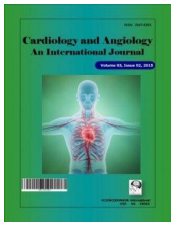

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Association of Adipose-derived Hormones with Atherosclerosis Indices in Metabolic Syndrome Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author KV designed the study, wrote the protocol and edited the final manuscript. Author SG managed the experimental process in the hospital under the guidance of authors SV and HSK and wrote the first draft of manuscript. Author J managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The study was aimed to determine the association of adipose derived hormones, adiponectin, leptin, and adiponectin/leptin (A/L) ratio with presence and degree of atherosclerosis in metabolic syndrome patients.
Study Design: Open label, pilot, case-control study.
Place and Duration of Study: Sadbhavna Medical and Heart Institute, Patiala and, Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, (INDIA), between January 2013 and December 2013.

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Methodology: Metabolic syndrome patients (n=55) with age ≥ 18 years, undergoing angiography for diagnosis and/or interventional treatment of atherosclerosis, and 25 matched control subjects were recruited. Evaluation of traditional and novel cardiovascular risk factors (adipose-derived hormones) and their association with angiographic-derived presence and degree of atherosclerosis indices (number of blocked vessels, severity index, and extent index) was carried out. Continuous variables were expressed as mean ± standard error mean and discrete variables were presented as frequencies and percentages. One way ANOVA was used to assess the difference b/w the groups characterized according to the number of vessels blocked. For each of the indices, the significant univariate predictors were entered into a forward stepwise multivariate regression model (model 1 and model 2) to determine the independent predictors. Statistical significance was accepted at $P \leq .05$.

Results: The independent predictors of atherosclerosis for number of blocked vessels were low serum adiponectin and high total cholesterol level. For extent and severity index, low adiponectin level was the only significant and independent predictor. Leptin and A/L ratio could not prove as significant predictors ($P \geq .05$).

Conclusion: Total cholesterol, adiponectin, leptin and A/L ratio might play a vital pathogenic role not only in the occurrence, but also in the severity, extent, number of vessels blocked complexity in metabolic syndrome patients.

Keywords: Adiponectin; leptin; novel; risk factors; independent predictors; angiography; metabolic syndrome; severity and extent index.

1. INTRODUCTION

Recent statistical reports have presented the facts that cardiovascular disease (CVD) is the leading cause of death [1]. Metabolic syndrome (MetS) is associated with a two-fold increased risk of CVD [2]. Information from many world regions suggests that about 20%-25% (more than 1 in 5) of adults have metabolic syndrome [3]. It lets in a constellation of insulin resistance, continuing inflammation and ectopic fat accumulation following saturation of adipose tissue with fatty acids [4]. The prevalence of MetS is increasing alarmingly because of adverse physical activity and dietary patterns [5].

Aside from various traditional CVD risk factors, several novel risk factors such as C-reactive protein (CRP), fibrinogen, homocysteine, lipoprotein (a), apolipoprotein (apo) A-1, apo B-100, have recently gained importance to predict sub-clinical atherosclerosis [6]. Increased low-density lipoprotein-cholesterol (LDL-C) [7], *triglycerides (TG)* [8], waist-to-hip ratio (WHR) [9], IR [10], systolic blood pressure (SBP) [11], diabetes [12], smoking [13], and decreased high-density lipoprotein cholesterol (HDL-C) [14] have been reported as major risk factors for coronary artery disease (CAD).

Among several novel risk factors, adipose-derived hormones have also acquired significant attention. Adipose tissue is now seen as an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases several hormones, particularly adiponectin (A) and leptin (L). Adiponectin may limit the advancement of coronary artery disease by direct stimulation of nitric oxide production in endothelial cells [15], suppression of lipid accumulation in macrophages [16] and, proliferation of vascular smooth muscle cells [17]. Leptin stimulates synthesis and secretion of endothelin-1 [18], lipoprotein lipase secretion in macrophages and accumulation of cholesterol esters in foam cells, particularly at high glucose concentration [19]. Leptin was previously described to be an independent predictor of CAD [20]. Two studies have found a substantial association between circulating plasma leptin with insulin resistance and inflammatory markers, suggesting leptin as a risk factor for CAD [21,22]. An association b/w adiponectin and CHD had not been fully understood [23,24]. Lack of association of adiponectin and CHD has been reported by Sattar *et al.* [25]. Based on these reported conflicting findings, further accumulation of data is required to resolve this issue. Therefore, the present study was directed to find out the association of adipocyte derived hormone with coronary angiography derived atherosclerosis indices in metabolic syndrome patients.

2. MATERIALS AND METHODS

A prospective, open label, pilot, case-control study was carried out in Sadbhavna Medical and

Heart Institute, Patiala, Punjab, (INDIA). Fifty five (n=55) metabolic syndrome patients fulfilling NCEP-ATP-III screening criteria for diagnosis of metabolic syndrome [26], of age ≥18 years that underwent coronary angiography as described by Babu *et al.* [27] for either diagnosis and/or Interventional treatment of CAD were included in this study. Patients were excluded if they were receiving dialysis and with organ transplant, immuno-suppressive therapy, jaundice, infected with HIV/AIDS, and patient refusing to make informed consent. The control group included 25 subjects, who were non-diabetics, non-hypertensive, with no history of a previous acute coronary syndrome, having normal electrocardiography, of matched age, sex, body mass index, and waist/hip ratio (WHR), and proved to have a completely normal coronary angiography. All subjects presented a written informed consent to the study protocol. All cases and control subjects were subjected to a complete history and clinical examination including measurement of body mass index {(BMI= Weight (kg) /Height (meter)^2 and waist to hip ratio {(WHR= waist circumference (inches) /hip circumference (inches)}.

2.1 Laboratory Measurements

Fasting blood samples were obtained before angiography. Serum was separated immediately by centrifugation and kept on –20°C until analysis. Serum adiponectin and leptin were assayed with ELISA kits (Ray-Biotech, Norcross, GA). Lipid profile, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and, fasting blood glucose levels (FBG) were measured by commercially available kits (ERBA Diagnostics Mannheim, Germany) according to manufacturer's recommended protocol.

2.2 Evaluation of Coronary Atherosclerosis by Angiogram

Angiographic evaluation of coronary atherosclerosis was carried out according to the criteria of Ringqvist *et al.* [28]. Three atherosclerotic indices, *i.e. number of stenosed vessels*, severity index and extent index were derived.

Number of *stenosed vessels:* The criterion for one, two, or three vessel diseases was a 70% or more reduction in the internal diameter of the right, left anterior descending, or left circumflex system. A 50% or more reduction in the internal diameter of the left main coronary artery was considered a double vessel disease (DVD). Patients with less severe disease, that is obstructions causing <70% reduction in the right, left anterior descending, or left circumflex coronary artery and <50% reduction in the left main coronary artery, were classified as a zero vessel disease for the purposes of this index. *Severity index* was defined as the average of the most severe stenosis in the left main, left anterior descending, left circumflex, and right coronary arteries. *Extent index* was *calculated as* the modified Gensini score for each patient according to coronary angiography results [29].

2.3 Statistical Analysis

All data were analyzed using SPSS (Statistical Program for Social Sciences, version 17, SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean ± standard error mean and discrete variables were presented as frequencies and percentages. One way ANOVA was used to assess the difference between the groups. The univariate predictors were found out by Pearson correlation for the continuous variables and Spearman correlation for discrete variables. For each of the indices, the significant univariate predictors were entered into a forward stepwise multivariate regression model (model 1 and model 2) to determine the independent predictors. Model 1 and 2 describes the inclusion of traditional and novel risk factors, respectively. Statistical significance was accepted at $P \leq 0.05$.

3. RESULTS

The clinical and laboratory characteristics of the study groups are shown in Table 1. All patients [(n=55, Male/Female=45/10)] of MetS included were in the age range of 30-55 years (mean age, 51.94±1.98 years).

All the traditional (waist circumference, SBP, TG, HDL, LDL, FBS, HDL/LDL ratio, waist/hip ratio) and new (leptin, adiponectin, leptin/Adiponectin (A/L) ratio) risk factors showed significant high serum levels ($P \leq 0.05$) in all patients irrespective of the presence of a number of risk factors. Fig. 1 shows the serum level of leptin (2.00±0.08 versus 3.37±0.17 ng/ml, $P<0.01$), adiponectin (6.99±0.14 versus 4.74±0.13 ng/ml, $P<0.01$) and an A/L ratio (3.60±0.18 versus 1.54±0.11, $P<0.01$) in MetS and control subjects, respectively.

Table 2 describes the univariate and multivariate predictors for each of the atherosclerotic indices. Number of stenosed/blocked vessels was found to have significant correlation with SBP, LDL and TC. It was found that among SBP, LDL and TC who showed significant univariate association, only one risk factor, *i.e.* TC was able to fit into regression model-1. TC was further added in model-2, which included novel risk factors, *i.e.* leptin, adiponectin and A/L ratio. Thus, 'n*umber of blocked vessels'* was predicted independently by both adiponectin (β= -0.714, *P*<0.001) and TC (β=0.27, *P*=0.003). But, only adiponectin was founded as the independent predictor for both extent index (β= -0.67, *P*<0.01) and severity index (β= -0.881, *P*<0.01).

Table 1. Clinical and laboratory characteristics of the patients and control subjects

Parameter	Control	Patients			
	(N=25)	1-Vessel disease (N=15)	2-Vessel disease (N=18)	3-Vessel disease (N=22)	*P* value
Age (yrs)	48.35±1.42	30.25±1.66	42.22±3.63	58.23±1.92	<0.001
BMI (kg/m^2)	28.60±4.50	29.31±2.70	28.60±2.50	29.40±2.50	0.84
Waist/Hip ratio	0.927±0.01	0.96±0.02	0.95±0.05	0.97±0.01	0.70
SBP (mm Hg)	113.50±3.2	130±2.62	132.22±2.49	136.46±1.82	0.15
DBP (mm Hg)	72.50±1.10	80.1±1.95	81.13±2.24	76.77±1.87	0.26
FGB (mg/dl)	68.00±1.26	105.00±3.06	116.60±3.27	112.38±3.69	0.36
LDL-C (mg/dl)	105.00±1.93	142.00±4.03	141.60±3.33	150.77±3.01	0.09
HDL-C (mg/dl)	56.20±1.81	36.7±2.46	35.10±1.67	37.69±1.74	0.59
TG (mg/dl)	110.5±1.20	206.14±14.88	191.80±14.95	226.61±11.38	0.16
TC (mg/dl)	171.00±3.19	220.43±10.17	215.70±7.54	239.46±7.30	0.08
LDL/HDL ratio	1.90±0.11	3.99±0.33	4.10±0.24	4.09±0.23	0.95

Values are represented as mean ± standard error mean or N (%); NS: not significant; BMI: Body Mass Index, SBP: Systolic Blood Pressure, TC: Total Cholesterol, TG: Triglycerides, HDL-C: High Density Lipoprotein cholesterol, LDL-C: Low Density Lipoprotein cholesterol, FBG: Fasting Blood Glucose.

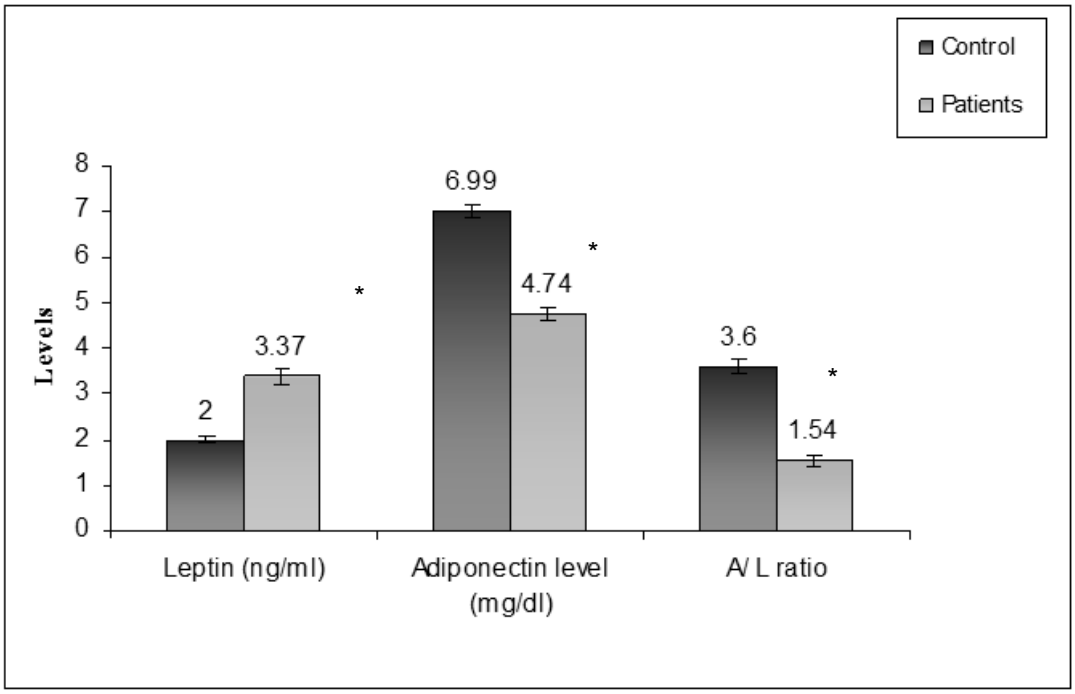

Fig. 1. Comparative levels of Adiponectin, Leptin, and A/L ratio
*(*P <0.001)*

Table 2. Univariate and Multivariate Predictors of angiographic derived indices

Variables	Number of blocked vessels					Severity index					Extent index				
	Univariate predictor		Multivariate predictor			Univariate predictors		Multivariate predictor			Univariate predictor		Multivariate predictor		
	R	*P*	B (95% CI)	β	*P*	R	*P*	B (95% CI)	β	*P*	R	*P*	B (95% CI)	β	*P*
						Model 1									
Age (yrs.)	-0.09	NS				-0.67	NS				0.006	NS			
BMI (kg/m^2)	0.34	NS				0.003	NS				0.30	NS			
Waist/hip ratio	O.10	NS				0.02	NS				-0.04	NS			
SBP (mmHg)	0.35	0.05				0.34	0.05				0.26	NS			
FBG (mg/dl)	0.25	NS				0.37	0.04				0.37	0.04			
LDL-C (mg/dl)	0.40	0.02				0.33	0.04				0.22	NS			
HDL-C(mg/dl)	0.11	NS				0.04	NS				0.01	NS			
TG (mg/dl)	0.24	NS				0.31	0.05				0.16	NS			
TC (mg/dl)	0.34	0.05	0.008	0.28	0.04	0.25	NS				0.15	NS			
LDL/HDL RATIO			(.001 to.016)			0.09	NS				0.04	NS			
	0.28	NS													
						Model 2									
Leptin	0.41	0.02				0.36	0.04				0.26	0.01			
Adiponectin	-0.74	0.01	-0.8	-0.71	.01	-0.88	0.01	-15.35	-0.88	0.01	-0.67	0.01	-13.68	-0.68	.01
			(-1.07 to -0.53)					(-18.54 to -12.15)					(19.42 to -7.93)		
A/L ratio															
	-0.67	0.01				-0.66	0.01				-0.49	0.01			

4. DISCUSSION

The present study addressed that several serum biomarkers could be predictive of CAD in patients with metabolic syndrome, and among which serum levels of leptin and adiponectin appeared to be more useful in clinical practice. We found that leptin had significant association with severity index and vessel disease, but poor association with extent index, whereas, adiponectin had significant association with all three angiography indices *i.e.* severity, extent and vessel disease. Overall, adiponectin but not leptin remains an independent risk factor for predicting risk of CAD. The analysis revealed that, traditional risk factors SBP, LDL and TC were individually found to have significant association with number of stenosed vessels, but when multiple factors considered all together, only TC was found as independent predictor of number of blocked vessels. This clarified that all risk actors do not act simultaneously to worsen the disease. Among novel risk factors, leptin and A/L ratio were univariately correlated with CAD severity, but after taking risk factors all-together, these did not fit into the regression model to behave as linear and important predictors.

This study supports the previous reports of low plasma adiponectin levels in patients with coronary atherosclerosis [30,31] and, being an independent predictor of both extent and severity of CAD [24,32]. Still, Lim *et al.* [33] found no significant relation between adiponectin and the extent or severity of coronary atherosclerosis. This controversy can be in part explained by the divergences in the methods of assessment of the atherosclerosis indices. Present results of predictability of CAD severity by leptin are in opposition to a previous finding [34]. Leptin could not prove as independent predictor of angiographic CAD. Thus, it revealed that reduction in adiponectin is more disturbing than the increase in leptin, as both are not exactly linearly dependent on each other *i.e.* per unit decrease in adiponectin will not lead to per unit increase in leptin. Other major factors may play a strong role simultaneously than leptin or A/L ratio.

Studies have reported a high A/L ratio in MetS than healthy Asian subjects [34,35]. Jung *et al.* [36] had found decreased A/L ratio in MetS subjects and gradually decrease according to the number of MetS components, suggesting an A/L ratio as the predictive marker for MetS. But, in the present study A/L ratio could not act as independent predictor of angiographic CAD severity. The present findings are in conformity with the previous findings of Chudek *et al.* [37], who had reported that A/L ratio was not significantly different in stable-angina patients with and without angiographic evidence of CAD severity.

A few studies have shown diverse effects of physical, dietetic and pharmacological therapies on adipose-derived hormone levels. It has been reported that lifestyle modifications (hypocaloric diet combined with moderate usage) [38], and surgical removal of fat (dermolipectomy) [39] led to fall in leptin and an increase in adiponectin levels, respectively. Certain drugs such as cyclosporine in psoriatic patients [40] and, resperidone in schizophrenic patients [41] has also been found associated with enhancement of adiponectin levels.

In the present work, none of the traditional risk factors (age, gender, SBP, DBP, BMI, waist/hip ratio, FBS, LDL, HDL, TC, TG, LDL/HDL and waist/hip ratio) could predict the angiographic presence and severity of CAD, except the TC as independent predictor of number of occluded vessels. It purports that only these traditional risk factors are not true risk factors for CAD development, rather other novel factors may play important role in predicting CAD. A single factor may have a deleterious effect of CAD risk, but when another factors cluster, the individual predictability of that factor may lose because only one factor will never predispose the patient towards severity. The present work suggests that adiponectin is capable of reflecting the clinical manifestation of CAD in patients with multiple cardiac risk factors. These results substantiate the concept that adiponectin plays a crucial role in the pathophysiology of CAD, and a useful marker of instability and adverse prognosis.

5. LIMITATIONS

Several confounding factors were not taken into account here, such as effect of exercise, gender differences, diet, alcohol consumption, and medications on adipose derived hormone levels. This was an observational study and we could not reach to a concrete determination. The prognostic value of leptin and adiponectin certainly at this level needs to be assessed during long-term follow up in large population based survey. As follow up of patients had not been carried out and consequently the present regression model for CAD prediction could not

test the patients' long term effect and disease progression.

6. CONCLUSION

Adiponectin may act as a potential useful marker for predicting CAD severity & extent and vessel disease in patients with multiple cardiac risk factors.

ETHICAL APPROVAL

The study was approved by the institutional ethics committee (IEC) for human research, Punjabi University, Patiala, and was conducted in accordance with "ethical guidelines for biomedical research on human participants" issued by ICMR and was performed in accordance with the declaration of Helsinki and the code of good clinical practice.

COMPETING INTERSTS

Authors have declared that no competing interests exist.

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