A STUDY ON SERUM FIBRINOGEN AS AN INDEPENDENT PREDICTOR OF MAJOR ADVERSE CARDIAC EVENTS (MACE) IN KNOWN DIABETIC CORONARY ARTERY DISEASE PATIENTS

Dissertation submitted to

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For the award of the degree

M.D GENERAL MEDICINE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON SERUM FIBRINOGEN AS AN INDEPENDENT PREDICTOR OF MAJOR ADVERSE CARDIAC EVENTS (MACE) IN KNOWN DIABETIC CORONARY ARTERY DISEASE PATIENTS"** submitted by **Dr. AMUDHAN .M** to The Tamil Nadu Dr. M.G.R Medical University is in partial fulfillment of the requirement of the award of **M.D DEGREE [GENERAL MEDICINE]** BRANCH 1 and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I, **Dr. AMUDHAN .M,** solemnly declare that the dissertation titled **"A STUDY ON SERUM FIBRINOGEN AS AN INDEPENDENT PREDICTOR OF MAJOR ADVERSE CARDIAC EVENTS IN KNOWN DIABETIC CORONARY ARTERY DISEASE PATIENTS",** is a bonafide work done by me at Govt. Stanley Medical College and Hospital from april 2012 to november 2012 under the guidance and supervision of my unit chief, Prof. **Dr. K. Madhavan, M.D.,** Professor of Medicine, This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of the requirements of M.D. Branch I,General medicine degree examination.

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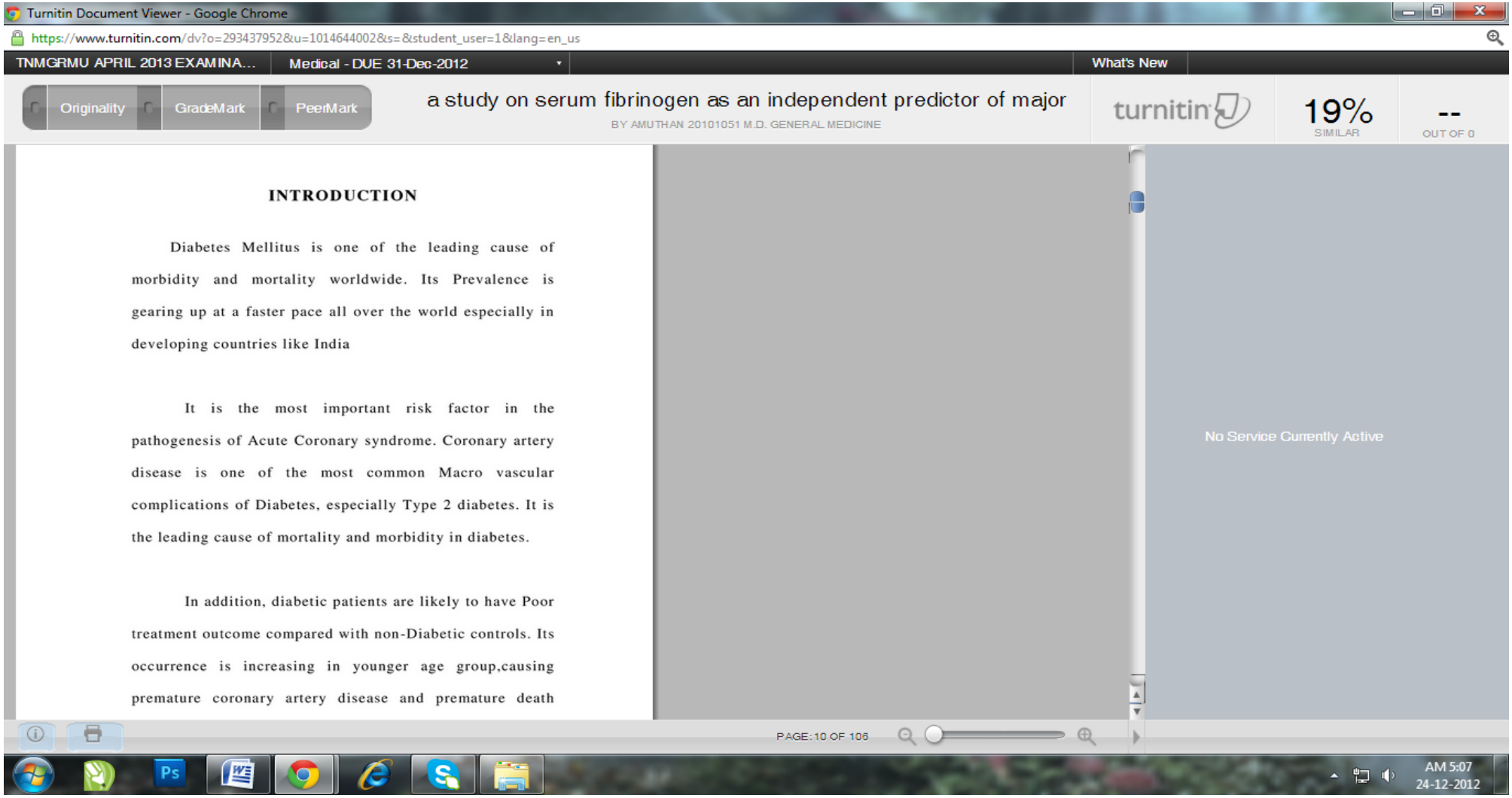
Last but not the least I would like to thank **my patients** with gratitude for their cooperation during the study.

PLAGARISM SNAP SHOT



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LIST OF ABBREVIATIONS

T1DM : TYPE 1 DIABETES MELLITUS

MODY : MATURITY ONSET DIABETES OF YOUNG

HNF : HEPATOCYTE NUCLEAR TRANSCRIPTION FACTOR

IPF : INSULIN PROMOTER FACTOR

DNA : DEOXY RIBO NUCLEIC ACID

ATP : ADENOSINE TRI PHOSPHATE

NK : NATURAL KILLER

PPAR : PEROXISOME PROLIFERATOR ACTIVATOR RECEPTOR

IRS : INSULIN RECEPTOR SUBSTRATE

TNF α : TUMOUR NECROSIS FACTOR α

PAI : PLASMINOGEN ACTIVATOR INHIBITOR

IR : INSULIN RESISTANCE

TGF β : TISSUE GROWTH FACTOR β

ACEI : ANGIOTENSIN CONVERTING ENZYME INHIBITOR

NCS : NERVE CONDUCTION STUDY

MI : MYOCARDIAL INFARCTION

CT : COMPUTER TOMOGRAPHY

t- PA : TISSUE PLASMINOGEN ACTIVATER

BMI : BODY MASS INDEX

WBC : WHITE BLOOD CELL

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INTRODUCTION

Diabetes Mellitus is one of the leading cause of morbidity and mortality worldwide. Its Prevalence is gearing up at a faster pace all over the world especially in developing countries like India

It is the most important risk factor in the pathogenesis of Acute Coronary syndrome. Coronary artery disease is one of the most common Macro vascular complications of Diabetes, especially Type 2 diabetes. It is the leading cause of mortality and morbidity in diabetes.

In addition, diabetic patients are likely to have Poor treatment outcome compared with non-Diabetic controls. Its occurrence is increasing in younger age group,causing premature coronary artery disease and premature death inflicting economic burden to the family and to the society.

Recently studies are focussing on serum Fibrinogen and its role in the pathogenesis of Coronary artery disease in Diabetes. Fibrinogen being an acute phase reactant is

also a pro-coagulant. It plays a major role in coagulation of blood. It has a significant role in Athero-thrombosis. Hence its role in adverse cardiac events in Diabetics and its prognostic value is currently the study of interest.

AIMS & OBJECTIVES

- To determine the concentration of Fibrinogen in diabetic CAD and its causal relationship to adverse cardiac events.

- To ascertain serum fibrinogen’spredictive value of major adverse cardiac events in Diabetic CAD.

- To ascertain the prognostic value of serum fibrinogen in Diabetic patients presenting with subsequent major adverse cardiac events.

- To evaluate the relation between serum Fibrinogen and other factors that cause adverse cardiac events.

REVIEW OF LITERATURE

DIABETES MELLITUS

It is a metabolic disorder of varied aetiology characterised by chronic hyperglycaemia and altered metabolism of carbohydrates, protein and fat leading to vascular syndrome affecting small and large sized blood vessels. It results from

Defective insulin secretion

Defective insulin action or

Both

EPIDEMIOLOGY

The prevalence of diabetes is increasing worldwide and in particular, developing countries like India. It has now become an important public health problem in India. With this pace, the Diabetic population in India would be around 70 million by 2030.At present, India heads the list of countries with highest population of Diabetics. The prevalence of DM is progressively stepping up and in particular T2DM prevalence is stepping up with rapid phase due to following factors

- Social habits leading to obesity
- Idle nature of daily routine activities
- Industrialisation
- Ageing of people
- Geographic status
- Genetic factors
- Environmental factors

CLASSIFICATION[1]:

CLASSIFICATION[1]:

I. Type 1 diabetes (β 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 cell function characterized by mutations in:
1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY
2. Glucokinase (MODY 2)
3. HNF-1 (MODY 3)
4. Insulin promoter factor-1 (IPF-1; MODY 4)
5. HNF-1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA
8. Subunits of ATP-sensitive potassium channel
9. Pro-insulin or insulin conversion
B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes
C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis,

hemochromatosis, fibrocalculouspancreatopathy, mutations in carboxyl ester lipase
D.Endocrinopathies-acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
E.Drug- or chemical-induced—Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, beta-adrenergic agonists, thiazides, hydantoin, alpha-interferon, protease inhibitors, anti-psychotics(atypicals and others), asparaginase, epinephrine
F. Infections—congenital rubella, cytomegalovirus, coxsackie
G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies
H. Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Inspite of ongoing research and advent of newer Antidiabeticdrugs , Diabetes is still considered high risk , causing high occurrence of Coronary artery disease and cerebrovascular accidents. [2,3,4]

Incidence of microvascular complication such as Retinopathy, neuropathy and Nephropathy are also much higher in Diabetes.[5,6,7]

TYPE I DIABETES:

Various genetic factors, environmental and immunological components contribute to its development causing ultimately, pancreatic beta cell damage and absolute insulin deficiency as a result.

The immune mechanism that underlies the development of T1DM is auto immunity mediated by T – cell, where autoantibodies attacks beta cells of pancreatic islets and destroys them.

In most individual there is autoimmune destruction of beta cells and may have evidence to it, in form of

autoantibodies. Some may not have evidence or markers for autoimmune process and they might have developed insulin deficiency due to idiopathic or non-immune mechanism.

The Autoimmune pancreatic pathology in development of T1DM is evident from pathological changes in pancreas of persons with impaired fasting glucose and impaired glucose tolerance. It is characteristically shows[8]

- Inflammatory cell infiltration of Islet cell such as -
  - Activated macrophages
  - Helper T cells
  - Cytotoxic T cells
  - Suppressor T cells
  - NK Cells
  - B Lymphocytes
- Selective destruction of Beta cells sparing cells that secrete Glucagon and other hormones.
- Patchy lesion with infiltrated lobules amidst unaffected lobules.

T1DM may co-exist with Auto immune diseases such as

- Autoimmune thyroiditis
- Coeliac disease
- Addisons disease
- Pernicious anaemia
- Vitiligo

Which further support pathological mechanism of Autoimmunity in the etiopathogenesis of T1DM.

Clinical course of type I DM:

At birth, all individuals have normal beta cell mass, later as age advances they lose their beta cell mass due to autoimmune mechanism, which is initiated by some environmental or infectious stimuli, that demands increased insulin requirement

Until 70% - 80% of beta cells are destroyed, the individuals will be asymptomatic. As age and immunological processes advances, the percentage of destroyed beta cells reach a point at which the remaining viable beta cells are not enough to tolerate glucose load and they exhibit the clinical signs and symptoms.

Rate of destruction of beta cell mass varies with individuals.

TYPE II DIABETES:

Two important pathological events that contributes to development of T2DM are

- Insulin resistance
- Defective insulin secretion

The presence of these two events may not be sufficient to cause T2DM unless there is extensive beta cell dysfunction. This has led to the observation , where Genetics play a contributory role in the pathogenesis of T2DM.

Though Genetic factor is considered a special position in the etiology, the chance that a patient with Genetic susceptibility to develop Diabetes is largely decided by other factors such as

- Environmental factors
- Social factors
- Obesity
- Diet
- Age
- Pregnancy

In fact insulin resistance occurs long before defective insulin secretion. T2DM manifests only after insulin secretion becomes defective.

It has a significant genetic association as evidenced by prevalence of insulin resistance in non-diabetic close relatives of T2DM patients. Other than genetic factors there are other factors that contribute to its development.

- Obesity
- Sedentary lifestyle
- Food habits
- The culprit genes are not yet completely identified. But recent studies have identified some associate genes such as

- [1]*Transcription factor 7- like 2 gene*

Genetic polymorphism of genes encoding,

- PPAR-γ
- Zinc transporter
  - IRS
  - Calpain10

are associated with T2DM.

[1]DIAGNOSTIC CRITERIA

- Symptoms of diabetes plus random blood glucose concentration of 11.1 mmol/L (200 mg/Dl or more)*or*
- Fasting plasma glucose 7.0 mmol/L (126 mg/dL or more)*or*
- Two-hour plasma glucose 11.1 mmol/L (200 mg/dL or more) during an oral glucose tolerance test using 75g anhydrous glucose
- A1C > 6.5%

Diabetic men have two times the risk of adverse cardiovascular events than non-diabetic control group. In women , the risk is three times in diabetic group than non-diabetic control group.[2]

Cardiovascular risk factors such as obesity and hypertension are co- existing in a higher frequency and level in diabetic than non-diabetic.[5,9-16]. This contributes to the increased risk and occurrence of adverse cardiovascular events in Diabetics than control group with conventional risk factor alone.

In addition to this , there is a significant difference in the serum levels of HDL , LDL and VLDL between Diabetics and Non Diabetic group, where HDL is low and LDL ,VLDL are high in Diabetics when compared to non diabetics in whom HDL is higher and LDL ,VLDL is lower than the Diabetic group.[2]

There are still other studies which confers only little correlation between the quantitative status of the risk factor and the occurrence of Adverse cardiac events , which has individual variation both in diabetic and non-diabetic.[2]

DIABETES & INFLAMMATION

Inflammation plays an important role in the evolution of T2DM. Diabetes is now linked with chronic inflammatory state and this has been attributed to abnormal lipid metabolism[1].

Insulin mediates its action by binding to insulin receptor in the surface of the Insulin responsive cells. The receptor in turn gets phosphorylated by itself and insulin receptor substrate family. This marks the initiating event in downstream signaling pathway.

Recent studies have shown some metabolic components involved in interference of signalling pathway. For instance in obesity metabolic overload puts endoplasmic reticulum in an incapacitant state. This burden, that is inflicted upon endoplasmic reticulum, activates inflammatory signal pathway and finally leading to Insulin resistance.[17,18,19]

Another mechanism by which metabolic factor involves in this inflammatory pathway is increased production of Reactive oxygen species by mitochondria in obesity leading to enhanced activation of inflammatory pathway.[20,21]

Obesity and diabetes share common features of insulin resistance. In obesity there will be excessive accumulation of saturated fat in white adipose tissue resulting in increased synthesis and release of saturated fatty acids and TNF-α.

High level of free fatty acid and TNF-α activates inhibitory phosphorylation of serine residues of IRS – I[22,23]. This inhibits insulin stimulated tyrosine phosphorylation of IRS-I to interact with insulin receptor. This results in inhibition of insulin action[22,24,25].

Development of insulin resistance, T2DM and cardiovascular disease to a great extent are mediated by inflammatory processes. This is evident from high levels of circulating inflammatory markers such as CRP, cytokines,

fibrinogen, IL-6, IL-8, PAI & TNF-α seen in T2DM patients[21] .

Visceral obesity, which is common in diabetes leads to excess adipose tissue producing various adipokines including inflammatory cytokines. These inflammatory agents are a key component to the development of IR, obesity, diabetes[21], atherosclerosis, heart disease and fatty liver.

DIABETES COMPLICATIONS

Prolonged hyperglycaemia seen in diabetic is a key feature which poses deleterious effect in the human body.

Its adverse effects affecting the vascular anatomy are main events contributing to micro vascular and macro vascular diseases.

COMPLICATIONS OF DIABETES :

- *Acute*

  Diabetic ketoacidosis

  Hyperglycemic hyperosmolar state

Hypoglycemia

Diabetic coma

- *Chronic*

Microvascular :

Diabetic cardiomyopathy

Diabetic nephropathy

Diabetic neuropathy

Diabetic retinopathy

Macrovascular disease :

Coronary artery disease

Diabetic myonecrosis

Peripheral vascular disease,

Stroke

Both Microvascular and Macrovascular :

Diabetic sexual dysfunction

MICROVASCULAR COMPLICATION :

Pathogenesis

The development of micro vascular complication depends on degree and duration of hyperglycaemia. Four possible mechanismshave been postulated. They are

- Metabolic overload in form of excess Sorbitol and other Polyols within the endothelial layer.
- Increased production of Prostaglandin products as a result of up regulation of Protein kinase C.
- Nonenzymatic glycosylation of protein leading to increased production of advanced glycation end products and thereby increased production of TGF β.

Consequently all these factors lead to Glucose mediated oxidative damage.

However there are still some studies which contradict the role of Hyperglycaemia in the aetiopathogenesis of diabetic complications. This fact was arrived from a study, where 40 % of the Diabetics even after meticulous optimal Glycaemic status develop Neuropathy eventually.[27]

This holds the same for development of Nephropathy, where some study shows progression to Nephropathy despite good Glycaemic control.[28]

MICROVASCULAR COMPLICATIONS

Diabetic retinopathy

It is the commonest micro vascular complication. Degree of hyperglycaemia and its duration predicts the risk of developing retinopathy. Development of diabetic retinopathy in T2DM may also require other risk factor such as hypertension.

The process of diabetic retinopathy starts well before the diagnosis of T2DM was made in T2DM patient[1] .

Proposed mechanism

Increased concentration of Sorbitol, which is a glucose alcohol derived from Glucose by POLYOL pathway is one mechanism. Here high sorbitolconcentration lead to osmotic stress which is thought to be the basic mechanism in most micro vascular complication including Diabetic Retinopathy.

Other postulated mechanisms are

- Oxidative stress by production of free radicals and reactive Oxygen species

Increased production of

- Growth factors such as Vascular Endothelial derived Growth factor.
- Growth Hormone
- TGF β
- Product of advanced glycosylated end product

The role of Vascular endothelial growth factor[29,30,31]and TGFβ are also implicated as evidenced by certain studies.

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Diabetic retinopathy can have major impact on the patient to the extent of blindness, especially if proliferative retinopathy sets in. so close monitoring for diabetic retinopathy is needed.

Diabetic nephropathy

It is characterised by proteinuria of more than 500ms in 24 hours in diabetic patients. Usually it follows micro albuminuria, where there is excretion of albumin of 30-300mg/day.

Micro albuminuria starts well early in the clinical span of T2DM. soit is prudent to screen for micro albuminuria very early, as 7% of T2DM patients are positive for micro albuminuria at diagnosis.

If no intervention has been taken during the time of micro albuminuria, the disease will worsen to proteinuria and finally end in diabetic nephropathy. ACEI therapy retards the progression to nephropathy in T2DM and prevent them in type I DM[32,33]. So ACEI is considered in the first line management of micro albuminuria, even in normotensive patient[33].

Diabetic neuropathy

It is often unrecognised micro vascular complication of diabetes.

Peripheral neuropathy of diabetes is often a diagnosis of exclusion. Numerous works up is necessary to arrive at the diagnosis of diabetic neuropathy.

In some people often present with foot ulcer before diagnosis is made. It accounts for more than 80% of amputation[34]. Exact mechanism by which diabetes causes neuropathy is not known, but the risk of diabetic neuropathy has a linear relationship with degree and duration of diabetes

Distal symmetric sensorimotor polyneuropathy is the commonest type of neuropathy. Patient gives a history of tingling, burning pain or numbness. There is involvement of posterior column as evidenced by hypoaesthesia to total sensory loss to light touch, temperature and vibration. Ankle reflex is absent[34]. Diabetes with sensory loss to 10-g monoplanes are more prone for foot ulcer.

Other types

- Pure sensory neuropathy
- Mononeuropathies
- Diabetic amyotrophy[34]
- Autonomic neuropathy

NCS shows reduction in amplitude and conduction of nerve impulse.

Differential diagnosis[34]

- Hypothyroidism
- Vitamin B12 deficiency
- Chronic inflammatory polyneuropathy
- Uraemia

Glycaemic control is main treatment strategy to prevent and to retard the progression of diabetic neuropathy. Other contributing factors such as high blood pressure and dyslipidemia should be corrected[1]

MACROVASCULAR COMPLICATION

The key underlying pathological mechanism that leads to the development of macro vascular disease is atherosclerosis.

The process involves injury to endothelium by chronic inflammatory process causes deposition and aggregation of oxidised lipids in LDL within the endothelial wall. This followed by monocyte infiltration and macrophage transformation. This process along with oxidised lipid lead to foam cell generation. Foam cell formation is followed by proliferation of macrophage and attraction of T-lymphocytes which cause increased smooth muscle proliferation and collagen deposition.

Final product is atheromatous plaque rich in lipids with a fibrous envelope. Rupture of this plaque causes acute vascular occlusion. Diabetes have high incidence of plaque ulceration and intra coronary thrombus formation[35].

Other factor that contribute to vasculopathy are

- Increased platelet adhesion
- Hyper coagulopathy due to increased fibrinogen.
- Increased free radical formation & platelet aggregation.
- Increased PAI -1

So combined additive effects of pronounced coagulability and defective fibrinolysis cause the incidence of vascular obstruction and major adverse cardiac events to be higher in diabetes, especially T2DMpatients[36]

Metabolic syndrome, comprising early spectrum of Diabetes as one of its components poses a major risk factor for Atheromatous vascular disease.

It is a group of adverse medical events which when co-exist together enhances the occurrence of adverse cardiac events in addition to Diabetes. It is also known as

- Cardiometabolic syndrome
- Syndrome X
- Insulin resistant syndrome
- Reaven's syndrome

Other conventional risk factors such as smoking, obesity, Hypertension, Microalbuminuria, Hypercholesterolemia and increased lipoprotein (a) may coexist or some can be a consequent to it.

The number of risk factors in a person has a linear relationship with chance of developing major adverse cardiac events. In the presence of these factors *Diabetes* magnifies the adverse events caused by them.

Coronary heart disease is the commonest macro vascular complication in T2DM.

Risk of Myocardial infarction in a person with Diabetic is same as that of a Non Diabetic with prior history of Myocardial infarction. Hence diabetes is considered as angina equivalent. Presence of diabetes

confers a risk of MI equivalent to the risk of MI in a non-diabetic with past history of MI.

CORONARY ARTERY DISEASE

It is the most common heart disease. It is caused by narrowing of coronary arteries by atherosclerotic process. It is a chronic pathological process which begins in early life and manifests in early of late adulthood.

"Atherosclerosis" literally refers to localized aggregation of lipids and this affects the intimal layer of epicardial coronary artery thereby causing thickening of intimal layer.

Large and medium sized arteries are commonly involved. Atherosclerosis initiates inflammatory process in the vessel wall and cause endothelial dysfunction. This attracts lipids, cholesterol, inflammatory cells and calcium within the intimal layer of blood vessel.

This leads to the genesis of plaque, which is made up of fat, cholesterol, calcium deposits and inflammatory

cells. It starts as fatty streak which later develops into fibrous plaque, a lipid rich core composed of inflammatory cells, smooth muscle cells and cellular debris within it.

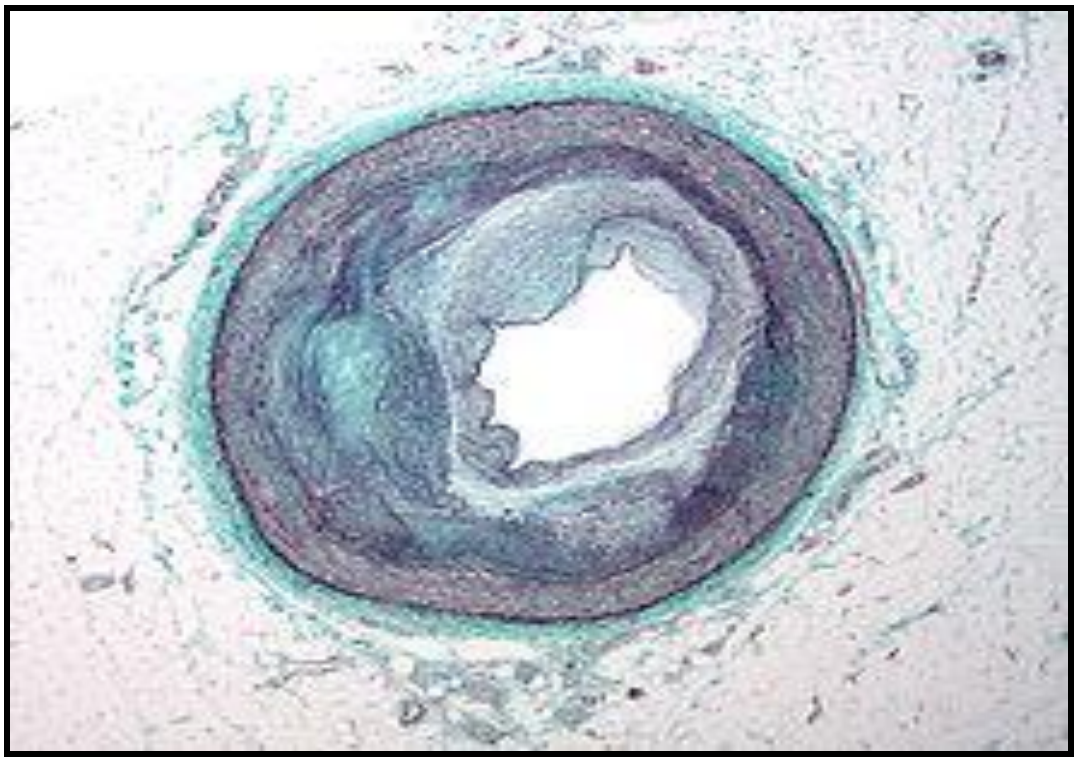
In patients with diabetes the inflammatory changes are marked. The degree of lipid composition in the plaque is more in diabetic CAD than non-diabetic CAD. Also there is increased inflammatory cell infiltration and thrombosis in them when compared to non-diabetics with coronary artery disease[37.]

These atheromatousplaque accumulate progressively and in advanced stage of the process, it causes luminal obstruction. The hemodynamics of the coronary blood flow is affected and there is reduced oxygen supply to the organs. Myocardial oxygen supply cannot meet increasing demands during exertion initially.

There is enough evidence to suggest high incidence of coronary artery disease in patients with conventional risk factors[38] such as

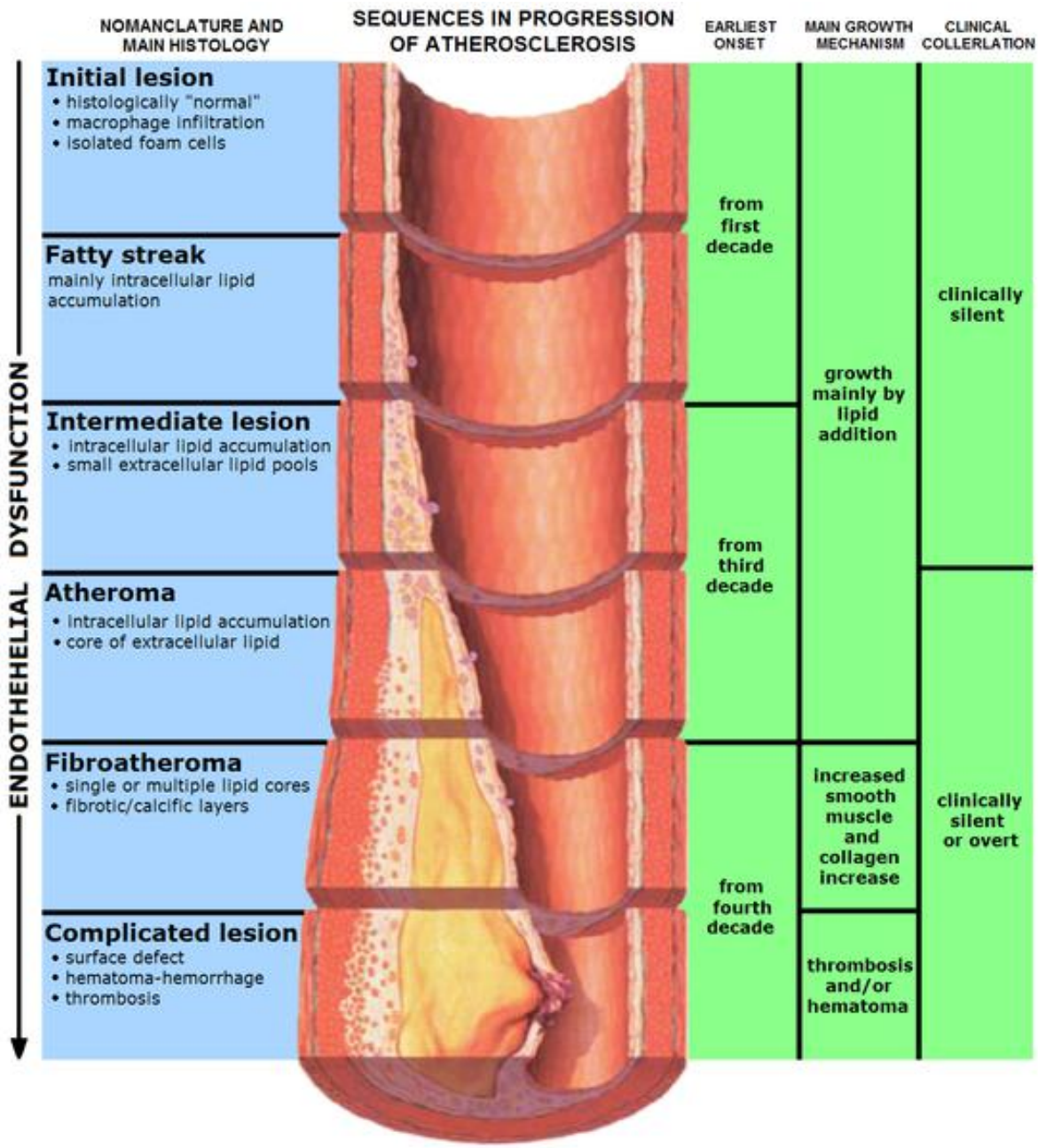
- Smoking
- obesity
- Dyslipidemia (increased LDL)
- Hyperfibrinogenemia& increased factor VII[39]
- Hyperlipoprotein (a)[40]
- Hepatic lipase[41]
- Advancing age

The role of alcohol in the causation of atherosclerotic coronary artery disease is controversial. Though alcohol causes altered metabolism, a mild to moderate intake of alcohol has been associated with decreased incidence of adverse cardiac events such as CAD[42]



Micrograph of a coronary artery with marked atherosclerosis and luminal narrowing.

Pathophysiology of Atherosclerosis



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Aerobic exercise reduces the risk of coronary artery disease. This is supported by some studies where reduction in the serum level of lipids and inflammatory markers such as C-reactive protein, fibrinogen were observed after an aerobic exercise program.[43]

The pathological mechanisms by which some risk factors lead to coronary artery disease are mediated through fibrinogen in common. This is evidenced by some studies which showed higher level of fibrinogen in smokers[44] and in diabetics[45].

CLINICAL MANIFESTATION:

Coronary artery disease has diverse clinical symptoms and signs[46] ranging from stable angina to sudden death. Depending upon the anatomical viability of atheromatous plaque.

Chest pain with diaphoresis is the most common presentation. A typical anginal pain is that of a retrosternal pain with a sense of heaviness, brought on exertion radiating to the neck, lower jaw, left shoulder, left arm or epigastrium and is relieved by rest and nitrates in stable angina.

But however this typical symptom need not be present always. They may have other symptoms which appear unrelated. They are termed angina equivalents.

Anginal equivalents are[46]

- Dyspnea
- Diaphoresis
- Fatigue
- Atypical chest pain

INVESTIGATION:

Patients basic investigations such as complete blood count, Thyroid function test, Fasting lipid profile and Glycemic status should be ascertained by fasting and postprandial blood sugar. Patients should be subjected to ECG both at rest and during stress. Cardiac evaluation using ECHO should be done, Thallium scintiography and CT Coronary Angiogram should be done where feasible.

DIABETES AND FIBRINOGEN IN CORONARY ARTERY DISEASE:

As diabetes and fibrinogen share most of the conventional risk factor[38] such as obesity, smoking, dyslipidemia, etc. contribution of diabetes and hyperfibrinogenemia[45] together causes significantly increased risk of atherosclerotic coronary artery disease.

Role of fibrinogen in Atherosclerosis and Thrombosis has been postulated due to [46] factors given below

- Magnified aggregation of platelet.

- Escalated Fibrin synthesis.
- Increased vascular smooth muscle cell proliferation.

So Hyperfibrinogenemia causes Atherothrombosis of varying degree depending upon its level.

FIBRINOGEN

Fibrinogen is a key component in coagulation process. It is a glycoprotein synthesized in liver by liver cells. It is about 340 kDa. Its normal serum level is 1.5 – 4.0 g/L.

It has an important role in final path of coagulation cascade where thrombin converts fibrinogen to fibrin. This fibrin is cross linked by factor VIII to form a clot. Thrombin and t-PA activates factor VIII and this is catalyzed by fibrin[47.]

Factor Xa and thrombin, which is involved in fibrinolysis, are transiently inhibited by fibrin, which engulf them within the fibers. There they remain viable to be released during fibrinolysis[48.]

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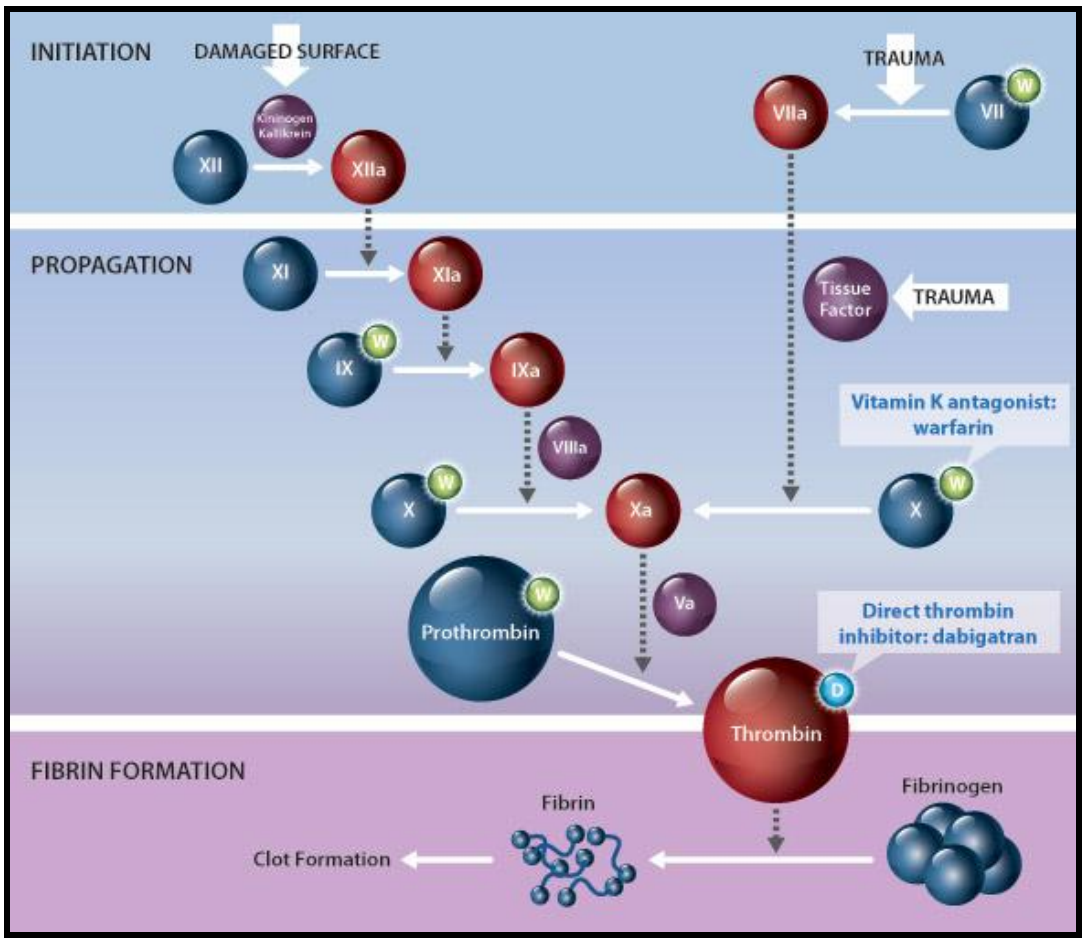
COAGULATION CASCADE :



Fibrinogen deficiency

- It can be congenital or acquired. Congenital deficiency is rare and been reported in few.

Dysfibrinogenemia

Gene controlling synthesis of Fibrinogen in liver undergoes mutation and causes Dysfibrinogenemia, a rare coagulopathic condition.

It causes failure of degradation of fibrinogen,while being converted to fibrin. These patients are prone for venous thrombosis and bleeding in rare instance.

Genetic molecular testing is used to detect the culprit genetic mutation, responsible for

– Inherited Dysfibrinogenemia

– Hypofibinogenemia (or)

– Afibrinogenemia

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Causes of Acquired deficiency

- Sepsis
- Severe trauma with extensive tissue loss
- Disseminated intravascular coagulation
- Massive blood loss
- Post Hemodilution.
- Drugs

- Anabolic steroids
- Phenobarbitol
- Streptokinase
- Valproic acid

Estimation of Fibrinogen

It can be ascertained using venous blood. Normally it ranges from 1.5 – 4 g/L depending upon the laboratory method adopted. It can be estimated with blood serum or plasma.

In plasma, it is measured by CLAUSS method which shows an inverse relationship between clotting time and plasma Fibrinogen level.

Fibrinogen level increases with BMI, smoking, fasting insulin levels, LDL,WBC Count, Diabetes and Pregnancy. Whereas it is reduced in moderate alcohol usage, exercise, high level of high density lipoprotein and hormone replacement therapy [49,50,51]

Fibrinogen poses significant risk for cardiovascular disorders.[52,53]. It's positive relationship with BMI has been established by a study which showed decrease in fibrinogen level following low calorie healthy diet for 6 months [54] and this may be the mechanism by which obesity increases the risk of cardiovascular disease. Also fibrinogen level are high in diabetes[55] than controls.

Obesity can be a link between diabetes and fibrinogen in causing adverse cardiac event mediated by fibrinogen and other traditional cardiovascular risk factor such as BMI, obesity, etc.

Poor glycemic status are often associated with increased fibrinogen level[(56)] and this is evidenced by the observation of increased platelet reactivity in Diabetics and this may be due to high fibrinogen level which cross bridges platelets.

Fibrinogen as a predictor of adverse coronary events in angina patients has been established by a study conducted by Thompson &colleagues[57]. This further

establishes T2DM as a high risk event for cardiovascular disease.[58,59]

Increased risk for cardiovascular disease in smokers can be attributable to high level of fibrinogen found in smokers than in non-smokers. This association has been established by study conducted by Fogari et al[60] which showed a linear relationship between fibrinogen level and number of cigars smoked.

It is well established that Diabetes have increased risk of adverse cardiac events. Plaque rupture and thrombosis are the key components in acute coronary syndrome. Pathogenesis of these events are largely contributed by inflammatory pathology as evidenced by increased level of fibrinogen and C-reactive protein in patients with unstable angina[61].

A study by Emansh et al, suggest a strong link between high plasma fibrinogen level and Premature CAD[62].Role of Fibrinogen in the causation of

Atheroembolic events is further accomplished by several studies showing strong link between Fibrinogen level and

- Ischemic Cerebrovascular accident[63,64,65]
- Peripheral vascular disease[66,67]

Fibrinogen, an acute phase reactant and a procoagulant in addition, is being centered around the pathophysiology of atherosclerosis. Hence it is being considered as a significant factor in the pathogenesis of coronary artery disease, especially in T2DM patients where its serum level is higher than non diabetic population.

Recently the role of fibrinogen level in serum in predicting subsequent major adverse cardiac events in known Diabetics with coronary artery disease patients is being studied extensively .

MATERIALS AND METHODS

Study site

Department of General Medicine, Government Stanley Medical college and Hospital, Chennai.

Collaborating Departments

- Department of Cardiology
- Department of Medical Biochemistry

Study Design

- Cross sectional study

Study Period

- June 2012 to November 2012

Selection of study population

- Inclusion criteria

Diabetic inpatients with past history or evidence of Coronary artery disease.

Exclusion Criteria

- Disseminated intravascular coagulation
- Pregnancy
- Liver disease
- Sepsis
- Drug abuse like OCP,Antifibrinolytic, hormones
- Dysfibrinogenemia

Investigations done

- Complete blood count
- Blood sugar – Random, fasting and post prandial
- Glycosylated Hb
- Blood urea
- Serum creatinine
- Urine routine analysis
- ECG
- ECHO
- Serum fibrinogen

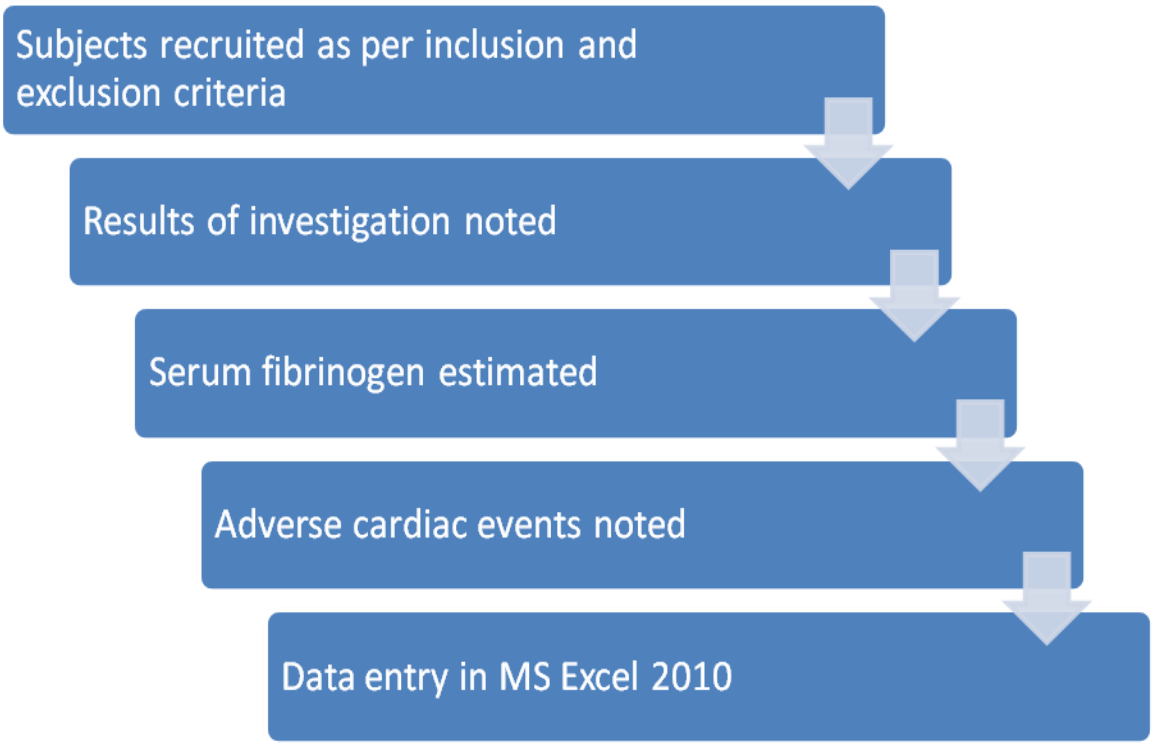
Sample size

- Using the above mentioned criteria 50 subjects were recruited

Sampling method

- Convenience sampling method was adopted

Study protocol



Estimation of Serum fibrinogen

Clauss method

The determination of fibrinogen with thrombin clotting time is based on the method originally described by Clauss; in the presence of an excess of thrombin, fibrinogen is transformed into fibrin and clot formation time is inversely proportional to the concentration of fibrinogen in the sample plasma.

Reagents

Fibrinogen reference

- Lyophilized human plasmacontaining buffer and preservative

Thrombin reagent

- Lyophilized preparation containing bovine thrombin, approximately 75 NIH U/ml, buffer, stabilizers and preservative

Imidazole buffer

- Imidazole 30 mmol/L
- Sodium chloride 125 mmol/L
- Sodium azide 0.1% as preservative, pH 7.35

Sample

- Venous blood collected in 3.8% sodium citrate in a ratio of 9 parts of blood to 1 part of anticoagulant(1:10)

Procedure

- Reconstitution of Thrombin agent done and maintained at room temperature(18-26°C) during testing
- To the fibrometer cup 0.2ml of the diluted plasma sample added
- To the fibrometer cup 0.2ml of the diluted plasma sample added
- This is incubated for 1-3 minutes at 37°C for not more than 5 minutes
- After incubation 0.1 ml of Thrombin reagent is added rapidly into the fibrometer while simultaneously starting the timer
- Clotting time results recorded in seconds
- Extrapolation of concentration done from calibration curve
- Results evaluated and tabulated

Major adverse cardiac events

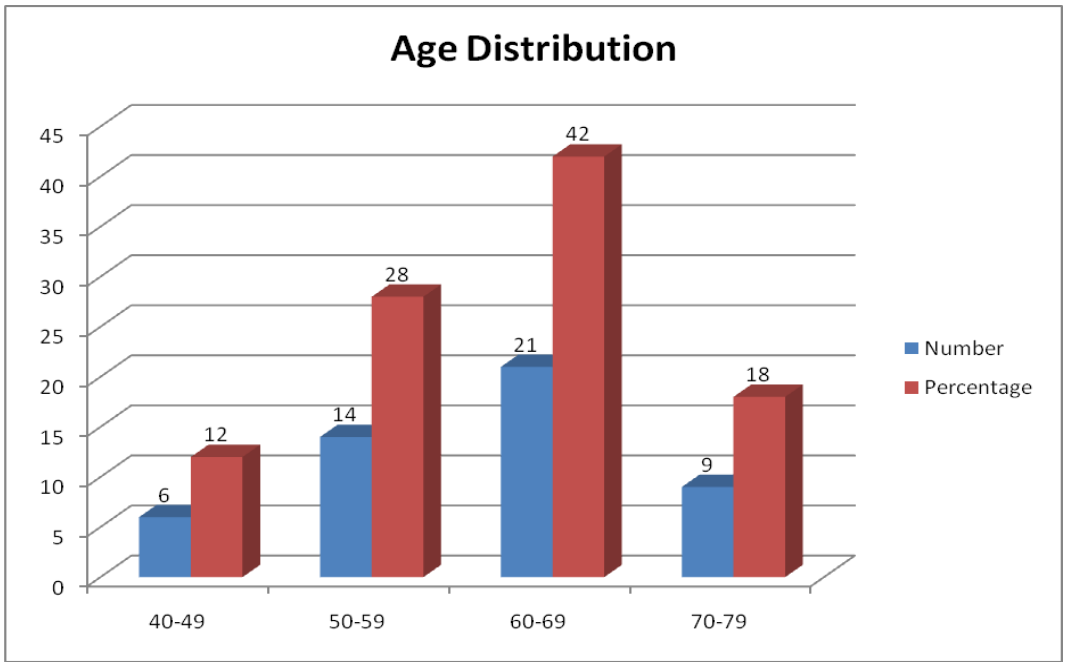
- Recurrent angina(RA)
- Congestive cardiac failure(CCF)
- Arrhythmia(AR)
- Death(CD)

RESULTS

This study was done to correlate the plasma fibrinogen levels in major adverse cardiac events occurring in known diabetic coronary artery disease patients who were admitted as in patients in Department of Medicine, Government Stanley Medical College, Chennai.

Age distribution

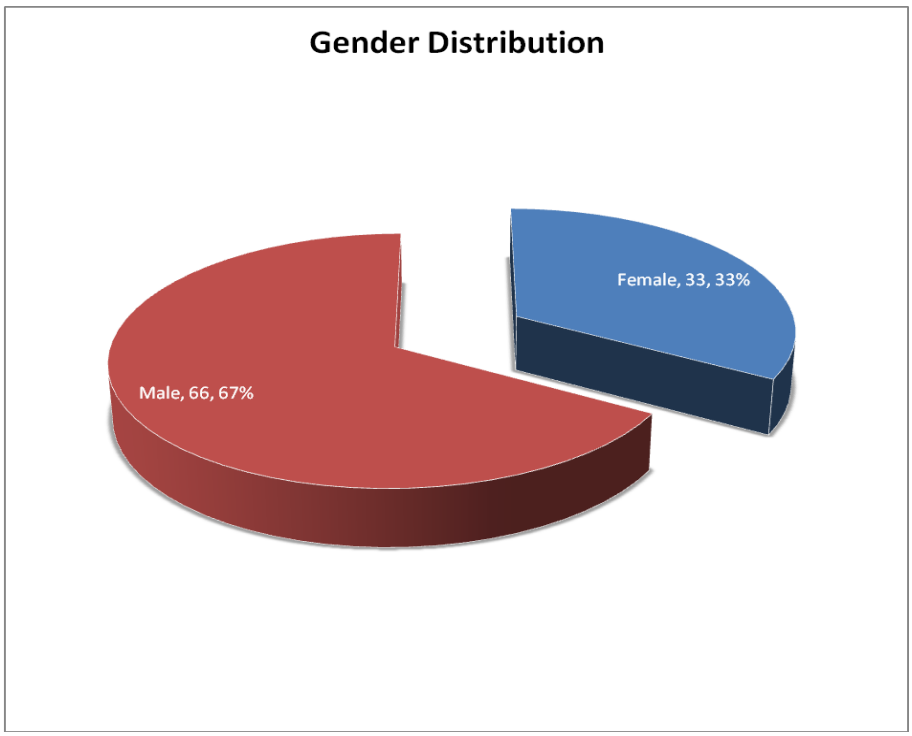
Chart 1



The total number of study subjects is N=50. Among them the age distribution ranges from 44 to 78 years. The majority of the patients belonged to the 44-78 years age group (42%) (Chart 1)

Gender distribution

Chart 2



As far as the gender distribution is concerned 66% of the study subjects are males and 34% of them are females. (Chart 2)

Group wise distribution of study population demographic characteristics

Table 1

	No MACE (n=24)	Recurrent Angina (n=11)	Congestive Cardiac Failure (n=15)	Arrhythmia (n=0)	Death (n=0)
Age	57.33	63.92	65.2	0.00	0.00
Duration of Diabetes	11.4	13.54	15.55	0.00	0.00
Fasting Blood Sugar	139.78	187.85	213.68	0.00	0.00
Post Prandial Blood Sugar	250.87	299.54	332.18	0.00	0.00
HBA_{1C}	9.22	9.98	10.03	0.00	0.00
Serum Fibrinogen	306.07	344.08	426.32	0.00	0.00

Table 1 displays the demographic data with mean values of age of patients, duration of diabetes, fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin (HBA_{1C}) and serum fibrinogen levels.

The mean values have been matched against the major adverse cardiac events (MACE) groups – recurrent angina, congestive cardiac failure, arrhythmia and death. Patients who do not develop MACE are captured in a separate group.

Prevalence of Major Adverse Cardiac Events

Table 2

MACE	**No of Patients**	**Percentage (%)**
No MACE	24	48
Recurrent Angina	11	22
Congestive cardiac failure	15	30
TOTAL	50	100

The observations made by Table 2 suggests that, the highest prevalence is that of patients who do not develop MACE(48%). This group is followed by the congestive cardiac failure group (30%). Arrhythmia and death groups will no longer be considered in this study due to no responses.

Relationship between MACE and patient age

Table 3A

Age	**40-49**	**50-59**	**60-69**	**70-79**	**TOTAL**
No MACE	5	11	9	1	26
Recurrent Angina	1	1	3	2	7
Congestive cardiac failure	0	2	9	6	17
TOTAL	6	14	21	9	50

X^2= 17.97 P=0.0063

From Table 3A the following observations can be made:

- 26 patients did not suffer from MACE
- 7 had recurrent angina and 17 had congestive cardiac failure
- In the group which did not have MACE more numbers clustered around the age groups of 50-59 and 60-69
- RA group has more numbers clustered around 60-69 age group
- Similarly the CCF group is clustered around 60-69 age group

Statistical Comparisons

Table 3B

Comparisons	**'t'**	**'p'**
No MACE - Recurrent Angina	2.77	<0.001
Recurrent Angina - Congestive cardiac failure	0.83	>0.05
Congestive cardiac failure - No MACE	4.44	<0.001

From Table 1 it can be seen that the mean ages of study groups No MACE, AR and CCF are 57, 64 and 66 respectively.

The above mentioned mean age groups were compared with each other as shown in table 3B using Student's unpaired t test.

On comparison of the No MACE and RA group a p value of <0.001 was arrived at and similarly comparing the age groups of RA and CCF yield a p value of <0.001 both highly significant.

Relationship between MACE and sex of the patient

Table 4

	Male	**Female**	**TOTAL**
No MACE	20(40%)	8(16%)	28
Recurrent Angina	4(8%)	4(8%)	8
Congestive cardiac failure	9(18%)	5(10%)	14
TOTAL	33(66%)	17(44%)	50

X^2= 2.37 P=0.305

Table 4 revealed the following details:

- In the No MACE group there were 20 men and 8 women
- The RA group consisted of 4 men and 4 women
- CCF group had 9 men and 5 women
- In total there were 33 men and 17 women
- The numbers when analysed statistically, yielded a chi squre value of 2.37 and a p value of 0.305(not significant)

Relationship between MACE and duration of Diabetes

Table 5

	5-10y	**11-15y**	**>15y**	**TOTAL**
No MACE	6	19	4	29
Recurrent Angina	1	2	5	8
Congestive cardiac failure	1	3	9	13
TOTAL	8	24	18	50

X^2= 14.87 P=0.005

From Table 5 the following can be gathered

- No MACE group consists of 29 patients and clustering is seen in the 5-10 and 11-15 years duration group
- In contrast RA group showed only 1 patient who developed recurrent angina within 10 years of diabetes and majority developed it after 15 yearsof diabetes
- CCF group showed the same picture as RA group
- Chi square test was used to analyse and revealed a p value of 0.005(statistically significant)

Relationship between MACE and Fasting blood sugar

Table 6

FBS(mg/dl)	**90-140**	**141-190**	**191-240**	**241-290**	**TOTAL**
No MACE	15	11	0	0	26
Recurrent Angina	0	3	4	0	7
Congestive cardiac failure	0	1	9	7	17
TOTAL	15	15	13	7	50

X^2= 56.30 P= <0.0001

From the above table, it can be seen that:

- Majority of the patients in the No MACE group belonged to the FBS 90-140 range
- In the RA group, highest number of patients belonged to FBS 191-240 range
- In the CCF most of the clustering was around 191-240 and 241-290 range
- However the last FBS group, 241-290 range had only 7 patients

Relationship between MACE and Post Prandial blood sugar

Table 7

PPBS	**190-240**	**241-290**	**291-340**	**341-390**	**TOTAL**
No MACE	12	8	5	0	25
Recurrent Angina	0	2	4	0	6
Congestive cardiac failure	0	1	7	7	15
TOTAL	12	11	16	7	50

X^2= 55.69 P= <0.0001

It can be seen from this table:

- Among the No MACE group, large number of patients belong to the 190-240 and 241-290 PPBS range. 341-390 range did not have any patients.
- RA group shows 4 patients in 291-390 range and nil patients in 190-240 and 341-390 ranges
- CCF group shows equal presence of patients in 291-340 and 341-390 range

Relationship between MACE and Glycemic control

Table 8

	Well controlled	**Uncontrolled**	**TOTAL**
	HBA_{1C} 6.2-8.3	**HBA_{1C}>8.3**	
No MACE	20	8	28
Recurrent Angina	1	7	8
Congestive cardiac failure	0	14	14
TOTAL	9	41	50

X^2= 8.21 P= <0.0165

From this table it can be clearly seen that more patients under the No MACE group are under the well-controlled H BA_{1C}group(20 out of 28). But in the RA and CCF groups very few patients are under the well-controlled H BA_{1C} group (1 and 0 respectively). The category of poorly maintained H BA_{1C} group has the largest number of patients (41 out of 50). Chi square test was used to analyse and revealed a p value of 0.0165(statistically significant)

Relationship between Serum Fibrinogen levels &patient age

Table 9

Serum Fibrinogen(mg/dl)	**Age of the patient (years)**			
	40-49	**50-59**	**60-69**	**70-79**
200-250	1	0	1	0
251-300	1	4	1	1
301-350	3	7	3	1
351-400	0	1	1	0
>400	1	3	15	6
	6	15	21	8

X^2= 3.47 P= >0.05

The serum fibrinogen levels were recorded in 50 patients with major adverse cardiac events. It can be seen that serum fibrinogen levels 200-250 range has only 1 patient in 40-49 and 60-69 age groups with other groups recording nil entries. In the serum fibrinogen levels 251-300 category, majority of the patients are seen in the 50-59 age groups. Similar picture is reflected in serum fibrinogen levels category 301-350. There are nil patients in the age groups 50-59 and 60-69 under serum fibrinogen levels category 351-400. In contrast serum fibrinogen levels category >400 shows the highest number of patients in the 60-69 age group.

Relationship between Serum Fibrinogen levels and sex of the patient

Table 10

	Mean serum fibrinogen (mg/dl)		
	Male	**Female**	**P value**
No MACE	299.71	311.29	0.29
Recurrent Angina	349.33	339.57	0.64
Congestive cardiac failure	431.39	419.00	0.41

It can be seen from the above table that, among the No MACE group, the women had a mean serum fibrinogen level of 311, while the men had a mean serum fibrinogen level of nearly 300. In the RA group, , the women had a mean serum fibrinogen level of 339, while the men had a mean serum fibrinogen level of 349. Finally in the CCF group , the women had a mean serum fibrinogen level of 419, while the men had a mean serum fibrinogen level of 431. The three groups had p values of 0.29, 0.64 and 0.41, all of them not statistically significant.

Relationship between Serum Fibrinogen levels and duration of Diabetes

Table 11

Mean serum fibrinogen (mg/dl)	**No of cases according to duration of disease**		
	5-10	11-15	>15
No MACE	6	19	4
Recurrent Angina	1	2	5
Congestive cardiac failure	1	3	9
Mean serum fibrinogen	319	337	375

X^2= 14.87 P=0.01

Table 11 reveals the following

- Patients with diabetes for 5-10 years have a mean serum fibrinogen level of 319 mg/dl with maximum patients having no MACE
- Patients with diabetes for 11-15 years have a mean serum fibrinogen level of 337 mg/dl with maximum patients having no MACE
- Patients with diabetes for more than15 years have a mean serum fibrinogen level of 375 mg/dl with maximum patients in the CCF group

- Statistical comparisons yielded a chi square value of 14.87 and p value of <0.01(statistically significant)

Relationship between Serum Fibrinogen levels and Fasting blood sugar

Table 12A

FBS	**90-140**	**141-190**	**191-240**	**241-290**
Mean serum fibrinogen	298.71	333.31	406.62	424
No of Cases	15	21	12	2

Statistical comparisons

Table 12B

Comparisons	**Z value**	**P value**	
(90-140) – (141-190)	3.46	<0.01	
(141-190) - (191-240)	5.22	<0.001	
(191-240) - (241-290)	1.3	>0.05	

From the above table, it can be seen that:

- 15 patients belonged to the FBS 90-140 range with mean serum fibrinogen kevel of 299 mg/dl nearly
- 21 patients belonged to the FBS 141-190 range with mean serum fibrinogen kevel of 333mg/dl
- 12 patients belonged to the FBS 191-240 range with mean serum fibrinogen kevel of 406 mg/dl
- 2 patients belonged to the FBS 241-290 range with mean serum fibrinogen kevel of 424 mg/dl
- Statistical comparisons were performed between categories (90-140) – (141-190), (141-190) - (191-240) and (191-240) - (241-290). The z value obtained was 3.46, 5.22 and 1.3 respectively. The corresponding p values were <0.01, <0.001(both statistically significant) and >0.05

Relationship between Serum Fibrinogen levels and Post Prandial blood sugar

Table 13A

PPBS	**190-240**	**241-290**	**291-340**	**341-390**
Mean serum fibrinogen	295.77	332.1	365.18	425.1
No of Cases	13	12	18	7

Statistical comparisons

Table 13B

Comparisons	**Z value**	**P value**	
(190-240) – (241-290)	2.9	<0.01	
(241-290) - (291-340)	2.15	<0.05	
(291-340) - (341-390)	3.81	<0.001	

From the above table, it can be seen that:

- 13 patients belonged to the PPBS 190-240 range with mean serum fibrinogen kevel of 295.77 mg/dl
- 12 patients belonged to the PPBS 241-290 range with mean serum fibrinogen kevel of 332mg/dl
- 18 patients belonged to the PPBS 291-340 range with mean serum fibrinogen kevel of 365 mg/dl
- 7 patients belonged to the PPBS 341-390 range with mean serum fibrinogen kevel of 425 mg/dl
- Statistical comparisons were performed between categories (190-240) – (241-290), (241-290) - (291-340) and (291-340) - (341-390). The z value obtained was 2.9, 2.15 and 3.81 respectively. The corresponding p values were <0.01, <0.05 and <0.001(all statistically significant)

Relationship between Serum Fibrinogen and Glycemic control

Table 14

	Well controlled	**Uncontrolled**	**TOTAL**
	HBA_{1C} 6.2-8.3	**HBA_{1C}>8.3**	
Mean fibrinogen values	315.06	354.10	28
No of Cases	11	39	8
Z value	2.67		
P value	<0.01		

In this table, it is seen that mean serum fibrinogen value for the category of well controlled (11 patients) HBA_{1C} was 315.06, while the mean serum plasma fibrinogen value for the category of poorly controlled (39 patients) HBA_{1C} was 354.10. Statistical comparisons of mean serum fibrinogen values of the two categories yielded a z value of 2.67 and a p value of <0.001(statistically significant).

Relationship between Serum Fibrinogen levels and MACE

Table 15A

MACE	**No of Patients**	**Mean serum fibrinogen levels**
No MACE	24	306.07
Recurrent Angina	11	344.08
Congestive cardiac failure	15	426.32

Statistical comparisons

Table 15B

Comparisons	't'	'p'
No MACE - Recurrent Angina	3.89	<0.001
Recurrent Angina - Congestive cardiac failure	6.63	<0.001
Congestive cardiac failure - No MACE	14.84	<0.001

Tables above reveal that

- No MACE category has 24 patients with mean serum fibrinogen level of 306.07 mg/d
- RA category has 11 patients with mean serum fibrinogen level of 344.08 mg/dl
- CCF category has 15 patients with mean serum fibrinogen level of 426.32 mg/dl
- Comparisons between mean serum fibrinogen levels of No MACE - Recurrent Angina category yielded a t value of 3.89
- Comparisons between mean serum fibrinogen levels of Recurrent Angina - Congestive cardiac failure category yielded a t value of 6.63
- Comparisons between mean serum fibrinogen levels of Congestive cardiac failure - No MACE category yielded a t value of 14.84
- All of the comparisons had a p value of <0.001

DISCUSSION

The present study, which is cross sectional in design, has a sample size of 50 patients of Diabetes mellitus with coronary artery disease. Among the 26 patients with major adverse cardiac events 11 had recurrent angina (22%) and 15 had congestive cardiac failure(30%).

The relationship between patient age and major adverse cardiac events among 50 patients were obtained from table 3. They revealed that the severity of major adverse cardiac events increased with the increasing age of the patients in a statistically significant manner.

Although there is a higher number of males than females with regard to total number of patients, it is evident that there is no significant variation in major adverse cardiac events in relation to gender of the patient

More patients with recurrent angina and congestive cardiac failure were among those patients with diabetic age more than 15 years(table 6). The findings prove that worsening of major adverse cardiac events with increasing duration of diabetes in these individuals is statistically significant.

Regarding the relationship of fasting blood sugar and post prandial blood sugar levels with the severity of major adverse cardiac events, it was observed that there is a statistically significant increase in the severity of major adverse cardiac events with increasing values of FBS and PPBS.

One of the studies conducted previously in this regard found that risk of major adverse cardiac events six times more among patients with poor glycemic control. [68]

Serum fibrinogen is one of the important factors that leads to the increased viscosity of blood, especially in diabetics. It is known for its role in end organ diseases. In this study serum fibrinogen levels was compared with various parameters and statistically analysed. The observations and interpretations are as follows

- No correlation found between the age of the patients and gender of the patients with their levels of serum fibrinogen

- When serum fibrinogen levels were correlated with various parameters regarding the diabetic age, blood sugar and glycemic control, mean serum fibrinogen was found to be in correlation with all the above parameters. It means that with progression and increase in severity of diabetes, there is a noticeable rise in mean serum fibrinogen titres.

- This could be attributed to the reason that long standing and poorly controlled diabetes is associated with greater incidence of macro vascular pathologies. It is seen in a related study that serum fibrinogen levels were higher in those diabetics with poor metabolic control [69]

- There is a positive correlation between major adverse cardiac events and mean serum fibrinogen levels. Increase in severity of major adverse cardiac events causes simultaneous increase in serum fibrinogen. Other similar studies have concluded stating that fibrinogen may be involved in increased cardiovascular risk of patients with diabetes[70,58]

SUMMARY &CONCLUSION

The summary of results obtained is as follows:

- The study included 50 diabetic patients with coronary artery disease.
- Age varied from 44 to 78 years
- 52% of the patients suffered from major adverse cardiac events(recurrent angina and congestive cardiac failure)
- Older patients had more severe forms of major adverse cardiac events
- There is no significance between gender of patients and severity of major adverse cardiac events
- Longer the duration of diabetes more severe the major adverse cardiac events
- Higher blood sugar levels and poorer glycemic control leads to severe major adverse cardiac events
- No correlation between mean serum fibrinogen level and age or gender of the patient

- Mean serum fibrinogen levels was significantly higher in patients with longer duration of diabetes, higher blood sugars and poor glycemic control
- Increase in severity of major adverse cardiac events correlates with increase in serum fibrinogen titres

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PROFORMA

S.NO :

DATE:

AGE:

IP NO:

NAME:

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UNIT:

PHONE NO.:

ADDRESS:

OCCUPATION:

EDUCATION

INCOME

INVESTIGATIONS:

CBC:

HB:

PCV:

TC:

DC:

ESR

BLOOD SUGAR- RBS

FBS

PPBS

Hb A1C:

FIBRINOGEN:

UREA:

CREATININE:

LIPID PROFILE:

URINE ROUTINE:

ECG:

ECHO:

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

"இதய நோய் உள்ள சர்க்கரை நோயாளிகளின் எதிர்மறை இதய நிகழ்வுகளை கணிக்கும் ஃபைப்ரினோஜன் என்றும் இரத்த புரதத்தின் கணிப்புத்தன்மையின் ஆய்வு"

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது :

பங்கு பெறும் நோயாளியின் எண் : பாலினம் : ஆண் ☐ பெண் ☐

நோயாளியின் விலாசம் :

நோயாளி இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

நோயாளியின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

.....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study on serum fibrinogen as an independent Predictor of Major Adverse cardiac events (MACE) In known diabetic coronary Artery Disease patients

Principal Investigator : Dr.M.Amudhan

Designation : PG in M.D (GM)

Department : Department of General Medicine Government Stanley Medical College, Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.06.2012 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

16/10/12

MEMBER SECRETARY,
IEC, SMC, CHENNAI

MASTER KEY

SBP : SYSTOLIC BLOOD PRESSURE

DBP : DIASTOLIC BLOOD PRESSURE

FBS : FASTING BLOOD SUGAR

PPBS : POSTPRANDIAL BLOOD SUGAR

ECG : ELECTROCARDIOGRAM

ECHO: ECHOCARDIOGRAM

TC : TOTAL CHOLESTROL

LDL : LOW DENSITY LIPOPROTEIN

HDL : HIGH DENSITY LIPOPROTEIN

VLDL : VERY LOW DENSITY LIPOPRITEIN

TGL : TRIGLYCERIDES

MACE: MAJOR ADVERSE CARDIAC EVENT

IWMI : INFERIOR WALL MYOCARDIAL INFARCTION

PRWP : POOR R WAVE PROGRESSION

EF : EJECTION FRACTION

T2DM : TYPE 2 DIABETES MELLITUS

SHT : SYSTEMIC HYPERTENSION

CAD : CORONARY ARTERY DISEASE

DCMP : DILATED CARDIOMYOPATHY

IDCMP : ISCHEMIC DILATED CARDIOMYOPATHY

CCF : CONGESTIVE CARDIAC FAILURE

RWMA : REGIONAL WALL MOTION ABNORMALITY

LVSE : LEFT VENTRICULAR SYSTOLIC FUNCTION

UA : UNSTABLE ANGINA

NSR : NORMAL SINUS RHYTHM

WNL : WITHIN NORMAL LIMIT

LVH : LEFT VENTRICULAR HYPERTROPHY

CKD : CHRONIC KIDNEY DISEASE

LVF : LEFT VENTRICULAR FAILURE

CVA : CEREBRO VASCULAR ACCIDENT

COPD : CHRONIC OBSTRUCTIVE PULMONARY DISEASE

PT : PULMONARY TUBERCULOSIS

ADD : ACUTE DIARRHOEAL DISEASE

LL : LOWER LOBE

DD : DIASTOLIC DYSFUNCTION

GERD : GASTRO ESOPHAGEAL REFLUX DISEASE

RA : RECURRENT ANGINA

AR : ARRRYTHMIAS

CD : DEATH

OCP : ORAL CONTRACEPTIVE PILLS

COPD : CHRONIC OBSTRUCTIVE LUNG DISEASE

S.No.	Name	Age	Sex male=1 female=2	SBP	DBP	Urine		Duration of Diabetes inYears	FBS	FBS	PPBS	PPBS	Glycosylated Hb	ECG	Echo	Fasting Lipd Profile					Urea	Creatinine	S. Fibrinogen	Diagnosis	MACE NIL=0 RA=1 CCF=2 ARR=3 CD=4
						Albumin nil=1 trace=2 1+=3 2+=4 3+=5	Sugar nil=1 trace=2 1+=3 2+=4 3+=5									TC	LDL	HDL	VLDL	TGL					
1	Nagammal	44	1	140	96	1	3	5	178	233	182	292	6.1	Old IWMI, PRWP in V1 - V3	Thin hypokinetic mid IW, EF 30%	151	87	45	19	99	21	0.7	462	T2DM/SHT/CAD/IDCMP/CCF	0
2	Palliappan	46	1	140	96	1	2	6	175	230	219	329	9.6	ST ↓ II,III, aVF	No RWMA, Normal LVSF	136	90	30	16	81	32	1.2	377.8	SHT/T2DM/COPD/CAD	0
3	Jayalakshmi	47	1	130	86	1	1	6	89	144	108	218	8.9	ST ↓ V2 - V5	Normal LVSF	131	87	28	16	81	17	0.8	395.2	T2DM/CAD/UA	0
4	Kothandaraman	47	1	140	94	1	1	6	120	175	162	272	8.4	NSR, WNL	No RWMA, Normal LVSF	120	68	30	22	77	35	0.9	380	T2DM/SHT/CAD/UA	0
5	Balakrishnan	47	1	160	102	2	4	7	155	210	210	320	9.1	NSR, LVH, ST ↓ & T wave ↓ V1 - V4	Global hypokinesia of inferobasal wall, EF 32%	137	87	26	24	120	36	1.2	423	T2DM/ CAD/ DCMP/ CCF	0
6	Sivasamy	51	1	200	120	3	1	7	112	167	140	250	7.2	NSR,LVH with strain	Concentric LVH	148	108	20	20	160	55	1.4	360	T2DM/CAD/CKD/Acc.HT/LVF	0
7	Selvam	52	1	150	94	1	1	8	120	175	160	270	8.8	NSR,LVH	No RWMA,Conc.LVH	135	87	28	20	86	35	0.8	382	T2DM/CAD/Old CVA/UA	0
8	Mani	54	1	130	84	1	4	9	155	210	233	343	9.3	ST↓L2,L3 & Avf	No RWMA,Normal LVSF	138	90	30	18	90	40	1.1	374	T2DM/CAD/UA/Inferior wall ischemia	0
9	Daniel	54	1	140	100	1	1	11	140	195	192	302	9.1	T↓L1,Avl, LVH	No RWMA,Conc.LVH	137	88	30	19	104	50	1	375	T2DM/SHT/COPD/CAD/Recurrent angina	0
10	Purushothaman	55	1	140	90	1	4	11	140	195	182	292	7.8	T↓L1,aVL, V5,V6	No RWMA,Normal LVSF	136	88	28	20	140	40	1	398	T2DM/CAD/UA/Lateral wall ischemia	0
11	Thangappan	56	1	130	86	1	1	11	104	159	136	246	8.8	WNL	Normal LV function	125	80	26	19	130	26	0.8	356	T2DM/CAD/UA	0
12	Mallika	56	1	160	94	1	4	11	10	65	200	310	8.5	NSR, LVH with strain pattern	No RWMA, conc. LVH	141	98	20	23	160	36	0.9	364	T2DM/ CAD/ SHT/ LVF	0
13	Munusamy	56	1	130	90	1	1	11	102	157	136	246	9	NSR, LV strain pattern	Hypokinesia of infero-posterior segment of LV, EF 46%	144	98	20	26	160	38	0.9	368	T2DM/ CAD/ LVF	0
14	Chinnasamy	58	1	168	96	2	3	11	130	185	184	294	6.9	NSR, LVH with strain pattern	No RWMA, conc. LVH	112	60	30	22	160	36	1.2	392	T2DM/ SHT/ CAD/ LVF	0
15	Saleem Basha	58	1	130	86	1	1	11	120	175	184	294	8.4	NSR, no specific ST-T changes	No RWMA, Normal LV function	187	122	45	20	84	40	1	310	T2DM/CAD/ UA	0
16	Manalan	56	1	140	86	1	1	12	120	175	162	272	8.5	NSR, ST↓, T↓ I, avL, V5, V6	hypokinesia of inferolateral segment of LV, EF 50%	146	96	30	20	81	50	1	366	T2DM/ CAD/ OLD PT/ LVF	0
17	Punitha	55	1	130	86	1	1	12	102	157	156	266	8.1	NSR, T wave↓ avL V5 - V6	No RWMA, Normal LV function	143	92	33	18	82	36	0.8	302	T2DM/COPD/ UA	0

18	Krishnamoorthy	57	1	172	96	3	4	12	146	201	220	330	9.2	NSR, LVH with strain pattern	hypokinesia of mid inferior wall, MR trivial, EF 32%	145	98	28	19	168	38	1.2	392	SHT/T2DM/CAD/ LVF	0
19	Nagavalli	57	1	160	100	1	1	12	132	187	180	290	9.3	NSR, LVH with strain pattern	No RWMA, Normal LV function	113	68	25	20	102	42	0.9	388	T2DM/CAD/OLD IWMI/ LVF	0
20	Munusamy	57	1	200	100	1	3	12	132	187	198	308	9	NSR, LVH with strain pattern	No RWMA, Normal LV function	113	45	48	20	100	36	0.9	393.2	T2DM/ SHT/ CAD/ LVF	0
21	Buvana	59	1	140	92	1	1	12	112	167	136	246	9.1	NSR, no specific ST-T changes	No RWMA, Normal LV function	123	58	45	20	170	40	0.9	276	T2DM/ SHT/ CAD/ ADD	0
22	Kanniappan	61	1	150	88	1	1	12	130	185	156	266	8.9	NSR, Qs III, avF	Hypokinesia of mid inferior wall, EF 46%	160	98	40	22	170	38	1.1	292.2	T2DM/ Old IWMI/ fever for evaluation	0
23	Valliammal	61	1	154	88	1	3	13	132	187	164	274	9	NSR, WNL	No RWMA, Normal LV function	140	90	30	20	90	38	1.1	280	T2DM/CAD/COPD EXACERBATION	0
24	Muthappan	61	1	148	86	1	1	13	107	162	148	258	8.8	NSR, WNL	No RWMA, Normal LV function	141	80	42	19	132	46	1	274.3	T2DM/CAD/COPD CHRONIC BRONCHITIS	0
25	Pushpa	61	1	160	92	3	4	13	136	191	180	290	9.1	NSR, no specific ST-T changes	No RWMA, Normal LV function	148	98	28	22	162	56	1.2	299.2	T2DM// CAD/ LRI	1
26	Govindasamy	61	1	150	88	3	3	13	130	185	168	278	9.2	Qs in V1 - V4	Hypokinesia of antero basal segment, Ef 45%	146	98	28	20	160	55	1.2	312	T2DM/ CAD/ OLD IWMI/ VIVAX MALARIA	1
27	Natarajan	61	1	136	88	3	1	14	130	185	156	266	7.8	Qs II, III, avF	mild hypokinesia of inferobasl wall, EF 50%	130	80	30	20	146	55	1.1	310	T2DM/CAD/OLD IWMI/COPD EXACERBATION	1
28	Valluvan	62	1	142	86	1	1	14	103	158	136	246	8.7	NSR, WNL	No RWMA, Normal LV function	149	86	45	18	132	36	0.9	298.2	T2DM/CAD/COPD EXACERBATION	1
29	Gunalan 55	64	1	152	90	1	1	15	162	217	162	272	9.2	NSR, WNL	No RWMA, Normal LV function	120	60	40	20	100	36	1	312	T2DM/CAD/ old PT/ COPD EXACERBATION	1
30	sundaram	64	1	154	92	1	1	15	120	175	156	266	7.7	NSR, no specific ST-T changes	No RWMA, Normal LV function	138	88	30	20	90	50	1	334.2	T2DM/CAD/ LEFT LL PNUEMONIA	1
31	Karpagam	64	1	140	82	1	1	15	120	175	142	252	8.8	NSR. WNL	No RWMA, Normal LV function	130	82	32	16	80	32	0.8	282.2	T2DM/AD/ bronchial asthma exacerbation	1
32	Karnan	64	1	160	88	1	3	15	112	167	182	292	8.7	NSR, T wave↓ I, avL	No RWMA, Normal LV function	146	98	28	20	156	50	1.1	282.2	T2DM/CAD/ acute febrile illness	1
33	Lalitha	64	1	140	86	1	1	16	108	163	136	246	8.4	NSR. WNL	No RWMA, Normal LV function	124	68	38	18	98	38	1	274.4	T2DM/CAD/ acute febrile illness for evaluation	1
34	Chellatha	65	2	162	92	3	4	16	142	197	199	309	9.1	Qs II, III, avF	Hypokinesia of inferobasal segment, EF 45%	152	102	28	22	162	51	1.3	332.2	T2DM/ OLD IWMI/ fever for evaluation	1
35	Krishnan	65	2	140	80	1	1	16	102	157	132	242	6.4	NSR. WNL	No RWMA, Normal LV function	123	66	38	19	120	36	1	286	T2DM/CAD/ ADD WITH MILD DEHYDRATION	1
36	Maragadam	66	2	154	92	1	3	17	130	185	182	292	9.1	NSR, T↓ v5, v6	No RWMA, Normal LV function	121	72	29	20	135	55	1.1	332	T2DM/CAD/ COPD EXACERABATION	2
37	Elavarasi	66	2	142	86	1	1	17	120	175	156	266	8.9	NSR. WNL	No RWMA, Normal LV function	126	68	38	20	110	42	0.9	270	T2DM/CAD/ COPD EXACERABATION	2
38	Muthusamy	66	2	154	88	1	1	17	122	177	155	265	8.4	T ↓ V2 - V4	No RWMA, Normal LV function	112	60	32	20	134	50	1	311.2	T2DM/CAD/ acute febrile illness for evaluation	2

39	Kannagi	68	2	140	82	1	1	18	106	161	142	252	9	NSR. WNL	No RWMA, Normal LV function	130	76	38	16	102	50	0.9	283.2	T2DM/CAD/ MALARIAL FEVER	2
40	Natarajan	69	2	148	88	1	1	18	130	185	184	294	9.4	NSR. WNL	No RWMA, Normal LV function	266	92	32	142	20	38	1.1	323.2	T2DM/CAD/FEVER WITH ARTHRALGIA	2
41	Krishnamoorthy	67	2	130	88	1	1	18	120	175	146	256	8.5	Qs V1-V5	Hypokinesia of AW septum, EF 45%	126	76	30	20	126	35	0.8	312	SHT/CAD/ OLD AWMI/LVF	2
42	Krishnaraj	70	2	150	100	1	1	19	132	187	193	303	7.2	T ↓ avL, V5,V6	No RWMA, conc. LVH	152	102	25	22	110	40	1	273.2	SHT/UA/ LATERAL WALL ISCHEMIA	2
43	Mani	70	2	140	86	1	3	19	140	195	200	310	8.8	NSR. WNL	No RWMA, Normal LV function	132	84	28	20	130	42	0.9	297	SHT/UA	2
44	Krishnaveni	71	2	110	84	1	1	21	132	187	155	265	8.4	Low voltage complex with PPRW	Global hypokinesia of LV, EF 35%	132	84	28	20	132	45	1.1	325.2	T2DM/SHT/CAD/ISCHEMIC DCMP/CCF	2
45	Muthukannan	73	2	156	96	1	3	21	146	201	206	316	9.5	ST↓v2-v5	Grade 1 DD	119	67	34	18	98	36	1.1	298	T2DM/SHT/CAD/RECURRENT ANGINA	2
46	Rajappa	74	2	136	94	1	1	21	133	188	156	266	9.1	NSR,T↓L1,Avl	No RWMA, Normal LV function	151	102	26	23	145	42	1	326	T2DM/CAD/DYSLIPIDEMIA/SHT/LW ISCHEMIA	2
47	Lalitha	75	2	138	94	1	1	22	123	178	156	266	8.9	WNL	Normal LV function	146	88	38	20	124	40	0.8	286	T2DM/CAD/ENTERIC FEVER	2
48	Santhanam	76	2	124	78	1	1	23	106	161	137	247	8.6	WNL	Normal LV function	140	76	46	18	97	37	0.9	256	T2DM/CAD/GERD	2
49	Henry	77	2	156	94	3	3	24	133	188	187	297	9.1	QS L1,Avl,v5,v6	Hypokinesia of Laterobasal segment, EF 43%	117	67	30	20	138	56	1.1	334	T2DM/CAD/UA	2
50	Rasiya bebum	87	2	100	70	1	3	24	155	210	224	334	9.8	QS L2,L3 & aVF	Hypokinesia of Inferior segment of LV, EF 28%	132	82	32	18	122	34	1	390.4	T2DM/CAD/OLD IWMI/DCMP/CCF	2