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Original Research Article.

Role of IL-6 and Insulin Resistance in the Etiopathogenesis of Atherosclerosis

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ABSTRACT

Objectives: Our study attempts to evaluate the role of Nuclear Factor-kappa Beta(NF-κB), Interleukin-6 and Homeostatic model assessment of insulin resistance (HOMA-IR) in assessment of severity of atherosclerosis currently assessed by angiography.

Methods: 50 cases of angiographically significant atherosclerosis (>50% obstruction in coronary arteries) and 50 age, sex, BMI matched patients with insignificant atherosclerosis (<50% obstruction) on angiography were selected from G.B Pant Hospital. Serum IL-6, NF-κB was estimated by ELISA and serum insulin was estimated by CLIA.

Results: Serum IL-6, NF-κB, Insulin and HOMA-IR were significantly raised in cases (p=0.003, 0.05, 0.003, 0.012 respectively). Upon correlation analysis, we observed that IL-6 has statistically significant correlation (Pearson's coefficient, r=0.196 and p=0.04) with NF-κB. Upon binomial logistic regression analysis, NF-κB emerged as the best predictor of severity of atherosclerosis (OD=19.2).

Conclusion: Our study shows that atherosclerotic progression is associated with inflammation, insulin sensitivity and endothelial dysfunction. The study also asserts a significant correlation between inflammation and NF-κB, thereby throwing light on critical role of NF-κB in pathways of inflammation promoting atherosclerosis. Further studies in larger sample size are required to assess NF-κB as marker of severity of atherosclerosis.

Keywords: Inteleukin-6, NF-κB, Insulin Resistance, Atherosclerosis.

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INTRODUCTION

IHD is the generic designation for a group of closely related syndromes resulting from myocardial ischemia--an imbalance between the supply (supply ischemia or low-flow ischemia) and demand of the heart for oxygenated blood (demand ischemia or high-flow ischemia).It is most commonly observed that myocardial ischemia is caused by atherosclerosis of the coronary arteries.[1]

Most of the developing countries have witnessed a dramatic increase in the prevalence of IHD.[2] Cardiovascular diseases have assumed epidemic proportions in India as the estimated burden of Coronary Heart Disease is more than 32 million patients.[3] According to the estimates from the GBD Study, by 2020 85% of the global cardiovascular disease burden is expected to be borne by developing nations out of which India is predicted to bear the greatest IHD burden.

Over the past few decades, the management of atherosclerosis mainly has been reduction of Low Density Lipoprotein (LDL)-cholesterol by HMG-CoA synthetase inhibitors like statins. But in spite of success in lowering LDL, the epidemic of IHD continued to surge. Therefore, the focus of research has been shifted from dyslipidemia to inflammatory processes. Studies show inflammatory processes might have a key role in the initiation and progression of atherosclerosis.

Inflammatory processes have a key role not only in the initiation and progression of atherosclerosis but also in the stability of the established atherosclerotic plaques.[4] Risk factors for cardiovascular disease like Diabetes Mellitus, smoking trigger a chronic inflammatory process, which leads to loss of vasodilatory and antithrombotic properties of the vascular endothelium (Endothelial dysfunction).[5]

The interplay between inflammatory processes and hormonal effects of insulin is emerging as key factors in etiopathogenesis. The inflammatory processes are mediated by cytokines like IL-6.

Interleukin (IL)-6 is a pleiotropic cytokine with a broad range of humoral and cellular immune effects relating to inflammation, host defense, and tissue injury.[6]

In a prospective study in apparently healthy men, Ridker et al[7] proposed that elevated levels of IL-6 were associated with increased risk of future myocardial infarction.

Various studies suggests that Insulin resistance (IR) contributes to atherosclerosis and is an important factor in its pathogenesis. It is postulated that impaired insulin sensitivity results in atherosclerosis by various mechanisms. They include the anti-aggregating platelet effect of insulin[8], the effect of the hormone on nitric oxide release from the endothelium[9], the inhibition of migration of vascular smooth muscle cells[10], and the inhibitory effect on fibrinogen synthesis[11] which are impaired in insulin-resistance.

Rel or NF-kappaB (NF-kB) proteins comprise a family of structurally-related eukaryotic transcription factors that are involved in the control of normal cellular processes such as immune and inflammatory responses by increasing the expression of specific cellular genes. These include genes encoding cytokines, receptors involved in immune recognition such proteins involved in antigen presentation and receptors required for neutrophil adhesion and migration.[12] NF-κB regulation of genes involved in the inflammatory response and cellular proliferation likely plays an important role in the initiation and progression of atherosclerosis.

Therefore, we studied IL-6, NF-κB and HOMA-IR (marker of insulin resistance) in patients with clinically significant atherosclerosis to understand further the etiopathogenesis of atherosclerosis and whether any of these can be used as biomarker to predict the severity of atherosclerosis.

MATERIALS AND METHODS

It was Descriptive Observational case control study conducted in the Department of Biochemistry in Lady Hardinge Medical College in collaboration with the Department of Cardiology, GB Pant Hospital after approval by the ethical committee of LHMC, New Delhi.

We enrolled 50 non diabetic cases diagnosed with angiographically significant atherosclerosis (>50% obstruction in coronary artery) and 50 age and sex matched controls with insignificant atherosclerosis (<50% obstruction) on angiography after informed written consent. The patients on statins were excluded from the cases. The study was approved by institutional ethical committee of LHMC.

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 IL-6 was estimated by ELISA using kit from Diaclone Research (France) while NF-κB was estimated using a kit from Biomedical Medical assay (Beijing, China). Insulin level was estimated by chemilumniscence based immunoassay (CLIA) from Beckman Coulter (United States) and HOMA-IR was calculated for estimating insulin resistance. According to Homeostasis model assessment score of insulin resistance (HOMA-IR), IR= fasting serum insulin (μIU/ml) × fasting plasma glucose (mg/ml)/405.

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. Binomial logistic regression was applied to obtain the best predictor of Atherosclerosis.

RESULTS

In the present study, we observed significantly (p=0.003) higher levels of IL-6 in study population (33.19±5.77 pg/ml) when compared to control (13.73±2.65 pg/ml) (figure 1) (table 1).In addition the mean serum NF-κB levels were also significantly (p=0.03) higher in the study group (0.33±0.10 ng/dl) as compared to control group (0.29±0.11 ng/dl) (figure 2) (table 1).Upon correlation analysis, we observed that IL-6 has statistically significant correlation (Pearson's coefficient, r=0.296 and p=0.05) with NF-κB (figure 3).The mean serum insulin level raised significantly (p=0.003) in study group as compared to controls (9.96±5.25 vs 6.85±4.9 μIU/ml) (table 1).The mean serum HOMA-IR level in the study group (cases) was 2.95 ±0.26 and in the control group was 1.95±0.29 . The difference between the two was significant (p=0.012) (table1).

Table 1: Parameters in Study Population

Parameter	Study Group	Mean	S.E.M	P Value
Il-6	**Case (n=50)**	33.188	5.77	
	Control (n=50)	13.732	2.65	0.003*
Insulin	**Case**	9.96	0.74	0.003*
	Control	6.85	0.69	
HOMA-IR	**Case**	2.95	0.26	0.012*
	Control	1.95	0.29	
NF-κB	**Case**	0.33	0.014	0.050*
	Control	0.29	0.015	

*p value≤0.05 is considered statistically significant

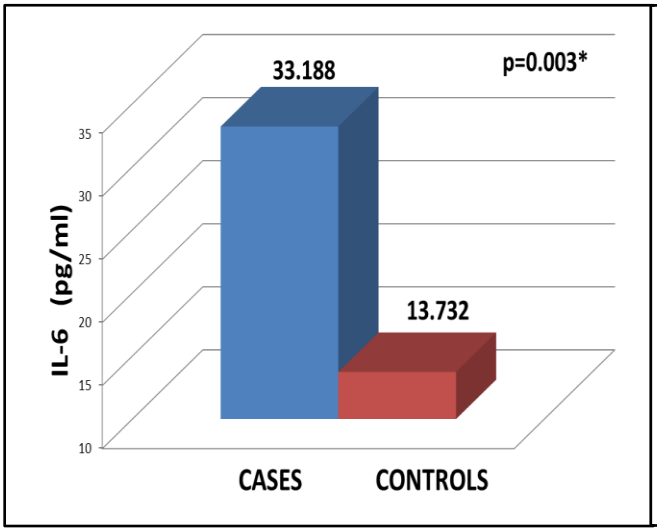

Figure 1: Serum IL-6 Level in Study and Control Group

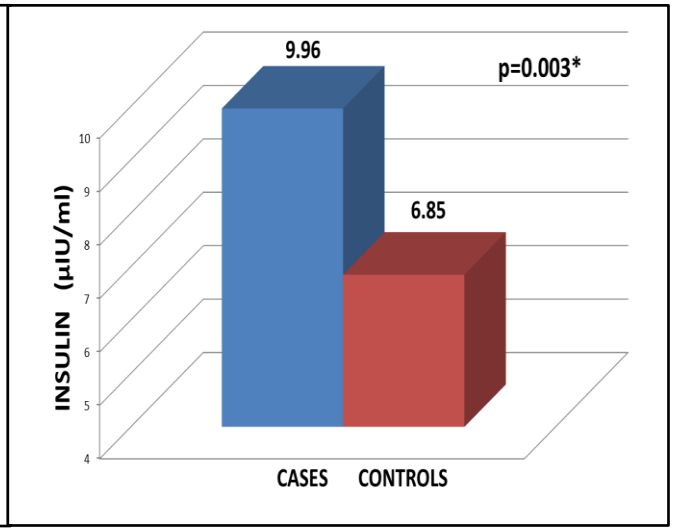

Figure 2: Serum Insulin Levels in Cases and Control Group

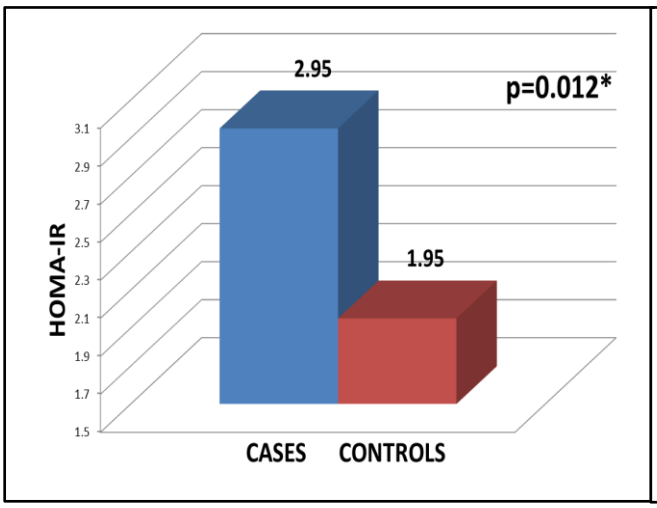

Figure 3: HOMA-IR Levels in Cases and Control Group

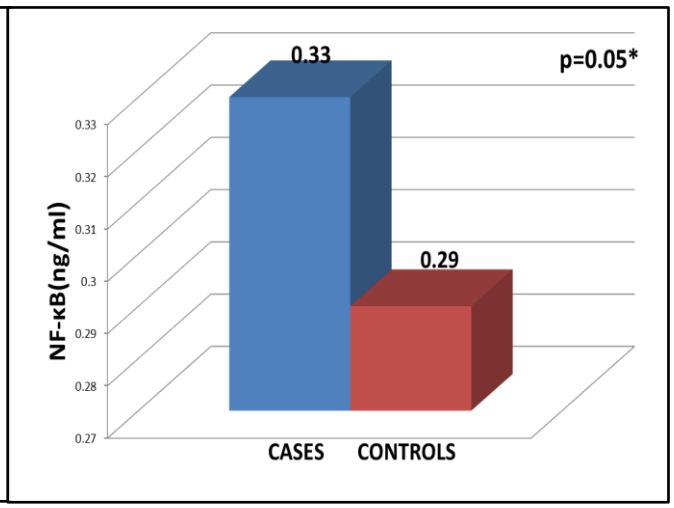

Figure 4: Serum NF-κB Levels In Cases And Control Group

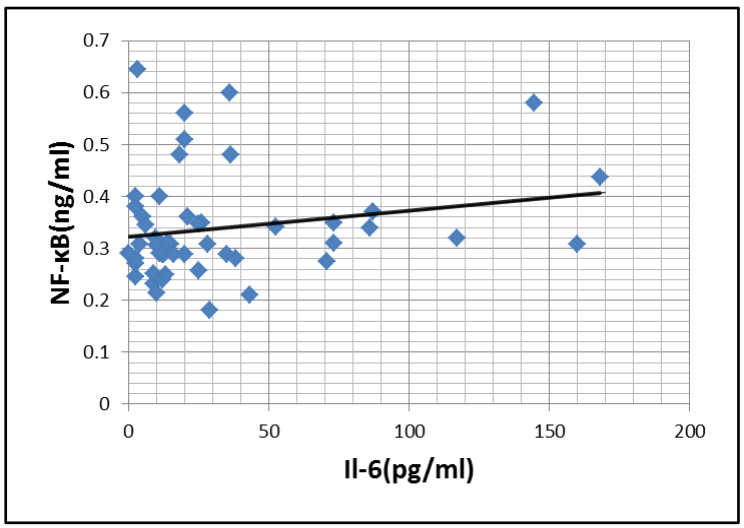

Figure 5: Correlation Between IL-6 and NF-KB

DISCUSSION

In our study we found increase in pro-inflammatory marker (IL-6), NF-κB, markers of insulin resistance (HOMA-IR and serum insulin) in cases of significant atherosclerosis as compared to controls. The inflammatory marker, IL-6 level in the study group (cases) was significantly higher as compared to controls. My findings are substantiated by different studies that confirm a close relationship between inflammation and atherosclerosis in an independent way. Ridker et al[7] found an independent correlation

between IL-6 levels and coronary risk in healthy men. Yudkin et al[13] also reported that IL-6 might play a key role in the development of coronary disease though a number of metabolic and endothelial mechanisms.

In 2003, Fernandez-Real et al[14] 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.[15] These findings emphasize the role of IL-6 as a potential marker of inflammation in diagnosis of ischaemic heart disease.

The mean serum NF-κB level in the study group (cases) was 0.33 ± 0.10 and in the control group was 0.29±0.11μM which was statistically significant (p=0.05). Worldwide there are very few clinical studies evaluating the role of NK-κB in ischaemic heart disease. In 2001,Tak et al[16] proposed that transcription factor nuclear factor-κB (NF-κB) is a key regulator of inflammation and plays a key role in various inflammatory diseases. In 2004 Jian Jun et al[17] studied NF-κB levels in Chinese patients with stable angina. He postulated that NF-κB were raised in cases as compared to controls (p<0.01). In support of this Gerondakis S et al[18] proposed that NF-κB regulates host inflammatory and immune responses and cellular growth properties by increasing the expression of specific cellular genes encoding for cytokines, major histocompatibility complex (MHC), proteins for antigen presentation, and receptors for neutrophil adhesion and migration.[19] This indicates a positive correlation between NF-κB and IL-6 (pronflammatory cytokines) with r=0.097 and p=0.05.

The markers of insulin resistance were markedly raised in cases as compared to controls. The mean serum HOMA-IR level in the study group (cases) was 2.95 ±0.26 and in the control group was 1.95±0.29 μM. The difference between the two was significant (p=0.012). The mean serum insulin level in the study group (cases) was 9.96±5.25 and in the control group was 6.85±4.9 μM. The difference between the two was significant (p=0.003). Ducimetiere[20] also showed that Insulin resistance and/or compensatory hyperinsulinemia predict CHD risk in non-diabetic population. In other study by Abbasi et al[21] in 314 non-diabetic population, it was proposed that insulin resistance at any given degree of obesity accentuates the risk of CHD. Recently, in 2010, Bertoluci et al[22] suggested that increased HOMA-IR is positively associated with angiographic coronary artery disease, and may be useful for risk stratification as a high-specificity test for coronary artery disease.

CONCLUSION

Thus, we postulate that atherogenesis is interplay between pro-inflammatory and anti-inflamatory markers. Insulin resistance further predisposes to atherosclerosis due to decreased anti-inflammatory and insulin sensitizing effects of insulin. Our study also highlighted the critical role of the novel marker, NF-κB which is a mediator of inflammation in etiopathogenesis of atherosclerosis.

So, these findings suggest that inflammation, endothelial dysfunction and insulin resistance interact with each other to promote atherogenesis in an individual predisposed to cardiovascular risk. This indicates that these novel biomarkers of non-invasive diagnosis of atherosclerosis.

These parameters must be further evaluated in larger sample size for their potential as biomarkers of severity of atherosclerosis

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