Original research article

High Sensitivity C-Reactive Protein In Type-2 Diabetes Mallitus Patients with Peripheral Vasculopathy

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Abstract

Background: Systemic inflammatory activity has turned out to play a key pathogenic role in vascular atherosclerosis, insulin resistance, and type 2 diabetes mellitus. Inflammatory biomarkers may therefore be a valuable tool for risk evaluation. Among them, the best evidence to date supports the use of high-sensitivity C-reactive protein (hs-CRP) to monitor insulin resistance and cardiovascular risk in diabetic and nondiabetic individuals.

Aims and Objectives: To assess the relation of symptomatic peripheral arterial disease and high sensitivity c-reactive protein in known type 2 diabetes patients and to study the passive smoking as an additional risk factor for peripheral vasculopathy and elevated high sensitivity c-reactive protein.

Materials and Methods: A cross sectional, case-control study conducted on patients with (100 cases) or without (100 controls) type 2 diabetes. The data regarding detailed history, physical examination, Brachial and ankle systolic blood pressures and Routine investigations were recorded, tabulated and statistically analyzed using appropriate statistical tools.

Result: The prevalence of low ABI was significantly higher in diabetics (16%) in comparison with non-diabetic controls (4%) ($p<0.05$). PAD was more common among women (11.2%) compared to men (6.8%). The mean hsCRP for the study group was 6.51 ± 1.02 significantly higher than the control group 1.74 ± 0.78 ($p<0.05$).

Conclusions: Changes in CRP levels provide cardiovascular risk prediction, and may be useful to refine cardiovascular risk stratification in high-risk patients with type 2 diabetes mellitus.

Keywords: Type 2 diabetes, peripheral vascular disease, ankle-brachial index, high-sensitivity C-reactive protein

Introduction

Type 2 Diabetes Mellitus is an important public health problem worldwide because of its high prevalence and complications.[1] The disease is characterized by metabolic alterations that correlate hyperglycaemia to other risk factors that contribute to complications in the circulatory system.[2] The number of deaths related to DM2 represents 9% of the world total, with four million cases each year. Cardiovascular diseases (CVD) are the most prevalent cause of death in DM2 patients[3][4] including myocardial infarction, ischaemic stroke, peripheral arterial obstructive disease and several other related diseases. Currently, atherosclerosis is indicated as the main cause for CVD development.[5] The main hypothesis for the origin of atherosclerosis considers it to be an inflammatory process that occurs in different forms, leading to vascular endothelium injury.[6][7]

Researchers have hypothesized that inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) may provide an adjunctive method for global assessment of cardiovascular risk.[8][9] In support of this hypothesis, several large-scale perspective epidemiological studies have shown that plasma levels of hsCRP are a strong independent predictor of risk of future peripheral arterial disease, Myocardial infarction, stroke and vascular death among individuals without known cardiovascular disease.[10][11][12] However, clinical application of hsCRP testing will depend not only on demonstration of independent predictive value, but also on demonstration that addition of hsCRP testing to traditional screening methods improves vascular disease risk prediction.

There is a positive association between hsCRP levels and T2DM among adult suburban-dwellers of South India.[13][14] Elevated hsCRP levels frequently cluster with well- established risk factors of T2DM such as obesity and insulin resistance.[15] Higher HbA1c levels were observed in all the South Indian subjects with an increase in hsCRP levels. Also, as seen by multiple regression analysis, HbA2c was the major determinant of hsCRP level in controls. Earlier studies have also shown the association of elevated hsCRP levels with obesity[16] and insulin resistance[17] in North Indian adolescents and South Indian adults, respectively. Association of increasing hsCRP levels with increasing fasting insulin, C-peptide, and HOMA-IR highlights coexistence of subclinical inflammation and insulin resistance. There is also ample evidence to suggest that hsCRP may be associated with an increasing risk of future cardiovascular events in otherwise healthy individuals.[18]

This study was performed to assess the relation of symptomatic peripheral arterial disease and high sensitivity c-reactive protein in known type 2 diabetes patients. And to study the passive smoking as an additional risk factor for peripheral vasculopathy and elevated high sensitivity c-reactive protein.

MATERIALS AND METHODS

It was a cross sectional, case-control study conducted on patients attending tertiary care hospital with (cases) or without (controls) type 2 diabetes patients from June 2016 to June 2018.

Total 100 diabetic patients with clinical evidence of peripheral vascular disease identified using Edinburgh claudication questionnaire were included as cases and an equal number of non-diabetics attending general medicine OPD for other ailments were included as controls.

Patients with established atherosclerotic diseases like coronary artery disease, stroke or peripheral vascular diseases, Smokers, Patients with history of collagen vascular disease, Patients with absent lower limb pulses, Bed-ridden patients, Diabetic foot ulcer patients were excluded from this study.

The purpose and objectives of the study were explained to the patients. After taking appropriate written consent, detailed history including duration of diabetes, vascular diseases, dyslipidaemia, smoking, alcohol use and drugs was taken and a thorough physical examination including all peripheral pulses and carotid pulses were done. Blood pressure measured using aneroid/ digital sphygmomanometer using a stethoscope. Brachial and ankle systolic blood pressures were measured using a hand held Doppler. Routine investigations including blood sugars, lipids, RFT, and ECG were done. The data was recorded in a proforma, tabulated and statistically analyzed using appropriate statistical tools.

RESULTS

A total of 100 diabetic patients (cases) and 100 non-diabetic controls participated in the study. All the 100 cases had more than five year type2 diabetes history. The mean age of Diabetic cases was 51.9 ± 11.18 years and Non diabetic control was 61.37 ± 9.56 years.

Clinical history of peripheral vasculopathy was elicited using Edinburgh claudication questionnaire and Ankle Brachial Index was measured for all 200 participants. Total 20 persons (10%) had ABI value < 0.9. The prevalence of low ABI was significantly higher in diabetics (16%) in comparison with non-diabetic controls (4%) ($p<0.05$). (Chart 1)

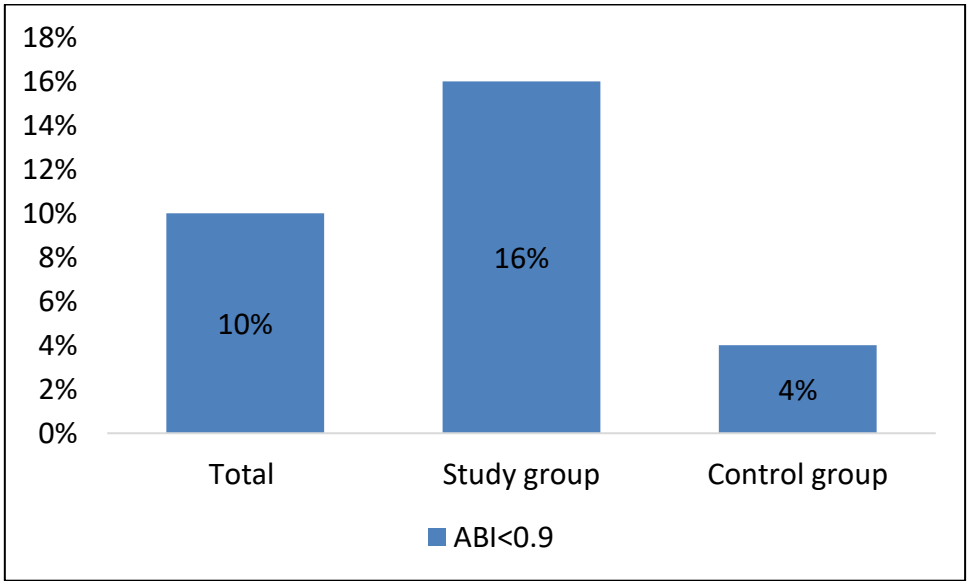

Chart 1: Symptomatic PAD as evidenced by ABI<0.9

Our cohort contained more females (71%) than males (29%), probably as a result of the exclusion criteria of tobacco use. The difference in the prevalence of PAD between diabetic and non-diabetic was statistically significant among women ($p=0.0478$), whereas the same in men was not statistically significant ($p=0.2939$). Also, PAD was more common among women (11.2%) compared to men (6.8%). This is an important observation when the fact was that a number of these women were passive smokers as their spouses where smoking. (Table 1)

Table 1: Sex distribution of PAD in Diabetic and Non Diabetic

PAD	Study group (N=100)	Control group (N=100)	Total (N=200)	P value
Women (N = 142)	13/78 (16.6%)	3/64 (4.6%)	16/142 (11.2%)	.0478
Men (N = 58)	3/22 (13.6%)	1/36 (2.7%)	4/58 (6.8%)	0.2939

Prevalence of elevated levels of high sensitivity c-reactive protein was observed in type 2 diabetes patients with symptoms such as claudication. The mean hsCRP for the study group was 6.51 ± 1.02 significantly higher than the control group 1.74 ± 0.78 ($p<0.05$). (Table 2)

Table 2: Comparison of hsCRP in the study and control group

High sensitivity C-reactive protein	Mean	Standard Deviation	Student Independent t test
Study group	6.51	1.02	t=26.15 p value = 0.001
Control group	1.74	0.78	

Passive smoking assessed by the presence of active smoker in family was seen in 46.5% women in the study. The peripheral arterial disease was common in these passive smoker both in diabetics (69.2%) and non-diabetics (66.7%) group. (Table 3)

Table 3: Relationship of passive smoking with PAD among women

Women	DM		No DM		Total
	PAD	No PAD	PAD	No PAD	
Passive Smoking	9 (69.2%)	27 (41.5%)	2 (66.7%)	28 (45.9%)	66 (46.5%)
No smoking	4 (30.8%)	38 (58.5%)	1 (33.3%)	33 (54.1%)	76 (53.5%)
Total	13 (100%)	65 (100%)	3 (100%)	61 (100%)	142 (100%)

DISCUSSION

Diabetes mellitus is a very common disease all over the world and especially so in India. Peripheral arterial disease is a very common macro vascular complication of diabetes and can result in morbidities like chronic ulcers, amputation etc. The inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) in type 2 deabetes patients with symptoms of peripheral vasculopathy adds prognostic information on cardiovascular risk comparable to blood pressure or cholesterol. Values <1, 1 to 3, and & >3 mg/l indicate lower, average, or higher relative cardiovascular risk, respectively. Global risk algorithms that include hsCRP outperform those solely using Framingham covariates. Ankle-brachial index, the ratio of ankle pressure to the brachial pressure is an easily done clinical test with sufficient sensitivity and specificity and is easily reproducible. Only simple tools like sphygmomanometer and a doppler probe are required for doing this test. A low ankle brachial index and an established

complaint of claudication as determined by Edinburgh claudication questionnaire diagnose peripheral arterial diseases in patients.

In this study high plasma hs-CRP levels showed a positive and significant correlation with DM2 cases ($p = 0.001$). A homogenous population was assessed with respect to gender and showed that plasma hs-CRP levels were significantly higher in patients with type 2 diabetes mellitus than in normal subjects. The prevalence of low ABI was significantly higher in diabetics (16%) in comparison with non-diabetic controls (4%). Number of females was more in the study as a result of the exclusion criteria of smoking, which excluded most men. However, among those included, men had a lower incidence of peripheral arterial disease compared to females. Analysis of history revealed that passive smoking is an important risk factors for females with peripheral artery diseases.

A possible mechanism by which DM2 might induce inflammation is by increasing advanced glycation end products that may activate macrophages and increase oxidative stress and interleukin-6 synthesis, resulting in the production of CRP.[19] The association of chronic low-grade inflammation with the progress of atherosclerosis in patients with DM2 has not been confirmed. However, Wakabayashi & Masuda showed that CRP levels were associated with arterial stiffness in patients with DM2.[20]

CRP is a sensitive acute-phase reactant although its function is not well defined. It binds to damaged tissue and nuclear antigens in a calcium-dependent manner, activating complement and generating proinflammatory cytokines.[21] It is thus believed to have a proinflammatory role.[22] Several prospective studies have found CRP to be a strong predictor of major cardiovascular adverse events, independent of lipid abnormalities, in apparently healthy men and women.[23][24] It is probable that CRP itself plays a significant role in the progression of atherosclerosis.[25] In contrast to the report by Erren *et al*.[26], who did not find significantly increased CRP levels in patients with CAD and PVD, compared with patients with CAD alone, this study found significantly increased CRP in the PVD group, and this significant association persisted in multivariate analysis. Our data support the hypothesis that CRP reflects the extent and severity of atherosclerosis in diabetic subjects.[24]

A number of large, prospective epidemiologic studies have examined inflammatory markers as predictors of CVD events in different clinical settings. At present, the best characterized biomarker is hs-CRP. Low-level increases in C-reactive protein appear to be a strong independent predictor of future cardiovascular events, including myocardial infarction, ischemic stroke, peripheral vascular disease, and sudden cardiac death among individuals with and without prior evidence of cardiovascular disease.[27][28][29]

Extensive analysis has demonstrated that hs-CRP adds prognostic information to traditional risk assessment and predicts cardiovascular risk independently of traditional risk factors, including low-density lipoprotein cholesterol.[30][31] A further analysis in 15,632 participants of a prospective cohort study yielded, after adjustment for age, blood pressure, smoking, diabetes, and obesity, that hs-CRP added prognostic information beyond that conveyed by all lipid measures.[32]

CONCLUSION

In conclusion, this prospective study provides evidence that baseline and serial changes in CRP levels represent important risk markers for future adverse cardiovascular outcomes, in addition to traditional cardiovascular risk factors, in high-risk patients with type 2 diabetes mellitus, and may be useful in refining cardiovascular risk stratification.

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