ateroskleroz ile ilişkilendirilen bir adipokindir. Bu çalışmada visfatinin koroner arter hastalığı ile ilişkisini araştırmayı amaçladık.
Hastalar ve Yöntem: Koroner arter hastalığı sebebiyle koroner arter baypas greftleme planlanan 20 hasta anjiografik olarak koroner arter hastalığı olmayan 20 bireyle kıyaslandı. Cinsiyet, yaş, vücut kitle indeksi ve serum visfatin seviyesi gruplar arasında karşılaştırıldı. Visfatin seviyesinin koroner arter hastalığının ciddiyeti, aortic kros klemp zamanı ve kardiyopulmoner baypas zamanı ile ilişkisi de incelendi.
Bulgular: Gruplar arasında yaş, cinsiyet, vücut kitle indeksi ve kan basınçları arasında fark saptanmadı. Serum visfatin seviyeleriyse anlamlı farklı bulundu (47,31±33,03 ng/ml ve 9,04±7,18 ng/ml, p=0,0001). Gensini skoru ile preoperative visfatin seviyesi arasında güçlü korelasyon saptandı (r=0,81; p=0,0001). Visfatin seviyesi ile kardiyopulmoner baypas ve aortic kros klemp zamanı arasında ilişki saptanmadı.
Sonuç: Artmış serum visfatin seviyesi inflamasyon ve aterosklerotik kardiyovasküler hastalıklarla ilişkili olabilir. Dolaşımdaki visfatin seviyesi koroner arter baypas greftleme yapılan hastalarda artmıştır. Serum visfatin seviyesinin koroner arter hastalığı ile ilişkisi ve tedavi hedefleri arasındaki yerini belirleyebilmek için büyük ölçekli çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Adipoz doku; adipokin; visfatin; ateroskleroz; koroner arter hastalığı

INTRODUCTION

Adipose tissue was considered as an energy source only until the last two decades and it was first identified as the source of the hormone leptin in 1994[1,2]. Nowadays it is described as active endocrine organ by releasing numerous bioactive substances, named as adipokines, that include hormones such as leptin, adiponectin, apelin, resistin, vaspin, hepcidine, chemerin, omentin, TNF-alfa, IL-6 and IL-8, and various others[3,4]. Accordingly, adipokines, which are signaling proteins secreted by adipose tissue, have versatile regulatory functions throughout the body in and for different disease states.

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Submitted: 24.04.2014
Accepted : 22.06.2014

Visfatin is a recently discovered adipokine. It is secreted from the visceral fat. It exhibits insulin-like functions[5,6]. Visfatin was also recognized as the formerly described nicotinamide phosphoribosyl transferase (NAMPT), which is the rate-limiting enzyme in the nicotinamide dinucleotide (NAD) biosynthetic pathway starting from nicotinamide and catalyzes the synthesis of nicotinamide mononucleotide (NMN) from nicotinamide and 5-phosphoribosyl pyrophosphate (PRPP)[7,8]. Visfatin, other than the fat tissue, is expressed by various other cells and tissues such as neutrophiles, liver, heart and muscles as well as accepted as a growth factor for the maturation of pro-cells of the B-lymphocytes[9,10].

Cardiovascular disorders are the main cause of mortality and morbidity in the current era[11,12]. There are multiple factors for the development of coronary heart disease. Adipokines and other various inflammatory and proinflammatory molecules that affect cardiovascular functions through not only as endocrine manner, but also by autocrine and paracrine mechanisms[13]. Consequence ends up with cytokine-mediated and systemic inflammation and atherosclerosis. Various studies revealed association of visfatin with inflammation[14], metabolic syndrome[6,15], endothelial dysfunction[15], atherosclerosis[8,15,16] and ischemia reperfusion injury[15-18].

In this study we aimed to investigate the correlation between circulating visfatin levels in patients with coronary artery disease who underwent on-pump coronary artery bypass grafting (CABG). Cohort was compared based on the Gensini scores with the findings of cases with angiographicaly normal coronary arteries.

PATIENTS and METHODS

The study was approved by the institutional ethics review board. The patients were informed about the protocol and following their consent they were included into the research. The study was conducted between April 2012-August 2012 at our institution. Twenty consecutive patients who underwent elective on-pump CABG after coronary angiography constituted the study group (group 1) where as control group (group 2) was randomly chosen 20 patients with angiographically normal coronary arteries. All the patients were operated by the same surgical team. The indications for surgical revascularization was in accordance with international guidelines.

The following demographic, laboratory and operative findings were analyzed: gender, age, body mass index (BMI), serum visfatin levels, cross-clamp ve cardiopulmonary bypass times (Table 1). Patients having BMI ≥ 30, diabetes mellitus, hepatic and renal dysfunction (creatinine >2.2 mg/dl), malignant states, active infections, and hyperlipidemia were excluded from the study. Body mass index was calculated by division of body weight to square of body length and the normal range is accepted 19-24.9 kg/m^2, where as with overweight and obesity were identified as 25-29.9 kg/m^2 and ≥30 kg/m^2, respectively. Hyperlipidemia is as increased low density lipoprotein above 130 mg/dl or total cholesterol above 200 mg/dl. The coronary artery disease was evaluated with Gensini scores (Table 1)[19].

Blood Sampling

The blood sampling was performed puncture of an antecubital vein after 12 hours fasting in all patients. In the study group, additional samples were collected during cardiopulmonary bypass, following release of aortic cross clamp and on the 3rd postoperative day from the central venous line. All the samples were stored at -20 °C for analysis following separation of the serum and cell parts by centrifugation. Serum visfatin levels were measured with ELISA method according to the manufacturer's protocol.

Operative Technique

All patients were operated by same surgical teams. Extracorporeal circulation was established with aortic and two-stage cannulations. A Stockert S3 roller pump (Sorin Group, Deutschland GMBH, München, Germany) was used for extracorporeal circulation. Myocardial protection was achieved with antegrade blood cardioplegia and moderate hypotermia (32 ^{o}C). Standart linear flow cardiopulmonary bypass was performed with the achieving 60-80 mmHg mean pressure. The left internal mamarian artery was anastomosed to left anterior descending coronary artery in all patients and remaining revascularizations were fashioned by greater saphenous vein. Proximal anastomosis were done with aortic side clamping.

Statistical Analysis

The results are presented as mean ± standart deviation. For ordinal variables, the frequencies of each value for each group were calculated. Categorical variables were compared by the x^2-test. Paired t test was used for comparison of preoperative and postoperative scores; student t test (independent sample test) was used for comparison of groups. Correlation calculations were done with Pearson test for data with normal distribution, and spearman test for data not suitable distrubition. A two-tailed p less than 0.05 was considered significant.

Table 1. Demographic variables and laboratory findings of the control and study group patients

Variables	Control Group (n=20)	Study Group (n=20)	p value
Gender (F/M)	9/11	5/15	0.185
Age	65.4±6.1	66.9±5.4	0.43
BMI	25.1±3.2	25.9±3.5	0.42
Gensini score	4.3±2.8	56.9±26.2	0.0001
V1	9.0±7.2	47.3±33.0	0.0001
V2	-	32.1±22.5	
V3	-	89.5±48.6	
V4	-	135.9±180.1	
CC	-	44.1±19.7	
CPB	-	73.4±26.7	

Data presented as mean ± standard deviation, (BMI: Body mass index; V1: Visfatin level at the preoperative period; V2: Visfatin level during cardiopulmonary bypass; V3: Visfatin level following the release of cross clamp; V4: Visfatin level on the third postoperative day; CC: Cross-clamp; CPB: Cardiopulmonary bypass.)

RESULTS

Demographic variables of the patients were compared between the two groups. Mean age of the patients was 66.9±5.42 years in the study group and 65.4±6.1 years in the control group. There were 5 females and 15 males in the study population where as this ratio was 9/11 among the controls. The BMI was calculated 25.9±3.5 kg/m^2 and 25.1±3.2 kg/m^2 in group 1 and and group 2, respectively. Age, gender, BMI, and blood pressures were not significantly different between the groups (p>0.05) (Table 1). The aortic cross clamp time was 44.1 (19.7) minutes and CPB time was 73.4 (26.7) minutes in the study group.

The visfatin level measured at the preoperative period in the study group was 47.3±33.0 ng/ml where as mean visfatin was 9.0±7.2 ng/ml in the control group. The difference was significant (p=0.0001) and visfatin levels were significantly elevated in patients with coronary artery disease. Consecutively, the visfatin levels during cardiopulmonary bypass, following the release of aortic cross clamp and on the 3rd postoperative day 32.1±22.5 ng/ml, 89.5±48.6 ng/ml, and 135.9±180.1 ng/ml. In the study group, there was not a significant difference between the preoperative and during cardiopulmonary bypass levels of visfatin (p=0.075); however, visfatin was found to be significantly elevated at the measures right after the cross clamp (p=0.042) and on the postoperative day (p=0.015).

The Gensini score was 56.9±26.2 in group 1 and 4.3±2.8 in group 2 (p=0.0001). There was no significant correlation between the visfatin level and the Gensini score in the control group (r=0.38; p=0.098). On the other hand there was significant strong correlation between the Gensini score and visfatin levels measured at the preoperative period (r=0.81; p=0.0001).

The overall mean visfatin level of whole population (n=40) was 29.5 (31.0) ng/ml. The mean Gensini score of the patients was 30.6±67.9. The correlation between the mean Gensini score and visfatin in the blood was strong and significant (r=0.85; p=0.0001). No significant correlation was detected between the BMI and visfatin (p=0.506), and corresponding values of visfatin and cardiopulmonary bypass and cross clamp times (p>0.05).

DISCUSSION

Adipocytes produce hormones, peptides, and other molecules, which affect cardiovascular function, through endocrine, autocrine, and paracrine mechanisms[13]. Visfatin is recently discovered adipokine which is excreted by the visceral adipocytes[5,6]. It is known that blood vessels express receptors for most of the adipocyte-derived factors. Thus, adipose tissue seems to play a key role in cardiovascular physiology. The circulating metabolites activate monocytes which in turn increases the secretion of inflammatory cytokines. As a consequence cytokine-mediated inflammatory reactions, systemic inflammation and atherosclerosis may ensue. In a recent study, it has been shown that transplantation of visceral adipose tissue from genetically obese mice into Apoe-deficient mice increased atherosclerosis in the recipient animals. The finding suggested that inflamed adipose tissue exerted distinct vascular effects most probably through inflammatory cells such as macrophages within the visceral adipose tissue[20].

Evidence indicates that increased release of proinflammatory cytokines from adipose tissues such as IL-6, IL-1, and TNF-α may lead to vascular wall inflammation and pro-atherogenic gene expression[21]. In the obese population adipose tissue express higher amounts proinflammatory proteins when compared with fit individuals[22,23]. There is strong clinical and experimental base supporting a correlation between systemic inflammation and endothelial dysfunction. Additionally, endothelial dysfunction might be an early indicator of atherosclerosis. Thus, impaired endothelial functions have been identified to play a vital role in the course of atherosclerotic cardiovascular disorders. Inflammatory cytokines are one of the most important insults in atherosclerotic plaque formation affecting throughout the endothelium of the atherosclerotic vessel. It is known that regardless of risk factors such as diabetes, hypertension, obesity etc, development of atherosclerotic lesions begin with the disruption of the endothelial cells. The findings of our study population when compared with the controls supported a prominent endothelial dysfunction in the study group. However, in a study by Choi et al.[24], circulating visfatin levels were not found to be significantly related with cardiovascular risk factors such as obesity, hypertension, lipid profile, and insülin resistance. Additionally, the auhors findings were not significantly different between patients with heart disease and control subjects[24].

Endothelial dysfunction is a mixture of complex events and may involve ischemia/reperfusion injury as well. Well established atherogenic risk factors include smoking, obesity, hypertension, diabetes mellitus, physical inactivity, and hypercholesterolemia. Endothelial dysfunction is accepted as an early indicator and stage of atherosclerosis which is a chronic inflammatory disease[25].

Several studies have shown that increased visfatin is associated with coronary artery disease in patients with asymptomatic coronary artery disease, patients devoid of risk factors presenting especially with acute coronary syndrome[26,27]. Various disorders may lead to altered plasma levels of visfatin and visfatin plasma concentrations may be related with lipid metabolism[28] and the inflammatory response[29]. Additionally, Dahl et al.[15] indicated increased expression of visfatin in macrophages of unstable carotid and coronary atherosclerosis in humans and Takebayashi et al.[30] has shown a negative association between the plasma levels of visfatin and vascular endothelial function. Findings may indicates visfatin might play a role in plaque destabilization[2,15,30].

Chronic inflammation is accepted as a mediator in the development of coronary artery disease[31] and NAMPT has been isolated in the pathogenesis of various acute and/or chronic inflammatory states such as atherosclerosis and cardiovascular disorders[32], hence NAMPT may act as a pro-inflammatory cytokine.

Visceral fat produces adipokines more actively than subcutaneous adipose tissue. Increased abdominal fat around the visceral organs has been identified to increase the risk of metabolic and cardiovascular problems[33]. There are studies in the literature indicating a correlation between circulating visfatin and metabolic parameters. It has been shown a positive correlation between the visceral adipose tissue visfatin gene expression and BMI and a negative correlation between BMI and subcutaneous fat visfatin[34]. Plazma visfatin levels are associated with age, weight, BMI, and waist-to-hip ratio[24,35,36]. However, in the present study we failed to find a correlation between serum visfatin levels and BMI. Of note the finding may be attributed that our study included subjects with relatively narrow range of BMI compared with the prior study subjects.

The results of our study are suggestive of increased serum visfatin levels as an indicator of coronary artery disease[3,7,8,13-16,20,24,26,30,32,33,36]. The association has been first identified in patients with carotid artery disease[2,14] and results of different studies including visfatin and coronary artery disease have been published in recent years[7,15,26,27]. Since visfatin is secreted from the macrophages in the fat tissue it is positively correlated with systemic inflammation[3,15]. Additionally, a negative correlation between visfatin and endothelial functions has been presented[4,5,18,30,31]). Although the low number of patients, as a major limitation of our study, our findings together with the guidance of the available literature are suggestive of visfatin as a trigger for inflammation at the initiation of the coronary artery disease. The decrease in serum visfatin levels during cardiopulmonary bypass may be attributed to the lowering effect of hypothermia as presented by David et al.[37] in their animal study. Similarly, there is inrease in serum visfatin in the early postoperative period as an early inflammatory response.

Both adipocytes and macrophages within fat tissue secrete numerous cytokines that may contribute to the inflammation and atherosclerosis. Identification and characterization of disease-specific proteins in the adipose tissue may a novel therapeutic target for prevention and/or treatment of acquired cardiovascular diseases. Increased visfatin levels are associated with inflammatory and atherosclerotic cardiovascular diseases. The circulating visfatin is found increased in patients undergoing coronary artery bypass grafting. Further multicenter prospective studis with higher number of patients is warranted to determine the predictive value of serum visfatin as a biomarker and potential therapeutic target for metabolic and cardiovascular diseases.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

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