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ORIGINAL ARTICLE

Leptin to Adiponectin ratio as Atherogenic Index in Ischemic Heart Disease Patients

Muhammad Kashif Nisar [1], Erum Afaq [2], Humera Afaq [3], Anila Jaleel [4], Adnan zuberi [5]

[1] Associate professor, Department of Biochemistry, Liaquat National Hospital & Medical College
[2] Assistant Professor, Department of Physiology, Liaquat National Hospital & Medical College
[3] Post graduate resident medical officer, Internal Medicine, Abbasi Shaheed Hospital, Karachi
[4] Professor &HOD, Department of Biochemistry, FMH College of Medicine and Dentistry, Lahore
[5] Professor, Department of Chemical Pathology, Ziauddin University

ABSTRACT

Objective: To determine plasma adiponectin and leptin levels in subjects with and without ischemic heart disease (IHD) and to find the correlation between leptin, adiponectin to the number of coronary vessels disease-using angiography.

Patients and Methods: This is a cross-sectional study conducted Ziauddin University. 80 subjects were recruited who were undergoing angiography. Height, weight, Waist and hip circumference were measured. BMI and WHR were calculated accordingly. Venous blood was drawn to measure adiponectin and leptin using ELISA.

Results: Leptin to adiponectin ratio (LA ratio) was significantly increased in three and two vessel disease compared with single vessel and non-significant groups.

Conclusion: The study shows that adiponectin decreases and leptin increases in multivessel disease. LA ratio has been found to correlate well in two and more than two vessel disease.

Key words: Adeponectin, IHD, LA ratio Leptin

Author`s Contribution
[1-2] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[3-5] Data analysis, interpretation and manuscript writing, Active participation in data collection.

Address of Correspondence
Muhammad Kashif Nisar
Email: dr.kashifnisar@gmail.com

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Introduction

Cardiovascular disease is the leading cause of death worldwide. Genetic tendency, sedentary life style, age, hypercholesterolemia, insulin resistance, smoking, diabetes mellitus and hypertension are the most common determinants for these disorders.[1]An imbalance between oxygen demand and supply to myocardial vessels due to atherosclerosis results in coronary artery disease.[2] According to WHO report, prevalence of cardiovascular disease is increasing in both developed and developing countries.[3] By 2020, Pakistan will be ranked 4th most heavily populated country in terms of diabetic patients and every 3rd person above 45 years of age will be hypertensive.[4] Since both are risk factors for ischemic heart disease, the burden of disease on our population can be easily foreseen. People from the Asian subcontinent are especially prone to cardiovascular disease due to certain risk factors incurred with a variation in lifestyle including, lack of a balanced diet, health awareness, exercise, and inaccessibility to modernized health care.[5,6] More specifically, The National Health Survey of Pakistan showed that obesity, hypercholesterolemia, and atherosclerosis are the most important determinants of ischemic heart disease.[7] It also indicated that increasing prevalence of obesity,

hypertension, diabetes, and ischemic heart disease are not only due to diets rich in salt and sugar, but also due to the lack of recreational/physical activities.[8] Previously adipocytes were considered to be an inert storage site for triglycerides. In numerous studies adipocytes have now been demonstrated to have an endocrinological function by which they release two hormones notably, leptin and adiponectin, which are thereby termed as adipocytokines.[9] These hormones are considered important in the regulation of cardiovascular function and homeostasis.[10]

Leptin was one of the first adipocytokine discovered.[11] Leptin is a protein, containing 167 amino acid belonging to cytokine family, encoded by Obesity gene at 7q31.3 locus.[12] Adiponectin is a 244-residue protein that is produced mainly by white adipose tissue.[13] Several studies demonstrated that high plasma leptin levels alone can indicate acute cardiovascular conditions, reocclusions after angioplasty, without association of traditional risk factors.[14] In contrast to this, low levels of serum adiponectin levels (due to genetic and environmental causes) results in obesity, type 2 diabetes, metabolic syndrome and atherosclerosis. This paradox in leptin and adiponectin concentrations suggests that leptin may trigger the process of vascular injury while adiponectin have protective role in the development of atherosclerosis.[11] More recently LA ratio is recognized as an index of atherogenesis in diabetic patients.[15] In this study would evaluate the role of LA ratio in ischemic heart disease and its correlation with the extent of coronary artery disease.

M: meter, Kg: kilogram, Cm: centimeter, BMI: body mass index, WHR: waste hip ratio

L/A ratio: Leptin to adiponectin ratio

Table 1: Descriptive characteristics of Ischemic heart disease patients (n=80)

Variables	Mean±SD	Range
Age (years)	48.81±6.15	35-60
Height (m)	1.64±0.98	1.45-1.82
Weight (kg)	73.23±9.32	58-105
BMI (kg/ m^2)	27.23±3.42	20.50-38.10
Waist circumference(cm)	91.15±7.06	74-107
Hip circumference(cm)	90.48±6.27	76-102
WHR	1.01±0.08	0.87-1.20

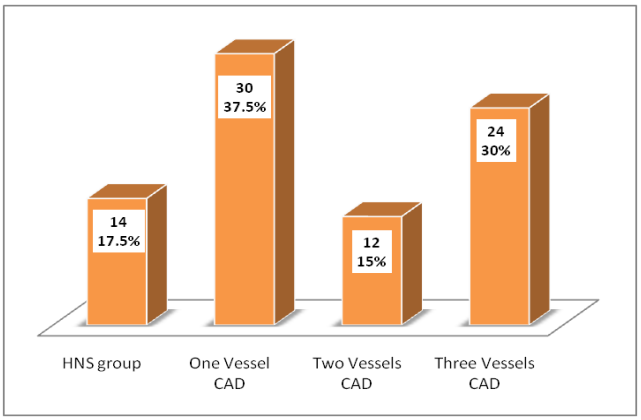

Figure-1: Graphical distribution of pattern of extent of CAD

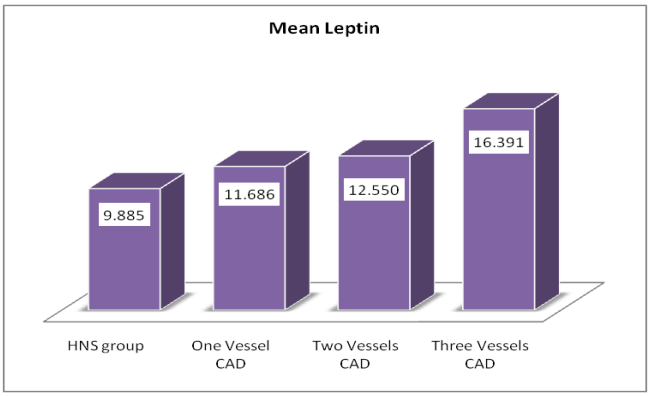

Figure-2: Graphical representation of mean leptin level according to multi vessel disease involvement

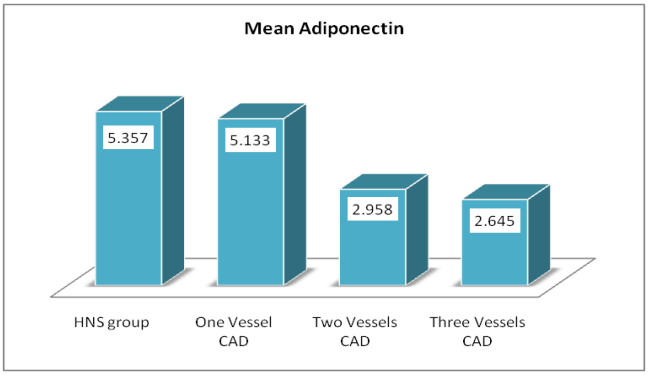

Figure-3: Graphical representation of mean Adeponectin level according to multi vessel disease involvement

Patients and Methods

This cross sectional study was conducted at Ziauddin University. Study duration was 2 years. Ethical approval was taken from ethical review committee of Ziauddin University. Individuals with age range between 40 -55 years from both genders diagnosed as a patient of CVD

on the basis of standard diagnosis protocol including ECG, cardiac enzyme and stress tests from angiography unit were inducted in the study. Exclusion criteria was Subjects with endocrine disorders or on anti-diabetics or lipid lowering drugs. Sampling was done through non-probability purposive sampling technique. Written consent was taken. A detailed history was entered on a detailed prescribed study proforma. Height, weight, Waist and hip circumference were measured. BMI and WHR were calculated by standard formulae. They were classified obese if BMI > 30 kg/m^2 and non-obese if BMI <30 kg/m^2.[16] Waist to hip ratio >0.95 in women and > 0.80 in men was considered obese.[17] Total 10 ml blood was taken by venipuncture at the time of angiography in a vacutainer tube. After centrifugation at 3000rpm for 15 minutes' serum was stored at -70˚C for future use. Samples were analyzed for leptin and adiponectin concentrations by using ELISA immunoassay kits (DRG diagnostics, Germany). Commercially available ELISA kit (DRG instrument GmbH, Marburg, Germany) was used to determine plasma adiponectin concentration. Manufacturer instructions were followed strictly and all tests were performed in duplicate on 96 well plates. Adiponectin values were expressed as µg/ml. Angiography was performed on TOSHIBA Infinix 2000A. Intra coronary guide wire was selected by the operator on the basis of coronary anatomy and morphology of the lesion. After crossing target lesion, the guide wire was fixed and appropriate sized balloon (balloon/artery ratio 1:1) was advanced to lesion site. After that balloon was inflated by inflation device filled with 50% mixture of contrast and saline. Data analysis was performed by using SPSS (Statistical program for social sciences) version-21.0.

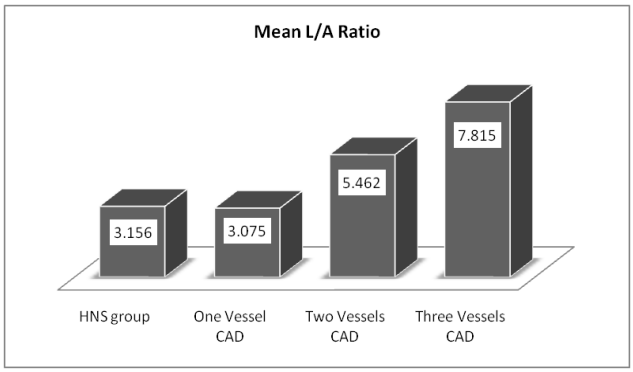

Figure-4: Graphical representation of mean L/A ratio according to multi vessel disease involvement

For continuous variables like age, height, weight, BMI, waist circumference, hip circumference, WHR, serum adiponectin, leptin and LA ratio were presented by mean ± standard deviation. One-way ANOVA and Post hoc Tukey HSD were performed to compare mean level among four study groups according to extent of CAD. Regression analysis was done to estimate relationship of serum levels with extent of CAD. Statistical significance was considered if $p \leq 0.05$

Results

Out of 80 subjects, large number of patients (37.5%) had one vessel followed by (30%) three vessels CAD (Figure 1). Table 1 showed basic characteristics of all the participants expressed as mean and standard deviation. Waist circumference and WHR was significantly more in three vessels CAD group (Table 2). Mean serum adiponectin level was significantly decreased in 2 & 3 vessels CAD groups ($p<0.001$) compared with two other groups. High L/A ratio in 3-vessels CAD was observed compared with the other three groups (Table 3). Positive significant correlation of serum leptin level was found with extent of CAD ($r = 0.298$). Regarding serum adiponectin levels, negative but significant correlation was present with extent of CAD ($r = -.496$). LA ratio also showed positive significant correlation ($r = 0.498$) (Table 4). (Figure 2) showed that serum leptin levels increased with progression of disease. Figure 3 indicates low levels of adiponectin with the progression of multi vessels disease. L/A also increased as the disease advances from 1 vessels to 3 vessels stage (Figure 4).

Discussion

Our study is focused on the variations in leptin and adiponectin levels and the ratio of leptin to adiponectin with the extent of occlusion of coronary arteries. According to our data serum adiponecctin levels decreased significantly with the progression of disease that is two vessels or three vessel disease compared with one vessel and non-significant group (Table-3). Adiponectin has been anticipated to protect against cardiovascular diseases. Adiponectin exerts strong anti-inflammatory effects through nuclear factor κ-B pathway,[18,19] down regulates adhesion molecules expressions on endothelial cells and enhances lipid

clearance.[20,21] Endothelial dysfunction is the first stage of atherogenesis.[22] Adiponectin holds protective actions on every stage of atherogenesis.[23] NO (Nitric Oxide) is the key endothelium derived relaxing factor which plays a central role in the regulation of vasomotor function and vascular tone. Alteration in NO levels in the endothelium mediates anti-inflammatory properties of adiponectin. In vitro, adiponectin induces NO production in human aortic endothelial cells via activation of MAPK(Mitogen activated protein kinase) pathway and enhanced endothelial Nitric oxide synthase mRNA and protein expression[10, 24] Adiponectin is prone to suppress superoxide generation and enhances Nitric oxide synthase activity in endothelial cells that are treated with oxidized LDL. Adeponectin is reported to down regulate acetyl Co A, Cholesteryl acyltransferase-1 in macrophages, thereby reducing the formation of foam cells.[25]

Our study shows that serum leptin concentration increases with the number of vessels involve. Our data suggest that there is significant increase in two vessel disease and three vessel disease when compared with one vessel and non-significant diseases (p value of <0.001) Leptin is secreted by white adipose tissues, the most frequent form of adipose tissues in mammals.[26] Cardiovascular risk is increasingly implicated by increased levels of leptin. Increased leptin levels are well associated with obesity related cardiovascular diseases such as atherosclerosis.[27, 28] Leptin exerts atherogenic effects, including endothelial dysfunction,[29] smooth muscle cell proliferation [30] generation of inflammatory mediators and platelet function modulation.[31,32] The key event which contribute to the formation of atherogenic plaque is the formation of lipid laden macrophages.[31]

Antagonism of leptin and adeponectin actions on cardiovascular system is shown above, there are evidences that high plasma leptin and low plasma adiponectin levels reflects poor cardiovascular outcome.[33] Kappelle et al proposed L:A ratio is a useful parameter to evaluate the cardiovascular event.[34] According to Norata et al, the L:A ratio can be used as a marker to predict thickness of intima media and its possible cardiovascular outcome.[35] In one study it was found that increased peritoneal dialysis patients markedly elevated L: A ratio is consistent with high risk for cardiovascular disease.[36]

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Table 2: Characteristics of Ischemic heart disease patients according to multi vessel disease involvement (n=80)

	HNS group (n=14) mean±SD	One vessel CAD (n=30) mean±SD	Two vessels CAD (n=12) mean±SD	Three vessels CAD (n=24) mean±SD	p-value
Age (years)	47.42±5.89	49.13±6.62	49.25±5.24	49.00±6.35	0.837
Height (m)	1.61±0.10	1.62±0.09	1.71±0.09	1.65±0.08	0.024
Weight (kg)	70.14±14.02	71.76±7.61	77.58±8.69	74.70±7.58	0.138
BMI (kg/ m^2)	26.84±4.65	27.15±3.91	26.30±1.87	28.03±2.41	0.505
Waist circumference(cm)	85.64±5.74	90.13±5.98	92.66±8.15	94.87±6.33	0.000
Hip circumference(cm)	89.50±6.72	91.83±7.27	90.66±5.92	89.29±4.65	0.463
WHR	0.94±0.06	0.98±0.07	1.06±0.04	1.07±0.05	0.000

Table 3: Plasma Levels of Adiponectin, Leptin and L/A ratio according to functioning of multi vessel disease (n=80)

Variables	HNS group (n=14) mean±SD	One vessel CAD (n=30) mean±SD	Two vessels CAD (n=12) mean±SD	Three vessels CAD (n=24) mean±SD
Adiponectin (µg/mL)	5.36±2.41	5.13±3.42	2.96±1.05*,**	2.65±1.03*,**
Leptin (ng/mL)	9.89±5.53	11.69±9.05	12.55±4.67*,**	16.39±10.9*,**,***
L/A Ratio	3.15±5.75	3.08±2.68	5.46±3.95*,**	7.81±6.29*,**,***

Post hoc Tukey HSD was applied
*p-value < 0.05 -Significant compared with hemodynamically non-significant group
**p-value < 0.05 Significant compared with one vessel disease group
***p-value <0.05 Significant compared with two vessels disease group

Table 4: Spearman's correlation of CAD group with quantitative variables (n=80)

Variables	Correlation coefficient®	p-value
Leptin (ng/mL)	0.298	0.007
Age (years)	0.076	0.501
BMI (kg/ m^2)	0.200	0.075
WHR	0.558	0.000
Adiponectin (µg/mL)	-0.496	<.001
L/A Ratio	0.498	<.001

Conclusion

LA ratio may be used to assess the cardiovascular status of the subjects recommended for angiography by the cardiologist.

References

1. Ignarro LJ, Balestrieri ML, Napoli C. Nutrition, physical activity, and cardiovascular disease: an update. Cardiovascular research. 2007;73(2):326-40.
2. Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J. Harrison's Principles of internal medicine. 2008, Single Edition Book ISBN 978-0-07-159991-7: MHID 0-07-159991-6.
3. Riley L, Guthold R, Cowan M, Savin S, Bhatti L, Armstrong T, et al. The World Health Organization STEPwise approach to noncommunicable disease risk-factor surveillance: methods, challenges, and opportunities. American journal of public health. 2016;106(1):74-8.
4. Khealani BA, Hameed B, Mapari UU. Stroke in Pakistan. Journal of the pakistan medical association. 2008;58(7):400.
5. Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. Jama. 2007;297(3):286-94.
6. Bhardwaj R, Kandoria A, Sharma R. Myocardial infarction in young adults-risk factors and pattern of coronary artery involvement. Nigerian medical journal: journal of the Nigeria Medical Association. 2014;55(1):44.
7. Jafar TH, Haaland BA, Rahman A, Razzak JA, Bilger M, Naghavi M, et al. Non-communicable diseases and injuries in Pakistan: strategic priorities. The Lancet. 2013;381(9885):2281-90.
8. Yaseen F. Association of resistin & interleukin 6 in ischemic heart disease and diabetic patients. Pak J Med Dent. 2014;3(1):17-22.
9. Zahorska-Markiewicz B. Metabolic effects associated with adipose tissue distribution. Adv Med Sci. 2006;51(2):111-4.
10. Szmitko PE, Teoh H, Stewart DJ, Verma S. Adiponectin and cardiovascular disease: state of the art? American Journal of Physiology-Heart and Circulatory Physiology. 2007;292(4):H1655-H63.
11. Conde J, Scotece M, Gómez R, López V, Gómez-Reino JJ, Lago F, et al. Adipokines: biofactors from white adipose tissue. A complex hub among inflammation, metabolism, and immunity. Biofactors. 2011;37(6):413-20.
12. Al-Jumaily EF, Zgaer SH. A Review Ratical: Leptin Gene And Obesity. World Journal of Pharmacy and Pharmaceutical Sciences. 2014;3(9).
13. Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes, obesity and metabolism. 2007;9(3):282-9.
14. Beltowski J. Leptin and atherosclerosis. Atherosclerosis. 2006;189(1):47-60.
15. López-Jaramillo P, Gómez-Arbeláez D, López-López J, López-López C, Martínez-Ortega J, Gómez-Rodríguez A, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Hormone molecular biology and clinical investigation. 2014;18(1):37-45.
16. Banks WND. Global Data Base on Obesity and Body Mass index (BMI) in Adults.(Accessed at htpp://www. who. Int/nut/db_bmi. htm). August; 2002.
17. Organization WH. Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008. 2011.
18. Wang X, Chen Q, Pu H, Wei Q, Duan M, Zhang C, et al. Adiponectin improves NF-κB-mediated inflammation and abates atherosclerosis progression in apolipoprotein E-deficient mice. Lipids in health and disease. 2016;15(1):33.
19. Pamukcu B, Lip GY, Shantsila E. The nuclear factor–kappa B pathway in atherosclerosis: a potential therapeutic target for atherothrombotic vascular disease. Thrombosis research. 2011;128(2):117-23.

20. Balsan GA, Vieira JLdC, Oliveira AMd, Portal VL. Relationship between adiponectin, obesity and insulin resistance. Revista da Associação Médica Brasileira. 2015;61(1):72-80.
21. Ouedraogo R, Gong Y, Berzins B, Wu X, Mahadev K, Hough K, et al. Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules in vivo. The Journal of clinical investigation. 2007;117(6):1718-26.
22. Choi B-J, Matsuo Y, Aoki T, Kwon T-G, Prasad A, Gulati R, et al. Coronary endothelial dysfunction is associated with inflammation and vasa vasorum proliferation in patients with early atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2014:ATVBAHA. 114.304445.
23. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. Circulation. 2002;105(5):546-9.
24. Wang X, Pu H, Ma C, Jiang T, Wei Q, Duan M, et al. Adiponectin abates atherosclerosis by reducing oxidative stress. Medical science monitor: international medical journal of experimental and clinical research. 2014;20:1792.
25. Motoshima H, Wu X, Mahadev K, Goldstein BJ. Adiponectin suppresses proliferation and superoxide generation and enhances eNOS activity in endothelial cells treated with oxidized LDL. Biochemical and biophysical research communications. 2004;315(2):264-71.
26. Coelho M, Oliveira T, Fernandes R. State of the art paper Biochemistry of adipose tissue: an endocrine organ. Archives of Medical Science. 2013;9(2):191-200.
27. Wannamethee SG, Tchernova J, Whincup P, Lowe GD, Kelly A, Rumley A, et al. Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. Atherosclerosis. 2007;191(2):418-26.
28. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. Journal of the American College of Cardiology. 2008;52(15):1201-10.
29. Morioka T, Emoto M, Yamazaki Y, Kawano N, Imamura S, Numaguchi R, et al. Leptin is associated with vascular endothelial function in overweight patients with type 2 diabetes. Cardiovascular diabetology. 2014;13(1):10.
30. 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-κB. Acta Biochim Biophys Sin. 2010;42(5):325-31.
31. Maya-Monteiro CM, Almeida PE, D'Ávila H, Martins AS, Rezende AP, Castro-Faria-Neto H, et al. Leptin induces macrophage lipid body formation by a phosphatidylinositol 3-kinase-and mammalian target of rapamycin-dependent mechanism. Journal of Biological Chemistry. 2008;283(4):2203-10.
32. Schafer K, Konstantinides S. Mechanisms linking leptin to arterial and venous thrombosis: potential pharmacological targets. Current pharmaceutical design. 2014;20(4):635-40.
33. Li AC, Glass CK. The macrophage foam cell as a target for therapeutic intervention. Nature medicine. 2002;8(11):1235.
34. Kappelle PJ, Dullaart RP, van Beek AP, Hillege HL, Wolffenbuttel BH. The plasma leptin/adiponectin ratio predicts first cardiovascular event in men: A prospective nested case–control study. European journal of internal medicine. 2012;23(8):755-9.
35. Norata GD, Raselli S, Grigore L, Garlaschelli K, Dozio E, Magni P, et al. Leptin: adiponectin ratio is an independent predictor of intima media thickness of the common carotid artery. Stroke. 2007;38(10):2844-6.
36. Park JT, Yoo T-H, Kim J-K, Oh HJ, Kim SJ, Yoo DE, et al. Leptin/adiponectin ratio is an independent predictor of mortality in nondiabetic peritoneal dialysis patients. Peritoneal Dialysis International. 2013;33(1):67-74..