CRP, AN INFLAMMATORY BIOMARKER IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

Objective: To find out hs-CRP levels in type 2 diabetic patients with and without CHD and to further evaluate association of hs-CRP with glycosylated hemoglobin and lipid profile.

Methodology: A cross-sectional/analytical study was conducted. Group A comprised of 100 type 2 diabetic patients without CHD and Group B comprised of 100 type 2 diabetic patients with CHD. All the patients were randomly selected from Khyber teaching hospital (KTH) and Hyatabad Medical Complex (HMC). Blood Glucose, Glycosylated Hemoglobin, Lipid profile and hs-CRP levels were assessed.

Results: The mean hs-CRP, FBS and glycosylated hemoglobin values were significantly (P< 0.05) high in type 2 diabetic patients having CHD than type 2 diabetic patients without CHD. Moreover, hs-CRP also showed a significant (P< 0.05) positive association with FBS and HbAlc and negative association with HDL-C (P< 0.05).

Conclusion: Raised levels of plasma hs-CRP in type 2 diabetic patients may contribute to ongoing atherosclerotic processes leading to the development of coronary heart disease in these patients and this can be used as a marker of development of atherosclerosis in patients with diabetes mellitus.

Key Words: Type 2 diabetes mellitus, Coronary heart disease, hs-CRP, HbAlc, Lipid profile.

INTRODUCTION

Diabetes mellitus is a chronic disorder which is characterized by hyperglycemia and disturbance in carbohydrate, fat and protein metabolism due to relative or absolute deficiency of insulin secretion or its actions or both.¹³ It is emerging as a serious health problem with the prevalence rate of about 10% among the adult population of Pakistan and if proper health strategies are not adopted, this can rise to about 14.5 million by the year 2030.⁴⁵

Coronary heart disease is the most common cause of death and disability among type 2 diabetic patients in this region of world and will become the leading cause of morbidity and mortality by the year 2020.⁶

As diabetics are more prone to develop CHD thus there is a need to find out new biomarkers which would help in diagnosing the disease. C-reactive protein (CRP) is the first acute phase reactant protein and a sensitive systemic marker of inflammation, tissue damage and various malignancies.⁷⁸

Insulin resistance and inadequate insulin secretion are the two main factors leading to type 2 diabetes mellitus. Basic research studies are in tune with the hypothesis that chronic subclinical inflammation is the main cause of insulin resistance leading to development of overt type 2 diabetes mellitus⁹¹¹. The inflammatory process considered to be a part of insulin resistance, also explains the high risk of atherosclerosis and CHD in diabetic population.¹²

Aim of the present study was to find out hs-CRP levels in type 2 diabetic patients with and without CHD and to further evaluate association of hs-CRP with glycosylated hemoglobin and lipid profile.

METHODOLOGY

A cross-sectional/analytical study was performed among the outdoor and indoor patients of Khyber teaching hospital (KTH) and Hyatabad Medical Complex (HMC). Biochemical analysis was carried out in the Research Laboratory of Biochemistry Department, of Khyber Medical College, Peshawar. Study population was
divided into two groups. Group A comprised of 100 patients having type 2 diabetes mellitus for at least 4 years and Group B comprised of 100 type 2 diabetic patients with CHD, who had first attack of myocardial infarction in the last 10 days. Patients having thyroid disorders, liver dysfunction, inflammatory diseases and those using lipid lowering drugs and oral contraceptive pills were not included in the study. The study was approved by Institutional Ethical Research Board (IERB) of Khyber Medical College, Peshawar.

Venous blood was obtained after an overnight fasting under aseptic techniques for measuring fasting blood sugar (FBS), total cholesterol (TC), triglycerides (TG), High density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin (HbAlc) and hs-CRP. Fasting Blood Sugar and lipid profile were estimated by enzymatic colorimetric method on semi auto chemistry analyzer Metrolab 1600 DR on the kits provided by Eli Tech diagnostics, France. Glycosylated Hemoglobin was determined by ion exchange resin colorimetric method using kit provided by Human Diagnostic, Germany. Serum C-reactive protein was detected by kit provided by Bio-Check USA on Elisa Reader Bio Tek ELX-800.

Analysis of data was done on SPSS version 19. Data was expressed as mean ±SD. Student “t” test was applied to compare variables between groups. Pearson correlation coefficient values were detected to find out the association amongst different variables.

Table 1 shows biochemical profile of the studied groups. Group B patients had a significant (P< 0.05) increase in age as compared to Group A patients. On looking for body mass index and Hypertension no statistical difference was found between the two groups while FBS and HbAlc levels were significantly (P<0.05) higher in patients of Group B as compared to Group A. Similarly, levels of hs-CRP were also found to be significantly higher (P< 0.05) in patients of Group B (diabetic with CHD) as

Table 1: Demographic, clinical and biochemical characteristics of the two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group-A (Mean±SD)</th>
<th>Group-B (Mean±SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dL)</td>
<td>175.61±59.13</td>
<td>213.80±91.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>8.308±3.03</td>
<td>10.166±3.452</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>272.06±121.15</td>
<td>279.61±151.82</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>290.02±203.23</td>
<td>324.37±142.60</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>44.32±15.24</td>
<td>40.67±16.53</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>171.58±125.13</td>
<td>176.09±154.09</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12.67±6.16</td>
<td>18.43±4.22</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Note: significant P value = <0.05, NS = non-significant

Table 2: Correlation of CRP with different parameters in studied groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CRP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>.053</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>.033</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>.103</td>
<td>NS</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>.154*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>.154*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>.125</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>.003</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>-.101</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>.129</td>
<td>NS</td>
</tr>
</tbody>
</table>

*(P<0.05)
compared to Group A (diabetic without CHD).

The correlation of hs-CRP with different variables separately in both groups showed significant positive (P < 0.05) correlation of hs-CRP with Total cholesterol in type 2 diabetic patients with CHD. On looking for correlation of hs-CRP with HDL-C, it was found to be significantly (P < 0.05) negative in group A (type 2 diabetic patients without CHD).

Table 2 shows the association of hs-CRP with various parameters in the studied population as a whole. There was a positive significant (P < 0.05) association of hs-CRP with FBS and HbA1c in both the studied groups.
DISCUSSION

Type 2 diabetes mellitus is emerging as a serious health problem all over the world\textsuperscript{11}. The incidence of congestive heart failure, cardiomyopathy and CHD is more in patients of type 2 diabetes mellitus\textsuperscript{14}. The mortality rate of CHD in patients of type 2 diabetes mellitus is two times more in males and four times more in females according to Framingham heart study\textsuperscript{15}. As diabetics are more at risk for CHD so there is a need to search out for new biomarkers which would help to assess the risk for development of CHD in these patients.

Elevated level of CRP is a better and strong indicator of CHD in type 2 DM than any other risk markers due to its basic role in atherosclerosis\textsuperscript{16,17}. It enhances the release of tissue factor from macrophages, leads to activate the complement system and causes the aggregation of LDL-C and VLDL-C by binding with them\textsuperscript{18,20}.

Due to involvement of inflammatory mechanisms in diabetogenesis and atherosclerosis, CRP levels tend to be increased in patients of type 2 diabetes mellitus with CHD\textsuperscript{21,22}. Our results show high levels of hs-CRP in patients having type 2 diabetes mellitus with CHD as compared to patients having type 2 diabetes mellitus without CHD. These results are in tune with the reports presented by Mohan et al\textsuperscript{23}, Haffner\textsuperscript{24} and Leipold et al\textsuperscript{25}.

A meta analysis of 2000 studies, comprised of about 1953 coronary accidents also showed that a single initial base line CRP value in upper third suggests the risk of 2.0 for future coronary accident as compared to a CRP value in lower third of the distribution, as seen in general population\textsuperscript{26}. These observations were not consistent with Layer et al\textsuperscript{1} who did not find any significant difference in CRP values after they compared normal subjects with diabetic population.

Our results show high levels of HbAlc in patients having T2DM with CHD than the patients having type 2 diabetes mellitus without CHD. There are different metabolic cascades e.g. polypathways, hexosamine pathway, protein kinase C and advanced glycosylation end-products which cause hyperglycemia\textsuperscript{17,27,28}. Hyperglycemia leads to glycosylation of various proteins especially LDL-C making them available for oxidation and enhancing the process of atherosclerosis\textsuperscript{29}. Similar association of hyperglycemia with CHD was reported by Honolulu heart study\textsuperscript{30} and Bedford study\textsuperscript{31}. The Chennai-Urban population study also claimed the strong association of high plasma glucose level with increased coronary events\textsuperscript{32}.

The positive association of hs-CRP with FBS and HbAlc can be explained by the fact that inflammation is the main hallmark state of insulin resistance which is observed in obesity and type 2 diabetes mellitus\textsuperscript{33}. There are two mechanisms which lead to inflammation. First, chronic over-nutrition and intake of glucose produce a state of oxidative stress and pro-inflammatory state and second, release of TNF-\(\alpha\) (tumor necrosis factor \(\alpha\)) and IL-6 (interleukin-6) suppress the transduction of insulin signals and inhibit its action\textsuperscript{34,35}. Our results are in tune with Dana et al\textsuperscript{36} and Meshram et al\textsuperscript{37} who also confirmed linear association of hs-CRP with HbAlc. On the contrary, Karthryn et al\textsuperscript{38} and Rodriguez et al\textsuperscript{39} showed that levels of inflammatory markers remain high inspite of achieving good glycemic control.

It can be concluded from the study that high levels of inflammatory markers such as CRP in type 2 diabetes mellitus predict the development of coronary heart disease. Therefore, inflammatory markers should be estimated in order to recognize diabetic patients who are at increased risk of coronary heart disease.

CONCLUSION

It can be concluded from the study that raised levels of plasma hs-CRP in type 2 diabetic patients may contribute to ongoing atherosclerotic processes leading to the development of coronary heart disease in these patients and this can be used as a marker of development of atherosclerosis in patients with diabetes mellitus.

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**CONTRIBUTORS**

SA participated in planning of study, data analysis and manuscript writing. MAK\(^2\) supervised the study and helped in manuscript writing. MAK\(^3\) helped in data management. All authors contributed significantly to the final manuscript.