

## ORIGINAL ARTICLE

## ASSOCIATION OF SERUM RESISTIN WITH LIPIDS IN HYPERTENSIVES AND CORONARY ARTERY DISEASE PATIENTS

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**Background:** Resistin, an adipocytokine was initially discovered in rodents as a regulator of lipidogenesis but now different clinical researches have proved its controversial role in inflammation also. Resistin is found to be involved in processes leading to atherosclerotic changes and ultimately to hypertension (HTN) and coronary artery disease. The present study was designed to observe the association of serum resistin with lipid levels in patients of hypertension and coronary artery disease.

**Methodology:** Eighty participants in four groups of equal number were selected including normal blood pressure, newly diagnosed cases of hypertension, hypertensive patients having myocardial infarction and angina pectoris respectively. After consent, history taking and general physical examination of the subjects (to rule out any ongoing disease process), their fasting blood samples were collected. Serum resistin was determined by using standard technique of enzyme linked immunosorbent assay, while lipid parameters were estimated by kits based on enzymatic methods. **Results:** The collected data were analyzed using SPSS-17. The values (mean±SD) of serum resistin, triglycerides and low-density lipoproteins were found progressively and significantly increased while serum high-density lipoproteins were significantly decreased in study groups with increased severity of disease.

**Conclusions:** Serum levels of resistin, triglycerides and LDL are significantly raised while serum HDL levels are significantly lowered in patients of hypertension and coronary artery disease.

**Keywords:** Resistin, hypertension, HTN, coronary artery disease, lipid profile, decrease

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## INTRODUCTION

According to 'Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure' (JNC-7), hypertension (HTN) is defined as systolic and diastolic blood pressure more than 140 and 90 mm Hg respectively.<sup>1</sup> Considered as a global epidemic, HTN is a disease which mainly affects heart and vasculature of the body. In 1990-1994, a survey conducted by Pakistan Medical Research Council reported that 33% of adults above 45 years of age were hypertensive.<sup>2</sup>

Ischemic heart disease (IHD) also known as Coronary artery disease is a condition of coronary vessels which results in the decreased blood supply to cardiac muscle. Atherosclerosis is chronic inflammatory process in the intimal layer of major arteries caused by metabolic risk factors and immune mechanism interaction. Gradual narrowing and obstruction of coronary arteries occur due to atherosclerotic plaques leading to impaired myocardial blood flow and thus producing clinical manifestations of angina pectoris (AP) and myocardial infarction (MI).<sup>3</sup>

Over the last century, the circulating lipids are thought to be associated with the pathogenesis of atherosclerosis. Dyslipidemia is one of the modifiable risk factors in patients of CAD. Blood lipids are considered as a link between inflammation, atherosclerosis and resistin.<sup>4</sup> Triglycerides have

atherogenic property and if raised they are an independent risk factor for CAD. High-density lipoprotein shows atheroprotective role by having reverse cholesterol transport property. Lipids trapped in atheromas are known to be broken down and neutralized by HDL by transferring antioxidant enzymes such as acetyl hydrolase and platelet-activating factor.<sup>4</sup>

Resistin is a cysteine rich adipocytokine which was discovered in obese mice during a research on a nuclear receptor, peroxisome proliferator activated receptor  $\gamma$  (PPAR  $\gamma$ ). This nuclear receptor is mainly expressed in adipocytes and is a major controller of adipogenesis.<sup>5</sup> So, the term of 'adipose secretory factor' was given to resistin.<sup>6</sup> In humans, resistin is found to own the amino acid sequence identical to a family of proteins known as "FIZZ - found in inflammatory zone" and this involvement in inflammation was also proved by different researches as well.<sup>7</sup> In human body resistin is chiefly secreted by bone marrow, monocytes and macrophages while to a lesser extent by adipocytes.<sup>8</sup>

The circulating macrophages infiltrate the intimal layer of arteries and secrete resistin. There resistin activates nuclear transcription factor-kappa B (NF $\kappa$ B) and causes an increased mobilization of intracellular calcium and activation of both protein kinase C as well as 1,4,5 inositol triphosphate leading to release of various inflammatory cytokines. These cytokines initiate multiple intracellular cascades

accelerating monocyte migration and formation of lipid laden foam cells in the arterial intima. Resistin also causes the increased hepatocytic production of lipoproteins especially LDL and triglycerides.<sup>9</sup> As a result there is increase trapping of the cholesterol and triglyceride in the infiltrated macrophages.<sup>10</sup> All these factors promote endothelial dysfunction, proliferation of vascular smooth muscle cell (VSMC) and migration leading to atherothrombosis, HTN and coronary artery disease (CAD).<sup>11</sup>

## MATERIALS AND METHODS

We conducted this comparative study in the department of Physiology of PGMI, Lahore with the assistance of Punjab Institute of Cardiology, Lahore after approval from the Advanced Science and Research Board of the University of Health Sciences (UHS), Lahore.

In this study 80 participants between the ages 30–55 years were recruited and divided into four groups. Twenty participants with equal number of males and females were included in each group. Groups were categorized as Group A, which included normotensive participants (BP≤120/80 mm Hg); group B comprised of freshly established cases of HTN, group C consisted of diagnosed cases of stable angina pectoris with HTN while patients of acute myocardial infarction with hypertension were assigned group D. (Newly diagnosed case is the patient who has been diagnosed for the first time within last thirty days or one month).

Participants with smoking, obesity (BMI ≥30 Kg/m<sup>2</sup>)<sup>12</sup>, acute or chronic inflammation, underlying cardiac or endocrinological disorder were excluded from the above groups. After taking written informed consent and detailed history of the study participants, their estimation of blood pressure was done using standard technique with mercury sphygmomanometer. A subject with blood pressure ≥140/90 mm Hg was taken as hypertensive.

By using aseptic technique, 5 ml of fasting blood sample was drawn with a disposable syringe and kept in the serum vial. After centrifugation, serum was stored at -20 °C. Sandwich ELISA technique was used to determine Resistin by using kit from Creative Diagnostics (USA) with Stat Fax 303 of Awareness Technology (USA).

Serum lipid profile was determined by enzymatic colorimetric method (precipitation method)

using Fluitest kit, Analyticon Biotechnologies for serum LDL and HDL, while kit of Crescent Diagnostics, Jeddah, Saudi Arabia was used for serum triglyceride estimation. The estimations were made with Microlab 300 (Spinreact), USA.

Data analysis was performed using SPSS-17. Results were presented as Mean±SD and analyzed with one-way ANOVA along with Post-hoc Tukey's test for comparison between the groups. Correlation between resistin and serum LDL, HDL and triglyceride was observed by applying Pearson's correlation coefficient, and  $p \leq 0.05$  was considered as statistically significant.

## RESULTS

Our study comprised of 80 participants equally divided into 4 groups. Determined values of serum resistin, LDL, HDL and triglyceride of the participants are presented in Table-1. Progressive and statistically significant increase in the levels of resistin ( $p < 0.001$ ), LDL ( $p < 0.001$ ) and triglyceride ( $p = 0.001$ ) was seen in hypertensives (group B), stable angina pectoris with HTN (group C), and MI with HTN (group D) as compared to normotensives (group A). Serum HDL levels were significantly decreased in study groups compared to normal ones ( $p < 0.001$ ).

Table-2 summarized the comparison of these parameters by Post hoc analysis. It revealed significant differences of serum resistin ( $p < 0.001$ ) between normotensive group (A) and groups having freshly established cases of hypertension (B), hypertensive patients having angina pectoris (C) and patients diagnosed with myocardial infarction having hypertension (D). Similar comparison of serum HDL levels revealed significant difference between group A and C ( $p < 0.001$ ), A and D ( $p < 0.001$ ), B and C ( $p = 0.014$ ), and between B and D ( $p = 0.001$ ). For serum LDL, the comparison was significant among groups A and C ( $p = 0.002$ ), A and D ( $p < 0.001$ ), B and C ( $p = 0.046$ ), and groups B and D ( $p = 0.011$ ).

Multiple comparisons of mean serum triglyceride levels between the groups revealed statistically significant differences amongst groups A and B ( $p = 0.046$ ), A and C ( $p = 0.007$ ), and between groups A and D ( $p = 0.001$ ).

Pearson's correlation coefficient showed non-significant correlation between serum resistin and HDL, LDL, and triglyceride levels in all groups (Table-3).

**Table-1: Comparison of serum resistin, HDL, LDL and triglyceride values (Mean±SD)**

Parameter	Group A	Group B	Group C	Group D	<i>p</i>
Resistin (ng/ml)	6.80±1.01	16.73±3.78	17.51±8.04	21.07±7.12	<0.001*
HDL (mg/dl)	66.00±27.37	56.80±13.87	40.10±12.79	34.90±6.60	<0.001*
LDL (mg/dl)	132.05±32.71	149.75±56.01	193.55±49.37	202±64.86	<0.001*
Triglyceride (mg/dl)	142.65±42.79	199.95±84.44	214.80±64.54	230.60±73.39	0.001*

\*Significant

**Table-2: Post hoc comparison of serum resistin, HDL, LDL triglyceride**

Parameter	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D
Serum Resistin	<0.001*	<0.001*	<0.001*	0.973	0.086	0.208
HDL (mg/dl)	0.322	<0.001*	<0.001*	0.014*	0.001*	0.767
LDL (mg/dl)	0.706	0.002*	<0.001*	0.046*	0.011*	0.956
Triglyceride (mg/dl)	0.046*	0.007*	0.001*	0.901	0.488	0.883

\*Significant

**Table-3: Correlation between serum resistin and HDL, LDL, and triglyceride levels**

Parameters	Group A		Group B		Group C		Group D	
	r	p	r	p	r	p	r	p
Resistin and HDL	-0.088	0.713	-0.049	0.837	-0.049	0.838	-0.030	0.899
Resistin and LDL	0.044	0.852	0.121	0.612	0.139	0.560	-0.330	0.156
Resistin and Triglyceride	0.421	0.065	0.120	0.613	0.097	0.683	0.319	0.170

r = Pearson's correlation coefficient

**DISCUSSION**

Atherosclerosis is subclinical low grade inflammation of the vascular endothelium which leads to pathological changes in diameter and flow of circulatory passages ultimately narrowing and occluding the vessels. Progression of these changes in the peripheral and cardiac vasculature can lead to diseases like hypertension and coronary artery disease.<sup>1</sup> Resistin is mainly expressed from blood leucocytes and is thought to participate in the release of a wide array of cytokines revealing its possible involvement in inflammation leading to atherosclerosis.<sup>13</sup>

Our results demonstrated increase in the levels of serum resistin in hypertensive patients and CAD compared to normal participants. The results are in agreement with the results of an analytical research which revealed raised resistin levels in hypertensive patients as compared to normotensives.<sup>14</sup> Resistin is thought to play this role by vascular remodeling and altering the renin angiotensin pathway.<sup>14</sup> In another study, strong association of raised resistin levels with increased future risk of developing hypertension was observed.<sup>15</sup>

Different researches derived similar relationship of resistin with myocardial impairment when strong association of raised serum resistin levels was observed in Spanish adults with the increased future risk of CAD<sup>16</sup> as well as in another multiethnic research, with the severity and outcome of cardiovascular disease. The exact role of resistin in causation of cardiac disease could not established.<sup>17</sup>

In the present research the association between serum levels of resistin, HDL, LDL and triglyceride was explored in normal participants and in patients with varying degree of cardiovascular disease. The results revealed significantly raised serum levels

of LDL and triglyceride and significantly lower levels of HDL in study participants but no correlation was observed between serum resistin and lipid parameters. In a study conducted on females with metabolic syndrome, positive association of resistin was found with serum triglyceride, cholesterol and VLDL while negative association was observed with HDL.<sup>18</sup> Parallel results were observed in a study conducted in hypertensive patients with peripheral arterial disease when significant positive association of resistin with waist circumference and serum LDL was observed.<sup>19</sup> Another study revealed negative correlation of resistin with serum HDL in patients suffering from dementia due to vascular inflammation.<sup>20</sup>

Resistin enhances the hepatocytic production of circulating lipids and atherogenesis through intracellular SREBP1 and SREBP2 pathways while apoB VLDL synthesis via PI3 kinase and MAP kinase pathways.<sup>21</sup> In an observational study serum resistin was positively correlated with LDL and triglycerides in the first degree relatives of diabetic patients suggesting its involvement in the causation of dyslipidemia even in normal participants.<sup>22</sup>

Despite lot of supporting data, we come across with controversial results also as in a study, no relationship between serum resistin and CAD was observed in obese participants. It was explained on the basis of sample size.<sup>23</sup> Inverse association was witnessed amongst serum lipid levels and resistin in another study. It is thought that sequestration of lipids in macrophages decreased their serum levels.<sup>24</sup> In a research follow up of patients of CAD revealed that patients with raised resistin levels had poor prognosis, but in these patients resistin was not correlated with lipid parameters which was due to its association with inflammation rather than serum lipids.<sup>25</sup>

Small sample size of this research limited the generalization of its results. Moreover association of resistin with various confounding and risk factors of hypertension and coronary artery disease was not observed. By overcoming the limitations of study, future ventures will help in better understanding of the links between the triad of resistin, atherosclerosis and coronary artery disease.

**CONCLUSIONS**

The present study revealed significantly raised levels of serum resistin and lipid parameters with increasing severity of the coronary artery disease. As increase in circulating levels of resistin is parallel to increase in serum lipids, it appears that resistin might be involved in the alteration of normal lipid metabolism and pathogenesis of atherosclerosis. So cause and effect relationship between resistin, lipid parameters and coronary artery disease is still to be explored.

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