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Research Article

Study of effects of metformin on C-reactive protein level in Type-2 diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus (DM) is extremely common; represent a significant global health problem. Type-2 DM is considered to be associated with a low grade inflammation, which may play a significant role in development of cardiovascular complications evidenced by C-reactive protein (CRP) is a an extremely sensitive marker of systemic inflammation. The study was undertaken to check the effect of metformin on CRP level in Type-2 DM.
Methods: The study was prospective and non-randomized. Thirty newly diagnosed Type-2 DM selected for metformin therapy by medicine personnel were enrolled in the study based on inclusion and exclusion criteria. Patients were divided into pre-treatment (before starting metformin therapy) and post-treatment group. Fasting blood sugar (FBS), postprandial blood sugar (PP_2BS), CRP level were measured at the time of enrolment and 3 months after starting metformin monotherapy.
Results: Results were analyzed using pair t-test. Metformin therapy was found to decrease CRP level significantly along with FBS, PP_2BS level. $p<0.05$ value considered as statistically significant. Value was expressed as mean ± standard deviation.
Conclusions: Treatment with 3 months metformin monotherapy for newly diagnosed Type-2 DM has shown a significant decrease in high-sensitivity-CRP level in Type 2 diabetes. This positive effect may be because of the decreased in the expression of proinflammatory cytokines and other mediators, including adhesion molecules, suggests that these processes may contribute to atherogenesis because atherosclerosis is also an inflammatory condition. However, this effect is probably dependent on improving glycemic control.

Keywords: C-reactive protein level, Type-2 Diabetes mellitus, Inflammatory marker, Atherosclerosis

INTRODUCTION

Diabetes mellitus (DM) is extremely common, represent a significant global health problem.[1] Type-2 DM is progressive and complex metabolic disorder characterized by chronic hyperglycemia and by disturbance in carbohydrate, lipid, and protein metabolism due to insulin resistance is caused by impaired insulin secretion and/or insulin action.[2] Insulin resistance is the prominent feature of Type-2 DM and result from combination of inflammation, genetic susceptibility and obesity. Type-2 DM has reached pandemic proportions involving 11% of the population in the United States, and it is estimated to increase to 20% by the year 2020.[3] The diabetes prevalence for 2013 has risen to 382 million, representing 8.3% of the world's adult population, with a prediction that by 2030 the number of people with diabetes will have risen to 439 million worldwide.[4-7] Diabetes has a prevalence of 2-5% in most western countries and is rapidly increasing in Asian countries due to changes in dietary habits during last years.[8] It is estimated that six people die every minute from the disease worldwide and up to 75% of patients with Type-2 DM will die from a cardiovascular complication, a figure that will soon make Type-2 DM one of the world's most prevalent cause of preventable mortality.[1,9,10] In India, according to the ADA criteria, the prevalence of diabetes was 4.7% in the urban compared to the 2.0% in the rural population while the prevalence of diabetes according to the WHO criteria was 5.6% and 2.7% among urban and rural areas respectively.[11] Globally, 529 million people (10% of adults) will have diabetes by 2035.[7] It is a proinflammatory, hypercoagulable state that predisposes patients to develop cardiovascular disease, a major cause

of morbidity and mortality.[2] Type-2 DM is considered to be associated with a low grade inflammation, which may play a significant role in development of cardiovascular complications evidenced by C-reactive protein (CRP) is a an extremely sensitive marker of systemic inflammation produced mainly by liver under the stimulation of adiposity-derived proinflammatory cytokines.[4,12-14] Data on elevated CRP level in diabetic patient with nephropathy, retinopathy, neuropathy and coronary artery disease, peripheral arterial disease, stroke providing link between inflammation and the development of micro vascular and macro vascular complication respectively[4,8-9,15-17] low grade inflammation has a pivotal role in atherosclerosis, associated with risk factors for atherosclerosis, including altered homeostasis, dyslipidemia, hypertension, and inflammation.[18,19]

Patient with Type-2 DM tend to have higher CRP concentration than those without it, suggesting that inflammation could contributes to the accelerated atherosclerosis and associated with an increased risk of myocardial infarction, coronary artery bypass grafting/angioplasty, and stroke in patient with Type-2 DM[2] during diabetes, chronic hyperglycemia causes increased formation of advanced glycated end products, increased glucose auto-oxidation and oxidative phosphorylation, which lead to oxidative stress. Thus intermittent glucose pulses, supporting the concept that an oxidative stress mechanism may cause tissue damage mediates the inflammatory effect of hyperglycemia in humans.

Oral hypoglycemic agents (OHAs) remain a mainstay in achieving glycemic control in diabetes.[20] some study suggest that OHAs reduce some CRP level in Type-2 DM patient.[2,20-24] Considering the above fact relationship among oral hypoglycemic agents and CRP level is complex. Thus this study is designed to know the effect of oral hypoglycemic agent, metformin on CRP level in Type-2 DM patients (where other possible factors influence on CRP level) are absent. If yes, to determine the effect of metformin treatment on CRP level in these patients. If metformin shows a positive impact on CRP level in diabetes patients, hypothesis about additional benefit of oral hypoglycemic agents in these patients can be made and tested by further research.

METHODS

Study subjects

The study was conducted at the New Civil Hospital, Surat during the period from April 2013 to March 2014. The study was approved by the local Institutional Ethics Committee. Mean age of thirty individuals participating in the study is 50.03±10.03 years. Informed consent of each participant was taken. The individuals participating in this study were divided into three groups: normal healthy volunteers, pre-treatment group (newly diagnosed Type-2 DM patients) and post-treatment group (newly diagnosed hypertensive patients started on motorman therapy). Selection of patient was based on inclusion and exclusion criteria.

Inclusion criteria

a. Freshly diagnosed Type-2 DM
b. Patients started on metformin monotherapy.

Exclusion criteria

a. Patients on statin and aspirin therapy
b. Any other medication affecting CRP level
c. Any other medication affecting blood sugar level
d. Type-1 DM
e. Any infective, inflammatory, allergic disorders, cardiovascular disorders necrosis, malignancy
f. Patients with trauma due to surgery, burns, fractures
g. Patient having habit of alcohol and smoking
h. Pregnant women.

After enrolment, hypertensive patients were treated with OHA (metformin-500 mg) and followed-up after 3 months period. The blood samples were collected for the estimation of high-sensitivity (hs) CRP level, fasting blood sugar (FBS) and postprandial blood sugar (PP_2BS) at the time of the first evaluation before starting metformin treatment and after 3 months therapy of metformin. Hs-CRP was measured by immunoturbidometry method by Erba XL-640 fully Autoanalyzer machine in the Clinical Biochemistry Department, Medical College, Surat.

Statistical analysis

All values are expressed as mean±standard deviation. Comparison of hs-CRP value between pre-treatment group and post-treatment group is performed by pair t-test and comparison of normal healthy volunteers (controls group) and metformin treated group (cases) is analyzed by unpair t-test. $p<0.05$ value is considered as a statistical significant.

RESULTS

Effect on FBS, PP_2BS

Thirty DM Type-2 patients were enrolled in the study. These 30 patients (mean age 50±10.03, 19 males and 11 females) received metformin treatment. Controls were 30 healthy volunteers (mean age 50±10.03, 19 males and 11 females) (Table 1).

FBS and PP_2BS mg/dl were 98.86±4.41 and 130±5.96 mg/dl in the control group respectively. FBS and PP_2BS were 148.5±28.0 mg/dl and 244.5±59.3 mg/dl in the before treatment group respectively (Table 1). After 3 months of metformin therapy, FBS and PP_2BS were 107±8.87 mg/dl and 145± 15.41 mg/dl. FBS and PP_2BS levels in the treatment

Table 1: General characteristics of the study population.

Variables	Controls (*n*=30)	Before metformin treatment (*n*=30)	After treatment
Age	50.03±10.03	50.03±10.03	
Gender			
Male	19	19	19
Female	11	11	11
FBS (mg/dl)	98.86±4.41	148.5±28.0*	107±8.87#
PP_2BS (mg/dl)	130±5.96	244.5±59.3*	145±15.41#

Values expressed as mean±SD. *p<0.05 as compared to control, #p<0.05 as compared to pre-treatment group.
FBS: Fasting blood sugar, PP_2BS: Postprandial blood sugar

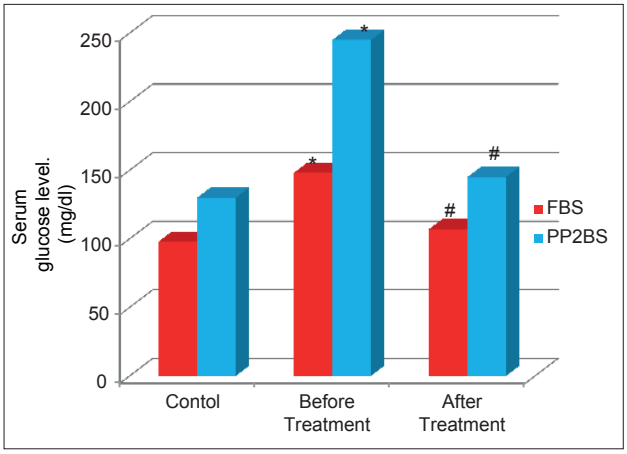

Figure 1: Effect on fasting blood sugar, postprandial blood sugar. Values expressed as mean±standard deviation. *p<0.05 as compared to control, #p<0.05 as compared to pre-treatment group.

the groups were higher than the control group but remained within normal limits (Table 1 and Figure 1).

Before the Type-2 diabetic mellitus therapy, mean serum has-CRP level was significantly raised in diabetes patients comparison to the control group (p<0.05). After 3 months of metformin therapy, the mean plasma has-CRP levels were decreased significantly from 3.08±1.62 to 2.30±1.07 mg/L (p<0.05) (Table 2 and Figure 2).

Grading of cardiovascular risk according to hs-CRP value (mg/L)

In our study, of 30 cases 12 have hs-CRP values more than 3 mg/L, before metformin treatment and after treatment with metformin for 3 months it reduce up to 6 cases which are fall under high risk group. Of 30 cases, 16 are in moderate risk group and 2 are in low risk group before metformin treatment. It increased up to 22 cases in moderate risk group at the end of 3 months treatment with metformin

Table 2: Hs-CRP in newly diabetics and healthy volunteers subjects and effect of metformin treatment on this parameter.

	Controls (*n*=30)	Metformin (*n*=30)	
		Before treatment	After treatment
Hs-CRP (mg/L)	0.61±0.31	3.08±1.62*	2.30±1.07#

Values expressed as mean±SD. *p<0.05 as compared to control, #p<0.05 as compared to pre-treatment group.
Hs-CRP: High-sensitivity-C-reactive protein

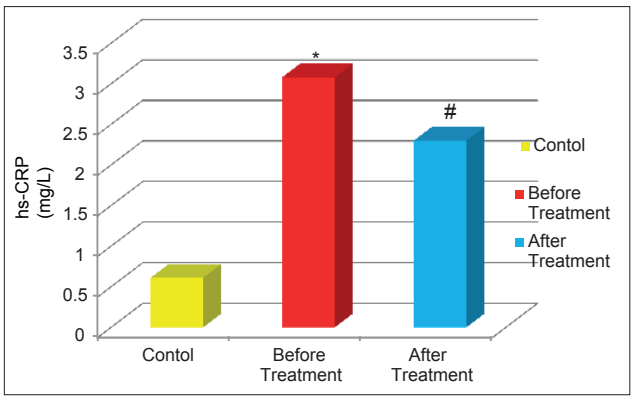

Figure 2: Effect of metformin treatment on mean plasma high-sensitivity-C-reactive protein level in Type-2 mellitus patients.

(Table 3). More number of cases falling under the moderate risk group might be due to control of underlying systemic illness like DM and controls of this might have impending atherosclerosis which is reflected in there hs-CRP values (Figure 3).

DISCUSSION

Elevated levels of high-sensitivity CRP emerged as a reliable biomarker for the subclinical inflammatory state, in patients of Type-2 DM and the effects of therapy with metformin on this parameter was examined in this study. The FBS and PP_2BS decreased within normal range with metformin therapy. Mean plasma hs-CRP level was significantly higher in patients of Type-2 diabetes compared to the control group before therapy, and it decreased significantly after the treatment of metformin therapy. Current evidence supports the usefulness of hs-CRP measurement for vascular risk and treatment efficacy assessment in insulin-resistant diabetic. Therapies that address insulin resistance may benefit individuals by reducing inflammation, atherogenesis, and thus macrovascular complications. Treatment aimed at improving the insulin-resistant state, whether non-pharmacological, such as exercise and weight reduction or pharmacological, such as metformin and thiazolidinediones, results in a decrease of CRP levels beyond mere glucose lowering. Among oral antidiabetic agents, accumulating evidence shows that metformin reduces CRP concentrations in patients with Type-2 DM. However, this effect is

Table 3: Grading of cardiovascular risk according to has - CRP value.

Hs-CRP (mg/L)	Controls (*n*=30)	Cases (*n*=30)	
		Before treatment	After treatment
<1 (low risk)	25	2	2
1-3 (moderate risk)	5	16	22
>3 (high risk)	0	12	6

Hs-CRP: High-sensitivity-C-reactive protein

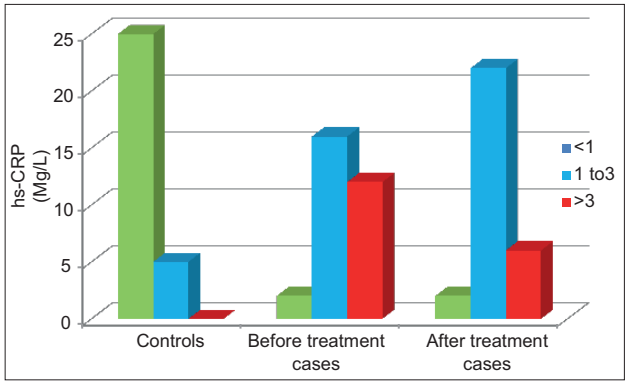

Figure 3: Grading of cardiovascular risk according to high-sensitivity-C-reactive protein value (mg/L).

probably dependent on improving glycemic control[2] CRP has numerous adverse cardiovascular effects that can contribute to the pathophysiology of cardiovascular disease. In experimental animals, metformin significantly improves survival rate in treated mice compared with untreated one.[25]

CONCLUSIONS

The anti-inflammatory role of OHAs is helpful in decreasing the disease related long-term complications in Type-2 diabetics. Keeping this fact in mind the present study was done to see the effect of antidiabetic drugs on hs-CRP level. The results of this study showed that a significant decrease in serum hs-CRP levels in newly-diagnosed patients with Type-2 DM after 3 months metformin therapy.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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