Serum leptin has no effect on coronary collateral development in patients with non-ST- elevation acute coronary syndromes: an observational study

Serum leptin düzeyinin ST yükselmesi olmayan akut koroner sendromlu hastalarda koroner kollateral gelişimi üzerine etkisi yoktur: Gözlemsel bir çalışma

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ABSTRACT

Objective: We attempted to investigate the potential association between leptin and coronary collateral vessel development in patients with non-ST elevation acute coronary syndromes (NSTE-ACS).

Methods: One hundred and nineteen consecutive patients with NSTE-ACS with high-grade coronary stenosis or occlusion in at least one epicardial coronary artery were prospectively enrolled in a cross-sectional observational study. Serum leptin levels measured in all patients. Collateral circulation was graded according to the Rentrop classification. Firstly, we divided patients into two groups as good and poor collateral group. Patients with Rentrop 2,3 were regarded as good collateral group. Patients in Rentrop grades 0, 1 classified as poor collateral group. Secondly, patients were divided into collateral (+) group and collateral (-) group. Collateral (+) group included the patients with grade 1, 2, 3 collateral development. Collateral (-) group was composed of the patients with Rentrop 0. Statistical analysis was performed using Student t-test, Mann-Whitney U test, Chi-square test, Kruskal -Wallis test and Spearman's correlation.

Results: We did not find statistically significant difference between good and poor collateral groups with regard to leptin levels [4.2 (1.8-8.6) ng/mL and 6.4 (2.4-12.6) ng/mL, p=0.22, respectively]. There was no statistically significant difference in leptin levels between collateral (+) group and collateral (-) groups [4.7 (1.7-10.5) ng/mL and 6.8 (2.7-12.1) ng/mL, p=0.33, respectively]. We observed that there was lower leptin level at higher Rentrop grades [Rentrop 0; 6.8 (2.5-12.5) ng/mL, Rentrop 1; 5.9 (1.7-14.1) ng/mL, Rentrop 2; 4.3 (1.7-8.7) ng/mL, Rentrop 3; 3.9 (2.1-9.7) ng/mL]. However, this difference did not reach statistically significant level (p=0.54). In addition, we did not find statistically significant correlation between Rentrop grades and leptin levels (p=0.246, r=-0.107).

Conclusion: The present study reveals no association between serum leptin level and coronary collateral development.

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Key words: Leptin, coronary collateral development, NSTE-acute coronary syndrome

ÖZET

Amaç: ST yükselmesi olmayan akut koroner sendromlu (NSTE-AKS) hastalarda serum leptin düzeyi ile koroner kollateral gelişimi arasındaki potansiyel ilişkiyi incelemeyi hedefledik.

Yöntemler: Bu kesitsel ve gözlemsel çalışmaya en az bir epikardiyal koroner arterinde ciddi darlık veya total oklüzyon olan 119 NSTE-AKS hastası alındı. Tüm hastalarda serum leptin düzeyleri ölçüldü. Kollateral gelişimi Rentrop klasifikasyonuna göre değerlendirildi. İlk olarak hastalar iyi ve kötü kollateral grup olarak ikiye ayrıldı. Rentrop 2 ve 3 hastalar iyi kollateral grup, Rentrop 0 ve 1 hastalar kötü kollateral grup olarak adlandırıldı. Daha sonra hastalar kollateral (+) grup ve kollateral (-) grup olarak sınıflandırıldı. Kollateral (+) grup Rentrop 1,2,3 hastalardan, kollateral (-) grup Rentrop 0 hastalardan oluştu. İstatistiksel analiz olarak Student t-testi, Mann-Whitney U testi, Ki-kare testi, Kruskal Wallis testi ve Spearman korelasyon analizleri kullanıldı.

Bulgular: Serum leptin düzeyleri bakımından iyi ve kötü kollateral grup arasında istatistiki anlamlı bir fark bulmadık [sırasıyla, 4.2 (1,8-8,6) ng/mL and 6,4 (2,4-12,6) ng/mL, p=0,22]. Kollateral (+) ve kollateral (-) grup arasında da leptin düzeyleri arasında istatistiki fark yoktu [sırasıyla, 4,7 (1,7-10,5) ng/mL and 6.8 (2,7-12,1) ng/mL, p=0,33]. Tüm Rentrop dereceleri ayrı ayrı değerlendirildiğinde, yüksek Rentrop derecelerinde düşük leptin düzeyleri saptadık [Rentrop 0; 6,8 (2,5-12,5) ng/mL, Rentrop 1; 5,9 (1,7-14,1) ng/mL, Rentrop 2; 4,3 (1,7-8,7) ng/mL, Rentrop 3; 3,9 (2,1-9,7) ng/mL]. Fakat bu fark da istatistiki anlamlılığa ulaşmadı (p=0,54). Bunların yanı sıra Rentrop dereceleri ile leptin düzeyleri arasında korelasyon olup olmadığı araştırıldı ve aralarında istatistiki anlamlı bir korelasyon saptanmadı (p=0,246, r=-0,107).

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Sonuç: Bu çalışmada serum leptin düzeyi ile koroner kollateral gelişimi arasında bir ilişki saptanmadı.
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Anahtar kelimeler: Leptin, koroner kollateral gelişimi, NSTE-akut koroner sendrom

Introduction

Coronary artery disease (CAD) is the most common cause of morbidity and mortality in developed societies. Classically, improving atherosclerosis leads to narrowing or total occlusion of coronary arteries, resulting in a broad clinic spectrum of chronic ischemic heart disease such as angina, myocardial infarction, or heart failure. As an adaptation to myocardial ischemia caused by coronary arterial narrowing and/or occlusion, coronary collateral vessels appear in some patients to protect myocardium. This is a protective and desirable mechanism because the subjects with well-developed coronary collaterals have been found to have preserved left ventricular function, improved survival rate and better cardiovascular outcomes compared to those with poorly developed ones (1, 2). However, there are considerable differences in the extent of the development of these natural bypasses among patients even with similar patterns of coronary artery disease (3). Unfortunately, there is limited data on the factors inducing the development of coronary collateral vessels although their functional importance in ischemic heart diseases is well known.

Though leptin primarily responsible for body weight regulation, this hormone has also a extremely widespread range of actions via its receptors on peripheral tissues such as endothelial cells, monocytes//macrophages and platelets (4, 5). The association between leptin and atherosclerosis, coronary artery disease, myocardial infarction, coronary vasodilatation and endothelial functions has been evaluated in numerous studies. Most studies reported that hyperleptinemia is positively correlated with atherosclerotic burden, cardiovascular events and endothelial dysfunction (4-7).

The effect of leptin on arteriogenesis and vascular functions has been addressed in some in-vivo and in-vitro researches and knowledge about this issue has steadily progressed during recent years. Leptin has been shown to induce angiogenesis (8). This hormone was also confirmed to stimulate vascular smooth muscle cell (VSMC) proliferation (9). Although exact mechanisms that effect sufficient coronary collateral development are still unknown, it is suggested that endothelial nitric oxide (NO) and reactive oxygen species have modulatory role on the development of coronary collateral vessels (10). It has been demonstrated in in-vitro studies that leptin induces oxidative stress and NO production in human endothelial cells (11).

However, current knowledge on association of leptin and coronary collateral development is limited.

Based on these aforementioned data, we attempted to investigate the potential association between leptin and coronary collateral vessel development.

Methods

Study design

This study was a cross-sectional observational study.

Study population

Between May 2008 and February 2009, one hundred and nineteen consecutive patients admitted to the cardiology department of Erciyes University School of Medicine with non-ST-elevation acute coronary syndrome (NSTE-ACS) who had high grade coronary stenosis or occlusion in at least one epicardial coronary artery at diagnostic angiography were prospectively enrolled into the present study. The patients with a greater than or equal to 80% obstruction in at least one epicardial coronary artery were included in the study (12). Patients were excluded if they had previous myocardial infarction, a history of past coronary intervention or coronary artery bypass grafting, chronic obstructive pulmonary disease, neoplastic or inflammatory disease.

The study was approved by local ethics committee, and a written informed consent was obtained from all patients enrolled in the study.

Patients were divided into four groups according to Rentrop collateral development classification: as good collateral group (Rentrop 2,3; 33 patients), poor collateral group (Rentrop 1,2; 86 patients); and further as collateral (+) group (Rentrop 1,2,3; 66 patients) and collateral (-) group (Rentrop 0; 53 patients).

Study protocol

Based on the above-mentioned inclusion and exclusion criteria, 119 subjects with NSTE-ACS were included in the present study.

The patients who had chest pain but no electrocardiographic evidence of ST elevation myocardial infarction (ST-elevation of ≥0.1mV in >1 limb leads or ≥0.2 mV in contiguous chest leads or left bundle branch block on presentation) as well as elevated cardiac enzymes were determined as NSTE-ACS patients. Each subject was questioned about the confirmed risk factors for atherosclerotic heart disease and coronary collateral development including hypertension, hyperlipidemia, diabetes mellitus, smoking status, chronic obstructive pulmonary disease and medications.

All angiographic procedures were performed within 24-48 hours of the onset of the subjects' chest pain.

Study variables

The baseline variables of our study were as following: age, gender, smoking status, waist circumference, hip circumference, waist/hip ratio, body mass index (BMI), levels of fasting blood glucose, plasma total cholesterol, high-density lipoprotein (HDL)

cholesterol, low-density lipoprotein (LDL) cholesterol, plasma triglycerides (Thermo clinical lab system with Konelab 60 I kits, Helsinki, Finland), hemoglobin, white blood cell count (XT 2000i® system, Japan) and high sensitivity C-reactive protein (Hs-CRP) (hs-CRP BN2, Dade-Boehring, Germany). The level of coronary collateral development was recorded as a predictor variable and serum leptin level was recorded as an outcome variable.

Leptin

Serum samples for the measurement of leptin level were drawn between 8^{00}-10^{00} hours and were preserved at -70°C. Serum leptin was determined using a commercially available radioimmunoassay kit (Diagnostic Systems Laboratories, Inc., Webster, TX). The reference values for leptin in our laboratory ranged from 2 to 17 ng/mL.

Coronary angiography and collateral grading

Left and right coronary angiography was performed in multiple projections by the Judkins or Sones technique via right femoral artery by Philips Integris 5000 equipment (Philips Medical Systems, Best, Netherlands). Arteriographies were recorded at a speed of 25 frames/sec. The degree of coronary artery diameter stenosis was evaluated visually by two independent cardiologists who had no knowledge of the patients' clinical information. Collateral circulation was graded according to the Rentrop classification (13). Grading of collateral filling was as follows: 0=no angiographically visible filling of any collateral channels, 1=collateral filling of the distal branches of the target artery without dye reaching the epicardial segment of that vessel, 2=partial filling of the epicardial portion of the recipient artery (dye enters but fails to completely opacify the target epicardial vessel), 3=complete filling of the epicardial segment (contrast enters and completely opacifies the target epicardial vessel).

Statistical analyses

SPSS for Windows version 13.0 software (Chicago, IL, USA) was used as the statistical software program. Kolmogorov-Smirnov test was used to determine whether the parameters fit with the normal distribution. Data within the normal distribution were expressed as mean±standard deviation (Mean±SD). Results of data without normal distribution are shown by median (interquartile range) expression. Mann-Whitney U test was used to compare data that did not fit with the normal distribution between two groups. Unpaired Student t test was used for comparing data within the normal distribution between two groups. ANOVA were used for comparisons between the four Rentrop groups. Kruskal Wallis test is used for data that not match with normal distribution among the four Rentrop groups. Chi-square test was used for comparison of categorical variables. The association between Rentrop grades and leptin values was evaluated by Spearman's correlation coefficient. A p value under 0.05 was accepted as the level of significance.

Results

Leptin levels in good collateral group vs poor collateral group

The baseline characteristics of patients with good and poor collateral groups are presented in Table 1. No statistically significant difference between the groups for age, sex, hypertension, diabetes mellitus, smoking, body mass index, waist and hip circumferences, waist-to-hip ratio, fasting glucose, creatinine level, hemoglobin, white blood cell level, lipid profile and high sensitive C-reactive protein was observed. In addition, we did not find statistically significant difference between good collateral group and poor collateral group with regard to leptin levels [4.2 (1.8-8.6) ng/mL and 6.4 (2.4-12.6) ng/mL, p=0.22, respectively] (Table 1, Fig.1).

Leptin levels in collateral (+) group vs collateral (-) group

All demographic, clinical and laboratory variables were similar between groups with and without collaterals as demonstrated in Table 2. Similarly there was no statistically significant

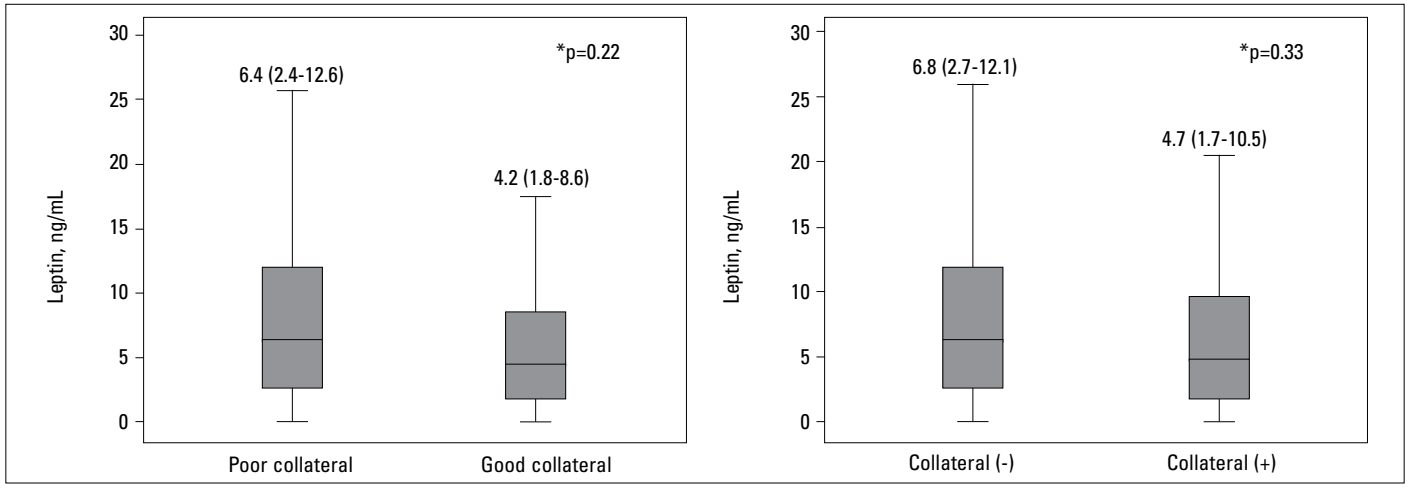

Figure 1. Comparison of serum leptin levels in good collateral group vs poor collateral group and in collateral (+) group vs collateral (-) group
Data are presented as median (range) values
*Mann-Whitney U test

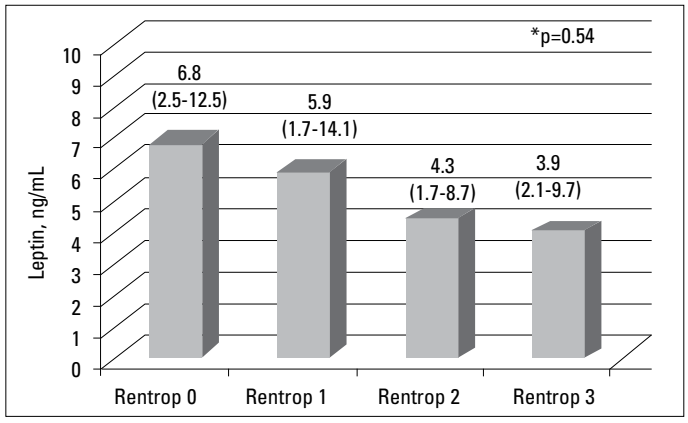

Figure 2. Serum leptin levels in all Rentrop groups
Data are presented as median (range) values
*Kruskal Wallis test

difference in leptin levels between collateral (+) group and collateral (-) group [4.7 (1.7-10.5) ng/mL and 6.8 (2.7-12.1) ng/mL, p=0.33, respectively] (Table 2, Fig.1).

Comparison of the leptin levels between all Rentrop`s grades groups

Lastly, we compared all Rentrop groups. There were no significant differences in baseline characteristics between Rentrop 0, 1, 2, 3 (p>0.05). We observed that there was lower leptin level at higher Rentrop grades [Rentrop 0; 6.8 (2.5-12.5) ng/mL, Rentrop 1; 5.9 (1.7-14.1) ng/mL, Rentrop 2; 4.3 (1.7-8.7) ng/mL, Rentrop 3; 3.9 (2.1-9.7) ng/mL]. However, this difference did not reach statistically significant level (p=0.54) (Fig. 2).

Correlation between Rentrop grades and leptin levels

We did not find statistically significant correlation between Rentrop grades and leptin levels (p=0.246, r=-0.107).

Discussion

In this cross-sectional observational study, which addresses -for the first time- the relationship of serum leptin level with coronary collateral circulation in patients with NSTE-ACS, we did not reach statistically significant association between leptin and coronary collateral development. However, patients with higher Rentrop grades were more likely to have lower leptin levels.

Because coronary collateral flow protect the myocardium against ischemia, the presence and adequacy of coronary collateral vessels is closely associated with better prognosis in patients with coronary artery disease (CAD). Good collateral vessels at the time of acute infarction lead to preserved myocardial function, limited infarct size, reduced ventricular aneurysm formation, improved survival rate and decreased cardiovascular events (1). Because of this clinical importance of collateral circulation, a variety of attempts was made to clarify underlying mechanisms leading to the development of coronary collateral vessel by many clinicians. So, therapeutic modalities can be improved to stimulate the growth of compensatory blood vessels.

Table 1. Comparison of baseline characteristics, laboratory parameters and leptin levels between the good collateral group and poor collateral group

Baseline characteristics	Good collateral (n=33)	Poor collateral (n=86)	*p
Age, years	61.8±15.5	63.0±11.5	0.65
Sex, male/female	23/10	59/27	0.90
Hypertension, n (%)	18 (54.5)	52 (60.5)	0.55
Diabetes mellitus, n (%)	13 (39.4)	32 (37.2)	0.82
Current smoker, n (%)	15 (45.5)	48 (55.8)	0.31
BMI, kg/m^2	26.5±3.7	26.4±5.3	0.89
Waist circumference, cm	93.0±9.9	93.3±12.8	0.90
Hip circumference, cm	102±10.4	102±13.5	0.98
Waist/hip ratio	0.91±0.2	0.91±0.1	0.58
Fasting glucose, mg/dL	111 (100-185)	107 (94-145)	0.17
Baseline creatinine, mg/dL	1.0 (0.9-1.3)	1.0 (0.9-1.3)	0.85
Total cholesterol, mg/dL	178.6±39.1	183.4±46.7	0.60
LDL cholesterol, mg/dL	115.3±29.6	119.1±33.5	0.57
HDL cholesterol, mg/dL	35.7±9.6	35.2±8.3	0.79
Triglyceride, mg/dL	131 (100-182)	128 (90-182)	0.51
Hemoglobin, g/dL	13.8 (12.7-14.8)	13.9 (12.6-14.7)	0.88
White blood cell,10^3/mm^3	9.4±4.3	9.9±3.6	0.50
Hs-CRP, mg/dL	5.9 (4.2-17.7)	12.7 (4-39.6)	0.25
Leptin, ng/mL	4.2 (1.8-8.6)	6.4 (2.4-12.6)	0.22
ACEI, n (%)	10 (30.3)	33 (38.4)	0.41
ARB, n (%)	3 (9.1)	8 (9.3)	0.97
β-Blockers, n (%)	10 (30.3)	17 (19.8)	0.21
CCB, n (%)	4 (12.1)	10 (11.6)	0.94
Statin, n (%)	5 (15.2)	21 (24.4)	0.27

Data are presented as the mean value±SD, median (interquartile range) or number or percentage of patients.
*Student t test, Mann -Whitney U test, Chi-square test p<0.05 considered statistically significant.
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, BMI - body mass index, CCB - calcium channel blocker, HDL - high-density lipoprotein, Hs-CRP - high sensitive C-reactive protein, LDL - low-density lipoprotein

Coronary collateral development occurs via two different processes. One of them is angiogenesis which describes the formation of new capillaries. Triggering mechanism in angiogenesis is hypoxia and it is less important than the other mechanism, arteriogenesis. Arteriogenesis is the leading underlying mechanism in collateral development. Arteriogenesis arises by means of the growth and remodeling of functional collateral arteries and it is activated mainly by physical forces. Subsequently, a complex cascade of molecular and cellular events breaks out (14).

Clinical studies suggested leptin as an independent risk factor for cardiovascular diseases (15, 16). Carotid intima-media thickness (CIMT) was found positively correlated with leptin concentrations regardless of other well-known cardiovascular

Table 2. Comparison of baseline characteristics, laboratory parameters and leptin levels between collateral (+) group and collateral (-) group

Baseline characteristics	Collateral (+) group (n=66)	Collateral (-) group (n=53)	*p
Age, years	61.4±14.1	64.3±10.6	0.21
Sex, male/female	45/21	37/16	0.84
Hypertension, n (%)	38 (57.6)	32 (60.4)	0.75
Diabetes mellitus, n (%)	20 (30.3)	25 (47.2)	0.06
Current smoker, n (%)	37 (56.1)	26 (49.1)	0.44
BMI, kg/m^2	26.7±4.1	26.1±5.8	0.53
Waist circumference, cm	93.8±11.6	92.4±12.6	0.52
Hip circumference, cm	102.7±12.2	10.2±13.3	0.52
Waist/hip ratio	0.91±0.02	0.91±0.1	0.84
Fasting glucose, mg/dL	108 (98-151)	107 (94-158)	0.67
Baseline creatinine, mg/dL	1.0 (0.9-1.3)	1.0 (0.9-1.3)	0.82
Total cholesterol, mg/dL	184.3±44.9	179.2±44.5	0.54
LDL cholesterol, mg/dL	118.5±32.9	117.4±32.0	0.85
HDL cholesterol, mg/dL	35.2±9.0	35.6±8.3	0.79
Triglyceride, mg/dL	128 (90-180)	131 (97-187)	0.94
Hemoglobin, g/dL	13.8 (12.7-14.7)	13.8 (12.6-14.6)	0.78
White blood cell,10^3/mm^3	9.5±3.6	10.1±3.8	0.38
Hs-CRP, mg/dL	9.7 (3.9-28)	11.1 (4-51.7)	0.43
Leptin, ng/mL	4.7 (1.7-10.5)	6.8 (2.7-12.1)	0.33
ACEI, n (%)	25 (37.9)	18 (34)	0.65
ARB, n (%)	6 (9.1)	5 (9.4)	0.94
β-Blockers, n (%)	19 (28.8)	8 (15.1)	0.08
CCB, n (%)	5 (7.6)	9 (17.0)	0.11
Statin, n (%)	13 (19.7)	13 (24.5)	0.52

Data are presented as the mean value±SD, median (interquartile range) or number or percentage of patients.
*Student t test, Mann-Whitney U test, Chi-square test P < 0.05 considered statistically significant.
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, BMI - body mass index, CCB -calcium channel blocker, HDL - high-density lipoprotein, Hs-CRP - high sensitive C-reactive protein, LDL - low-density lipoprotein

risk factors in a study conducted by Ciccone et al. (17). Since increased CIMT was reported to reflect increased atherosclerotic burden in many studies (18, 19), the association between leptin and atherosclerosis can be highlighted clearly. In addition, leptin receptors were identified in atherosclerotic coronary arteries although the aortic endothelium was lack of these receptors and hyperleptinemia was confirmed to result in significant coronary endothelial dysfunction (6, 20). The precise underlying mechanism by which hyperleptinemia promotes atherosclerosis has not been established yet. Increase in the cholesteryl ester amount in human macrophages via leptin induced acyl-coenzyme A: cholesterol acetyltransferase (ACAT-1) expression may be one of the causal links between leptin and atherosclerosis (21). In addition, the relationship between leptin and atherosclerotic risk factors such as hypercholesterolemia, diabetes mellitus, age, hypertension, genetic susceptibility were noted in numerous studies (4, 5). In an experimental study, leptin was showed to promote atherosclerotic lesions directly in wild-type mice although it had no effect on leptin receptor deficient mice (22). Besides promoting atherosclerosis, leptin has been reported to correlate directly and positively with adverse cardiac events such as myocardial infarction and angina pectoris (16). Prothrombotic role of leptin can contribute to increased cardiovascular adverse events. This prothrombotic role of leptin results from especially its effect on plasminogen activator inhibitor-1 (PAI-1) level in endothelial cells and platelet aggregation. Leptin increases PAI-1 level in endothelial cells and induces platelet aggregation via leptin receptors (23, 24). All findings mentioned above suggest that an inverse relationship should exist between leptin and coronary collateral development. In addition, it should be noted that an experimental study conducted by Bush et al. (7) showed acute leptin treatment did not provide any significant improvement in arteriogenesis in hypoperfused rat brain although it restored hemodynamic reserve of the cerebral vasculature.

However, some other researches support the thesis that leptin must be positively correlated with coronary collateral development. For instance, Schroeter et al. (25) demonstrated that leptin improve the ability of endothelial progenitor cells (EPCs) to promote vascular regeneration. That the EPC-mediated angiogenesis may contribute to coronary collateral development was reported in another study before (26). Nitric oxide (NO), which is synthesized from L-arginine by NO synthase (NOS), is a signal mediator and it is primarily responsible for endothelial functions. Decreased NOS activity and decreased production of NO in endothelial cells have been shown to be associated with impaired collateral development (10, 27). During the coronary collateral development, increased shear stress resulted from severe coronary narrowing is followed by increased NO production and a series of complex processes. In addition, leptin has been demonstrated to increase NO production via upregulation of NO synthase activity (11). One of the causal relations suggesting leptin may increase coronary collateral development is that leptin induces oxidative stress and enhance the level of reactive oxygen species (ROS) in endothelial cells (28). ROS activation is required for expression of some growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and for proliferation and migration of endothelial cells and vascular smooth muscle cells. Namely, ROS have critical role in angiogenesis and collateral development (29-31).

The reason for why we did not find any relationship between leptin and coronary collateral development is a considerable question that must be cleared by further studies which address the leptin functions comprehensively in human beings. Inter-individual variability in coronary collateral development and in

response to leptin hormone, leptin resistance and genetic differences may be responsible mechanisms for the complex effect of leptin on coronary collateral development. While leptin induces coronary collateral development via enhancing ROS activation and NO bioavailability in some patients, its suppressor effect can be dominant in other subjects via its promoting effect on atherosclerosis and endothelial dysfunction. In fact, in patients with higher Rentrop grades, there was a trend toward lower leptin levels. The failure to detect any statistically significant association between leptin and coronary collateral development do not prove that leptin do not effect collateral formation because the study population of our study was too small. Larger studies are necessary to confirm our findings.

Study limitations

'Firstly, this is a single center study with a small patient sample size. Secondly, the study population included acute coronary syndrome patients, but stable patients are lack. Thirdly, we evaluated collateral vessel formation only angiographically by Rentrop grading. But, Rentrop grading is a semi-quantitative technique which demonstrates only a fraction of the total collateral vessels since the vessels with the luminal diameter of 100 μm or smaller is not angiographically visible. Lastly, the degree of coronary artery stenosis was evaluated visually without using quantitative coronary angiography (QCA).

Conclusion

The current study reveals no statistically significant association between serum leptin level and coronary collateral development although the patients with low leptin levels prone to good collateral circulation. To assess this association in the more rational way, further studies examining leptin effect on angiogenesis and arteriogenesis in cellular, molecular and genetic basis are warranted.

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References

1. Meier P, Gloekler S, Zbinden R, Beckh S, de Marchi SF, Zbinden S, et al. Beneficial effect of recruitable collaterals: a 10-year follow-up study in patients with stable coronary artery disease undergoing quantitative collateral measurements. Circulation 2007; 116: 975-83. [CrossRef]
2. Kaya MG, Özdoğru I, Kalay N, Doğan A, İnanç T, Gül I, et al. Plasma B-type natriuretic peptide in diagnosing inferior myocardial infarction with right ventricular involvement. Coron Artery Dis 2008; 8: 609-13. [CrossRef]
3. Pohl T, Seiler C, Billinger M, Herren E, Wustmann K, Mehta H, et al. Frequency distribution of collateral flow and factors influencing collateral channel development. Functional collateral channel measurement in 450 patients with coronary artery disease. J Am Coll Cardiol 2001; 38: 1872-8. [CrossRef]
4. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. Circulation 2008; 117: 3238-49. [CrossRef]
5. Efstratiadis G, Nikolaidou C, Vergoulas G. Leptin as a cardiovascular risk factor. Hippokratia 2007; 11: 163-70.
6. Knudson JD, Dinçer UD, Zhang C, Swafford AN Jr, Koshida R, Picchi A, et al. Leptin receptors are expressed in coronary arteries, and hyperleptinemia causes significant coronary endothelial dysfunction. Am J Physiol Heart Circ Physiol 2005; 289: 48-56. [CrossRef]
7. Busch HJ, Schirmer SH, Jost M, van Stijn S, Peters SL, Piek JJ, et al. Leptin augments cerebral hemodynamic reserve after three-vessel occlusion: distinct effects on cerebrovascular tone and proliferation in a nonlethal model of hypoperfused rat brain. J Cereb Blood Flow Metab 2011; 31: 1085-92. [CrossRef]
8. Park HY, Kwon HM, Lim HJ, Hong BK, Lee JY, Park BE, et al. Potential role of leptin in angiogenesis: leptin induces endothelial cell proliferation and expression of matrix metalloproteinases in vivo and in vitro. Exp Mol Med 2001;33: 95-102. [CrossRef]
9. Huang F, Xiong X, Wang H, You S, Zeng H. Leptin-induced vascular smooth muscle cell proliferation via regulating cell cycle, activating ERK1/2 and NF-kappaB. Acta Biochim Biophys Sin (Shanghai) 2010; 42: 325-31. [CrossRef]
10. Güleç S, Karabulut H, Özdemir AO, Özdöl C, Turhan S, Altın T, et al. Glu298Asp polymorphism of the eNOS gene is associated with coronary collateral development. Atherosclerosis 2008; 198: 354-9. [CrossRef]
11. Yang R, Barouch LA. Leptin signaling and obesity: cardiovascular consequences. Circ Res 2007; 101: 545-9. [CrossRef]
12. Topsakal R, Kaya MG, Duran M, Günebakmaz O, Doğan A, İnanç T, et al. The relation between microalbuminuria and coronary collateral vessel development in patients with unstable coronary artery disease. Coron Artery Dis 2009; 20: 431-4. [CrossRef]
13. Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985; 5: 587-92. [CrossRef]
14. Heil M, Eitenmüller I, Schmitz-Rixen T, Schaper W. Arteriogenesis versus angiogenesis: similarities and differences. J Cell Mol Med 2006; 10: 45-55. [CrossRef]
15. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation 2001; 104: 3052-6. [CrossRef]
16. Gómez-Ambrosi J, Salvador J, Silva C, Pastor C, Rotellar F, Gil MJ, et al. Increased cardiovascular risk markers in obesity are associated with body adiposity: role of leptin. Thromb Haemost 2006; 95: 991-6.
17. Ciccone M, Vettor R, Pannacciulli N, Minenna A, Bellacicco M, Rizzon P, et al. Plasma leptin is independently associated with the intima-media thickness of the common carotid artery. Int J Obes Relat Metab Disord 2001; 25: 805-10. [CrossRef]
18. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991; 11: 1245-9. [CrossRef]

19. Crouse JR 3rd, Craven TE, Hagaman AP, Bond MG. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995; 92: 1141-7. [CrossRef]
20. Parhami F, Tintut Y, Ballard A, Fogelman AM, Demer LL. Leptin enhances the calcification of vascular cells: artery wall as a target of leptin. Circ Res 2001; 88: 954-60. [CrossRef]
21. Hongo S, Watanabe T, Arita S, Kanome T, Kageyama H, Shioda S, et al. Leptin modulates ACAT1 expression and cholesterol efflux from human macrophages. Am J Physiol Endocrinol Metab 2009; 297: 474-82. [CrossRef]
22. Schäfer K, Halle M, Goeschen C, Dellas C, Pynn M, Loskutoff DJ, et al. Leptin promotes vascular remodeling and neointimal growth in mice. Arterioscler Thromb Vasc Biol 2004; 24: 112-7. [CrossRef]
23. Singh P, Peterson TE, Barber KR, Kuniyoshi FS, Jensen A, Hoffmann M, et al. Leptin upregulates the expression of plasminogen activator inhibitor-1 in human vascular endothelial cells. Biochem Biophys Res Commun 2010; 392: 47-52. [CrossRef]
24. Bodary PF, Westrick RJ, Wickenheiser KJ, Shen Y, Eitzman DT. Effect of leptin on arterial thrombosis following vascular injury in mice. JAMA 2002; 287: 1706-9. [CrossRef]
25. Schroeter MR, Leifheit M, Sudholt P, Heida NM, Dellas C, Rohm I, et al. Leptin enhances the recruitment of endothelial progenitor cells into neointimal lesions after vascular injury by promoting integrin-mediated adhesion. Circ Res 2008; 103: 536-44. [CrossRef]
26. Matsuo Y, Imanishi T, Hayashi Y, Tomobuchi Y, Kubo T, Hano T, et al. The effect of endothelial progenitor cells on the development of collateral formation in patients with coronary artery disease. Intern Med 2008; 47: 127-34. [CrossRef]
27. Lamblin N, Cuilleret FJ, Helbecque N, Dallongeville J, Lablanche JM, Amouyel P, et al. A common variant of endothelial nitric oxide synthase (Glu298Asp) is associated with collateral development in patients with chronic coronary occlusions. BMC Cardiovasc Disord 2005; 5: 27. [CrossRef]
28. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. FASEB J 1999; 13: 1231-8.
29. Huang RP, Peng A, Golard A, Hossain MZ, Huang R, Liu YG, et al. Hydrogen peroxide promotes transformation of rat liver non-neoplastic epithelial cells through activation of epidermal growth factor receptor. Mol Carcinog 2001; 30: 209-17. [CrossRef]
30. Okuyama H, Shimahara Y, Kawada N, Seki S, Kristensen DB, Yoshizato K, et al. Regulation of cell growth by redox-mediated extracellular proteolysis of platelet-derived growth factor receptor beta. J Biol Chem 2001; 276: 28274-80. [CrossRef]
31. Wang Z, Castresana MR, Newman WH. Reactive oxygen and NF-kappaB in VEGF-induced migration of human vascular smooth muscle cells. Biochem Biophys Res Commun 2001; 285: 669-74. [CrossRef]