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ORIGINAL ARTICLE

A Study of Plasma Fibrinogen Level in Type-2 Diabetes Mellitus and its Relation to Glycemic Control

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Abstract The high prevalence of classic cardiac risk factors in patients with type 2 diabetes mellitus does not explain the increased cardiovascular related morbidity and mortality in these patients. Fibrinogen may have a role in this excess risk. This study is undertaken to know the fibrinogen levels in type 2 diabetes mellitus and its relations to glycemic control. In the present study fibrinogen levels (Clauss method) were estimated in 100 type 2 diabetic subjects and 100 age and sex matched controls. Fibrinogen was correlated with various parameters like glycosylated hemoglobin (cation exchange resin method), age, sex, smoking, body mass index (kg/m^2), hypertension and ischemic heart disease. Higher plasma fibrinogen levels were found in type 2 diabetes mellitus patients (656 ± 130 mg/dl) as compared to controls (324 ± 139 mg/dl) which were statistically significant. Fibrinogen levels were associated with age ($P < 0.01$), hypertension ($P < 0.01$), body mass index ($P < 0.01$), smoking ($P < 0.01$), ischemic heart disease ($P < 0.01$), and glycosylated hemoglobin ($r = 0.49$) in diabetics in a significant manner. But no correlation was found with sex ($P < 0.05$) in diabetes. In controls, association was found between fibrinogen levels and smoking ($P < 0.01$) and body mass index ($P < 0.01$). Patients with type 2 diabetes mellitus had a high prevalence of hyperfibrinogenemia. Fibrinogen levels were independently associated with hemoglobin A1c values, which suggests that fibrinogen may be involved in the increased cardiovascular risk of patients with type 2 diabetes mellitus.

Keywords Type 2 diabetes mellitus · Fibrinogen · Glycosylated hemoglobin

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Introduction

Diabetes mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades and it is projected that the number of individuals with diabetes will continue to increase in near future. Although the prevalence of both type 1 and type 2 diabetes mellitus is increasing worldwide, the prevalence of type 2 diabetes mellitus is expected to rise more rapidly in future because of increasing obesity and reduced activity levels [1]. In the past decade, the potential role of hemostatic factors, particularly fibrinogen, in atherosclerosis and its complications has generated considerable attention. Studies have shown that formation of an occlusive thrombus, on a damaged atherosclerotic lesion is the most common precipitating factor of acute myocardial infarction. Evidence also suggests that fibrinogen has a role, both in the early stages of plaque formation and late complications of cardiovascular disease [2]. The excess cardiovascular morbidity and mortality among diabetics have not been fully explained by major risk factors such as hypertension, cigarette smoking and hypercholesterolemia. Increased attention is being paid to, disordered hemostatic mechanism in pathogenesis of both large vessel and small vessel disease in diabetes [3]. Impaired glucose

tolerance exerts an influence by enhancing thrombogenic factors such as, fibrinogen in the diabetics [4].

Fibrinogen, itself is determined by several modifiable and non-modifiable determinants like age, sex, smoking, body mass index (BMI), hypertension, alcoholism, glycemic control, lipid profile and urine albumin excretion rate [5, 6]. The present study is undertaken to know the levels of fibrinogen in type 2 diabetes mellitus and its relation with glycemic control. Evidence of increased thrombotic tendency in diabetes would have etiological, preventive and therapeutic implications [3]. Cardiovascular complications account for nearly 50% of deaths in type 2 diabetes mellitus and 25% in type 1 patients. Therefore, it is important to recognize various cardiovascular risk factors and modify them if possible by primary and secondary intervention [5]. Diabetic patients have higher cardiovascular morbidity than non diabetic subjects. Several studies have shown that haemostatic factor especially hyperfibrinogenemia is implicated as a source of atherosclerosis and its complications [6–8].Studies have reported that fibrinogen levels were higher in diabetics than in controls [3–5]. Very few studies have been done regarding the association of fibrinogen with glycemic control in type 2 diabetes mellitus [6, 7, 9].In view of above concepts and due to paucity of similar studies, this study has been undertaken to know the significance of fibrinogen as risk factor in type 2 diabetes mellitus and its relation with glycemic control.

Materials and Methods

The objectives are to detect the plasma fibrinogen levels in type 2 diabetes mellitus patients and to compare and correlate the values of plasma fibrinogen levels with glycemic control in these patients. The source of data were patients attending diabetic clinic of B.L.D.E.A's Shri B.M.Patil Medical College, Hospital and Research Centre, who were diagnosed type 2 diabetes mellitus either newly detected or already on diet or treatment between February 2004 to February 2005. The method of collection of data was purposive sampling technique and it was a case control study. Sample size of the cases were hundred patients attending diabetic clinic of B.L.D.E.A's Shri B.M.Patil Medical College, Hospital and Research Centre who are diagnosed type 2 diabetes mellitus, newly detected or already on diet or treatment. The controls were hundred non diabetic healthy attenders (age and sex matched) accompanying the patients in B.L.D.E.A's Shri B.M Patil Medical College, Hospital and Research Centre. The procedure followed was detailed history, clinical examination and relevant laboratory investigations were done both in diabetic patients and in controls. The various parameters which were studied included age of the patient (year), sex, smoking, blood pressure (mm Hg), BMI (kg/m^2), Ischemic heart disease (IHD), plasma fibrinogen levels (mg/dl) by "Clauss method" and glycosylated hemoglobin (%) by "cation exchange resin method". Blood Sugar levels, plasma fibrinogen levels and glycated hemoglobin were measured in cases and controls.

Results

In the present study fibrinogen levels were estimated in 100 type 2 diabetes mellitus subjects and 100 age and sex matched controls. Fibrinogen levels were correlated with age, sex, smoking, hypertension (HTN), IHD, BMI and glycosylated hemoglobin (HbA1c). The patients were divided into five groups viz 30–40, 40–50, 50–60, 60–70 and >70 years for analytical purpose. Patients (diabetic) were categorized in three groups depending upon the HbA1c values i.e., into 5.5–6.8% (good control) 6.8–7.6% (fair control) and >7.6% (poor control).The mean age in the present series was 56.4 years for both cases and controls. The youngest age was 35 years. The eldest age was 80 years. The maximum numbers of patients were in the age group 51–70 years (69%). Among the 100 patients studied 57% were males and 43% were females. In this study M:F ratio is 1.3:1. The mean plasma fibrinogen in cases was 656 ± 130 mg/dl. Lowest value was 350 mg/dl and highest value was 880 mg/dl. The mean plasma fibrinogen in controls was 324 ± 139 mg/dl. Lowest value was 130 mg/dl and highest value was 680 mg/dl. Cases had a higher fibrinogen when compared to controls and normal range (200–400 mg/dl) and it was statistically highly significant ($P < 0.01$), Table 1.

In this, it was found in study population that, as age advances fibrinogen also increases and was statistically significant. In cases, males had mean fibrinogen of 653 ± 126 mg/dl and females had mean fibrinogen of 660 ± 137 mg/dl which were higher but was not statistically significant. In control, males had mean fibrinogen of 342 ± 156 mg/dl and females had mean fibrinogen of 301 ± 110 mg/dl which were lower but was not statistically significant. There were 15 (15%) smokers among cases and 16 (16%) in controls. In cases and controls, smokers had

Table 1 Descriptive statistics in diabetics and controls

	Controls	Diabetes
Number (%)	100	100
Age (years)	56.4	56.4
Fibrinogen (mg/dl)	324 ± 139	656 ± 130
HbA1c (%)	4 ± 1.6	8.5 ± 1.69

Table 2 Correlation between fibrinogen levels in diabetics and controls with various parameters

	Diabetes	Controls
Age (years)	$P < 0.01$	$P > 0.05$
Sex	$P > 0.05$	$P > 0.05$
Smoking	$P < 0.01$	$P < 0.01$
Hypertension	$P < 0.01$	–
IHD	$P < 0.01$	–
BMI (Kg/m2)	$P < 0.01$	$P < 0.01$
HbA1c (%)	$r = 0.49$	–

higher fibrinogen levels than non smokers and were statistically significant ($P < 0.01$). In cases, smokers had 720 ± 104 mg/dl and non smokers had 520 ± 113 mg/dl fibrinogen levels. In controls smokers had 630 ± 116 mg/dl and non smokers had 300 ± 108 mg/dl fibrinogen levels. In diabetic hypertensive patients mean fibrinogen level was 784.1 ± 68.9 mg/dl and in diabetic normotensive 640 ± 127 mg/dl. Diabetic hypertensive patients had higher fibrinogen level than diabetic normotensive which was statistically significant. Patients with IHD had higher mean fibrinogen when compared to patients without IHD and there was statistically significant correlation between fibrinogen and IHD in cases. In both cases and controls obese individuals had higher fibrinogen level than non obese and which was statistically significant. In diabetic obese individuals mean fibrinogen was 712 ± 114 mg/dl and in non obese individuals, mean fibrinogen was 593 ± 113 mg/dl. In controls, obese individuals mean fibrinogen was 660 ± 102 mg/dl and in non obese individuals mean fibrinogen was 296 ± 123 mg/dl, Table 2.

The mean HbA1c value in cases was 8.5 ± 1.69%. Lowest value was 5.6% and highest value was 12.5%. Cases had a higher HbA1c value when compared to normal range (4.2–6.2%). The correlation between HbA1c and fibrinogen levels of the diabetic patient is positive i.e., poorer the glycemic status, higher the fibrinogen levels ($r = 0.49$), Fig. 1.

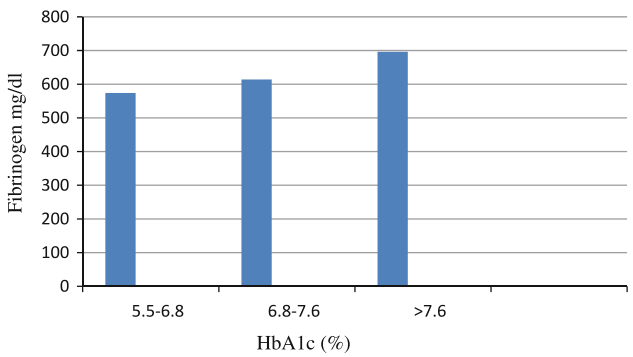

Fig. 1 Bar diagram showing relationship between mean fibrinogen levels and HbA1c in diabetics

Discussion

Increased cardiovascular morbidity and mortality in diabetics underscores and need to identify potential reversible cardiovascular risk factors in this group of patients. For many years, hemostatic factors especially fibrinogen, has been implicated as a cause of atherosclerosis and its complications i.e., MI, angina etc. In the present study diabetics had higher fibrinogen level than controls signifying increased cardiovascular risk. The various possible mechanisms for hyperfibrinogenemia in diabetics could be that a procoagulant state often exists in people of diabetes. There is an increase in a number of coagulation factors such as plasminogen activator inhibitor 1, von-Willebrand factor, fibrinogen, factor VII and thrombin antithrombin complexes particularly in association with macrovascular and microvascular disease and glycemic control. Plasma levels of lipoprotein(a) [Lp(a)] are elevated in people with diabetes, particularly those with poor glycemic control. The Lp(a) molecule is formed by the assembly of at least two major proteins, a molecule of apoB100 covalently linked to a molecule of apolipoprotein(a) [APO(a)] by a single disulfide bridge. It is structurally similar to low density lipoprotein (LDL) in protein and lipid composition, the essential difference between the two being APO(a). APO(a), a glycoprotein structurally similar to plasminogen, the precursor of plasmin has the capacity to bind to fibrin and to membrane protein of endothelial cells and monocytes. This inhibits plasminogen binding and plasmin generation which leads to decreased fibrinolysis and delays thrombolysis and contributes to the accumulation of Lp(a) and fibrin at the sites of vascular injury. Lp(a) has a major role in diabetes and its vascular complications by decreasing fibrinolysis and thus increasing plasma fibrinogen levels [10].

The mechanism by which fibrinogen increases cardiovascular risks are not fully understood. Fibrinogen plays important role in development of atherosclerosis starting from the stage of plaque formation till formation of occlusive thrombus over a ruptured atherosclerotic plaque, which is the most common precipitating cause of MI. The various mechanism by which fibrinogen has been found to promote atherosclerosis and thrombosis are (a) hyperfibrinogenemia increases plasma viscosity, (b) it induces reversible RBC aggregation, (c) it binds it receptors on platelet membrane and causes platelet aggregation, (d) it forms fibrin and fibrinogen degradation products (FDPs) which in turn bind LDL and sequester more fibrinogen and (e) fibrinogen and FDPs stimulate smooth cell proliferation and migration.

All these factors result in increased atherogenesity in patients of hyperfibrinogenemia i.e., diabetes and cause coronary artery disease. Besides, fibrinogen levels were

found to be associated with age, smoking, HTN, BMI, glycemic control and IHD [11]. The correlation between glycemic control and fibrinogen levels could be due to (a) glycosylate fibrinogen is less susceptible to plasmin degradation (b) relative insulin deficiency in diabetic's results in differential protein synthesis i.e., 29% decrease in albumin synthesis and 50% increase in fibrinogen synthesis [12]. Thus, a link between fibrinogen and atherosclerosis is undeniable, it is the nature of association that is debatable—risk factor or risk marker. Several determinants of fibrinogen in health and disease are life style dependent, e.g. BMI, smoking etc., and are amenable to change. The value of lowering fibrinogen levels by life style modifications or drugs is still unknown and future cardiovascular research in this area is warranted. To summarize diabetics had higher fibrinogen levels, which were found to be associated with glycemic control, age, hypertension, smoking, BMI and IHD.

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