A STUDY ON FIBRINOGEN LEVELS IN TYPE 2 DIABETES MELLITUS

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON PLASMA FIBRINOGEN LEVELS IN TYPE 2 DIABETES MELLITUS**" is a bonafide work done by **Dr. RAKESH.P.**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2009-2012.

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ABBREVIATIONS

DM – Diabetes Mellitus

SHT- Systemic Hypertension

CAD- Coronary Artery Disease

CVA- Cerebrovascular Disease

FPG- Fasting Plasma Glucose

PPPG- Post Prandial Plasma Glucose.

TC-Total Cholesterol

HDL- High Density Lipoprotein

PVD- Peripheral Vascular Disease

ECG- Electrocardiogram

RWMA- Regional Wall Motion Abnormality

CT- Computerised Tomogram

MRI- Magnetic Resonance Imaging

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INTRODUCTION

India is frequently referred to as the diabetic capital of the world as it has the highest number of cases in the world.

The worldwide prevalence of diabetes has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000.[1] Based on current trends greater than 360 million individuals worldwide will have diabetes by the year 2030.[1]

India had around 31.7 million cases in year 2000 which is expected to rise alarmingly to around 79.4 million in 2030 by which time every fifth diabetic subject in the world would be an Indian.[1] Indian studies puts these numbers at a much higher levels from estimated 51 million in 2010 to 87 million in 2030.[2]

The prevalence rate in India varies among urban and rural population. In the urban population, an Indian Council of Medical Research (ICMR) study in 1972 reported a prevalence of 2.3%.[3] which rose to 12.1% in the year 2000.[4] More recently, estimates from a nationwide surveillance study of T2DM found a prevalence of 7.3% in urban areas & 3.2% in peri-urban/slum areas (urban fringes).[5] In the rural population, an early study in 1991 indicated that the prevalence rate ranged from 0.4-1.5% in Delhi.[6] A multicentric study in 2008 estimated the prevalence to be 3.1%.[5]

In Tamilnadu the prevalence in 2008 is 18.6% in urban areas and 9.1% in rural areas.[7]

The incidence of T2DM in the urban south Indian population was 20.2 per 1,000 person years.[5]

Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death. In the United States, diabetes was listed as the seventh leading cause of death in 2007; a recent estimate suggested that diabetes was the fifth leading cause of death worldwide and was responsible for almost 4 million deaths in 2010 (6.8% of deaths were attributed to diabetes worldwide).

In India diabetes is responsible for 109 thousand deaths, 1.157 million years of life lost and 2.263 million disability adjusted life years (DALYs) during 2004.[8-9] WHO estimates that mortality from diabetes, heart disease and stroke costs about $210 billion in India in the year 2005. Much of the heart disease and stroke in these estimates was linked to diabetes. WHO estimates that diabetes, heart disease and stroke together will cost about $ 333.6 billion over the next 10 years in India.

Although the prevalence of both type 1 and type 2 diabetes is increasing worldwide, the prevalence of type 2 diabetes is rising much more rapidly because of increasing obesity and reduced activity levels.

The real burden of the disease is however due to its macro and micro vascular complications. Macrovascular complications are the most important causes of morbidity, mortality and disability in people with Type 2 diabetes mellitus.

Coronary artery disease is the leading cause of death among adult diabetics and accounts for about three times as many deaths among diabetics as among non-diabetics.[10]

it is now being increasingly appreciated that the traditional risk factors (smoking, obesity, hypercholesterolemia, family history, physical inactivity, diabetes mellitus, hypertension) for cardiovascular disease may account for only one half to two thirds of the actual risk. It becomes important to try and identify other risk factors, especially those that can be easily modified or corrected. Some of the factors whose role is being seriously investigated include estrogen deficiency, lipoprotein(a), plasma fibrinogen, plasminogen-activator inhibitor type 1, endogenous tissue plasminogen activator (tPA), C-reactive protein , and homocysteine.

Fibrinogen is one such factor. It is the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation. Elevation of plasma viscosity due to increase in fibrinogen concentration significantly contributes to the microvascular disorder in diabetics.[13-14] Similarly many studies have shown elevated fibrinogen to be an important risk factor for coronary artery disease.[15-17] Evidence also suggests that fibrinogen may be involved in the development of atherosclerotic lesions beginning with the early stages of plaque formation.[11]

To conclude among the various hematological factors, elevated fibrinogen as a risk factor in diabetes plays an important role in the development of

complications.[18] Fibrinogen levels can be reduced considerably by life style interventions and probably drugs there is possibility that measurement of fibrinogen may help in disease prediction or prevention.[12, 56]

AIMS AND OBJECTIVES

1. To estimate the levels of plasma fibrinogen in patients with diabetes mellitus.
2. To compare the levels of fibrinogen in patients with diabetes alone, diabetes with microvascular complications, diabetes with macrovascular complications.
3. To correlate levels of fibrinogen with age, body weight, Body Mass Index, total cholesterol and HbA1c levels.

REVIEW OF LITERATURE

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that is characterized by chronic hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems commonly the eyes, kidney, heart and blood vessels. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.

The word Diabetes in Greek means – "I run through Siphon". Indian name for Diabetes is Madhumeha – Honey in rain. In 16^{th} century, Susrutha in the Sanskirit book of surgery, and Charaka in the Sanskirit book of medicine have mentioned about Diabetes. The first person -Vaidys – tested the urine of diabetic patients.

Classification

DM is classified on the basis of the pathogenic process that leads to hyperglycemia. The two broad categories of DM are designated type 1 and type 2

Etiologic Classification of Diabetes Mellitus.[19]
I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency) A. Immune-mediated B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III. Other specific types of diabetes A. Genetic defects of beta cell function B. Genetic defects in insulin action C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia. D.Endocrinopathies- acromegaly, Cushing's syndrome, glucagonoma etc. E. Drug- or chemical-induced F. Infections—congenital rubella, cytomegalovirus, coxsackievirus. G. Uncommon forms of immune-mediated diabetes— "stiff-person" syndrome etc H. Other genetic syndromes sometimes associated with diabetes like Turners
IV. Gestational diabetes mellitus (GDM)

Diagnosis

Glucose tolerance is classified into three broad categories:

(1)Normal glucose homeostasis:

A Fasting plasma glucose < 100 mg/dl (5.6 mmol/l) [b], a plasma glucose < 140 mg/dl (11.1 mmol/L) following an oral glucose tolerance test [d], and an HbA1C < 5.6%[c] are considered to define normal glucose tolerance.

(2)Diabetes Mellitus: The International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation has issued the following diagnostic criteria.

Criteria for the Diagnosis of Diabetes Mellitus
1.Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/l (200 mg/dl) [a] *or*
2.Fasting plasma glucose ≥7.0 mmol/l(126 mg/dl)[b] *or*
3.HbA1c > 6.5%[c]*or*
4.Two-hour plasma glucose ≥11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test [d]

[a] Random is defined as without regard to time since the last meal.

[b] Fasting is defined as no caloric intake for at least 8 h.

[c] The test should be performed in a standard laboratory.

[d] The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

(3)Abnormal glucose homeostasis

It is defined as

(a) A Fasting plasma glucose = 5.6–6.9 mmol/l (100–125 mg/dl), is called as Impaired Fasting Glucose (IFG) (World Health Organization uses an FPG of 6.1–6.9 mmol/l (110–125 mg/dl);

(b)Plasma glucose levels between 7.8 and 11 mmol/l (140 and 199 mg/dl) following an oral glucose challenge, which is called impaired glucose tolerance (IGT);

(3) HbA1c of 5.7–6.4%.

A HbA1c of 5.7–6.4%, IFG, and IGT do not identify the same individuals, but individuals in all three groups are at greater risk of progressing to type 2 diabetes and have an increased risk of cardiovascular disease. The term "prediabetes," "increased risk of diabetes" (ADA), or "intermediate hyperglycemia" (WHO) are used for this category.

The current criteria for the diagnosis of DM emphasize that the HbA1c or the FPG as the most reliable and convenient tests for identifying DM in asymptomatic individuals. Oral glucose tolerance testing, although still a valid means for diagnosing DM, is not often used in routine clinical care

Screening

Widespread Fasting Plasma Glucose (FPG) or HbA1C as a screening test for type 2 DM is recommended because

(a) A large number of individuals who meet the current criteria for DM are asymptomatic.

(b) Epidemiologic studies suggest that type 2 DM may be present up to a decade before diagnosis.

(c) Some individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis.

(d) Treatment of type 2 DM may favorably alter the natural history of DM.

The ADA recommends screening all individuals > 45 years every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) >25 kg/m^2] and have one additional risk factor for diabetes . In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM.

Risk factors for type 2 Diabetes Mellitus

The risk factors for developing DM are as under.

Risk Factors for Type 2 Diabetes Mellitus[19]
Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
Obesity (BMI ≥25 kg/m^2)
Physical inactivity
Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
Previously identified with IFG, IGT, or an A1C of 5.7–6.4%
History of GDM or delivery of baby >4 kg
Hypertension (blood pressure ≥140/90 mmHg)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Polycystic ovary syndrome or acanthosis nigricans
History of cardiovascular disease

TYPE 1 DIABETES

Introduction

It constitutes roughly 5 – 10% of all the diabetic patients. Previously it was called as Insulin dependent Diabetes mellitus (IDDM). Rates of type 1 diabetes are increasing by around 2 – 2.5% per year worldwide and is common in males.

Type 1 DM usually starts in children aged 4 years or older, usually abruptly, with the peak incidence of onset at age 11-13 years. Also, a relatively high incidence exists in people in their late 30s and early 40s, when the disease tends to present in a less aggressive manner (ie, early hyperglycemia without ketoacidosis and gradual onset of ketosis) referred to as latent autoimmune diabetes of the adult (LADA).[28]

Pathogenesis

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to the destruction of the pancreatic beta cells and insulin deficiency.

Immunological Factors

Most (around 85%), individuals have evidence of islet-directed autoimmunity. Prevalence is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and Addison disease. Prevalence of

type 1 diabetes autoantibodies and newly diagnosed type 1 diabetes is higher in patients with autoimmune thyroiditis.[21] Some individuals have type 1 DM lack immunologic markers indicative of an autoimmune process .

Islet cell autoantibodies (ICAs) are a composite of several different antibodies directed at pancreatic islet molecules such as GAD, insulin, IA-2/ICA-512, and ZnT-8, and serve as a marker of the autoimmune process of type 1 DM.

Assays for autoantibodies to GAD-65 are commercially available. Testing for ICAs can be useful in classifying the type of DM as type 1 and in identifying non diabetic individuals at risk for developing type 1 DM. Islet cell antibodies are present in the majority of individuals (>85%) diagnosed with new-onset type 1 DM, in a significant minority of individuals with newly diagnosed type 2 DM (5–10%), and occasionally in individuals with GDM (<5%).

Genetic Factors

The concordance of type 1 DM in identical twins ranges between 40 and 60%, compared to 70 – 90 % in type2 diabetes mellitus. Most individuals with type 1 DM have the HLA DR3 and/or DR4 haplotype. Refinements in genotyping of HLA loci have shown that the haplotypes DQA1*0301, DQB1*0302, and DQB1*0201 are most strongly associated with type 1 DM.

In addition to MHC class II associations, genome association studies have identified at least 20 different genetic loci that contribute susceptibility to

type 1 DM (polymorphisms in the promoter region of the insulin gene, the CTLA-4 gene, interleukin-2 receptor, *CTLA4*, and PTPN22, etc.).

Genes that confer protection against the development of the disease also exist. The haplotype DQA1*0102, DQB1*0602 is extremely rare in individuals with type 1 DM (<1%) and appears to provide protection from type 1 DM.

Environmental and Other Factors

Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, mumps, rubella, coxsackievirus B4), toxic chemicals, exposure to cow's milk in infancy, and cytotoxins. A meta-analysis suggests a significant association between enterovirus infection and autoimmune/type 1 DM.[22]

Infant weight velocity has a small indirect effect on adult insulin resistance, and this is primarily mediated through its effect on BMI and waist circumference.[23]

Intensive dose statin therapy was associated with increased risk of new onset diabetes compared with moderate dose in a pooled analysis of data from 5 statin trials.[24]

Amino acid metabolism also plays a key role in the pathogenesis of diabetes. Amino acid profiles could help assess risk of developing diabetes.[25]

Recent evidence suggests a role for vitamin D in the pathogenesis and prevention of diabetes mellitus. Vitamin D deficiency is also an important independent predictor of development of coronary artery calcification in individuals with type 1 DM.[26-27]

The morbidity and mortality associated with diabetes are related to the short- and long-term complications. Such complications include hypoglycemia and hyperglycemia, increased risk of infections, microvascular complications (eg, retinopathy, nephropathy), neuropathic complications, and macrovascular complications like ischemic heart disease, cerebral vascular disease, peripheral vascular disease.

TYPE 2 DIABETES MELLITUS

Introduction

It constitutes around 85 – 90 % of all diabetes mellitus. Previously called as Non insulin dependent diabetes, Adult onset diabetes etc.

Etiology and Pathogenesis

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that insulin resistance precedes an insulin secretory defect but that diabetes develops only when insulin secretion becomes

inadequate. A recent study indicates Beta cell function happens early in the pathological process and does not necessarily follow stage of insulin resistance.[29]

Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin. In the progression from normal glucose tolerance to abnormal glucose tolerance, postprandial blood glucose levels increase first; eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

Genetic Considerations

Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. The disease is polygenic and multifactorial, since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition, and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified, but recent genome-wide association studies have identified a large number of genes that convey a relatively small risk for type 2 DM. Most prominent is a variant of the transcription factor 7–like 2 gene that has been associated with type 2 diabetes in several populations and with impaired glucose tolerance in one population at high risk for diabetes. Genetic polymorphisms associated with

type 2 diabetes have also been found in the genes encoding the peroxisome proliferators–activated receptor-γ, inward rectifying potassium channel, zinc transporter, IRS, and calpain 10. The mechanisms by which these genetic loci increase the susceptibility to type 2 diabetes are not clear.

Other factors

(a) About 90% of patients who develop type 2 diabetes mellitus are obese. However, a large, population-based, prospective study has shown that an energy-dense diet may be a risk factor for the development of diabetes that is independent of baseline obesity.[30] Compared with persons of European ancestry, persons of Asian ancestry are at increased risk for diabetes at lower levels of overweight.[31]

(b) Hypertension and prehypertension are associated with greater risk of developing diabetes in whites compared with African Americans.[32]

(c) Abnormal in utero environment resulting in low birth weight may predispose some individuals to develop type 2 diabetes mellitus.[33-34]

Some forms of diabetes, however, have a clear association with genetic defects. The syndrome previously known as maturity onset diabetes of youth (MODY) has now been reclassified as a variety of defects in beta-cell function. These defects account for 2-5% of individuals with type 2 diabetes who present at a young age and have mild disease. The trait is autosomal dominant

and can be screened for through commercial laboratories. To date, 6 mutations have been identified:

- HNF-4-alpha
- Glucokinase gene
- HNF-1-alpha
- IPF-1
- HNF-1-beta
- NEUROD1

During the induction of insulin resistance, such as is seen after high-calorie diet, steroid administration, or physical inactivity, increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance; however, postprandial glucagon like peptide-1 (GLP-1) response is unaltered.[5] This has physiologic implications; for example, if the GLP-1 level is unaltered, GLP-1 may be a target of therapy in the states mentioned above.

Chronic Complications of DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. The risk of chronic complications increases with the duration and degree of hyperglycemia; they usually do not become apparent until the

second decade of hyperglycemia in patients with type 1 DM but type 2 DM patients often have complications at the time of diagnosis.

Chronic complications can be divided into vascular and nonvascular complications.

The vascular complications of DM are further subdivided into microvascular and macrovascular complication.

Chronic Complications of Diabetes Mellitus
Microvascular
Eye disease
Retinopathy (nonproliferative/proliferative)
Macular edema
Neuropathy
Sensory and motor (mono- and polyneuropathy)
Autonomic
Nephropathy
Macrovascular
Coronary heart disease
Peripheral arterial disease
Cerebrovascular disease
Other
Gastrointestinal (gastroparesis, diarrhea)
Genitourinary (uropathy/sexual dysfunction)
Dermatologic
Infectious
Cataracts
Glaucoma
Periodontal disease
Hearing loss

Although the pathophysiology differs between the types of diabetes, it is similar in most of the complications, including microvascular, macrovascular, and neuropathic.

Hyperglycemia appears to be the determinant of microvascular and metabolic complications.

Macrovascular disease, however, is much less related to glycemia but a good glcemic control may produce improvement in the lipid profile.[95]

Insulin resistance with concomitant lipid abnormalities (elevated levels of small dense low-density lipoprotein cholesterol [LDL-C] particles, low levels of high-density lipoprotein cholesterol [HDL-C], elevated levels of triglycerides) and thrombotic abnormalities (ie, elevated type-1 plasminogen activator inhibitor [PAI-1], elevated fibrinogen), as well as conventional atherosclerotic risk factors (eg, family history, smoking, hypertension, obesity, sedentary life style), determine cardiovascular risk.

Unlike liver and smooth muscle, insulin resistance is not associated with increased myocardial lipid accumulation.[35]Persistent lipid abnormalities remain in patients with diabetes despite evidence supporting benefits of lipid-modifying drugs. Statin dose up-titration and the addition of other lipid-modifying agents are needed.[36]

Increased cardiovascular risk appears to begin earlier to the development of frank hyperglycemia, presumably because of the effects of insulin resistance. Stern[37] in 1996 and Haffner and D'Agostino in 1999[38]developed the "ticking clock" hypothesis of complications, suggesting that the clock starts ticking for microvascular risk at the onset of hyperglycemia, while the clock starts ticking for macrovascular risk at some antecedent point, presumably with the onset of insulin resistance.

Mechanisms producing chronic complications

Although chronic hyperglycemia is an important etiologic factor leading to complications of DM mainly the microvascular ones, the mechanisms by which it leads on to these varied involvement of multiple organ system is not fully understood. There are four prominent theories, though not mutually exclusive, have been proposed to explain how hyperglycemia may be leading to the chronic complications of DM.

(1)Formation of advanced glycosylation end products (AGEs)

This occurs due to nonenzymatic glycosylation of intra- and extracellular proteins from the interaction of glucose with amino groups on proteins. AGEs have been shown to cross-link proteins (e.g., collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce

nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as the glomerular filtration rate (GFR) declines.

(2)Sorbitol pathway

Hyperglycemia increases glucose metabolism via the sorbitol pathway by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species, and also leads to other types of cellular dysfunction. However, using aldose reductase inhibitors has not shown significant beneficial effects.

(3)Diacylglycerol pathway

Hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C which alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons. Inhibitors of PKC are being studied in clinical trials.

(4)Hexosamine Pathway

Hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, which may alter function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor or plasminogen activator inhibitor-1 (PAI-1).

Growth factors appear to play an important role in some DM-related complications.

- Vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic proliferative retinopathy.
- TGF-β is increased in diabetic nephropathy and stimulates production of collagen and fibronectin by mesangial cells.
- Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications.

An emerging hypothesis is that hyperglycemia leads to epigenetic changes in the affected cells.

Diabetic Retinopathy

DM is one of the leading cause of blindness in India. In India, the prevalence of Diabetic Retinopathy amongst diabetics is 17–27%. Prevalence of diabetic retinopathy at the time of diagnosis is 7.3%.[95] Individuals with DM are 25 times more likely to become legally blind than individuals without DM. Diabetic retinopathy is classified into two stages:

(1)Nonproliferative diabetic retinopathy

Usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots and progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia.

(2)Proliferative diabetic retinopathy

The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative disease. These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage,

fibrosis, and ultimately retinal detachment. Hence it is important to detect early and treat so as to prevent its progression.

(3).Clinically significant macular edema can occur when only nonproliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years.

Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy; hypertension is also a risk factor.

Diabetic Nephropathy

Diabetic nephropathy is the leading cause of end stage renal disease (ESRD) and a leading cause of DM-related morbidity and mortality. Both microalbuminuria and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy.

The pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to end stage renal disease (ESRD) is not fully understood. It is probably due to

- The effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs).

- Hemodynamic alterations in the renal microcirculation like glomerular hyperfiltration or hyperperfusion and increased glomerular capillary pressure.
- Structural changes in the glomerulus like increased extracellular matrix, basement membrane thickening, mesangial expansion and fibrosis.

Smoking accelerates the decline in renal function.

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM.

Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the GFR which then return to normal during the first 5 years of DM.

After 5–10 years of type 1 DM, nearly 40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30–299 mg/d in a 24-h collection or 30–299 μg/mg creatinine in a spot collection (preferred method). Although the appearance of microalbuminuria in type 1 DM is an important risk factor for progression to macroalbuminuria (>300 mg/d or > 300 μg/mg creatinine) Microalbuminuria is a risk factor for cardiovascular disease. Once macroalbuminuria is present, there is a steady

decline in GFR, and nearly 50% of individuals reach ESRD in 7–10 years. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely to be irreversible.

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects:

(1)Microalbuminuria or macroalbuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period.

(2)Hypertension more commonly accompanies microalbuminuria or macroalbuminuria in type 2 DM.

(3)Microalbuminuria is less predictive of diabetic nephropathy and progression to macroalbuminuria in type 2 DM.

Diabetic Neuropathy

Diabetic neuropathy occurs in 50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. The development of neuropathy correlates with the duration of diabetes and glycemic control. Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy

should be made only after other possible etiologies are excluded. It can be of many types.

(1)Polyneuropathy/Mononeuropathy

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss, hyperesthesia, paresthesia, and dysesthesia . Neuropathic pain develops in some of these individuals typically involves the lower extremities, is usually present at rest, and worsens at night. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Diabetic polyradiculopathies are usually self-limited and resolve over 6–12 months.

Mononeuropathy is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve.

Involvement of the third cranial nerve is most common and is heralded by diplopia. Other cranial nerves IV, VI, or VII are also affected. Mononeuritis multiplex may also occur.

(2)Autonomic Neuropathy

Individuals with long-standing DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension may be responsible for sudden cardiac death. Gastroparesis, bladder-emptying abnormalities, hyperhidrosis of the upper extremities and anhidrosis of the lower extremities and an inability to sense hypoglycemia appropriately - hypoglycemia unawareness may also occur.

Lower Extremity Complications

DM is the leading cause of non traumatic lower extremity amputation. Foot ulcers and infections are also a major source of morbidity in individuals with DM. The reason for the increased incidence of these disorders in DM is due to several pathogenic factors: neuropathy, abnormal foot biomechanics, Peripheral vascular disease, and poor wound healing. The peripheral sensory neuropathy interferes with normal protective mechanisms and allows the

patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulceration. Motor and sensory neuropathy lead to abnormal foot muscle mechanics and to structural changes in the foot (hammertoe, claw toe deformity, prominent metatarsal heads, Charcot joint). Autonomic neuropathy results in anhidrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation. PAD and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Approximately 15% of individuals with type 2 DM develop a foot ulcer and a significant subset will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration).

Risk factors for foot ulcers or amputation include: male sex, diabetes >10 years' duration, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation, and poor glycemic control.

Coronary Artery Disease

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in Coronary artery disease (CAD), Myocardial infarction, Congestive heart failure, Peripheral vascular disease and sudden death in DM. The American Heart Association has designated DM as a "CHD risk equivalent." Type 2 diabetes patients without a prior MI have a similar risk for coronary artery related events as non diabetic individuals who have had a prior MI. CHD is more likely to involve multiple vessels in individuals with DM.

The increase in cardiovascular morbidity and mortality rates appears to be due to the synergism of hyperglycemia with other cardiovascular risk factors. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking.

The presence of complications - microalbuminuria, macroalbuminuria, an elevated serum creatinine, and abnormal platelet function also plays a role in development of macrovascular complications.

Insulin resistance, as reflected by elevated serum insulin levels, is associated with elevated levels of plasminogen activator inhibitors (PAI-1) and

fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis.

Because of the extremely high risk of cardiovascular disease in individuals, any diabetic patient who has symptoms suggestive of cardiac ischemia or peripheral or carotid arterial disease should undergo thorough evaluation. The absence of chest pain ("silent ischemia") is common, and so a thorough cardiac evaluation is mandatory when undergoing major surgical procedures.

In both the DCCT (type1 diabetes) and the UKPDS (type2 diabetes), cardiovascular events were not reduced by intensive treatment during the trial but were reduced at follow-up 10 to 17 years later termed *legacy effect* or *metabolic memory*. During the DCCT, an improvement in the lipid profile of individuals in the intensive group (lower total and LDL cholesterol, lower triglycerides) during intensive diabetes management was noted. Other trials have also failed to show any reduction in cardiovascular morbidity and mortality.

The incidence of cerebrovascular disease is increased three times in individuals with DM than in non diabetics. The mechanisms operating in the development of coronary artery disease also acts here.

FIBRINOGEN AND DIABETES MELLITUS

Introduction

Fibrinogen is one of the most important coagulation factors in the final common pathway of coagulation. When fibrinogen is converted to fibrin, it forms the structural meshwork that consolidates an initial platelet plug into a solid hemostatic clot. The physiologic importance of fibrinogen is demonstrated by the bleeding diathesis associated with afibrinogenemia[61, 62] and some dysfibrinogenemias.[63]Other dysfibrinogenemias are associated with thromboembolic disease .[62, 64]

Fibrinogen is a dimeric glycoprotein synthesized in the liver and has a molecular weight of 340,000. It I made up of 2 subunits. Each subunit contains three disulfide-linked polypeptide chains[69] referred to as the Aα (66.5kD), Bβ (52kD), and γ (46.5kD) chains. Aμ, Bb, and γ are composed of 610, 461, and 411 amino acids, respectively. Fibrinopeptides A and B are released from the amino-termini of the A αand Bβ chains by thrombin cleavage of the Argl6-Glyl7 and Argl4-Glyl5 bonds, respectively to form the fibrin.[70]The genes for the three chains of fibrinogen are found within a 50-kb length of DNA on chromosome 4 at q23-q32.[71]

It is found in plasma and in platelet α-granules. In the platelets it is taken up from plasma by endocytosis mediated by glycoprotein IIb/IIIa. Platelet fibrinogen lacks γ chain. The plasma half-life of fibrinogen is 3 to 5 days.[65]

Fibrinogen plays an important role in the following processes.

1. The soluble fibrinogen molecule is converted into insoluble fibrin during the final common pathway of coagulation which stabilizes the initially formed platelet plug.

2. The polymerized fibrin acts as a template for the activation of the fibrinolytic system, which regulates fibrin deposition and clot dissolution.

3. Fibrinogen binds to cells such as platelets and causes platelet aggregation and to endothelial cells, where it participates in tissue repair.

Hyperfibrinogenemia

Fibrinogen plays a very crucial role in atherosclerosis and thrombosis related phenomenon like hemostasis, inflammation, aggregation of platelets, blood viscosity, smooth muscle proliferation and fibrinolysis. Though it is considered as a marker for the presence of vascular disease, it remains controversial whether fibrinogen is a cause or merely an association with the atherosclerotic process.[72]

Fibrinogen is an acute phase reactant, and its synthesis can be increased up to 20-fold with a strong inflammatory stimulus.[66, 67]IL-6 is an important mediator of increased fibrinogen synthesis during an acute phase response,[68] and IL-6 secretion can be up-regulated by fibrin degradation products. Thus, elevated fibrinogen levels may be a reflection of the low-grade inflammation associated with vascular disease. On the contrary, increased fibrinogen levels

(due to inflammation or other causes) may be responsible for the pathogenesis of vascular lesions, acting as a risk factor for the atherosclerotic disease and contribute to its progression. Moreover, fibrinogen and fibrin degradation products may enhance the inflammation in the vascular lesions by regulating cytokine mediated action and leukocyte-endothelial interactions.[73] A low grade inflammation secondary to Chlamydia or H.pylori infection have been suggested to raise fibrinogen levels and thus increase cardiovascular mortality and morbidity.[86]

One of the significant and common conditions associated with both elevated fibrinogen level and cardiovascular disease are type 2 diabetes mellitus and the insulin resistance syndrome.[74, 75]

Why type 2 diabetes mellitus produces elevated fibrinogen? The mechanisms leading to hyperfibrinogenemia in type 2 diabetes mellitus have not been elucidated so far. The potential mechanisms suggested include that of a low-grade inflammation, hyperinsulinemia and albuminuria.[76-78]

Zanetti et al and Schrem et al have suggested that the following mechanism - In diabetes patients develop albuminuria which leads to hypoalbuminemia leading to decrease in plasma oncotic pressure which in turn stimulates hepatic protein synthesis, though synthesis of all the plasma protein, the synthesis of fibrinogen is increased to a greater extent associated with a decreased clearance and this increased levels of fibrinogen is responsible for cardiovascular adverse effects.[77, 82]

Others have reported that fibrinopeptide is positively related to glucose and this is probably how hyperglycemia leads to elevated fibrinogen levels.[83-84] There is also controversy whether elevated fibrinogen levels are a consequence of Diabetic nephropathy and subsequent loss of albumin or nephropathy is worsened by elevated fibrinogen.[85]

Researchers have proposed the existence of "insulin resistance genes" which may be responsible for insulin resistance as well as hyperfibrinogenemia.[79]The putative genes include Lipoprotein lipase gene and the β fibrinogen gene.[80-81].

Multiple factors affect fibrinogen levels. It increases with age, body mass index, smoking, and post menopause, low-density-lipoprotein (LDL) cholesterol, lipoprotein (a) and leukocyte count. It decreases with physical activity[87], moderate alcohol intake[88], increased high-density-lipoprotein (HDL) cholesterol, and with hormone replacement therapy (HRT).[89-90]Higher levels of plasma fibrinogen were seen in non-drinkers or who drank > 60 g of alcohol per day.[88]

Interventions to lower fibrinogen levels

Lifestyle modifications can alter fibrinogen level, of which smoking cessation is by far the most effective; weight or stress reduction or an increase in regular physical activity has less effects; dietary modifications seems to have even less effect, moderate alcohol consumption causes a small reduction.[93]

Among the oral fibrinogen reducing medications, Fibrates (e.g. Bezafibrate reduces increased fibrinogen by around 40%), and Ticlopidine (reduces about 15%) are effective only if fibrinogen was elevated. The efficacy of these drugs when the fibrinogen levels are normal has not been fully evaluated. Finally, intravenous fibrinolytic agents or heparin-induced extracorporeal low-density lipoprotein precipitation will lower fibrinogen dramatically; yet these methods are not indicated for this purpose alone and needs further studies .[93] Aspirin therapy in low doses has no significant influence on plasma fibrinogen levels[91]

Eriksson at al in a study involving 292 women the levels of fibrinogen levels were elevated in post menopausal women than pre menopausal women and in women not taking Hormone replacement therapy than in women taking Hormone Replacement therapy.[43]Thus Hormone replacement therapy (HRT) has a beneficial effect in lowering fibrinogen.

Different antihypertensive drugs elicit different effects on fibrinogen and lipid profile, which variously influence the overall risk profile of these patients. Patients who were on 'lipid-neutral (ACE-I, Ca-blocker, Angiotensin-II blocker) or lipid friendly (alpha-blocker) anti-hypertensive drugs had significantly lower plasma fibrinogen levels, when compared with those who were on 'lipid-hostile' drugs (Beta-blocker, Thiazide diuretic).[98]

A recent study has shown that elevated plasma fibrinogen (≥375 mg/dl) in the presence of diabetes mellitus and increased BMI (≥25 kg/m^2) are associated

with lower platelet inhibition with Clopidogrel in patients with cardiovascular diseases.[94]

In a study by Zhao et al involving 1300 Chinese diabetic subjects it was found that APTT values decreased and fibrinogen levels increased with increasing HbA1c values and they recommended APTT and fibrinogen tests may potentially be used as screening tests for thrombotic complication risk in Type 2 DM patients.[97]

To conclude physiological importance of elevated plasma fibrinogen levels is not fully understood. There are various mechanisms through which fibrinogen may be involved in atherothrombosis. It may be due to rheological alterations, increased platelet aggregability, increased fibrin formation, and stimulation of vascular cell proliferation and migration but the association between fibrinogen and cardiovascular risk does not establish a cause-effect relation .Elevated fibrinogen levels, whatever the cause may be like genetic, inflammation , or some other reason may cause a hypercoagulable state that could produce various adverse effects.[92]These adverse effects are more pronounced in diabetes mellitus.

METHODOLOGY

Source of Data

The study was conducted on patients with of Type 2 diabetes mellitus with or without complications admitted in Medical wards / attending outpatient department at Rajiv Gandhi Government General Hospital, Chennai.

Study design : Cross sectional study

Ethical committee clearance : Obtained

Competing interest : Nil

Financial support : Nil

Method of Collection of Data

After obtaining consent the diabetic patients were subjected to detailed history, clinical examination and investigations as per the proforma.

The following criteria were applied for selection of patients in the study group.

Inclusion criteria

1. Patients with Type2 diabetes mellitus (newly diagnosed or known cases) with or without microvascular or macrovascular complications

Exclusion criteria

1. Patients with Coagulation abnormalities/ anticoagulant therapy.

2. Smokers

3. Alcoholic.

4. Obese individuals with BMI > 30.

5. Presence of features of active infection/inflammation like fever, diabetic foot ulcer, urinary tract infection.

Lab investigations

1. Fasting and post prandial blood sugar.
2. Fasting Lipid Profile.
3. Early morning Spot urine Albumin by immune turbidimetry.
4. HbA1c using H.P.L.C method.
5. Plasma fibrinogen using automated optical light scattering method.
6. Blood Urea and serum creatinine.
7. Complete Blood Counts (Total count, Differential count, Hemoglobin, Erythrocyte sedimentation rate, hematocrit, and platelet count).
8. Electrocardigram.
9. Echocardiography (wherever necessary).
10. Chest X ray.

Criteria/Case definition for classifying the patients

(1) **Diagnosis of Diabetes**

(a) Fasting Plasma Glucose > 126mg/dl and 2 Hours post prandial plasma glucose > 200mg/dl.

(b) Known cases of type 2 Diabetes Mellitus taking/not taking medications.

(2**) Hypertension**

(a) Blood Pressure > 140/90 mm of Hg recorded in sitting posture on each of 2 or more visits.

(b) Known hypertensive patients taking/not taking medications.

(3) **Obesity**

Body Mass Index (BMI) = Weight in Kgs / Height in (Meter)^2

(a) Over weight -25 – 30

(b) Obese > 30

(4) **Criteria for Microvascular complications**

Diabetic Retinopathy

Fundus examination by o

pthalmoscope after dilatation of pupils.

(a) Non proliferating Diabetic Retinopathy:

Microaneurysm, Haemorrhage, hard exudates

(b) Proliferative Retinopathy

- New vessels on disc (NVD)
- New vessels elsewhere (NVE)

(c) Clinically significant macular edema (CSME)

- Thickening of retina located 500µU/m from the center of macula.
- Hard exudates with thickening of adjacent retina located 500µU/m from the center of macula.
- Zone of retinal thickening of one disk area or larger in size, located one disc diameter from the center of macula.

Diabetic Nephropathy

(a) Macroproteinuria: Protein excretion of > 500 mg/day. Microlbuminuria was tested by early morning spot albumin concentration and values greater than 2mg/dl were taken as significant in patients who did not have macroproteinuria.[99]

(b) Serum Creatinine &Calculation of GFR done based on Cockcroft Gault formula

Estimated creatinine clearance (ml/min) =

$$\frac{(140 - \text{Age}) \times \text{body weight (kg)}}{72 \times \text{Plasma Creatinine (mg/dL)}}$$

(c) Ultrasonographic evidence of reduced kidney size.

Diabetic Neuropathy

History and Clinical examination was done for peripheral neuropathy, polyradiculopathy.

Criteria for Macrovascular complications

Cardiovascular disease

(a) History of Chest pain, breathlessness on exertion, prior myocardial infarction, congestive cardiac failure.

(b)ECG features

- Left ventricular hypertrophy.
- Ischaemic heart disease – ST – T changes
- Features of old myocardial infarction.

(c) Echocardiography (in selected situations only)

- Regional wall motion abnormalities (RWMA)
- Decreased Ejection Fraction

Peripheral Vascular Disease

Clinical examination of peripheral palpable arteries was done. Doppler study was done in relevant cases.

Stroke

History, clinical examination and imaging studies (CT/MRI) for stroke was done.

A total of 120 type 2 Diabetes mellitus patients were studied. Patients were divided into 3 groups:-

Group 1: Patients had Diabetes mellitus alone without any microvascular or macrovascular complications.

Group 2: Patients had Diabetes mellitus with predominant macrovascular complications (CVA / CAD).

Group 3 Patients had predominant microvascular complications (Retinopathy, Nephropathy, Neuropathy).

OBSERVATIONS AND RESULTS

Plasma fibrinogen levels were compared among the 3 groups. Other variables like age, sex, HbA1c, body weight, body mass index, total cholesterol and HDL were included.

Statistical analysis

Appropriate statistical analyses were made using Graphpad Instat3 software. The statistical significance of difference between the mean values of the groups were evaluated by Student's Unpaired 't' Test and Tukey-Kramer Multiple Comparisons Test .

The differences in the mean values of the two groups were regarded as statistically significant if the p value was less than 0.05 and highly significant if p value was less than 0.01.

The Baseline Characteristics of the study group is shown in table 1.

	Group1	**Group2**	**Group3**	**Total**
Number of patients	40	40	40	120
Males	26	27	26	79
Females	14	13	14	41
Mean age (years)	52.5 ± 5.5	61 ± 7.6	59.5 ± 5.2	57.6 ± 7.2
Mean body weight (Kg)	65.1 ± 6.1	66.2 ± 4.9	65.0 ± 4.8	65.4 ± 5.3
Mean Body Mass Index (Kg/m^2)	24 ± 2.7	25.1 ± 2.2	24.5 ± 2.5	24.4 ± 2.6
Hypertension – Yes	16	25	10	51
No	24	15	30	69

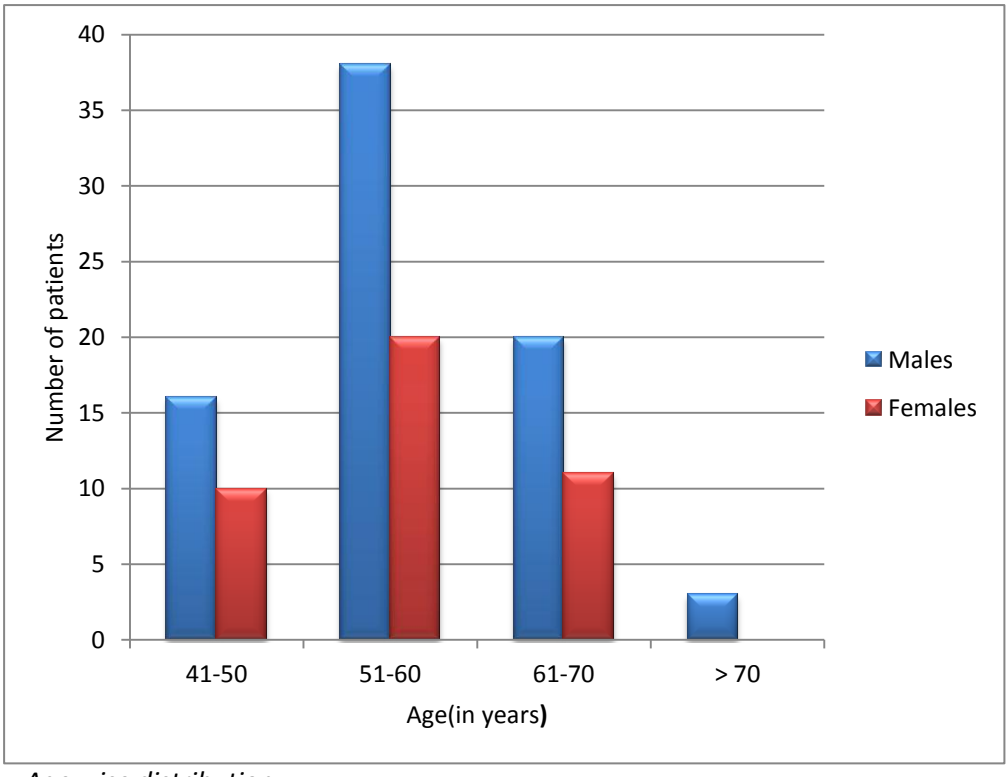
Table 1

Age wise distribution of the study population

The age wise distribution is shown in table 2.

Age(in years)	**Males**	**Females**	**Total**
41 – 50	16	10	26
51 – 60	38	20	58
61 – 70	20	11	31
>70	3	0	3

Table 2



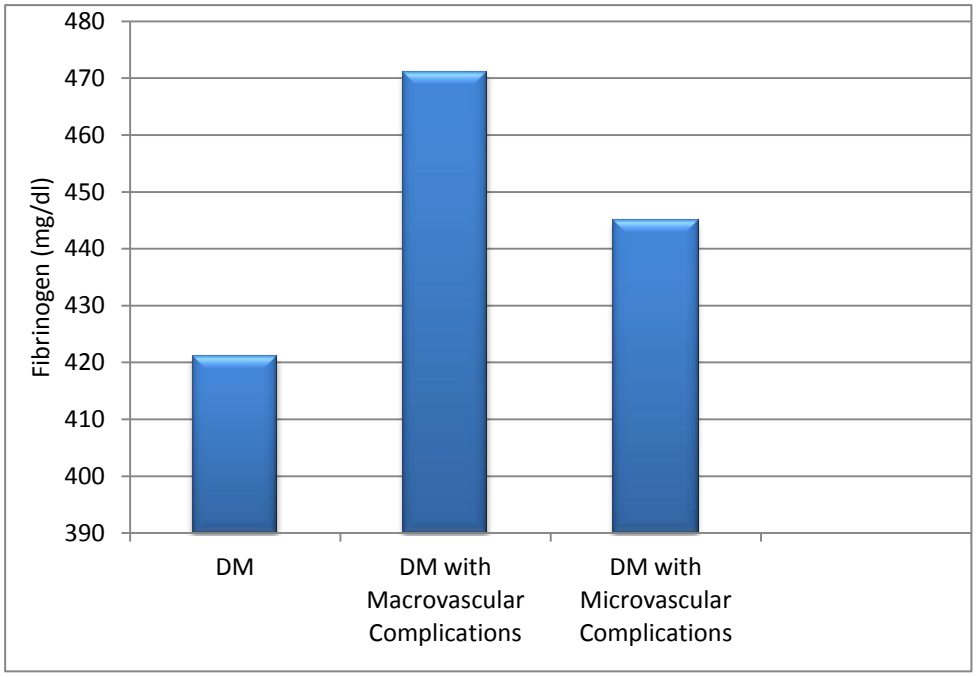
Age wise distribution

Plasma fibrinogen levels in Diabetes Mellitus

The mean fibrinogen levels in the 3 groups are given in table 3.The mean fibrinogen in patients with DM with macrovascular complication (group3) were elevated compared to the other groups.

	DM alone (Group 1)	**DM with macrovascular complication (Group2)**	**DM with microvascular complication (Group 3)**
Mean fibrinogen (mg/dl)	421.2125	471.3775	471.3775
Standard deviation (SD)	32.831	17.036	15.610
Std. error of mean(SEM)	5.191	2.694	2.468
Lower 95% conf. limit	410.71	465.93	434.55
Upper 95% conf. limit	431.71	476.83	444.54
Median(50th percentile)	423.75	469.05	442.35

Table 3



Mean plasma fibrinogen levels

In order to ascertain whether differences between the fibrinogen levels among 3 groups were statistically significant, p value was calculated using Tukey-Kramer Multiple Comparisons Test. The results are summarized in table 4.

Comparison Of Fibrinogen Levels	**'p' Value**
DM alone & DM with macrovascular complications	p<0.001 (very significant)
DM alone& DM with microvascular complications	p<0.01 (significant)
DM with macrovascular and microvascular complications	p<0.001(very significant)

Table 4

The p value is less than 0.01 in all the 3 comparisons indicating that differences in the mean fibrinogen levels are significant. Thus fibrinogen levels are potential markers of CAD/stroke as well as microvascular complications like retinopathy, nephropathy etc.

Age & Fibrinogen - Correlation and Regression Analysis:

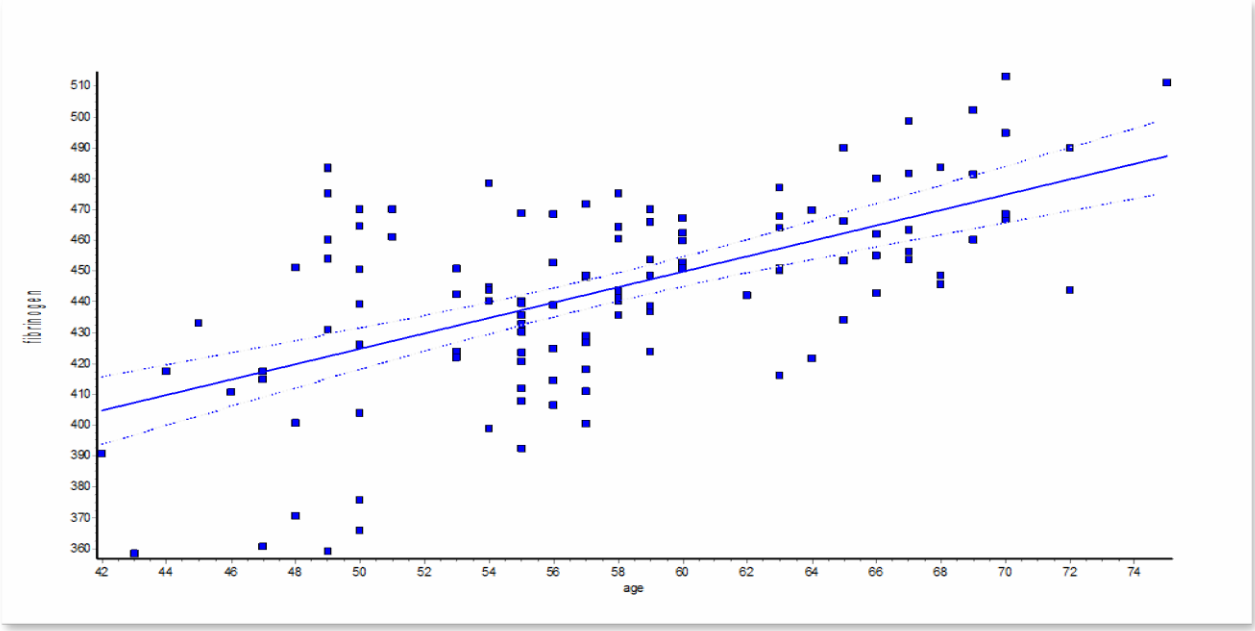
In order to assess whether fibrinogen levels vary with age correlation analysis were carried out with Pearson formula. The results are as under:

Correlation coefficient (r) = 0.5808

95% confidence interval: 0.4481 to 0.6884

Coefficient of determination (r squared) = 0.3373

The two-tailed p value is < 0.0001.



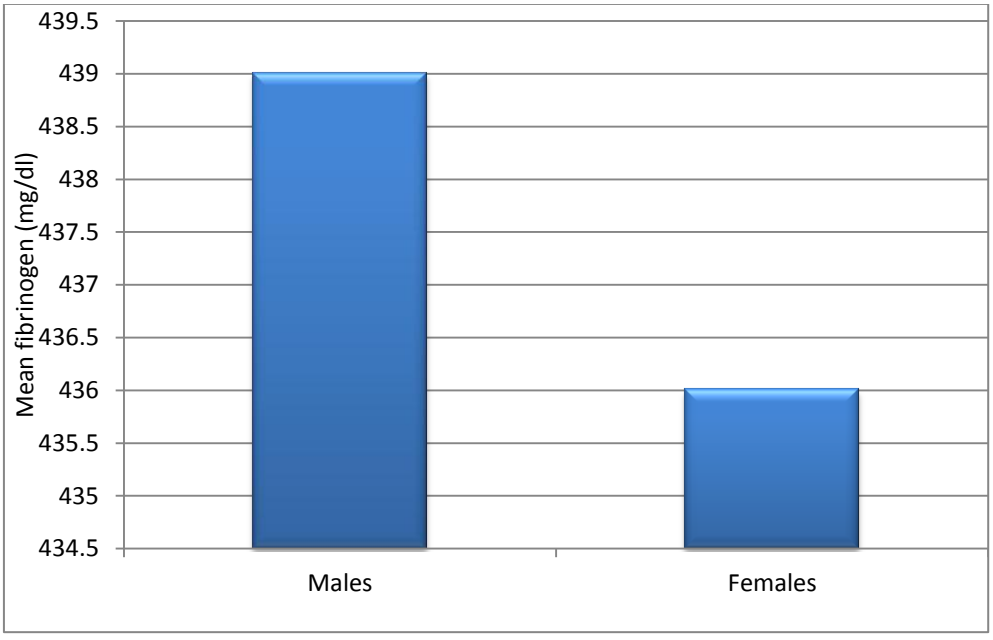
Thus Fibrinogen levels show a positive correlation with age implying that fibrinogen levels increase with age.

Fibrinogen levels in Males versus Females

The mean fibrinogen levels in male and female diabetics are given in table 5.

	Males	Females
Mean fibrinogen (mg/dl)	439.20 ± 27.6	436.47 ± 34.8
Number	78	42
'p' value	0.0799 (not significant)	

Table 5



Mean fibrinogen Levels in males & females

Though the mean fibrinogen is slightly higher in males than females the p value is greater than 0.05 indicating that the differences in male and female mean fibrinogen levels is not significant.

Body Weight & Fibrinogen – Correlation and Regression Analysis

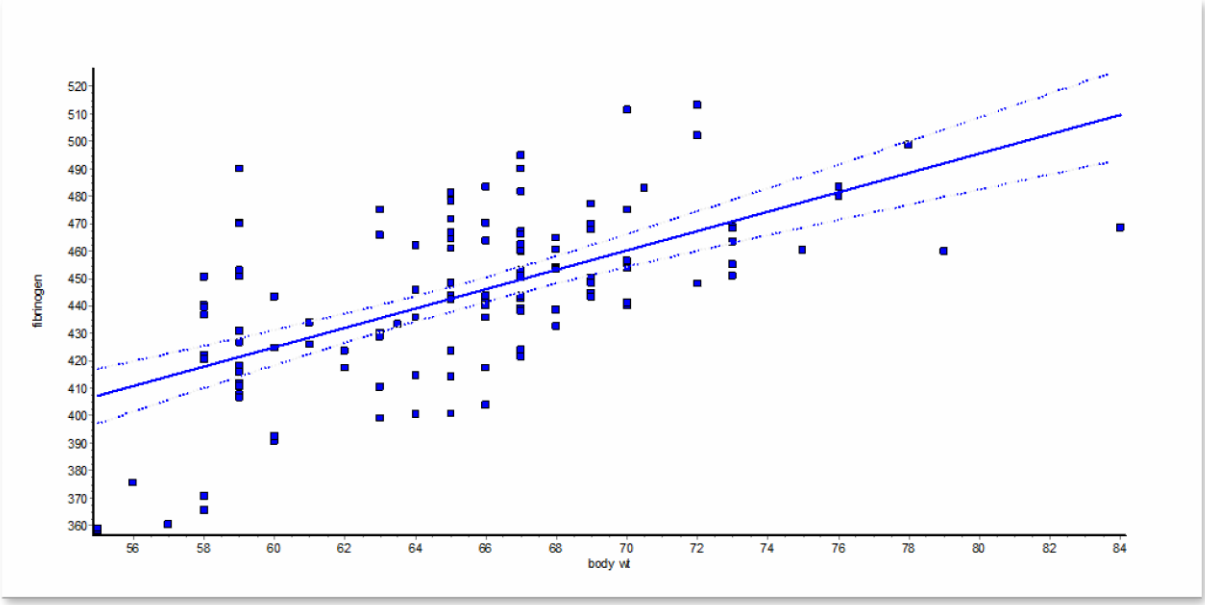
In order to assess whether fibrinogen levels vary with body weight correlation analysis was carried out using Pearson formula. The results are as under:

Correlation coefficient (r) = 0.6050

95% confidence interval: 0.4775 to 0.7075

Coefficient of determination (r squared) = 0.3660

The two-tailed P value is < 0.0001, considered extremely significant.



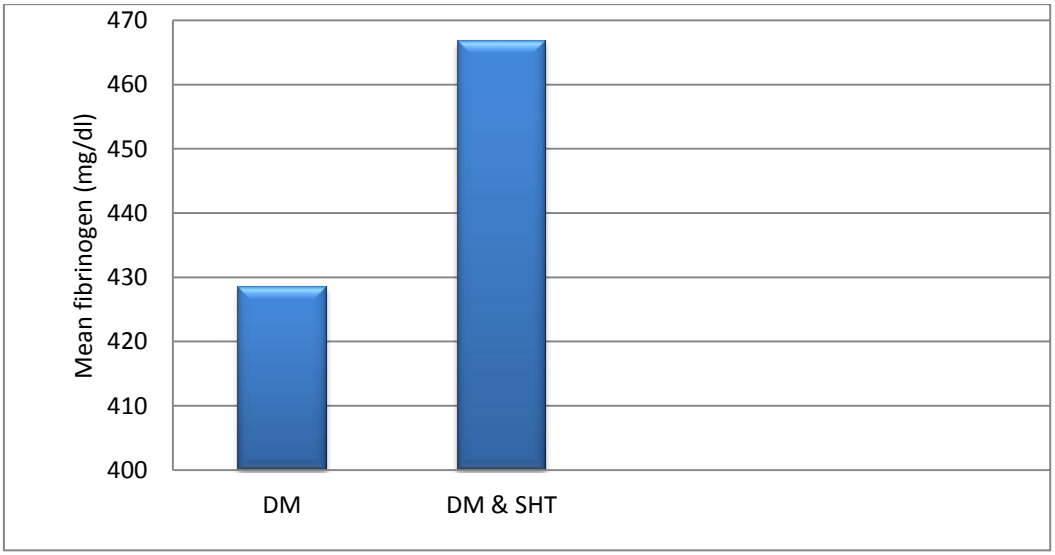
Fibrinogen levels show a positive correlation with body weight implying that its level increases with increasing body weight.

Fibrinogen Levels In Diabetes compared to Diabetes & Hypertension

The mean fibrinogen levels in patients with diabetes alone and diabetes with hypertension are summarized in table 6.

	DM & SHT	DM
Fibrinogen (mg/dl)	466.7 ± 20.3	428.5 ± 26.9
Number of patients	49	71
' p ' value	0.0400 (significant)	

Table 6



Fibrinogen levels in DM alone and DM with SHT

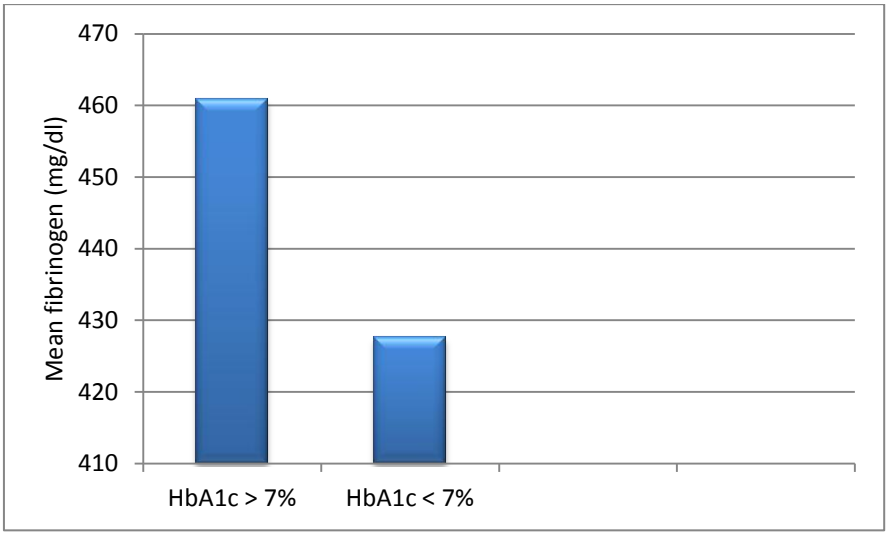
The p value is less than 0.05 indicating that hypertension is also a factor that causes elevation of fibrinogen levels.

Fibrinogen and HbA1c

In order to find out whether glycemic control affected fibrinogen levels ,the mean fibrinogen levels in patients with HbA1c > 7% was compared with HbA1c < 7% the results are shown in table 7.

	HbA1c > 7	**HbA1c < 7**
Fibrinogen (mg/dl)	460.82	427.56
Number of patients	61	58
'p' value	0.0118 (significant)	

Table 7



Fibrinogen Levels and HbA1c

The difference is statistically significant implying that fibrinogen levels increases with poor glycemic control.

Fibrinogen and HbA1c- Correlation and Regression Analysis

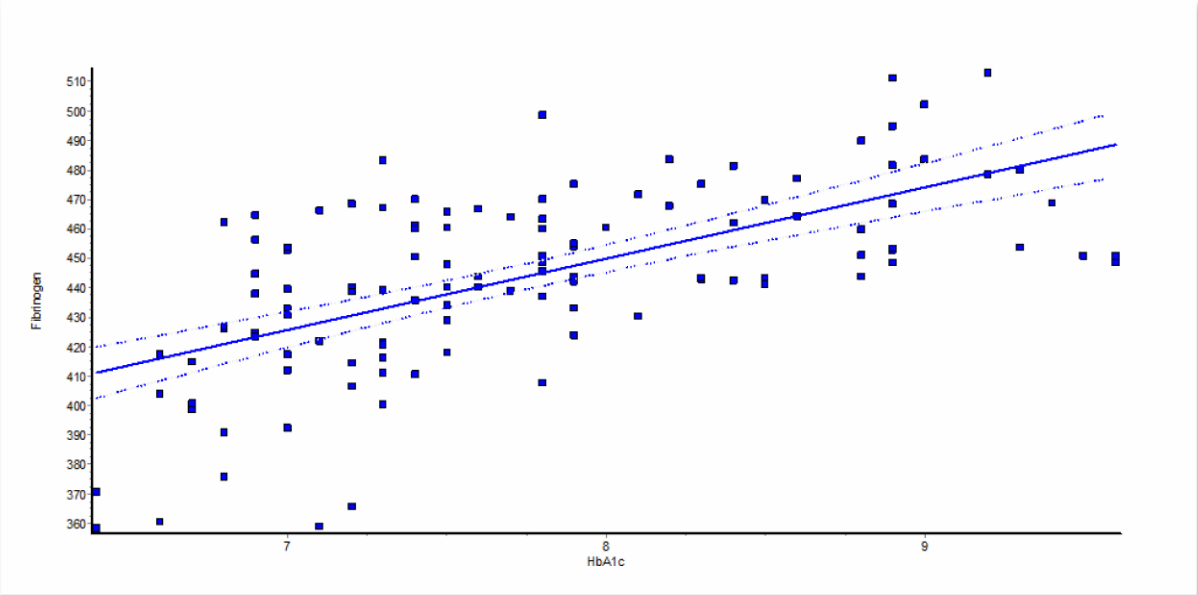
In order to assess whether Fibrinogen levels varies with HbA1c levels correlation analysis was carried using Pearson formula. The results are as under:

Correlation coefficient (r) = 0.6246

95% confidence interval: 0.5014 to 0.7229

Coefficient of determination (r squared) = 0.3901

The two-tailed P value is < 0.01 considered very significant.



The fibrinogen levels show a positive correlation with HbA1c implying Fibrinogen levels increase with Increasing HbA1c levels.

Body Mass Index and Fibrinogen - Correlation and Regression Analysis

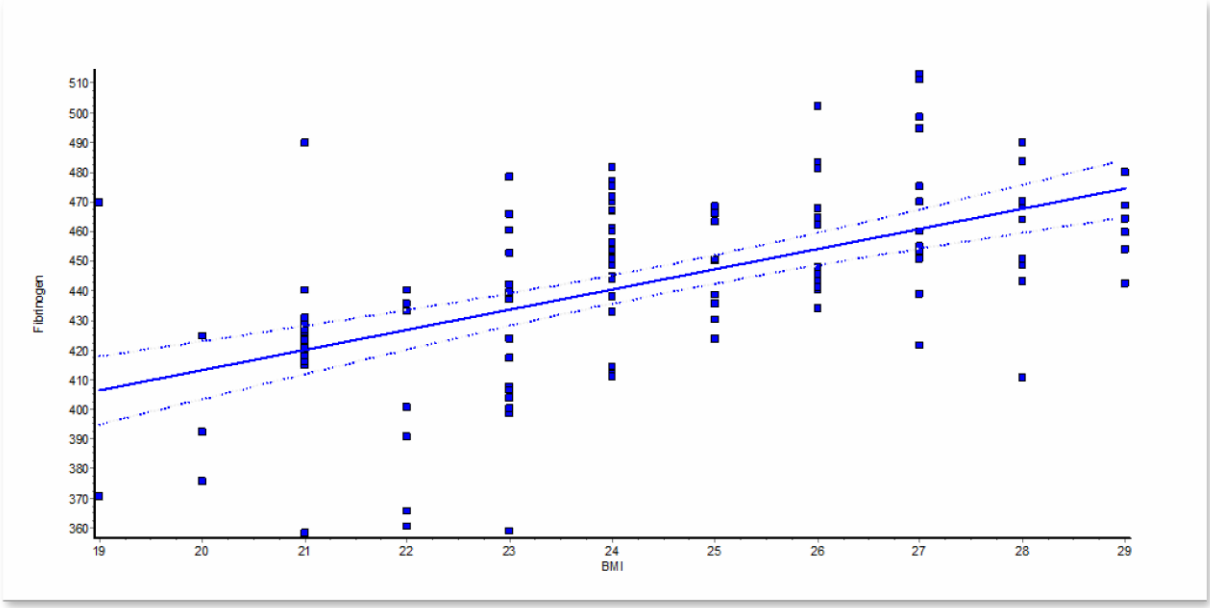
The Pearson Correlation formula was used.

Correlation coefficient (r) = 0.5484

95% confidence interval: 0.4094 to 0.6626

Coefficient of determination (r squared) = 0.3008

The two-tailed P value is < 0.0001, considered extremely significant.



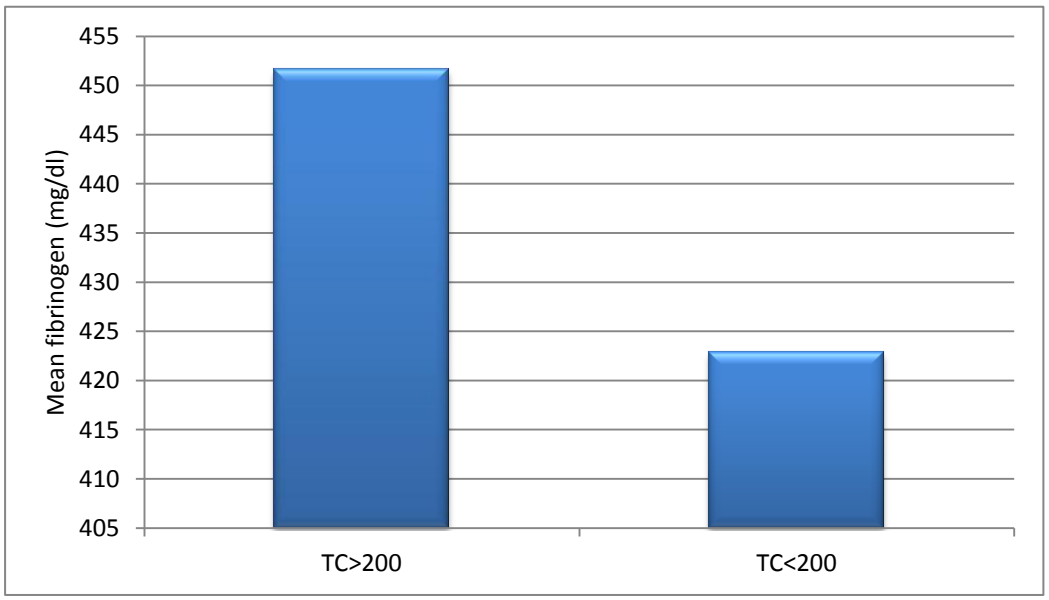
Fibrinogen levels showed a significant positive correlation with Body mass index.

Fibrinogen and Total Cholesterol (TC)

The fibrinogen levels in patients having total cholesterol >200 mg/dl was compared with patients having total cholesterol < 200mg/dl. The results are shown in table 8.

	TC > 200	**TC < 200**
Mean Fibrinogen (mg/dl)	451.67 ± 21.5	422.89 ± 31.8
Number of patients	73	47
'p' value	0.0028 (very significant)	

Table 8



Fibrinogen levels in patients with total cholesterol greater/less than200 mg/dl

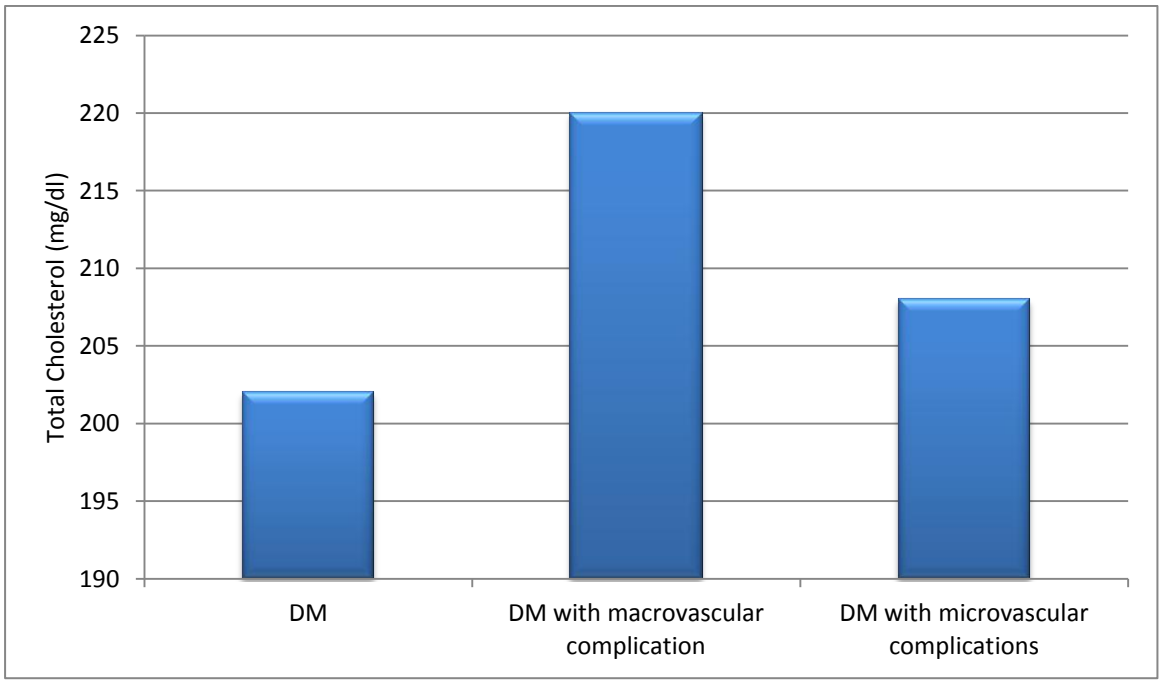
Fibrinogen levels are significantly higher in patients having total cholesterol greater 200 mg/dl.

Total Cholesterol in Diabetes alone versus Diabetes with Complications

Total cholesterol in the 3 groups of diabetic patients (DM alone, DM with macrovascular complications, DM with microvascular complication) were compared. The results are shown in table 9.

	DM	**DM with macrovascular complications**	**DM with microvascular complications**
Mean Cholesterol	202.43 ± 22.597	219.98 ± 18.564	207.68 ± 17.813

Table 9



Mean cholesterol levels

The p values were calculated using Tukey-Kramer Multiple Comparisons Test.

The results are shown in table 10.

Comparison	p value
DM & DM with macrovascular complications	P < 0.01
DM & DM with microvascular complications	P >0.05
Microvascular & Macrovascular complication	P < 0.01

Table 10

Total cholesterol is significantly elevated in Diabetic patients with macrovascular complications (CAD/CVA) compared to other diabetic patients.

HDL Cholesterol In Diabetes Alone Versus Diabetes With Complications

HDL cholesterol in the 3 groups of diabetic patients (DM alone, DM with macrovascular complications, DM with microvascular complications) were compared. The results are shown in table 11.

	DM	**DM with macrovascular complications**	**DM with microvascular complications**
HDL Cholesterol	48.525 ± 3.823	46.850 ± 3.085	48.650 ± 2.806

Table 11

The p values were calculated using Tukey-Kramer Multiple Comparisons Test. The results are shown in table 12.

Comparison	**p value**
DM & DM with macrovascular complications	p > 0.05
DM & DM with microvascular complications	p >0.05
Macrovascular & microvascular complication	P > 0.05

Table 12

There are no significant differences in the HDL levels among the three groups.

DISCUSSION

The study was a cross sectional study in 120 diabetic patients belonging to lower socio-economic group attending Rajiv Gandhi Government General Hospital. They were divided into 3 groups of 40 each. Group 1 patients had DM without microvascular complications. Group 2 had DM patients with macrovascular complications (CAD/CVA). Group 3 had patients with microvascular complications. There were 79 males and 41 females. The mean age of the study group was 57.6 ± 7.2 years. 42 % of the patients were hypertensives.

The results from this study showed fibrinogen to be significantly higher in diabetic patients who had macrovascular complications like coronary artery disease, and cerebrovascular disease than those who had only diabetes or diabetes with microvascular complications like nephropathy, neuropathy retinopathy etc.

The study also showed fibrinogen to be higher in patients with diabetes with microvascular complications than those who had diabetes only. Fibrinogen levels were also higher in Diabetes than reference values of fibrinogen (200 to 400 mg/dl[39]) in the general population.

"Fibrinogen studies collaboration" - a large meta analysis of large and comprehensive data comprising 6944 first nonfatal myocardial infarction or stroke events and 13210 deaths and various other studies have found that

increased fibrinogen levels are associated with major systemic morbidity like coronary artery disease, stroke etc.[56]

In a study by Bruno et al involving 1574 diabetics in north Italy, fibrinogen was found to be significantly elevated in diabetes mellitus patients compared to non diabetics.[41] Similarly, Jensen et al. reported a progressive increase in fibrinogen level in diabetics with complications.[42] In a study by Eriksson et al in Stockholm area to assess the relationship between plasma fibrinogen and coronary heart disease in women, found the mean value for plasma fibrinogen to be significantly higher in patients with coronary artery disease than in controls and it tended to be higher in diabetics than in nondiabetics.[43] Sanchez et al conducted a study to assess the prognostic relations between inflammatory markers and mortality in diabetic patients with non ST elevation acute coronary syndrome found fibrinogen and WBC count to be higher in diabetic than in non-diabetic patients on admission and among diabetic patient fibrinogen was higher in those who died during the follow up.[44] Similar studies by James et al[45], Kafle et al[46], Taj Muhammad Khan et al[49] showed fibrinogen to be elevated in diabetics with CAD compared to non diabetics with CAD and non diabetics.

Maresca et al observed elevated fibrinogen as a strong cardiovascular risk factor in diabetes mellitus and suggested that it accounts for a part of the excessive cardiovascular risk in type 2 diabetic patients that remains unexplained after considering the traditional risk factors.[40]

In our study we found that diabetic patients with microvascular complications had significant elevation of fibrinogen compared to diabetic patients without complications. In a study by Bruno et al involving 1574 type 2 diabetics in north Italy, fibrinogen was found to correlate well with albumin excretion rate.[41] Mattock et al and Neil et al in their studies showed increased cardiovascular-related morbidity and mortality in diabetic patients with microalbuminuria and macroalbuminuria.[50-51] This positive association seen between albumin excretion rate and fibrinogen could explain this increased cardiovascular risk.

In a study by Klein et al involving 909 patients with type 1 diabetes enrolled in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) it was found that fibrinogen correlated with albumin excretion rate and its levels were increased in patients with peripheral vascular disease and retinopathy but did not correlate with severity of retinopathy.[52] Asakawa et al and Fujisawa et al have shown that increased fibrinogen is associated with worsening renal function and also retinopathy.[53-54]Recent studies have shown that certain polymorphisms in fibrinogen gene is associated with elevated levels of fibrinogen in type 2 diabetes mellitus.

Similar findings have been shown in India by Neetha Kuzhuppilly et al in a study at Kasturba Medical College, Manipal, Karnataka.[55]

In our study we found that plasma fibrinogen correlated well with HbA1c levels with a correlation coefficient of 0.58. Fibrinogen levels also correlated with body mass index, body weight and age. This has been shown in studies by Bruno et al[41], Klein et al[52], Kafle et al.[46]

In our study we found that fibrinogen levels were slightly higher in males than females though the difference was not significant. This is in contrast to other studies by Klein et al[52], Jain et al[58] where the levels were slightly higher in females but the difference was also not significant as in our study.

Out of the 120 patients 49 patients had hypertension. The mean fibrinogen in patients with both diabetes and hypertension were significantly higher than diabetes alone. This has been seen various studies[58-60]This implies that hypertension itself is a risk factor for elevated fibrinogen levels and probably has a synergestic effect with diabetes mellitus in the development of complications.

The fibrinogen levels were elevated in presence of hypercholesterolemia. In our study it was found that mean fibrinogen levels were elevated in patients having total cholesterol > 200mg/dl. Similar observations were seen in studies by Klein et al and Jain et al.[52, 58]

In our study there was no significant relationship between HDL cholesterol and fibrinogen levels and development of microvascular complications. This is in contrast to Jain et al, Klein et al and Kafle et al where the levels of HDL were lower in patients with microvascular and macrovascular complications.[42, 52, 58]

CONCLUSION

1. A total of 120 cases of diabetes mellitus were involved in the study who were divided into 3 groups of 40 each – diabetes alone, diabetes with microvascular complications, and diabetes with macrovascular complications.
2. The mean fibrinogen levels in patients with macrovascular complications were significantly higher than with microvascular complications and diabetes alone indicating that elevated fibrinogen levels is risk factor for development of macrovascular complications and thus a marker of morbidity and mortality.
3. The mean fibrinogen levels in patients with microvascular complications were significantly higher than diabetes alone and thus it is a marker for development of retinopathy, nephropathy etc.
4. Of the 120 patients, there were 78 males and 48 females. The mean fibrinogen levels were slightly higher in males than in females but the difference was statically insignificant.
5. The age group ranged from 42 to 73 years. The plasma fibrinogen levels correlated well with age, body weight and body mass index indicating higher levels with older age and obesity.
6. The plasma fibrinogen levels correlated well with HbA1c levels indicating poor glycemic control is risk factor for developing elevated levels of fibrinogen.

7. The mean plasma fibrinogen levels were significantly higher in diabetic patient associated with hypertension than with diabetes alone.
8. Fibrinogen levels were significantly higher in patients with total cholesterol > 200 than with total cholesterol < 200.
9. There were no significant differences in mean HDL cholesterol level among the patients with diabetes alone, diabetes with microvascular complication.
10. The results of study indicate that plasma fibrinogen levels is an important risk factor for developing macrovasular complications mainly coronary artery disease and cerebrovascular accidents as well as microvascular complications like retinopathy, nephropathy . Fibrinogen levels also increases with age, body weight, hypertension, poor glycemic control and dyslipidemia.
11. From our study we can recommend estimation of fibrinogen in a subset of patients who have poor glycemic control, hypertension, obesity and if fibrinogen levels are found high strict control measures should be initiated.

FUTURE TRENDS

1. Further studies on the existing modalities which lower fibrinogen and finding newer treatment measures that can lower the fibrinogen levels without adverse effects, should be done.

2. Fibrinogen levels before initiating treatment and during on-going treatment could be a potential indicator for overall efficacy of therapy and life style modifications and the risk reduction.

3. Fibrinogen levels could be a potential marker for the prediction and prevention of macrovascular or microvascular complications.

4. Recent studies have shown that certain polymorphisms of fibrinogen genes are associated with elevated fibrinogen levels. The occurrence of these polymorphisms needs to be studied in Indian population.

LIMITATION OF STUDY

1. The results were predominantly obtained from a cross-sectional survey of small number of patients. Patients recruited here may not be representative of the entire population.
2. The duration of diabetes was not considered.
3. The sample did not include patients with type 1 diabetes mellitus.
4. Retinopathy could not be assessed in significant number of patients since they had cataract. The severity of retinopathy was not used for analysis.
5. The proteinuria was not quantified. The presence of microalbuminuria or macroalbuminuria was taken as the evidence of nephropathy.
6. The effect of treatment modality (insulin, oral hypoglycemic agents or both) could not be compared with fibrinogen levels as most patients were taking drugs irregularly without regular follow up.

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PROFORMA

FIBRINOGEN LEVELS IN DIABETES MELLITUS

Name: Age: Sex:

Address:

Mobile number:

Unit/Ward:

PRESENT HISTORY

DURATION OF DIABETES :

Symptoms

Polyuria	Oliguria	Visual disturbances
Polydipsia	Facial puffiness	Weight loss/gain
Polyphagia	Swelling of legs	High coloured Urine
Giddiness	Anorexia	Headache/loc/fits
Chest pain	Vomiting/hiccups	Sensory disturbances
Palpitations	Easy fatiguablity	Leg ulcers
Breathlessness	Altered bowel habits	Limb weakness
Fever	Dysuria	Abdominal pain

PAST HISTORY

SHT CAD KIDNEY DISEASE

CVA SEIZURE DISORDER PT

HYPOGLYCEMIC EPISODES

OTHERS

TREATMENT HISTORY:

COMPLIANCE : GOOD / POOR

PERSONAL HISTORY:

ALCOHOL:

DIET :

LIFE STYLE : ACTIVE / SEDENTRY

CLINICAL EXAMINATION

WEIGHT: HEIGHT: BMI:

VITALS

PULSE

BP

GENERAL EXAMINATION

CVS

RS

ABDOMEN

CNS

FUNDUS:

INVESTIGATIONS:

URINE ANALYSIS

Albumin

Sugar

Deposits

COMPLETE HEMOGRAM

HB (G/DL)

TC (CELLS/CMM)

DC

ESR

PLATELET(LAKHS/CMM)

RENAL FUNCTION TESTS

BLOOD SUGAR (RANDOM)

BLOOD UREA(MG/DL)

S. CREATININE(MG/DL)

FASTING PLASMA GLUCOSE:

POST PRANDIAL PLASMA GLUCOSE:

HBA1C:

ECG IN ALL LEADS:

CHEST X RAY PA VIEW:

ECHOCARDIOGRAPHY:

ULTRASONOGRAPHY:

FIBRINOGEN:

HDL: **TOTAL CHOLESTEROL**:

S.NO	NAME	AGE	SEX	WEIGHT	BMI	SHT	CVA	CAD	RETINOPATHY	NEPHROPATHY	NEUROPATHY	HbA1c	FIBRINOGEN	TOTAL CHOLESTE	HDL
1	Arumugam	49	m	70	26	y	n	n	n	n	n	7.3	483	226	46
2	Manokaran	49	m	76	28	y	n	n	n	n	n	8.2	483.5	243	42
3	Arunagiri	53	m	65	23	n	n	n	n	n	n	6.9	423.7	190	50
4	Jayanthi	50	f	58	22	n	n	n	n	n	n	7.2	365.7	178	47
5	Muruganathan	58	m	68	24	y	n	n	n	n	n	7.5	460.5	200	45
6	Ramasamy	54	m	63	23	n	n	n	n	n	n	6.7	398.9	180	49
7	Sargunam	55	f	59	24	y	n	n	n	n	n	7	411.8	178	53
8	Mayavel	45	m	63	22	n	n	n	n	n	n	7.9	433.1	200	52
9	Narayanan	57	m	72	26	y	n	n	n	n	n	7.5	448	203	45
10	Saraswathy	49	f	55	23	n	n	n	n	n	n	7.1	359.1	169	47
11	Ramakrishnan	47	m	64	21	n	n	n	n	n	n	6.7	414.7	183	49
12	Mukundan	55	m	68	24	y	n	n	n	n	n	7	432.7	200	48
13	Sundari	57	f	64	23	n	n	n	n	n	n	7.3	400.3	188	52
14	Shanmugam	47	m	66	23	n	n	n	n	n	n	7	417.5	196	45
15	Srinivasan	54	m	70	26	y	n	n	n	n	n	7.5	440	233	56
16	Ansar Basha	50	m	67	23	y	n	n	n	n	n	7.3	439.1	240	55
17	Madhavan	56	m	65	24	n	n	n	n	n	n	7.2	414.4	189	56
18	Bakkiyam	50	f	56	20	n	n	n	n	n	n	6.8	375.5	190	45
19	Aravindan	44	m	62	23	n	n	n	n	n	n	6.6	417.3	188	51
20	Rahima Begum	56	f	68	27	y	n	n	n	n	n	7.7	438.9	212	45
21	Chakravarthy	56	m	84	28	y	n	n	n	n	n	8.9	468.5	256	49
22	Kuppusamy	59	m	67	25	n	n	n	n	n	n	7.9	423.8	208	46
23	Lakshmanan	48	m	65	22	n	n	n	n	n	n	6.7	400.7	176	53
24	Rosy	64	f	67	27	n	n	n	n	n	n	7.3	421.4	211	55
25	Munusamy	57	m	63	21	n	n	n	n	n	n	7.5	428.9	209	43
26	Arokiadas	48	m	58	19	n	n	n	n	n	n	6.4	370.6	176	45
27	Ravikumar	50	m	61	21	n	n	n	n	n	n	6.8	426	202	47
28	Laxmiammal	58	f	60	28	y	n	n	n	n	n	8.5	443.1	232	48
29	Janaki	43	f	55	21	n	n	n	n	n	n	6.4	358.3	178	53
30	Krishnan	42	m	60	22	n	n	n	n	n	n	6.8	390.7	198	56
31	Nirmala	60	f	67	27	y	n	n	n	n	n	8.9	452.8	223	48
32	Manimaran	54	m	69	24	y	n	n	n	n	n	6.9	444.6	211	47
33	Rajendran	55	m	60	20	n	n	n	n	n	n	7	392.4	177	44
34	Kotti	63	m	69	25	y	n	n	n	n	n	7.8	450.2	234	46
35	Noshin	47	f	57	22	n	n	n	n	n	n	6.6	360.4	166	49
36	Kanchana	46	f	63	28	n	n	n	n	n	n	7.4	410.5	198	51
37	Arumugam	50	m	66	23	n	n	n	n	n	n	6.6	404	188	53
38	Sarasu	55	f	63	25	n	n	n	n	n	n	8.1	430.1	222	53
39	Loganayaki	49	f	68	29	y	n	n	n	n	n	7.9	454	235	49
40	Srinivasalu	60	m	79	29	y	n	n	n	n	n	8.8	459.8	211	48

S.NO	NAME	AGE	SEX	WEIGHT	BMI	SHT	CVA	CAD	RETINOPATHY	NEPHROPATHY	NEUROPATHY	HbA1c	FIBRINOGEN	TOTAL CHOLESTE	HDL
1	Mookaiah	67	m	67	24	y	y	n	n	n	n	8.9	481.6	223	45
2	Raja	63	m	69	24	y	y	n	n	y	n	8.6	477	218	43
3	Geethalakshmi	68	f	66	28	y	y	y	y	y	y	9	483.4	245	46
4	Kamaraj	58	m	63	24	y	n	y	n	n	n	7.9	475.1	212	47
5	Ansar Basha	70	m	72	27	y	y	y	y	y	y	9.2	513	243	47
6	Sumithra	63	f	66	28	y	n	y	y	y	n	7.7	463.8	221	42
7	Kumar	51	m	65	24	y	n	y	n	n	n	7.4	461	200	49
8	Kannikammal	66	f	64	26	y	y	n	y	y	y	8.4	461.9	243	50
9	Narasimman	65	m	67	25	y	n	y	n	n	n	7.1	466.2	211	53
10	Nissar Ahmed	67	m	78	27	y	y	y	n	n	n	7.8	498.4	209	45
11	Sumathi	56	f	59	23	n	n	y	n	n	n	7	452.8	212	46
12	Raman	49	m	67	24	n	n	y	n	n	n	7.4	460	234	43
13	Arul	55	m	58	21	n	n	y	n	n	n	7.6	440.1	189	44
14	Neelavathi	59	f	59	24	y	y	n	y	y	n	7.4	470.1	198	45
15	Suresh	49	m	70	27	y	n	y	n	n	n	8.3	475	202	47
16	Duraisamy	69	m	72	26	y	y	n	y	y	y	9	502	255	48
17	Arunan	75	m	70	27	y	y	y	y	y	y	8.9	511.2	221	42
18	Arumugam	57	m	65	24	y	n	y	n	n	n	8.1	471.5	200	45
19	Devika	55	f	58	23	n	y	n	n	n	n	7	439.5	202	50
20	Murugesan	60	m	67	26	n	n	y	n	n	n	6.8	462.3	215	54
21	Rangan	70	m	65	24	n	n	y	y	n	n	7.6	466.8	236	46
22	Senthamarai	70	f	67	27	y	y	n	y	y	n	8.9	494.6	254	47
23	Nathamuni	66	m	76	29	y	y	y	n	n	y	9.3	480	232	45
24	Venda	50	f	58	25	n	n	y	n	n	n	7.4	450.4	213	43
25	Lakshmi	58	f	65	29	y	y	n	n	n	n	8.6	464.2	246	47
26	Subramani	67	m	70	24	n	n	y	n	n	n	6.9	456.3	221	49
27	Ramamoorty	59	m	68	24	n	y	n	n	n	n	7	453.5	189	51
28	Arjunan	54	m	65	23	y	y	n	n	y	n	9.2	478.2	234	46
29	Noornisha	65	f	67	28	y	y	y	y	y	n	8.8	489.9	245	51
30	Kumaran	70	m	73	25	n	y	n	n	n	n	7.2	468.3	201	47
31	Palayam	72	m	59	21	y	y	n	y	y	y	8.8	489.8	200	48
32	Rajeshwari	50	f	66	28	y	n	y	n	n	n	7.8	470.1	234	43
33	Vishwanathan	58	m	67	23	n	n	y	n	n	n	8	460.3	215	44
34	Damodaran	64	m	59	19	y	n	y	y	y	n	8.5	469.8	203	46
35	Moorthy	50	m	68	26	n	y	n	n	n	n	6.9	464.6	224	45
36	Suseela	69	f	65	26	y	y	n	n	n	n	8.4	481.3	234	52
37	Nirmala	48	f	59	24	n	n	y	n	n	n	8.8	450.9	214	53
38	Ahmad	67	m	73	25	n	n	y	n	n	n	7.8	463.2	219	48
39	Sambandam	60	m	67	24	n	y	n	n	n	n	7.3	467	189	47
40	Shanmugam	51	m	69	27	y	n	y	n	n	n	7.8	470	243	45

1	aravindan	55	m	64	22	n	n	n	y	y	n	7.4	435.5	221	43
2	nagaraj	66	m	73	27	y	n	n	y	y	y	7.9	455	238	45
3	chandra	57	f	59	24	n	n	n	y	y	n	7.3	410.8	222	47
4	fathima	53	f	66	29	n	n	n	y	y	y	8.4	442.5	200	48
5	vijaya	65	f	68	27	y	n	n	n	y	y	8.9	453.4	212	45
6	moorthy	62	m	65	23	n	n	n	Y	y		7.9	442.2	194	46
7	shankar	59	m	67	24	n	n	n	n	y	y	6.9	438	188	46
8	manimaran	59	m	63	23	y	n	n	y	y	n	7.5	465.7	197	49
9	kumari	66	f	67	26	n	n	n	y	n	y	8.3	442.7	221	50
10	gopi	58	m	66	25	n	n	n	y	y	n	7.4	435.7	212	51
11	saroja	65	f	61	26	n	n	n	y	y	y	7.5	433.9	214	56
12	sundar	58	m	66	22	n	n	n	y	y	n	7.2	440	242	46
13	janakiraman	63	m	59	21	n	n	n	n	n	n	7.3	416	200	48
14	murali	53	m	67	24	n	n	n	y	y	y	7.8	450.6	219	49
15	robert	58	m	70	26	n	n	n	n	y	y	8.5	441.2	211	50
16	abdul	72	m	67	26	n	n	n	y	y	y	8.8	443.7	231	53
17	praveena	53	f	58	21	n	n	n	n	y	n	7.1	421.8	198	52
18	gowri	68	f	69	28	y	n	n	y	y	y	7.8	448.4	221	48
19	thangaraj	57	m	59	21	n	n	n	y	y	n	6.8	426.8	221	49
20	poorani	57	f	59	21	n	n	n	y	y	y	7.5	417.9	243	46
21	raju	69	m	75	27	n	n	n	y	y	y	7.8	460.2	231	48
22	shanmugam	58	m	65	24	n	n	n	y	n	n	7.9	443.7	189	45
23	surenderan	63	m	69	26	y	n	n	y	y	y	8.2	467.8	221	47
24	naseer	54	m	66	26	n	n	n	y	y	n	7.6	443.6	201	54
25	selvi	55	f	59	23	n	n	n	y	y	n	7.8	407.6	197	52
26	david	56	m	60	20	n	n	n	n	y	n	6.9	424.6	176	49
27	lakshmi	59	f	58	23	n	n	n	y	y	n	7.8	436.8	189	49
28	muruganathan	55	m	62	21	n	n	n	n	y	n	6.9	423.5	198	47
29	munusamy	67	m	70	24	n	n	n	y	y	y	9.3	453.7	189	48
30	suganthy	63	f	67	27	y	n	n	y	y	y	9.5	450.8	211	48
31	kalimuthu	68	m	64	26	n	n	n	y	y	n	7.8	445.7	211	47
32	saraswathy	57	f	69	28	n	n	n	y	y	y	8.9	448.5	219	48
33	alexander	55	m	73	29	y	n	n	y	y	y	9.4	468.8	211	46
34	duraisamy	58	m	69	26	n	n	n	y	y	n	8.3	443.4	198	46
35	rajan	49	m	59	21	n	n	n	n	y	n	7	430.8	189	53
36	meenakshi	56	f	59	23	n	n	n	n	y	n	7.2	406.5	178	51
37	sukumar	59	m	65	24	y	n	n	y	y	y	9.6	448.4	198	53
38	mohan	59	m	68	25	n	n	n	n	y	n	7.2	438.6	187	49
39	nirmala	55	f	58	21	n	n	n	n	y	n	7.3	420.5	178	49
40	raziya	60	f	73	28	n	n	n	y	y	y	9.6	450.7	231	50

PATIENT CONSENT FORM

Study detail:

"STUDY ON FIBRINOGEN LEVELS IN TYPE 2 DIABETES MELLITUS"

Study centre : Rajiv Gandhi Government general hospital, Chennai.

Patients Name :

Patients Age :

Identification Number :

Patient may check (√) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: Place Date

Signature of investigator :

Study investigator's Name : Place Date