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Original Research Article.

Role of Adiponectin and Pro-Inflammatory Cytokines in Ischemic Heart Disease

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ABSTRACT

Aims & Objectives: Recent studies have shown adiponectin to be an anti-inflammatory adipokine having insulin sensitising properties. It is seen that Insulin resistance and inflammation contributes significantly to atherosclerosis. In our study, we estimated the levels of adiponectin and proinflammatory cytokines in patients with angiographically proven ischemic heart disease.

Materials And Methods: 50 cases of angiographically proven ischemic heart disease and 50 age and sex matched controls with no evidence of ischemic heart disease on angiography were selected from GB Pant Hospital. Serum adiponectin, TNF-α and IL-6 levels were estimated by ELISA kit in both cases and controls.

Results: The mean serum adiponectin level was lower in cases (5.97±0.80 µg/ml) as compared to controls (6.60±0.4 µg/ml).The mean serum levels of TNF-α were higher in cases as compared to controls and the p value was significant. IL-6 was also elevated significantly in cases as compared to controls. p value of <0.05 was regarded as statistically significant.

Conclusion: Lower adiponectin levels in cases as compared to controls is suggestive of its role in reducing inflammation and insulin resistance in the etiopathogenesis of ischemic heart disease. Higher levels of pro-inflammatory cytokines in cases indicate that ischaemic heart disease is an inflammatory condition where glucose metabolism is deranged predisposing to atherosclerosis.

Keywords: Adiponectin, Cytokines, Ischemic Heart Disease.

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INTRODUCTION

Ischaemic heart disease (IHD) is the generic designation for a group of closely related syndromes resulting from myocardial ischaemia, which is an imbalance between the perfusion and the demand for oxygenated blood.[1] Most individuals with ischaemic heart disease are asymptomatic for decades[2] as the disease progresses before the first onset of symptoms often as a "sudden" heart attack.

IHD is now the leading cause of death worldwide claiming 25-30% of deaths in most industrialized countries.[3] It is on rise and has become a true pandemic that respects no borders. According to Burden of Disease Study conducted by Ministry of macroeconomics and health, it is estimated that 6.1 million of the world's IHD patients will be in india by 2015. It is hypothesized that Indians have exaggerated insulin insenstivity in response to traditional risk factors (hyperlipidemia, obesity, physical inactivity) predisposing them to increased cardiovascular risk.

Accumulating evidence suggests that atherosclerotic progression results from micro-inflammation[4] mediated by proinflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) via NF-κB pathway. Adiponectin (adipocyte-derived anti-inflammatory plasma protein) has a role in decreasing the progress of atherosclerosis. It has insulin sensitizing and vasodilatory actions by modulating endothelial cell responses and insulin sensitivity via suppressing NFκB signaling in response to TNF-α.[5,6]

TNF-α is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It is produced chiefly by activated macrophages, endothelial cells and adipose tissue. It is chemoattractant for neutrophils and increases the expression of cell adhesion molecules on endothelial cells.[7] In liver, it causes insulin resistance by serine phosphorylation of insulin receptor substrate

(IRS-1) which inhibits its tyrosine kinase autophosphorylating activity thereby imparing insulin signalling.[8] When TNF-α binds to its receptor, it releases NFκB which is a heterodimeric transcription factor that translocates to the nucleus mediating inflammation and insulin resistance.[9]

IL-6 is an interleukin that acts as a pro-inflammatory cytokine and is secreted by T cells and macrophages. It plays an essential role in the final differentiation of B-cells into Ig-secreting cells stimulating immune responses leading to inflammation. At high concentrations, IL-6 induces IRS-1 serine phosphorylation which inhibits phosphorylation of its tyrosine residues in response to insulin binding to its receptor and decreases transcription of IRS-1, GLUT-4. As a result IL-6 causes insulin resistance.[10]

ADIPONECTIN (ADIPO Q) (ACRP 30) is an adipocyte derived protein that is abundantly present in plasma.[11] It suppresses the expression of adhesion molecule on endothelial cells[12], proliferation of smooth muscle cells[13] and formation of foam cells.[14] It has been shown to have anti-diabetic, anti-atherosclerotic and anti-inflammatory functions by causing increase in glucose uptake into the cells, increased fatty acid oxidation and promoting insulin senstivity. Adiponectin stimulates protein kinase A by increasing cAMP levels inside the cell. The protein kinase suppresses TNF-α induced IκB-α phosphorylation. As a result NF-Kb IkB-α complex does not dissociate, thus inhibiting NFκB mediated signalling pathways.[15]

MATERIALS AND METHODS

The study was a Hospital based Observational case control study which was conducted in the Department of Biochemistry in Lady Hardinge Medical College in collaboration with the Department of Cardiology, GB Pant Hospital, New Delhi from November-2011 to March 2013.The study population comprised of the Adults of 35 yrs or above diagnosed angiographically with ischaemic heart disease in GB Pant Hospital during my study period.

The study subjects were divided into two groups.

Cases: A minimum of 50 angiographically diagnosed patients of ischaemic heart disease of age 35 years or above of either sex.

Controls: A minimum of 50 age and sex matched patients with no evidence of ischaemic heart disease on angiography.

Inclusion Criteria

All patients of 35 yrs or above with angiographically diagnosed ischaemic heart disease.

Exclusion Criteria

- History of any acute inflammatory disease.
- Any history of ongoing chronic inflammatory disease (Rheumatoid Arthritis, Connective tissue disorders, Inflammatory bowel disease, pelvic inflammatory disease)
- Any type of chronic diseases (chronic obstructive pulmonary disease, cirrhosis, chronic kidney disease, tuberculosis)
- Any type of debilitating illness(cancer).

Venous blood sample was collected from the subjects under sterile condition after overnight fasting of 8-12 hrs. The sample was processed immediately for the routine biochemical investigations, hemogram and lipid profile. For special investigations, the plasma samples were stored at -20ºC till subsequent analysis. Special investigation like TNF-α, IL-6 and Adiponectin were estimated by ELISA.

Statistical Analysis

It was done by using SPSS (statistical package for social sciences) 20 version. All the data was expressed as mean ±SE of mean. The p value of < 0.001 was considered highly significant. The data obtained was compared between two groups by student t-test. Pearson's correlation coefficient was applied for correlation between two quantitative variables.

Table 1: Serum Levels of TNF-α, IL-6 and Adiponectin in cases and controls

Parameter	Study Group (n=50)	Mean	S.D	S.E.M	p Value Independent Sample T Test
TNF-α	Case	362.20	236.45	33.43	0.000*
	Control	186.94	177.33	25.07	
IL-6	Case (n=50)	33.188	40.80	5.77	0.003*
	Control (n=50)	13.732	18.76	2.65	
ADIPONECTIN	Case (n=50)	5.97	5.69	0.80	0.486
	Control (n=50)	6.60	2.94	0.41	

Table 2: Correlation Coefficient of TNF-α, IL-6 and Adiponectin

Parameter		Pearson's Coefficient	p Value
TNF-α	IL-6	0.091	0.366
	ADIPONECTIN	-0.164	0.103
IL-6	TNF-α	0.091	0.366
	ADIPONECTIN	-0.098	0.334
ADIPONECTIN	TNF	-0.164	0.103
	IL-6	-0.098	0.334

RESULTS

The mean serum adiponectin level was lower in cases (5.97±0.80 µg/ml) as compared to controls (6.60±0.4 µg/ml).The mean serum levels of TNF-α were higher in cases as compared to controls and the p value was significant. IL-6 was also elevated significantly in cases as compared to controls. p value of <0.05 was regarded as statistically significant. The mean serum adiponectin level in the study group (cases) was 5.97±0.80 µg/ml and in the control group was 6.60±0.4 µg/ml. The Pearson correlation coefficient was calculated between the two quantitative variables and the value is given in the table (2).

DISCUSSION

In the study the mean plasma TNF-α level in the study group (cases) was 362.20±33.43 pg/ml and in the control group was 186.94±25.07 pg/ml. The difference between the two was statistically significant (p value=0.000*) (Table 1). Our findings are in accordance to Ross[16] and Skoog et al[17] who have also implicated TNF-α as an important contributor to the development of atherosclerotic lesions by promoting the expression of adhesion molecules on endothelial cells and initiating inflammatory cascade inside the arterial wall. In 2008, Kosmala et al[18] also observed significant rise in TNF levels in stable IHD cases. This signifies that TNF-α is an important novel marker of inflammation and has a potential in identifying individuals at high cardiovascular risk.

A positive correlation was found between TNF-α and IL-6 with Pearson's coefficient r= 0.091which was not statistically significant. The mean plasma IL-6 level in the study group (cases) was 33.19±5.77 pg/ml and in the control group was 13.73±2.65 pg/ml and the difference between the two was statistically significant (p = 0.003). Ridker et al[19] also found an independent correlation between IL-6 levels and coronary risk in healthy men. In 2003, Fernandez-Real et al[20] also confirmed plasma concentrations of proinflammatory cytokines like IL-6 are increased in patients with ischemic heart disease. This can be attributed to the reversible ischemia which triggers an initial rapid release of preformed IL-6 from circulating monocytes, or cardiac mast cells, followed by enhanced production of IL-6[21]. These findings emphasize the role of IL-6 as a potential marker of inflammation in diagnosis of ischaemic heart disease.

A positive correlation was found between IL-6 and TNF-α with Pearson's coefficient r=0.091which was not statistically significant.

In my study a negative correlation was found between IL-6 with Adiponectin with r= -0.098. Fernandez-Real et al[20] and many other studies have implicated proinflammatory cytokines to cause insulin resistance in humans in Caucasian population. J. Sean et al[22] showed for the first time that IL-6 exerts an inhibitory effect on both early insulin receptor (IR) signal transduction and downstream insulin action, thereby causing insulin resistance. My study also confirms similar correlation between IL-6 and insulin resistance though it is statistically not significant.

The mean serum adiponectin level in the study group (cases) was 5.97±0.80 µg/ml and in the control group was 6.60±0.4 µg/ml. The difference between the two was not statistically significant (p= 0.486). My findings were supported by Schulze et al[23] who postulated that high plasma levels of adiponectin were associated with a reduced risk for incident CHD events in 745 men with Type 2 diabetes .In addition Pischon et al[24] also observed similar findings in a non-diabetic population as well.

In my study a negative correlation was found between adiponectin and TNF-α, IL-6 with r= -0.164, r=-0.098 respectively which was not significant. Similar findings were suggested by Ouchi et al[25] who suggested that adiponectin suppresses TNF-α secretion from a number of cell types including macrophages which could be responsible for the negative correlation. The negative correlation of adiponectin with IL-6 has also been suggested by Engelis et al[26] in Germany but the study was done in obese females. These findings could explain the anti-inflammatory action of adiponectin. However more clinical studies are required to ascertain the molecular mechanisms that participate in anti -inflammatory action of adiponectin.

CONCLUSIONS

The high levels of proinflammatory cytokines in cases as compared to the controls indicate the role of ongoing chronic inflammation in the etiopathogenesis of ischaemic heart disease. It suggests the inflammatory processes mediated by proinflammatory cytokines plays role in atherogenesis leading to ischemic heart disease.Higher Adiponectin in cases as compared to controls is suggestive of its role in reducing inflammation and insulin resistance in the etiopathogenesis of ischemic heart disease. However, insignificant difference of adiponectin between cases and controls could be due to cases and controls were BMI matched. Further studies on a larger sample size are required for in depth evaluation of the possible role of TNF-α, IL-6 and Adiponectin as biomarkers of atherosclerosis. This pilot study needs to be substantiated with a larger sample size with different ethnicities.

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