PLASMA FIBRINOGEN AS A MARKER OF MAJOR ADVERSE CARDIAC EVENTS IN PATIENTS OF TYPE 2 DIABETES WITH UNSTABLE ANGINA.

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ABSTRACT

Unstable angina patients with type 2 diabetes have higher mortality and morbidity. The present study aimed at determining the differences in the inflammatory status between non-diabetic and diabetic patients with unstable angina, and evaluating fibrinogen concentration as predictor of in hospital major adverse cardiac events in diabetic patients.

142 cases of unstable angina were analyzed. 37 patients were found to be diabetic and 105 were non-diabetic. Plasma fibrinogen was determined in each patient at the time of admission. Unstable angina was diagnosed on the basis of typical history of chest pain and electrocardiographic changes. All the patients were followed during their hospital stay for major adverse cardiac events (MACE) such as myocardial infarction, recurrent angina, congestive cardiac failure, arrhythmias and cardiac death.

Out of 37 diabetic 16% patients were in Braunwald class I of unstable angina while 14 % and 70% were in class II and class III respectively. The mean fibrinogen levels in diabetic (344.72$\pm$80.57) were significantly higher than in non-diabetic (275.19$\pm$63.56) patients of unstable angina (p=<0.001). As compared to 27% of non-diabetic patients 60% of diabetic patients had MACE (p=<0.001). In multivariate analysis, other than diabetes (p=0.044, adjusted OR=2.760, 95%CI=1.029-7.408) age, plasma fibrinogen and past history of ischemic heart disease were independent predictors of MACE.

Unstable angina patients with type 2 diabetes had significantly higher chances of having MACE during their hospital stay. Plasma fibrinogen was a strong predictor of in-hospital major adverse cardiac events in our study.

KEY WORDS- Type 2 diabetes; Fibrinogen; Unstable angina; Inflammation.

INTRODUCTION

Diabetes mellitus is widely recognized as being perhaps the most significant risk factor for the development of acute coronary syndromes (1). Furthermore, when patients with diabetes develop clinical events, their prognosis is worse than that for non-diabetics (2).

The basis for the excess risk of cardiovascular disease among diabetic patients has not been completely determined. Firstly, there is a high prevalence of conventional risk factors such as dyslipidemia, hypertension, and obesity (3). Secondly, diabetic patients are at increased risk for thrombosis formation as a consequence of increased platelet reactivity, increased concentrations and activity of coagulation factors, and decreased activity of antithrombotic factors and fibrinolytic system (4, 5). Thirdly, insulin resistance, hyperinsulinemia, hyperglycemia, and advanced glycation end products also affect arterial wall physiology (6). All these mechanisms favor systemic and coronary inflammation and accelerated progression and precipitation of atherothrombosis (7). In fact, in diabetic patients with unstable angina coronary plaques have a higher incidence of plaque ulceration and intra-coronary thrombus formation than in non-diabetic patients. Diabetic plaques usually have a greater lipid core burden and a richer inflammatory component and are more commonly complicated by overlying thrombosis (8). In addition; inflammation is an important pathogenetic determinant of type 2 diabetes.

However, very limited information is available concerning the concentrations of fibrinogen in diabetic patients with unstable coronary artery disease. Thus, the present study aimed at determining the differences in the inflammatory status between non-diabetic and diabetic patients with unstable angina, and evaluating fibrinogen concentration as predictors of in hospital major adverse cardiac events in diabetic patients.

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MATERIAL AND METHODS

This study was carried out at Department of Medicine, Government Medical College and Hospital, Nagpur, from January 2002 to June 2003. The patients of unstable angina presenting during this period and satisfying study criteria were initially observed in ICCU and subsequently in medicine wards till discharge, for occurrence of major adverse cardiac events.

Patients admitted to ICCU or medicine wards of GMC with diagnosis of unstable angina were included in the study. Unstable angina (9, 10) was diagnosed clinically by history of typical ischemic chest pain/ discomfort with or without associated ECG changes.

The exclusion criteria were: raised levels of CPK-MB or LDH at admission, patients with ECG changes suggestive of acute myocardial infarction, recent acute myocardial infarction (within 4 weeks) (11), inter-current inflammatory or neoplastic conditions, valvular heart disease and patients presenting with congestive cardiac failure.

Patients satisfying the inclusion criteria and not having any of the exclusion criteria were entered in study as cases. Each of the patients was subjected to detailed history of type 2 diabetes mellitus, ischemic heart disease, and other risk factors and thorough physical examination. In this study patients were considered to be diabetic when they had history of diabetes or a fasting blood sugar greater than 126 mg/dl. Patients were considered hypertensive when they had history of hypertension diagnosed and treated with medication, diet or blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least two occassions. Height and weight was recorded. Waist circumference was measured one inch above the umbilicus (12). The maximum circumference over the buttock with minimum clothing was recorded as hip circumference (13). Waist-hip ratio of 0.9 or greater was considered abnormal.

Plasma fibrinogen was determined in all the patients at admission by modified Clauss's method with kit provided by DADE BEHRING, Germany (14).

In all patients, a 12 lead ECG was recorded on admission. Additional ECGs were performed whenever possible during an episode of angina. ECGs were classified as abnormal in case of ST depression more than 0.05 mV or T-wave inversions more than 0.2 mV in at least 2 adjacent leads. Patients were monitored in the intensive care unit for 48-72 hours and thereafter in the wards till discharge. All the patients received standard medical therapy for an unstable angina. The clinical end points were: in hospital recurrent angina, arrhythmias, congestive cardiac failure, new myocardial infarction and cardiac death. Recurrent angina was defined as occurrence of two or more episodes of typical chest pain, each lasting for more than one minute, twenty four hours after initiation of standard medical therapy. New myocardial infarction was diagnosed by history of typical chest discomfort consistent with a diagnosis of myocardial infarction, appearance of STelevation or new Q-wave on ECG and / or elevation of CPK-MB.

Statistical analysis was done by using the students''t' test for continuous variables and chi square test for categorical variables and results were obtained in the form of p (Probability) value. p value of <0.05 was considered significant. All these tests along with multilogistic regression analysis were done by using software Stata (version 7.0) © Stata Corporation 1997-2002.

RESULTS

The study included 142 patients of unstable angina admitted to Government Medical College and Hospital, Nagpur. Of the total 142 patients 50 (35%) developed major adverse cardiac events. 92 patients (65%) did not have such complication during their hospital stay.

The mean age of cases was 56 years with range of 32 years to 88 years. Among 142 cases studied 68% were male and 32% female. Male to female ratio was 2.1: 1.

37 patients (26%) had type 2 diabetes. Analysis of other risk factors showed 39% had abnormal waist-hip ratio. Hypertension (34%) was the next common risk factor. There were 30% smokers in the present study. 16% patients had dyslipidemia.

Maximum (46%) of patients presented with Braunwald's class III unstable angina. 28% patients had Braunwald's class I unstable angina and 26% patients had Braunwald's class II unstable angina. Out of 37 diabetics 70% patients were in Braunwald's class III of unstable angina while 16% and 14 % were in class I and class II respectively. Thus diabetics had severer grade of angina more commonly than non diabetics.

The plasma fibrinogen levels were significantly higher in cases with type 2 diabetes than non diabetics (344.72$\pm$80.57 vs. 275.19$\pm$63.56; p=<0.001).

Out of 37 diabetic patients 60%, and out of 105 non diabetic patients, 27% had in hospital major adverse cardiac events. Thus in hospital, major adverse cardiac events were significantly higher in diabetic patients of unstable angina as compared to non diabetic patients (p=<0.001). Recurrent angina was the commonest major adverse cardiac event observed in type 2 diabetes patients with unstable angina during hospital stay (48%). All the patients who developed myocardial infarction during hospital stay were diabetic.

Plasma fibrinogen was significantly higher in patients of type 2 diabetes with unstable angina who had in hospital major adverse cardiac events than diabetics with uneventful in-hospital stay (382.27 vs. 289.67 mg/dl; p=<0.001).

In multivariate analysis, diabetes was strong predictor of major adverse cardiac events (p=0.044, adjusted OR=2.760, 95%CI=1.029-7.408). Age, plasma fibrinogen and past history of ischemic heart disease were other independent predictors of in hospital major adverse cardiac events.

DISCUSSION

Coronary tissue from diabetic patients with acute coronary syndrome has more lipid rich atheroma, thrombosis, and macrophage cell infiltration than tissue from patients without diabetes (8). This higher incidence of inflammatory cell infiltration in coronary tissue from diabetic patients suggests not only that inflammation may play an important part in the pathophysiology of acute coronary syndrome but also that a more pro-inflammatory state is present in diabetic than in non-diabetic patients (15). The concentration of acute phase reactants like fibrinogen in diabetes is higher than non diabetics (16). Anuja Jain et al (17) proposed various possible mechanisms for hyperfibrinogenemia in diabetics. They could be that fibrinogen is acute phase reactant; it increases with early atherosclerosis, glycosylated fibrinogen is less susceptible to plasmin degradation, relative insulin deficiency in diabetics result in differential protein synthesis i.e. 29% decrease in albumin synthesis and 50% increase in fibrinogen synthesis and higher plasma cortisol levels in state of insulin deficiency cause increase in fractional synthesis of fibrinogen.

A variety of clinical studies have been carried out to investigate different markers of inflammation as predictors of coronary events in patients with unstable angina and after myocardial infarction. However, very limited information is available concerning diabetic patients. In a study by Sanchez et al (18**)** diabetic patients with acute coronary disease had enhanced C reactive protein concentrations, fibrinogen concentrations, and leucocyte counts at admission than the non-diabetics.

The goal of the present study was to evaluate the usefulness of fibrinogen concentration as predictors of major adverse cardiac events in diabetic patients with unstable angina. Thus we have attempted to correlate morbidity and mortality in diabetic patients of unstable angina with values of plasma fibrinogen. The mean fibrinogen levels in diabetic (344.72$\pm$80.57) was significantly higher than in non-diabetic (275.19$\pm$63.56) patients of unstable angina (p=<0.001). Diabetic patients of unstable angina had significantly higher in hospital major adverse cardiac events (p=<0.001) including recurrent angina. Myocardial infarction during immediate post angina period was also significantly higher in diabetics. Plasma fibrinogen was significantly higher in patients of type 2 diabetes with unstable angina who had in hospital major adverse cardiac events (382.27 vs. 289.67) than diabetics without it (p=<0.001). Plasma fibrinogen was strong predictor of in-hospital major adverse cardiac events in our study. Assessment of fibrinogen concentration also provides prognostic information in diabetic patients with unstable angina.

An important limitation of our study has been the small sample size; the findings therefore need to be confirmed by a large study. There is also need to follow up these patients and study whether their long term outcome is any different from patients without baseline elevation of plasma fibrinogen. This study also does not establish causal relationship in elevated plasma fibrinogen and in hospital major adverse cardiac events in type 2 diabetes patients of unstable angina. However, plasma fibrinogen values may have practical clinical applications in risk stratification and targeting of treatment of diabetic patients with unstable coronary disease.

Unstable angina patients with type 2 diabetes had significantly higher chances of having MACE during their hospital stay. This may be because of significantly higher levels of plasma fibrinogen in these patients. Plasma fibrinogen was a strong predictor of in-hospital major adverse cardiac events in our study. Assessment of fibrinogen concentration also provides prognostic information in diabetic patients with unstable angina. To establish the causal relationship between plasma fibrinogen and higher chances of

MACE in type 2 diabetic patients of unstable angina needs further studies.

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