Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2016/630

Original Article

Serum High-sensitive C-reactive Protein and Insulin Resistance in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease

P Mohan Kumaresh[1], Gowri Thilagam[2], J Latha[3]

[1]Associate Professor, Department of Biochemistry, Government Medical College, Pudukkottai, Tamil Nadu, India, [2]Assistant Professor, Department of Pharmacology, Government Theni Medical College, Theni, Tamil Nadu, India, [3]Assistant Professor, Department of Biochemistry, Madurai Medical College, Madurai, Tamil Nadu, India

Abstract

Introduction: Patients with Type 2 diabetes mellitus (DM) are characterized by insulin resistance (IR) and a low-grade inflammation, which is reflected by the levels of serum high-sensitive C-reactive protein (hsCRP). A single hsCRP measurement is a strong predictor of myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death, in individuals without a history of heart disease.

Aim: The aim of this study was to assess the correlation between serum hsCRP levels with IR (homeostasis model assessment-IR [HOMA-IR]) and various biochemical parameters such as fasting and postprandial plasma glucose, hemoglobin A1c (HbA1c), lipid profile (serum triglycerides, total cholesterol, high-density lipoprotein cholesterol [HDL-c], and calculated low density lipoprotein cholesterol [LDL-c]) in controls, patients with Type 2 DM without coronary artery disease (CAD), and patients with Type 2 DM with CAD.

Materials and Methods: Totally 150 patients with diabetes and 50 controls were included in the study. hsCRP was estimated with Latex turbidimetry method and IR was estimated by calculating HOMA-IR. Descriptive statistical analysis was done by one-way ANOVA *F*-test for *P*-value. *P*=0.05 was considered statistically significant. The comparison of levels of each parameter among the various groups was analyzed by Bonferroni *t*-test. Chi-square test was done to analyze the male:female ratio in various groups. Karl Pearson's correlation coefficient was used to analyze the correlation between various parameters.

Results: Serum hsCRP level was increased in patients with Type 2 DM when compared with controls. In patients with Type 2 DM with CAD, the serum hsCRP level was increased when compared with those without CAD. There was, however, a fair, positive correlation between hsCRP and IR, HbA1c, serum triglycerides, total cholesterol, and LDL-c, and a moderate negative correlation with HDL-c in Type 2 DM.

Key words: Coronary artery disease, Insulin resistance, Serum high-sensitive C-reactive protein, Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia.[1]

Access this article online

www.ijss-sn.com

Month of Submission : 10-2016
Month of Peer Review : 11-2016
Month of Acceptance : 11-2016
Month of Publishing : 12-2016

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of DM are designated Type 1 and Type 2.[1]

Type 1A DM results from autoimmune beta-cell destruction, which leads to insulin deficiency. Individuals with Type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta-cells. However, they develop insulin deficiency by unknown mechanisms and are ketosis prone. Relatively, few patients with Type 1 DM are in the Type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage.[1]

Corresponding Author: Dr. P Mohan Kumaresh, 3/385 Dinamani Nagar, Near KP School, Pothumbu Post, Madurai - 625 018, Tamil Nadu, India. Phone: +91-9444276950. E-mail: mohangowri07@yahoo.co.in

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance (IR), impaired insulin secretion, and increased glucose production.[1]

The worldwide prevalence of DM has risen dramatically over the past two decades. Likewise, the prevalence rates of impaired fasting glucose are also increasing. Although the prevalence of both Type 1 and Type 2 DM is increasing worldwide, the prevalence of Type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels.[1]

Patients with Type 2 DM show a 2- to 5-fold increase in coronary heart disease (CAD).[2] Both Type 2 DM and CAD are characterized by low-grade inflammation and IR.[3,4] Serum high-sensitive C-reactive protein (hsCRP) reflects low-grade inflammation.[5]

Serum hsCRP is increased in obese[6] and diabetic patients.[7-9] It predicts the onset of cardiovascular disease.[5,10-12]

With this background, the present study titled, "serum hsCRP and Insulin Resistance Levels in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease" was taken up.

IR

IR is defined as a decreased biological response to normal concentration of circulating insulin.[13] It is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle, and liver cells. It is found in both obese non-diabetic individuals and patients with Type 2 DM. There is a broad clinical spectrum of IR, ranging from euglycemia (with marked increase in endogenous insulin) to hyperglycemia despite the large doses of exogenous insulin.[14]

Measurement of IR

Measurement of IR in a routine clinical setting is difficult and needs surrogate methods, namely fasting insulin concentration or the euglycemic insulin clamp to provide an indirect assessment of insulin function.[14]

Simple fasting methods to measure IR, such as the homeostasis model assessment (HOMA), fasting glucose/insulin ratio (FGIR), and Quantitative Insulin Sensitivity Check Index (QUICKI) methods, have been widely promoted.[15]

The first is the HOMA, and a more recent method is the QUICKI. Both employ fasting insulin and glucose levels to calculate IR and both correlate reasonably with the results of clamping studies.[16] A simpler tool such as HOMA is more appropriate for large epidemiologic studies and is more reliable than FGIR and QUICKI methods.[15]

CRP

Tillet and Francis in 1930 described a substance that was present in the sera of acutely ill patients and able to bind the cell wall C-polysaccharide of *Streptococcus pneumonia*. In 1941, the substance was shown to be a protein and given the name CRP.[14]

CRP was subsequently shown to be an acute-phase reactant and important in the non-specific host defense against inflammation, especially in infections. Routinely used methods for CRP estimation have a detection limit of 3-8 mg/L.[14]

CRP consists of five identical, non-glycosylated polypeptide subunits non-covalently linked to form a disk-shaped polymer with a molecular weight of about 115 kDa (Figure 1). It contains little or no carbohydrate and is synthesized in the liver. Its production is controlled by interleukin-6.[14]

Each of the five subunits of CRP contains one binding site for a phosphatidylcholine molecule and two binding sites for calcium. These binding sites allow CRP to recognize and bind to a variety of biologic substrates, including phosphatidylcholine and phospholipids, components of damaged cell walls, chromatin and nuclear antigens, polysaccharides present in many bacteria, fungi, and protozoal parasites, resulting in the formation of CRP-ligand complexes. CRP-ligand complexes can activate the complement system, thereby facilitating phagocytosis and the removal of materials released from damaged cells as well as potentially toxic materials from invading microorganisms. CRP-ligand complexes also bind directly to neutrophils, macrophages, and other phagocytic cells,

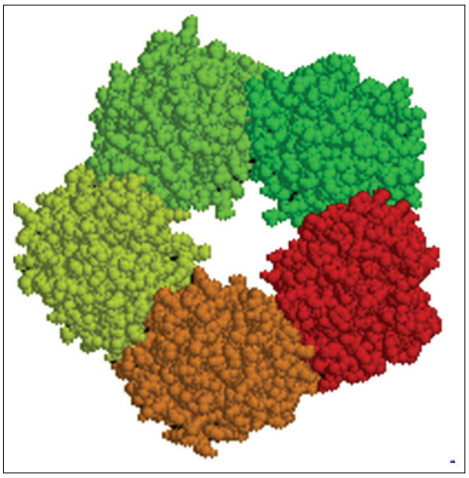

Figure 1: Structure of C-reactive protein

stimulating an inflammatory response and the release of cytokines.

The key functions of CRP within the innate immune system include the ability to:

1. Recognize and bind to phosphatidylcholine exposed in damaged cell walls and found in many bacteria, fungi, and parasites.
2. Act like an opsonin, marking bacteria, damaged cell walls, and nuclear debris for phagocytosis.
3. Bind to Cl, the first component of the classical pathway of the complement system that triggers phagocytic activity.
4. Bind to polymorphonuclear leukocytes and monocytes, which stimulate the production of inflammatory cytokines.

Serum CRP concentrations are positively associated with a risk of future coronary events such as CAD.[14] The use of CRP for this purpose requires the use of hsCRP assays having detection limits <0.3 mg/L. A number of automated immunoturbidimetric and immunonephelometric assays are commercially available for sensitive and precise measurement of low concentrations of CRP.[14]

A single hsCRP measurement is a strong predictor of myocardial infarction,[10,11,17,18] stroke,[10,11,18] peripheral vascular disease,[19,20] and sudden cardiac death,[21] in individuals without a history of heart disease. The association between hsCRP and future vascular events is linear and is independent of age, smoking, hypertension, dyslipidemia, and diabetes.[14]

Serum hsCRP value <1 mg/L is considered as low risk, 1-3 mg/L is considered as intermediate risk, and >3 mg/L as high risk for primary prevention of atherosclerosis. Recent data suggest that using hsCRP value with the calculated low density lipoprotein (LDL) is a potent way to predict the risk.[14]

Aim of the Study

The study was taken up after reviewing various literatures on serum hsCRP and IR in Type 2 DM and in CAD. The aim of the study is to assess the following:

1. To assess the levels of serum hsCRP and IR measured as HOMA-IR in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.
2. To assess the correlation between serum hsCRP levels and IR (HOMA-IR) in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.
3. To assess the correlation between serum hsCRP levels and various biochemical parameters such as fasting and postprandial plasma glucose, hemoglobin A1c (HbA1c), lipid profile (serum triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and calculated LDL-cholesterol [LDL-c]) in controls, patients with Type 2 DM without CAD, and patients with Type 2 DM with CAD.

MATERIALS AND METHODS

Study Population

The study was carried out in a total of 160 patients which included 110 patients with Type 2 DM and 50 controls.

For the DM group, patients with Type 2 DM were selected. The patients with DM were further categorized as those without CAD (normal electrocardiogram/treadmill test negative) $n = 48$ (Group 1) and those with CAD (coronary angiogram-proven cases) $n = 62$ (Group 2). The mean age of the DM group was 50.8 years.

For the control group (Group 0), age- and sex-matched apparently healthy controls were selected. The mean age of the controls was 49.4 years.

Inclusion Criteria

The minimum duration of diabetes was 5 years in all patients with Type 2 DM. The patients were on oral hypoglycemic treatment.

Exclusion Criteria

Patients who were on treatment with insulin and/or thiazolidinediones were excluded from the study.

Patients who had liver disorders, hepatitis, cirrhosis, renal failure, inflammatory disorder, or malignancy were also excluded from the study.

Protocol of the Study

The patients were clinically examined, and height and weight measurements were recorded. Blood pressure was also recorded. The body mass index was calculated from the height and weight measurements using the following formula:

$$\text{Body mass index} = \frac{\text{Weight in kilograms}}{\text{Height in metre}^2}$$

Fasting blood samples were collected in three different tubes - plain tube, one containing 1% ethylenediaminetetraacetic acid (EDTA) and one containing sodium fluoride-potassium oxalate mixture (1:3). 2 h post-prandial blood samples were collected in tubes containing sodium fluoride-potassium oxalate mixture. Spot urine was collected for the estimation of urine microprotein.

Plasma was separated from fasting, and post-prandial blood samples collected in sodium fluoride-potassium oxalate tubes and were used for estimating plasma glucose immediately. Serum was separated from fasting blood samples collected in the plain tubes and divided into two parts. One part of the serum was used for estimating hsCRP, urea, creatinine, total cholesterol, HDL-c, and triglycerides immediately. The other part of the serum was stored at -20ºC and was used for the estimation of insulin by enzyme-linked immunosorbent assay (ELISA) method. The ELISA procedure was carried out within 30 days of sample collection. HbA1c was estimated using blood collected in EDTA tubes.

Estimation of Serum Insulin

Methodology

ELISA method using Insulin ELISA kit from DiaMetra was used for measuring serum insulin.

Instrument

Triturus analyzer - an open-system automatic ELISA analyzer.

Estimation of Serum hsCRP

Methodology

Latex turbidimetry method for quantitative determination of hsCRP (low levels of CRP) in serum or plasma.

Estimation of Plasma Glucose

Kit used: Erba Mannheim XL Systems Packs
Method: Glucose oxidase-peroxidase method - 1-point assay.

Estimation of HbA1c

Kit used: Diatek glycohemoglobin
Method: Ion exchange resin method.

Estimation of Urea

Kit used: Erba Mannheim XL Systems Packs
Method: Urease - GLDH method.

Estimation of Serum Creatinine

Kit used: Erba Mannheim XL Systems Packs
Method: Modified Jaffe's method.

Estimation of Serum Triglycerides

Kit used: Erba Mannheim XL Systems Packs
Method: Enzymatic method, end point.

Estimation of Serum Total Cholesterol

Kit used: Erba Mannheim XL Systems Packs
Method: Enzymatic method.

Estimation of Serum HDL-c

Kit used: Erba Mannheim XL Systems Packs
Method: Immuno-inhibition method.

Determination of LDL-c

LDL-c was determined using Friedewald's formula:

$$\text{LDL-c} = \text{Total cholesterol} - (\text{HDL-c} + \text{VLDL-c})$$

$$\text{VLDL-c} = \frac{\text{Triglycerides}}{5}$$

Determination of HOMA-IR

$$\text{HOMA-IR} = \frac{\text{Serum insulin } (\mu\text{IU / mL}) \times \text{Plasma Glucose } (\text{mmol / L})}{22.5}$$

Estimation of Urine Microprotein

Method

Urine microprotein was estimated in spot urine sample by Pyrogallol Red microprotein kit method in semi-automated analyzer.

RESULTS AND STATISTICAL ANALYSIS

The mean and standard deviation for the various parameters evaluated, namely, BMI, fasting plasma glucose, post-prandial plasma glucose, HbA1c, blood urea, serum creatinine, lipid profile, serum hsCRP, fasting serum insulin, HOMA-IR, and urine microprotein in the entire study population, in the controls (Group 0), in patients with Type 2 DM without CAD (Group 1), in patients with Type 2 DM with CAD (Group 2) is presented in Table 1.

Descriptive statistical analysis was done by one-way ANOVA *F*-test for *P*-value. The comparison of levels of each parameter among the various groups was analyzed by Bonferroni *t*-test. Chi-square test was done to analyze the male:female ratio in various groups. Karl Pearson's correlation coefficient was used to analyze the correlation between various parameters. $P = 0.05$ was considered statistically significant.

DISCUSSION

One-way ANOVA *F*-test was used to analyze whether the three groups were age matched. The mean age of the control group (Group 0) was 49.92 ± 5.749 years. For the group composed of patients with Type 2 DM without CAD (Group 1), it was 50.94 ± 5.61 years, and in the group composed of patients with Type 2 DM with CAD, it was 51.79 ± 3.44 years. All the three groups were found to be age matched ($P = 0.14$).

Similarly, Chi-square test was performed to find any difference in the male:female composition among the

three groups. It was found that the three groups were sex matched ($P = 0.98$).

The mean BMI in control group was 24.26 ± 1.37 kg/m^2, in Group 1, it was 24.26 ± 2.08 kg/m^2, and in Group 2, it was 26.54 ± 2.35 kg/m^2. The control group and Group 1 were found to be similar as far as BMI was concerned. Group 2 patients had a significantly higher BMI when compared to the other groups.

One-way ANOVA *F*-test and multiple comparison Bonferroni *t*-test were used to analyze the serum hsCRP and IR levels among the three groups.

The mean serum hsCRP level of Group 1 (5.742 ± 1.8 mg/L) and Group 2 (6.803 ± 1.929 mg/L) was found to be increased when compared to the control group (2.714 ± 0.712 mg/L) and it was statistically significant ($P = 0.001$) (Table 2).

A single hsCRP measurement is a strong predictor of myocardial infarction.[17-20] Serum hsCRP value <1 mg/L is considered as low risk, 1-3 mg/L is considered as intermediate risk, and >3 mg/L as high risk for primary prevention of atherosclerosis.[14] Thus, patients with DM (Group 1 and 2) were found to be at a high risk for coronary heart disease. The Group 2 patients had significantly higher hsCRP levels than Group 1 patients.

IR as measured by HOMA-IR was found to be significantly increased in Group 1 and Group 2 when compared with the control group. When Group 1 and Group 2 were compared, Group 2 had significantly higher IR ($P = 0.001$) (Table 3).

In the control group, serum hsCRP had a significant positive correlation with HbA1c. However, serum hsCRP levels showed a poor correlation with plasma glucose levels and lipid profile.

Table 1: Mean value of parameters among the various groups

Parameter	Control	Overall Type 2 DM	Type 2 DM without CAD	Type 2 DM with CAD
Age (years)	49.92±5.75	51.42±3.48	50.94±5.61	51.79±3.44
Male:female ratio	28:22	60:50	26:22	34:28
Duration of diabetes (years)	-	8.74±2.89	8.33±3.15	9.05±2.98
Body mass index (kg/m^2)	24.26±1.37	25.54±2.16	24.26±2.08	26.54±2.35
Fasting plasma glucose (mg/dL)	90.80±5.71	153.16±36.09	152.38±44.92	153.77±42.54
Post-prandial plasma glucose (mg/dL)	134.68±6.11	218.29±56.28	215.38±69.11	220.55±64.41
HbA1c (%)	5.26±0.46	8.30±1.52	7.90±1.87	8.62±1.45
Blood urea (mg/dL)	28.56±5.86	27.77±7.58	28.85±7.10	26.94±7.73
Serum creatinine (mg/dL)	0.96±0.14	1.00±0.19	0.98±0.15	1.01±0.17
Serum triglycerides (mg/dL)	134.66±48.93	162.91±54.40	150.94±34.56	172.18±53.80
Serum total cholesterol (mg/dL)	172.66±21.25	203.46±67.10	182.69±51.82	219.55±65.37
Serum HDL-c (mg/dL)	44.82±6.07	39.87±7.63	42.27±6.36	38.02±7.66
Serum LDL-c (mg/dL)	100.91±24.02	131.01±65.37	110.23±49.42	147.10±63.57
Serum hsCRP (mg/L)	2.71±0.71	6.34±2	5.74±1.81	6.80±1.93
Serum insulin (μIU/mL)	8.85±1.20	8.80±2.39	8.36±2.90	9.15±2.33
HOMA-IR	1.99±0.34	3.20±1.21	2.91±0.68	3.43±1.21
Urine microprotein (mg/dL)	23.48±6.49	24.92±14.58	25.29±18.68	24.63±16.37

hsCRP: High-sensitive C-reactive protein, DM: Diabetes mellitus, CAD: Coronary artery disease, HOMA-IR: Homeostasis model assessment-insulin resistance, HbA1c: Hemoglobin A1c, HDL-c: Highdensity lipoprotein-cholesterol, LDL-c: Lowdensity lipoprotein-cholesterol

Table 2: Serum hsCRP levels among the various groups

Parameter	Group	N	Mean	Standard deviation	One-way ANOVA *F*-test	Multiple comparison Bonferroni *t*-test
Serum hsCRP mg/L	0	50	2.714	0.7126	*F*=93.48,	0 versus 1, 2,
	1	48	5.742	1.8058	*P*=0.001	1 versus 0, 2
	2	62	6.803	1.929		
	Total	160	5.207	2.3627		

hsCRP: High-sensitive C-reactive protein

Table 3: IR among the various groups

Parameter	Group	N	Mean	Standard deviation	One-way ANOVA *F*-test	Multiple comparison Bonferroni *t*-test
HOMA-IR	0	50	1.99	0.3406	*F*=39.41	0 versus 1, 2
	1	48	2.908	0.6758	*P*=0.001	1 versus 0, 2
	2	62	3.434	1.2069		
	Total	160	2.825	1.0468		

HOMA-IR: Homeostasis model assessment-insulin resistance

IR as calculated by HOMA-IR in the control group had a significantly positive correlation with BMI, fasting plasma glucose, serum triglycerides, total cholesterol, and LDL-c, and a significantly negative correlation serum HDL-c.

In the Group 1, serum hsCRP had significantly positive correlation with serum triglycerides and IR. There was a poor correlation between serum hsCRP and BMI, plasma glucose levels, HbA1c, total cholesterol, HDL-c, and LDL-c.

IR in the Group 1 had a significantly positive correlation with HbA1c and serum hsCRP.

In the Group 2, serum hsCRP had significantly positive correlation with HbA1c, serum triglycerides, total cholesterol, LDL-c, and IR, and a significant negative correlation with serum HDL-c. However, there was a poor correlation between serum hsCRP and BMI, fasting and post-prandial plasma glucose levels.

IR in the Group 2 had a significantly positive correlation with BMI, fasting and post-prandial plasma glucose, HbA1c, serum triglycerides, total cholesterol, LDL-c, and hsCRP, and a significantly negative correlation with HDL-c.

CONCLUSION

From the analysis of the data, the following conclusions were made:

1. Serum hsCRP level was increased in patients with Type 2 DM when compared with controls. In patients with Type 2 DM with CAD, the serum hsCRP level was increased when compared with those without CAD.
2. Serum hsCRP correlated poorly with IR in the controls. There was, however, a fair, positive correlation between hsCRP and IR in Type 2 DM.
3. Serum hsCRP was poorly correlated with plasma glucose levels and lipid profile parameters in the control group. In the patients with Type 2 DM, serum hsCRP had a positive correlation with HbA1c, serum triglycerides, total cholesterol, and LDL-c, and a moderate negative correlation with HDL-c.

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How to cite this article: Kumaresh PM, Thilagam G, Latha. Serum High-sensitive C-reactive Protein and Insulin Resistance in Patients with Type 2 Diabetes Mellitus with Coronary Artery Disease. Int J Sci Stud 2016;4(9):129-134.

Source of Support: Nil, **Conflict of Interest:** None declared.