"CORRELATION OF PLASMA FIBRINOGEN LEVEL IN TYPE II DIABETES MELLITUS PATIENTS WITH HBA1C LEVELS AND MICROVASCULAR COMPLICATIONS – A ONE YEAR CROSS SECTIONAL STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled **"CORRELATION OF PLASMA FIBRINOGEN LEVEL IN TYPE II DIABETES MELLITUS PATIENTS WITH HBA1C LEVELS AND MICROVASCULAR COMPLICATIONS – A ONE YEAR CROSS SECTIONAL STUDY"** is a bonafide research work done by **REG NO.BG0115015.**

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LIST OF ABBREVIATIONS

AACE	–	American Association of Clinical Endocrinologists
ADA	–	American Diabetes Association
AGE	–	Advanced glycation end products
ATP	–	Adenosine triphosphate
BMI	–	Body mass index
CAD	–	Coronary artery disease
cAMP	–	Cyclic adenosine monophosphate
CKD	–	Chronic kidney disease
DCCT	–	Diabetes Control and Complications Trial
DM	–	Diabetes Mellitus
EASD	–	European Association for the study of Diabetes
ESRD	–	End stage renal disease
FBS	–	Fasting plasma glucose
FPG	–	Fasting plasma glucose
GDM	–	Gestational diabetes mellitus
HDL	–	High density lipoprotein
IDF	–	International Diabetes Federation
IFG	–	Imparired fasting glucose
IGT	–	Impaired glucose tolerance
IL-6	–	Interleukin 6

NPH	–	Neutral protamine Hagedorn
PAD	–	Peripheral artery disease
PCOS	–	Polycystic ovarian syndrome
PPAR	–	Peroxisome proliferator activated receptor
PPBS	–	Post prandial blood sugar
SMBG	–	Self monitoring of blood glucose
SPSS	–	Statistical package for the social sciences
TGF-beta	–	Transforming Growth Factor beta
TNF	–	Tumor necrosis factor
UKPDS	–	United Kingdom Prospective Diabetes Study
VLDL	–	Very low density lipoprotein
WHO	–	World Health Organisation

ABSTRACT

BACKGROUND: Diabetes is considered one of the most common non communicable diseases globally. There are various complications of diabetes mellitus which may be microvascular or macrovascular, affecting all the systems in the body. Many studies have shown that hemostatic disturbance, including high fibrinogen levels, are associated with coronary heart disease in patients with diabetes.

AIMS AND OBJECTIVES:

1. To Study Plasma Fibrinogen levels in Type 2 Diabetes Mellitus patients with Microvascular complications.
2. To Study the association of Plasma Fibrinogen levels with Glycemic control.

METHODOLOGY: A one year cross sectional study was conducted in the KLEs Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi. 100 type 2 diabetes mellitus patients fulfilling the inclusion criteria were included in the study. These patients underwent history, clinical examination, FBS, PPBS, HBA1c and fibrinogen estimation. Descriptive statistics was used for data analysis.

RESULTS: In our study, the prevalence of hyperfibrinogenemia was found to be 88%. There was a significant association between fibrinogen levels and HBA1c levels(p value less than 0.0001). We also found a significant association between duration of diabetes and fibrinogen levels(p value less han 0.001). There was no significant association between gender and HBA1c, HBA1c and microvascular complications and fibrinogen and microvascular complications.

CONCLUSION: Thus plasma fibrinogen can be used as a marker for microvascular complications in type 2 diabetes mellitus as the prevalence of hyperfibrinogenemia among type2 diabetes patients with microvascular complications was 88%. There was also a significant association between duration of diabetes and plasma fibrinogen and glycaemic control and plasma fibrinogen.

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. The prevalence of diabetes has increased over the past decade and has been predicted to increase in the future. According to WHO, about 180 million people have diabetes. According to the current trend, more than 360 million people will have the disease by 2030[1].

Although the prevalence of both type 1 and type 2 diabetes mellitus is increasing worldwide, the prevalence of type 2 diabetes mellitus is expected to rise more rapidly in future because of increasing obesity and reduced activity levels[2]. Diabetes increases the morbidity and mortality due to its propensity to develop micro and macroangiopathy[3].

Diabetes has a major and deleterious impact on both individual and national productivity. The socio economic consequences of diabetes and its complications could have a seriously negative impact on the economics of developed and developing nations (WHO, 2011). Complications from diabetes such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, renal failure, and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society.

In the past decade, the suspected role of hemostatic factors, particularly fibrinogen, in atherosclerosis and its complications has invited considerable attention. Studies have shown that in acute myocardial infarction, formation of an occlusive thrombus, on a damaged atherosclerotic lesion is the most common precipitating

factor. Evidence also suggests that fibrinogen has a role, both in the early stages of plaque formation and late complications of cardiovascular disease[4].

Recently increased attention is being paid to, disordered hemostatic mechanism in pathogenesis of both large and small vessel disease in diabetes[5]. Impaired glucose tolerance and chronic hyperglycaemia exerts an influence on the pathogenesis of microvascular complications by increasing the thrombogenic factors like fibrinogen[6]. Cardiovascular complications account for nearly 50% of deaths in type 2 diabetes mellitus and 25% in type 1 patients.

OBJECTIVES

1) To study plasma fibrinogen levels in type II diabetes mellitus patients with microvascular complications.
2) To study the association of plasma fibrinogen levels with glycaemic control.

REVIEW OF LITERATURE

Diabetes mellitus (DM) refers to a group of common metabolic disordersthat share the phenotype of hyperglycemia. Factors contributingto hyperglycemia include reduced insulin secretion, decreasedglucose utilization, and increased glucose production.The metabolicdysregulation in diabetes mellitus causes secondary pathophysiologicchanges in multiple organ systems that impose a tremendous burdenon the individual with diabetes and on the health care system.

EPIDEMIOLOGY:

In the United States, DM is the leading cause of end-stage renal disease (ESRD), no traumatic lower extremity amputations, and adult blindness[7]. With over 20 million diabetic people, India leads the world in the number of individuals with Diabetes Mellitus[8].

Worldwide prevalence of diabetes mellitus. Global estimate is 382 million individuals with diabetes. Regional estimates of the number of individuals with diabetes (20–79 years of age) are shown (2013). *(Used with permission from the IDF Diabetes Atlas, the International Diabetes Federation, 2013.)*

Figure 1. Worldwide Prevalence Of Diabetes

CLASSIFICATION:

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset ortype of therapy. There are two broad categories of DM, designated type 1 and type 2.

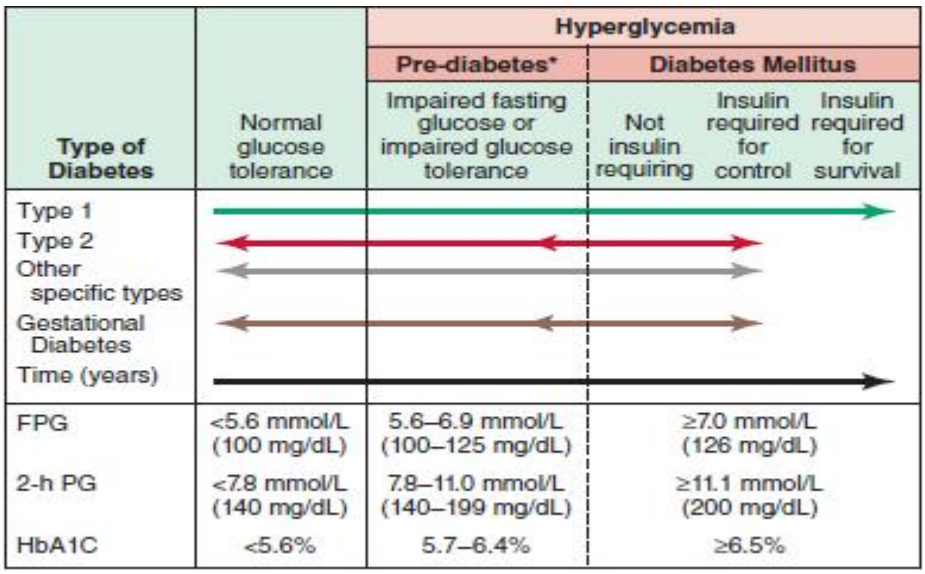


Figure 2. Spectrum Of Glucose Homeostasis And Diabetes Mellitus

Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.

PATHOGENESIS:

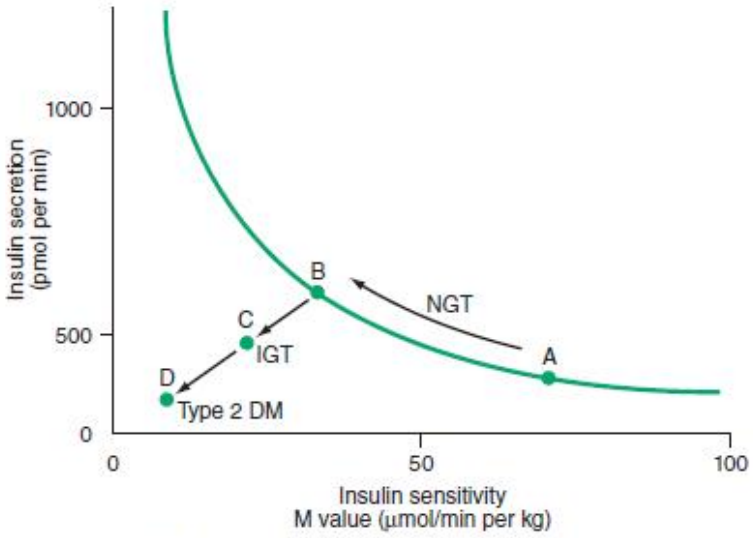
The pathogenesis to some extent depends on the ethnicity and descent of the individual for eg; Latinos have greater insulin resistance and East Asians and South Asians have more beta cell dysfunction, but both defects are present in both populations[9]. East and South Asians appear to develop type 2 DM at a younger age and a lower BMI. In some groups, DM that is ketosis prone (often obese) or ketosis-resistant (often lean) is seen.

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.In situations where resistance to insulin predominates, the mass of β-cells undergoes a transformation capable of increasing the insulin supply and compensating for the excessive and anomalous demand.

In absolute terms, the plasma insulin concentration (both fasting and meal stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to maintain normal glucose homeostasis. Keeping in mind the intimate relationship between the secretion of insulin and the sensitivity of hormone action in the complicated control of glucose homeostasis, it is practically impossible to separate the contribution of each to the etiopathogenesis of type 2 DM[10].

Type 2 DM is characterized by impaired insulinsecretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output.

As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure ensues.



Metabolic changes during the development of type 2 diabetes mellitus (DM). Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D). NGT, normal glucose tolerance. *(Adapted from SE Kahn: J Clin Endocrinol Metab 86:4047, 2001; RN Bergman, M Ader: Trends Endocrinol Metab 11:351, 2000.)*

Figure 3. Metabolic Changes During The Development Of Type 2 Diabetes Mellitus

Glucose tolerance impairement exerts an influence by increasing the thrombogenic factors like fibrinogen. Several studies have shown that thrombogenic factor especially hyperfibrinogenemia is implicated as a source of atherosclerosis and its complications[11,12,13]. Increase in Plasma Fibrinogenis thought to be one of the major factors associated with increase in blood viscosity.

ROLE OF FIBRINOGEN IN TYPE II DIABETES MELLITUS:

Fibrinogen plays an important role in a number of pathological processes in the body, including inflammation, thrombogenesis and atherogenesis. The proposed mechanisms are[14] vessel wall infiltration by fibrinogen, haemorheological effects

because of increase in blood viscosity, increased platelet aggregation and thrombus formation, augmentation of platelet degranulation etc[14].

Formation of an occlusive thrombus, on a damaged atherosclerotic lesion is the most important precipitating factor of acute myocardial infarction. Evidence also suggests that fibrinogen has a role, in the early stages of plaque formation and also late complications of cardiovascular disease[15]. Impaired glucose tolerance influences the pathogenesis by increasing the thrombogenic factors like fibrinogen[16].

There are a number of mechanisms to explain increased fibrinogen levels in DM: 1) Diabetes is associated with low grade inflammation and as a result Interleukin 6 are elevated in thesepatients. This cytokine stimulates hepatocytes to produce fibrinogen representing an important link between inflammation and hypercoagulation[17]. 2) Insulin resistance in type 2 DM is associated with increased hepatic fibrinogen production in response to insulin[17]. Increased fibrinogen synthesis has also been demonstrated postprandially in type 2 DM but not in healthy controls further suggesting hepatic dysregulation of fibrinogen synthesis in this condition[18]. 3) In diabetic patients there is increased rate of fibrinogen clearance with shorter fibrinogen circulating half life. This means that the rate of synthesis is even more than that indicated by plasma level. 4) An association between oxidative stress and plasma fibrinogen has been observed in diabetics[19]. Fibrinogen synthesis is regulated by a feedback mechanism by thrombin activation[20]. In diabetics thrombin formation is induced by free radicals[21]. Hyperglycemia and insulin resistance and the consequent oxidative stress may give rise to increased thrombin formation.

Fibrinogen binds specifically toactivated platelets via glycoprotein IIb/IIacontributing to platelet aggregation. Also increased fibrinogen levelspromote

formation of fibrin. Fibrinogen is a major contributor to plasma viscosity. Finally fibrinogen is an acutephase reactant that is increased in inflammatory states[22].

Fibrinogen and its metabolites may lead to endothelial dysfunction through various mechanisms[23]. Several atherosclerotic lesions contain large amounts of fibrin. This phenomenon is associated with a decrease in fibrinolyticactivity and plasminogen concentrations which are observed in CAD[24].It has been found that fibrin triggers cell proliferation, contributing to cell migration and bonds fibronectin which also triggers cell migration and adhesion[25]. In advanced atherosclerotic plaques, fibrin participates in the cross linkage of LDL and lipid accumulation leading to the creation of the lipid core of atherosclerotic lesions[24,26]. The Gothenburg study[27] and Framingham study[28]reported that plasma fibrinogen levels represent an independent risk factor for myocardial infarction and stroke in univariate analysis.

METABOLIC ABNORMALITIES:

ABNORMAL MUSCLE AND FAT METABOLISM:

Insulin resistance, the decreased ability of insulin to act effectively on target tissues (especially muscle, liver, and fat), is an important feature of type 2 DM and results from a combination of genetic susceptibility and obesity. Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia.

Increase in hepatic glucose output predominantly accounts for increased FPG levels, whereas decrease in peripheral glucose usage results in postprandial hyperglycemia[9]. The exact molecular mechanism leading to insulin resistance in type 2 DM has not been elucidated. Insulin receptor levels and tyrosine kinase activity in

skeletal muscle are reduced, but these alterations are most likely secondary to increased insulin levels and are not a primary defect.

Hence, "postreceptor" defects in insulin-regulated phosphorylation/ dephosphorylation appear to play the predominant role in insulin resistance. Abnormalities include the accumulation of lipid within skeletal myocytes, which may impair mitochondrial oxidative phosphorylation and decrease insulin-stimulated mitochondrial ATP production.

It is important to note that, not all insulin signal transduction pathways are resistant to the effects of insulin (e.g., those controlling cell growth and differentiation using the mitogenic -activated protein kinase pathway). Consequently, hyperinsulinemia may increase the insulin action through these pathways, potentially accelerating diabetes related conditions such as atherosclerosis.

The obesity accompanying type 2 DM, is considered to be part of the pathogenic process. The increased adipocyte mass leads to increased levels of circulating free fatty acids and other fat cell products like nonesterified free fatty acids, retinolbinding protein 4, leptin, TNF-α, resistin, IL-6, and adiponectin called adipokines. In addition to regulating body weight, appetite, and energy expenditure,adipokines also modulate insulin sensitivity.

Adipocyte products and adipokines also produce an inflammatory state and may explain why markers of inflammation such as IL-6 and C-reactive protein are often elevated in type 2 DM[29].

IMPAIRED INSULIN SECRETION:

The reason(s) for the decrease in insulin secretory capacity in type 2 DM is unclear. It is assumed that a second genetic defect—superimposed upon insulin resistance—leads to beta cell failure. Islet amyloid polypeptide called amylin, co secreted by the beta cell, forms the amyloid fibrillar deposit found in the islets of patients with long-standing type 2 DM. If such islet amyloid deposits are a primary or secondary event is yet to be known.

INCREASED HEPATIC GLUCOSE AND LIPID PRODUCTION:

Insulin resistance leads to increased hepatic gluconeogenesis which in turn leads to fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state. Insulin resistance also leads to increased lipolysis and free fatty acid flux from adipocytes, leading to increased lipid (very-low-density lipoprotein [VLDL] and triglyceride) synthesis in hepatocytes. This lipid storage in the liver may result in non alcoholic fatty liver disease and abnormal liver function tests[29].

DIAGNOSIS:

Glucose tolerance is classified under three broad categories: normal glucose homeostasis, DM, or impaired glucose homeostasis. An FPG ≥7.0 mmol/L (126 mg/dL), a glucose ≥11.1 mmol/L (200 mg/dL) 2 h after an oral glucose challenge, or an HbA1c ≥6.5% indicates the diagnosis of DM. Abnormal glucose homeostasis is defined by (1) FPG = 5.6–6.9 mmol/L (100–125 mg/dL), which is calledimpairedfasting glucose (IFG); (2) plasma glucose levels between 7.8 and 11 mmol/L (140 and 199 mg/dL) following an oral glucose challenge, which is termed as impaired glucose tolerance (IGT); or (3) HbA1c of 5.7–6.4%.

RISK FACTORS FOR THE DEVELOPMENT OF DIABETES MELLITUS:

- Family history of DM (i.e., parent or sibling with type 2 diabetes).
- Obesity i.e., BMI ≥25 kg/m2 or ethnically relevant definition for overweight.
- Physical inactivity.
- Race or ethnicity (e.g., African American, Latino, Native American, AsianAmerican).
- Previously history of IFG, IGT, or a hemoglobin A1c of 5.7–6.4%.
- History of GDM or delivery of baby >4 kg (9 lb).
- Hypertension i.e.,blood pressure ≥140/90 mmHg.
- HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level of >250 mg/dL (2.82 mmol/L).
- PCOS or acanthosis nigricans.
- History of cardiovascular disease[30].

TREATMENT:

The goals of therapy for diabetes mellitus (DM) are:

1. Eliminate symptoms due to hyperglycemia,
2. Reduce and/or eliminate the long-term complications of dm, and
3. Allow the patient to achieve as normal a lifestyle as possible[31].

It is a *comprehensive diabetes care* which is essential in the management of diabetes rather than strict glycemic control alone.

Comprehensive Medical care for patients with diabetes consists of:

- Individualised glycemic control
- Self monitoring of blood glucose
- Hba1c testing every 3 months
- Diabetes self management education and support
- Medical nutrition therapy
- Eye examination(yearly or twice in a year)
- Foot examination(twice a year by the physician and daily by the patient)
- Screening for diabetic nephropathy
- Blood pressure measurement
- Lipid profile and serum creatinine measurement
- Influenza/pneumococcal/hepatitis b immunization
- Antiplatelet therapy.

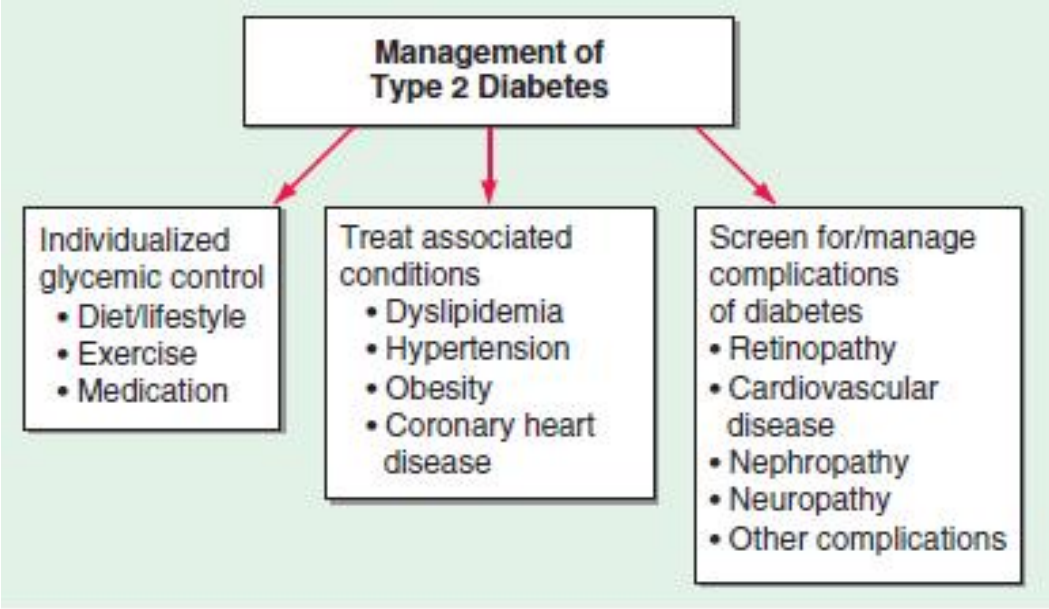


Figure 4. Essential Elements In Comprehensive Care Of Type 2 Diabetes

GLUCOSE LOWERING AGENTS:

A) BIGUANIDES: Metformin being the main drug in this class, acts by reducing hepatic glucose production and increasing the peripheral utilization of glucose. By antagonizing glucagon's ability to generate cAMP, it decreases hepatic glucose production. It should not be used in renal failure, acidosis, liver disease, severe hypoxemia, unstable heart failure.

B) SULFONYLUREAS: Stimulate insulin secretion by interacting with the ATP sensitive potassium channels on the beta cells. These drugs reduce both fasting and postprandial blood glucose. They have a tendency to cause hypoglycemia especially the longer acting ones[32].

C) GLP1 RECEPTOR AGONISTS: These drugs are called as incretins. They act by increasing glucose related insulin release. These drugs have a lesser tendency of causing hypoglycaemia because of the glucose related insulin release. The drugs in this group are Exanetide and Liraglutide. These drugs also suppress glucagon and delay gastric emptying.

D) ALPHA-GLUCOSIDASE INHIBITORS: These drugs decrease postprandial hyperglycaemia by delaying the glucose absorption. They do not influence glucose utilization or insulin secretion. They inhibit the enzyme which cleaves the oligosaccharides in the intestine and thus reduce the glucose absorption.

E) THIAZOLIDINEDIONES: These drugs reduce the insulin resistance by binding to the PPAR-gamma receptor, highest levels of these receptors are found in the adipocytes. These drugs cause a redistribution of fat from central to peripheral location. They also decrease the levels of circulating insulin indicating a decrease in the insulin resistance. Thiazolidinediones are associated with weight gain, decrease in haematocrit and increase in plasma

volume. They are therefore contraindicated in liver disease and class III to IV heart failure.

F) SODIUM GLUCOSE CO-TRANSPORTER 2 IHIBITORS:By inhibiting this cotransporter which is mainly present on the proximal convoluted tubules of the kidney, these drugs reduce the renal threshold of glucose and increase the urinary excretion of glucose. Because of the increase in the urinary levels of glucose, there may be an increased risk of urinary tract infections.

G) OTHER THERAPIES: These include bile acid binding resins and bromocriptine.

H) INSULIN THERAPY: Insulin must be considered as the initial therapy in type 2 DM patients especially in those who are lean, those with severe liver or kidney disease in whom oral hypoglycemic agents are contraindicated. Usually the therapy is started with a single daily dose of long acting insulin like NPH or glargine as single evening or bedtime dose with a dose of 0.3 to 0.4 units/kg body weight. Glargine has lesser incidence of hypoglycaemia than NPH when given as bedtime dose. Some physicians prefer starting at a low initial dose of long acting insulin and then increasing the dose according to SMBG values, the usual dose being 5 to 15 units/day or 0.2 units/kg/day.

CHOICE OF INITIAL GLUCOSE LOWERING AGENT:

The level of hyperglycemia and the patient's individualized goal should be the main factors influencing the initial choice of therapy. Usually the following principle is followed that patients with mild to moderate hyperglycemia (FPG <11.1–13.9 mmol/L [200–250 mg/dL]) often respond well to a single, oral glucose-lowering agent. Patients with more severe hyperglycemia (FPG >13.9 mmol/L [250 mg/dL])

may respond partially but are unlikely to achieve normoglycemia with oral monotherapy.

Insulin may be used as initial therapy in patients with severe hyperglycemia (FPG <13.9–16.7 mmol/L [250–300 mg/dL]) or in those who are symptomaticfrom the hyperglycemia. Treatment algorithms from several professional societies (ADA/European Association for the Study of Diabetes [EASD], IDF, AACE) suggest metformin as initial therapy because of its efficacy, known side effect profile, and its low cost.

A number of combinations of therapeutic agents are proven useful in type 2 DM (metformin + second oral agent, metformin + GLP-1 receptor agonist, or metformin + insulin), and the dosing of agents in combination is the same as when the agents are used alone. If proper and efficient control is not achieved with the combination of two agents (based on reassessment of the HbA1c every 3 months), a third oral agent or basal insulin should be added.

Insulin becomes necessary as type 2 DM progresses to the phase of relative insulin deficiency (as seen in long-standing DM) and is indicated by inadequate glycemic control with one or two oral glucose-lowering agents. Patients who require >1unit/kg per day of long-acting insulin should be considered for combination therapy with metformin or a thiazolidinedione. The addition ofmetformin or a thiazolidinedione may reduce insulin requirements in some individuals with type 2 DM, while maintaining or even improving glycemic control.

COMPLICATIONS:

Diabetes related complications affect multiple systems in the body. These complications do not appear until atleast second decade of the disease i.e, hyperglycaemia. Because type 2 diabetes mellitus (DM) usually has a long asymptomatic period of hyperglycemia before diagnosis, many patients with type 2 DM often have complications at the time of diagnosis.

Diabetes-related complications can be divided into vascular and nonvascular complications. The vascular complications of diabetes are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease [CAD], peripheral arterial disease [PAD], cerebrovascular disease).

The UKPDS demonstrated that each percentage point reduction in HbA1c was associated with a 35% decrease in microvascular complications. As in the DCCT, there was a continuous relationship between glycemic control and development of microvascular complications. Efficient glycemic control also reduced the cardiovascular event rate in the follow-up period of >10 years.

The mechanism by which hyperglycaemia leads to complications is not well understood but it is proposed that hyperglycaemia leads to epigenetic changes which influence gene expression in affected cells.

Four theories have been proposed on how hyperglycaemia leads to complications:

1. Increased intracellular glucose leading to the formation of advanced glycosylation end products, which bind to a cell surfacereceptor, via the nonenzymatic glycosylation of intra- and extracellularproteins, which in turn leads to cross-linking of proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and alteredextracellular matrix composition.
2. Hyperglycemia increasing glucose metabolism through the sorbitol pathway related to the enzyme aldose reductase. But, testing of this theory in humans, using aldose reductaseinhibitors, has not demonstrated beneficial effects.
3. Hyperglycemia leading to increase in 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.
4. Hyperglycemia leading to increase in the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production, leading to altered function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in the gene expression of transforming growth factor β (TGF-β) or plasminogen activator inhibitor-1.

Growth factors play an important role in diabetes complications. Vascular endothelial growth factor A is increased in proliferative diabetic retinopathy and its levels decrease following laser photocoagulation. Transforming growth factor beta causes increased basement production of collagen and fibronectin by mesangial cells and is increased in diabetic nephropathy.

DIABETIC RETINOPATHY:

Diabetic retinopathy is divided into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the hyperglycemia and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots. The pathophysiologic mechanisms proposed in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in blood flow of retina, and abnormal retinal microvasculature, all of which lead to ischemia of retinal tissue.

Retinal neurovascular unit, which consists of neurons, glia, astrocytes, Muuller cells, and specialized vasculature are the site of inflammation, according to a new concept. The hallmark of proliferative retinopathy is the development of neovascularisation. The new blood vessels formed are fragile and can rupture easily leading to vitreous haemorrhage and ultimately retinal detachment.

Duration of diabetes and degree of glycemic control are the best factors to predict the development of retinopathy. Hypertension and nephropathy have also been found to be risk factors. Although there is genetic susceptibility for retinopathy, this confers lesser influence when compared to the duration of diabetes or the degree of glycemic control.

DIABETIC NEPHROPATHY:

Diabetic nephropathy is the leading cause of chronic renal impairment in the form of chronic kidney disease (CKD), ESRD, and CKD requiring renal replacement

therapy. The main factor in the pathogenesis of diabetic nephropathy is chronic hyperglycaemia.

The exact mechanism is not well understood but involve the effects of soluble factors (growth factors, angiotensin II, endothelin, advanced glycation end products [AGEs]), alterations in the renal microcirculation like glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure, and structural changes in the glomerulus like increase in extracellular matrix, thickening of basement membrane, mesangial expansion, fibrosis.

Smoking leads to rapid decline in renal function. Since only 20-40% of diabetic patients develop nephropathy, the other factors implicated are not yet identified. Some of the risk factors include race and family history of diabetic nephropathy.

There is a stage of microalbuminuria followed by macroalbuminuria. Recently these terms have been replaced by 'persistent albuminuria' by the ADA. Screening for albuminuria should begin 5 years after the onset of type 1 diabetes and at the time of diagnosis of type 2 diabetes.

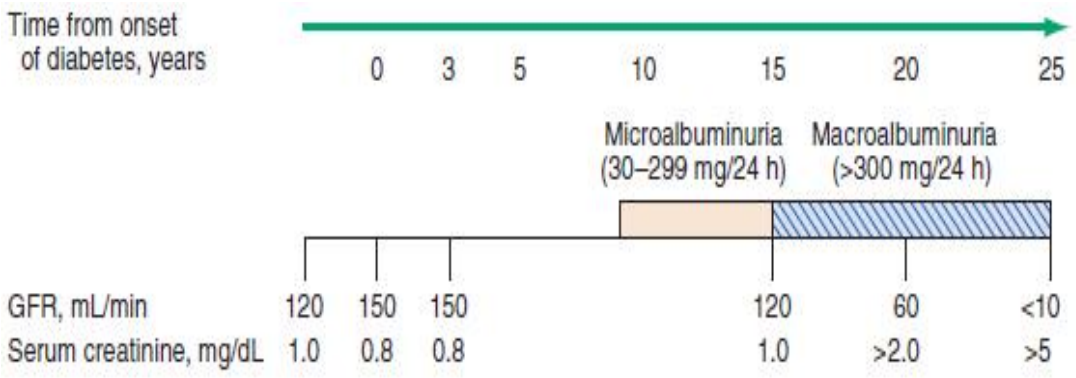


Figure 5. Time Course Of Development Of Diabetic Nephropathy

DIABETIC NEUROPATHY:

Diabetic neuropathy occurs in ~50% of individuals with long-standing diabetes. The ways of manifesting may be as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. The development of neuropathy is related with the duration of diabetes and glycemic control.Additional risk factors are body mass index (BMI) (the greater the BMI, the greater the risk of neuropathy) and smoking.

Both myelinated and unmyelinated nerve fibers are affected.Distal symmetric polyneuropathy is the most common form of diabetic neuropathy. It most commonly presents as distal loss of sensations and pain. Symptoms may be in the form of numbness, tingling, sharpness or burning that begins in the feet and progresses proximally. Neuropathic pain may also be present in some, which is present in the lower extremities, more at rest and worsens in the night.

Syndrome of diabetic polyradiculopathy is characterized by severe disabling pain in the distribution of one or more nerve roots which may be accompanied by motor weakness. They are usually self limited and resolve within a period of 6 to 12 months. Mononeuropathy which is less frequent when compared to polyneuropathy manifests as pain along the distribution of a single nerve. The third cranial nerve is the most frequently involved.

Long standing diabetes may cause autonomic dysfunction by affecting cholinergic, noradrenergic or peptidergic systems. Involvement of the cardiovascular system may manifest as resting tachycardia and orthostatic hypotension. Anhidrosis of the feet can promote drying of skin with cracking, which in turn leads to increased risk of foot ulcers.

Autonomic neuropathy may lead to impairment in release of counter regulatory hormones especially the catecholamines leading to 'hypoglycaemia unawareness' i.e, inability to sense hypoglycaemia appropriately.

MATERIAL AND METHODS

STUDY DESIGN:

This is a one year cross sectional study conducted in the KLEs Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

STUDY SITE AND AREA:

Data was collected from the patients presenting to Department of Internal medicine at KLES Dr Prabhakar Kore Hospital & MRC, Belagavi fulfilling inclusion criteria.

Duration of study: One year

Period of study: January 2016 to Dec 2016

STUDY POPULATION AND SAMPLING:

Sample Size:100

Sample Size Calculation:$z\alpha^2pq/d2$

Where zα-1.96(Constant),

P-prevalence (50%)-as obtained from previous studies , q-(100-p),

D-Absolute Error (20% Of P)

SAMPLE SELECTION CRITERIA:

INCLUSION CRITERIA:

- Patients aged 18 years to 60years.
- Patients with Type 2 Diabetes Mellitus with Microvascular complications like Retinopathy or Nephropathy or Neuropathy.

EXCLUSION CRITERIA:

- Type 2 Diabetes Mellitus patients with cigarette smoking, pregnancy and obesity.
- Type 2 Diabetes Mellitus patients without microvascular complications.
- Type 1 Diabetes Mellitus patients.
- Any ongoing infection.
- Any Acute Coronary or Cerebrovascular event.
- Any evidence of Cancer.

DATA COLLECTION:

After obtaining a written informed consent from all the patients, the candidates fulfilling the inclusion criteria were included in the study. The study participants were subjected to detailed history taking and physical examination.

After history and physical examination, the patients underwent routine blood tests like complete blood count and other tests needed for the study like HBA1c, plasma fibrinogen, urine routine examination, fundoscopy, monofilament testing, FBS, PPBS.

At very beginning it was clarified that the participant had the right to refuse to answer any question during completing questionnaire. They could withdraw from the study at any time. It was also clarified to all participants about the aim of the study.

DATA ANALYSIS:

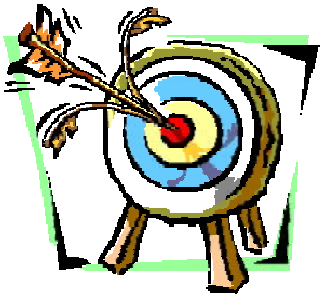
Descriptive statistics was used to analyze data. Data were analyzed with the software named Statistical Package for the Social Science (SPSS) version 16.0.Data was analyzed by descriptive statistics and calculated as percentages and presented by using table, bar graph etc. Microsoft office Excel 2007 is used to decorating the bar graph.

ETHICAL CONSIDERATION:

Ethical committee clearance was taken before starting the study. During the course of this study, interested subjects were given consent forms and the purpose of the research and the consent form were explained to them verbally in Kannada, Marathi or Hindi. The participants were informed that their participation would be fully voluntary and they had the right to withdraw or discontinue from the research at any time without any hesitation or risk. They were also informed that confidentiality would be maintained. Information might be published in any presentations or writing, but their personal identity such as their name and address will not be mentioned in the study. The participants were informed that the data was collected by written questionnaire. The supervisor also checked the consent form and questionnaire. The participants were informed about their role in the research process. The participants were informed about the aim of the research and procedures involved in the study.

They were also informed that if they wish they were free to withdraw from the study any time. The study information only discusses with the supervisor but this would not be shared with any other person. These materials were disposed off after completion of the research project. The study results might not have any direct effects on them. Participants were also informed that they would not get any harmful things from the study.

Introduction



Objectives

Review of Literature

Methodology

Results

Discussion

Conclusion

Summary

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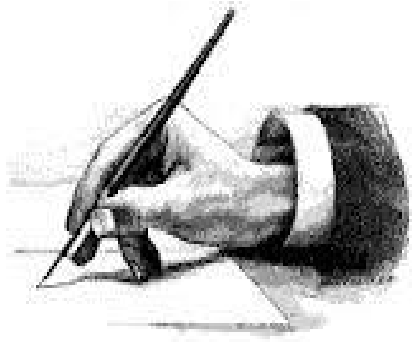


Annexure-I

Annexure-II

Annexure-III

Annexure-IV

Annexure-V

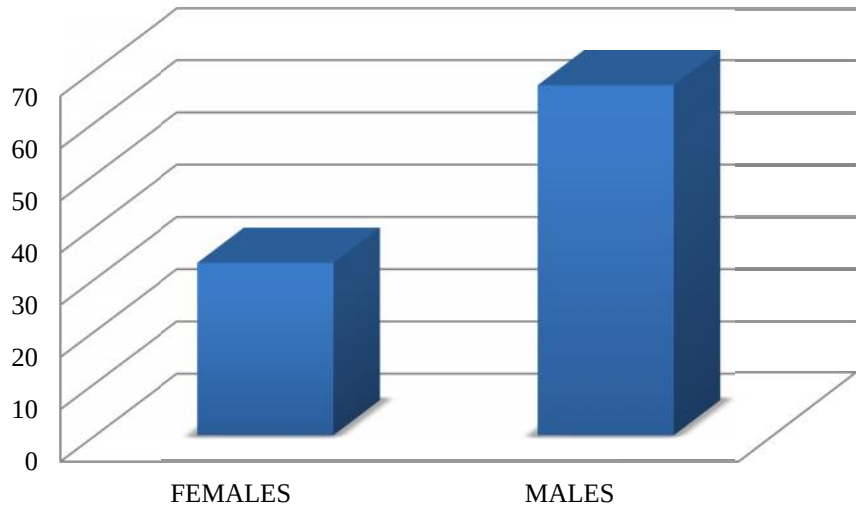
RESULTS

In this study conducted in the KLEs Dr.Prabhakar Kore Hospital and Medical Research Centre, from January 2016 to December 2016, the following results were observed.

Table 1: Sex Distribution

Sex	Distribution(n=100)	
	Number	**Percentage**
Males	67	67
Females	33	33
Total	100	100

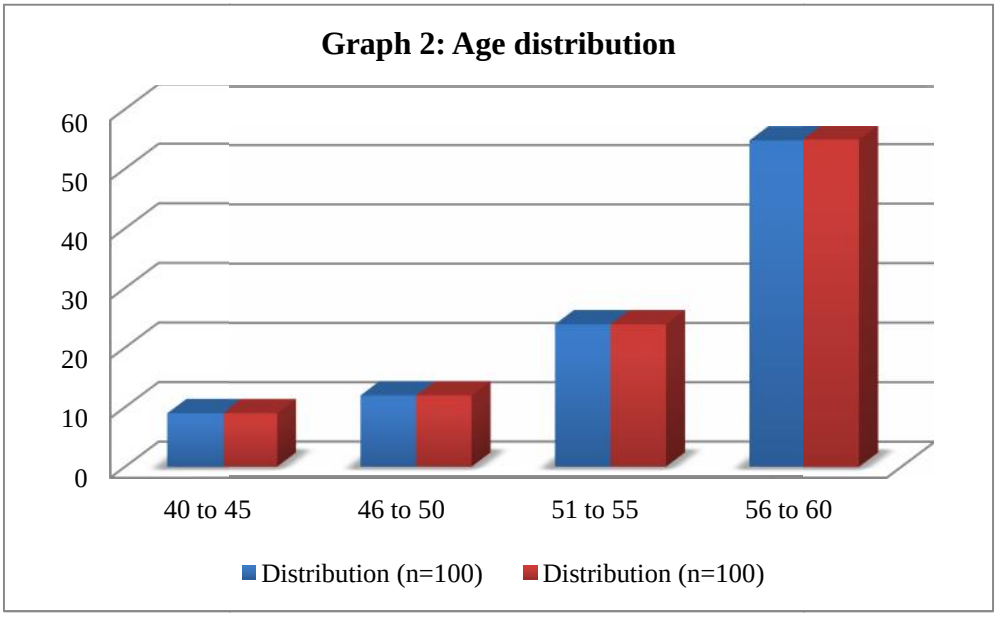
Graph 1: Gender



In our study, among 100 patients, 33 were females (33%) and 67 were males (67%).

Table 2: distribution of study population according to age:

Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
40 to 45	9	9.00
46 to 50	12	12.00
51 to 55	24	24.00
56 to 60	55	55.00
Total	100	100.00

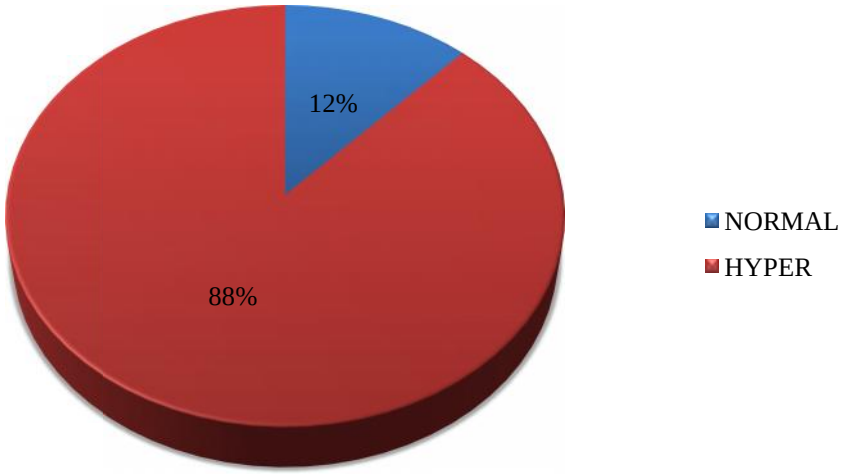


In our study, there were 9 patients in the age group of 40-45years, 12 patients in the age group of 46-50years, 24 patients in the age group of 51-55years and 55 patients in the age group of 56-60years.

Table 3: Prevalence Of Hyperfibrinogenemia:

Fibrinogen	Number	Percentage
Normal	12	12%
Hyper	88	88%
Total	100	100%

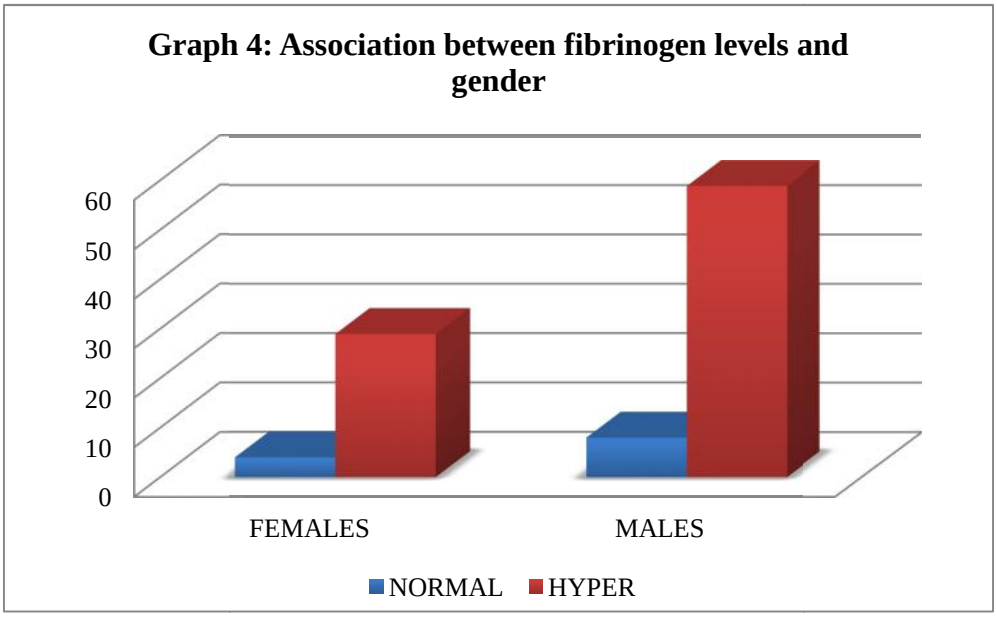
Graph 3: Prevalence of hyperfibrinogenemia



In our study, the prevalence of hyperfibrinogenaemia was 88%.

Table 4: Association between Fibrinogen Levels and Gender:

Fibrinogen	Males	Females	Total
Normal	8	4	12
Hyper	59	29	88
Total	67	33	100

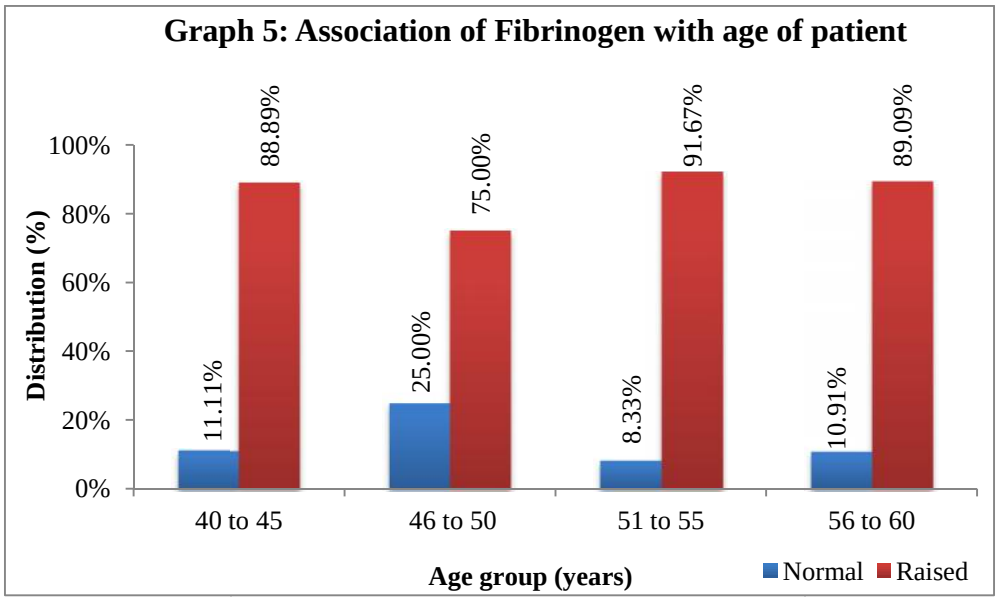


This bar graph shows association between fibrinogen levels and gender. It shows that among the patients who had hyperfibrinogenaemia, 29 were females (32.95%) and 59 were males (67.04%).

p value = 0.7634, statistically not significant.

Table 5: Association Of Fibrinogen With Age Of The Patients:

Age group (years)	Fibrinogen (mg/dL)				Total	
	Normal (<360)		Raises (≥360)			
	No	%	No	%	No	%
40 to 45	1	11.11	8	88.89	9	9.00
46 to 50	3	25.00	9	75.00	12	12.00
51 to 55	2	8.33	22	91.67	24	24.00
56 to 60	6	10.91	49	89.09	55	55.00
Total	12	12.00	88	88.00	100	100.00



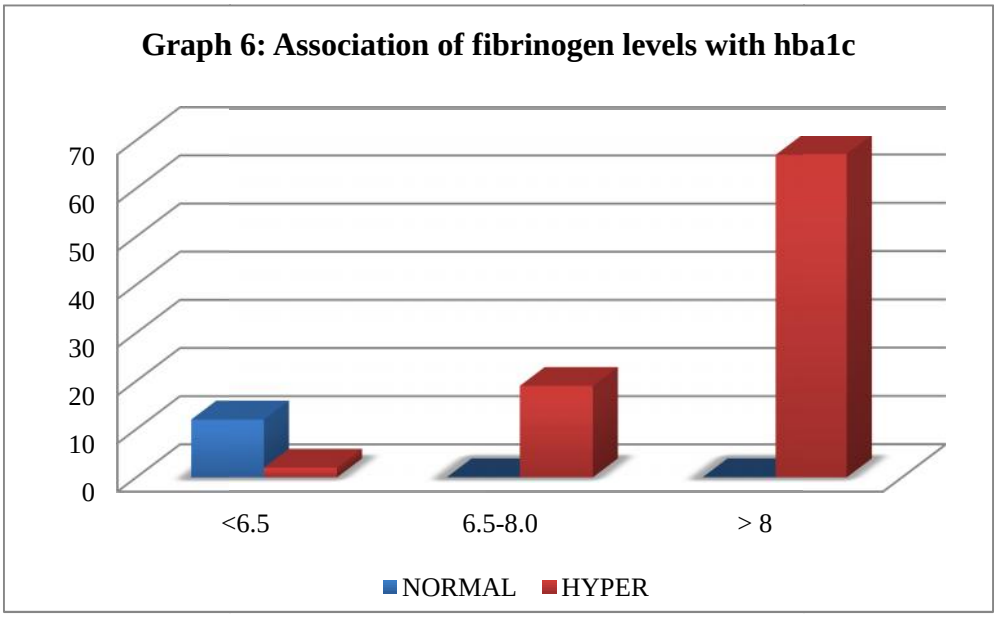
p = 0.483

In our study, there was no significant association between the age of the patient and fibrinogen levels.

p value = 0.483, statistically not significant.

Table 6: Association Of Fibrinogen Levels With Hba1c Levels:

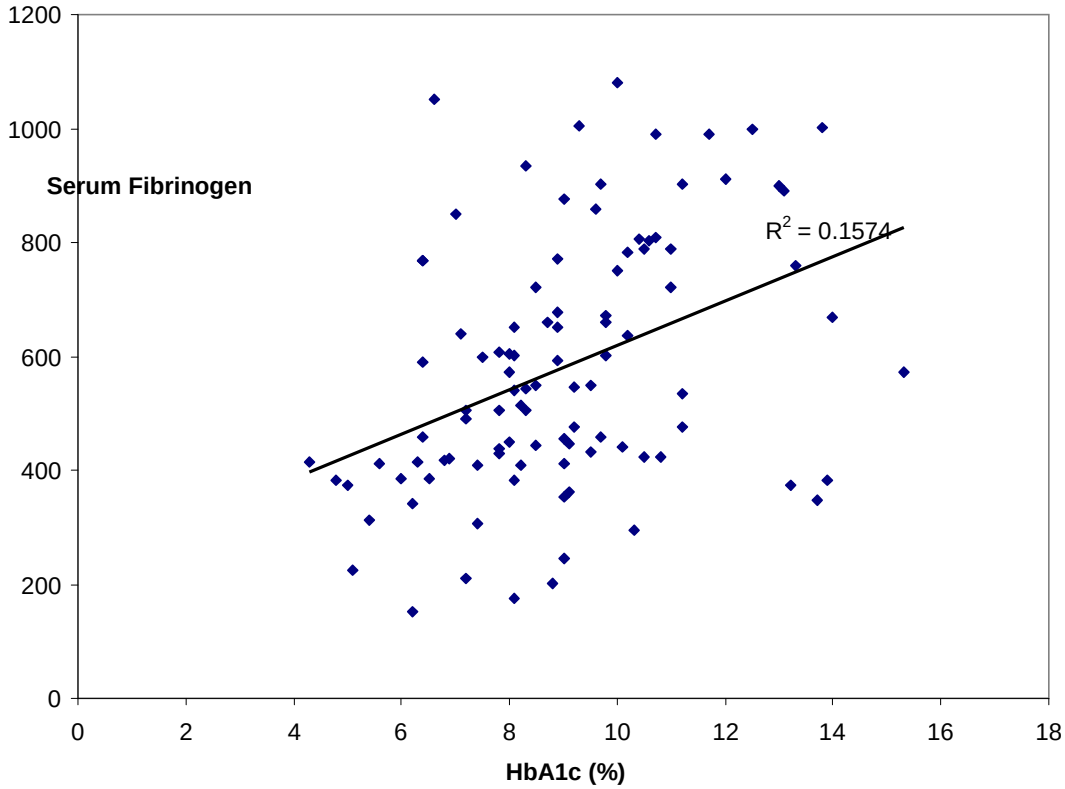
	HBA1C			
Fibrinogen	**Less than 6.5**	**6.5-8.0**	**More than 8.0**	**Total**
Normal	12	0	0	12
Hyper	2	19	67	88
Total	14	19	67	100



This bar chart shows the correlation between fibrinogen levels with HBA1c. It shows that all patients who had HBA1c levels more than 8% had hyperfibrinogenemia.

p value less than 0.0001, statistically highly significant.

Graph 7: Correlation of HbA1c with Serum fibrinogen



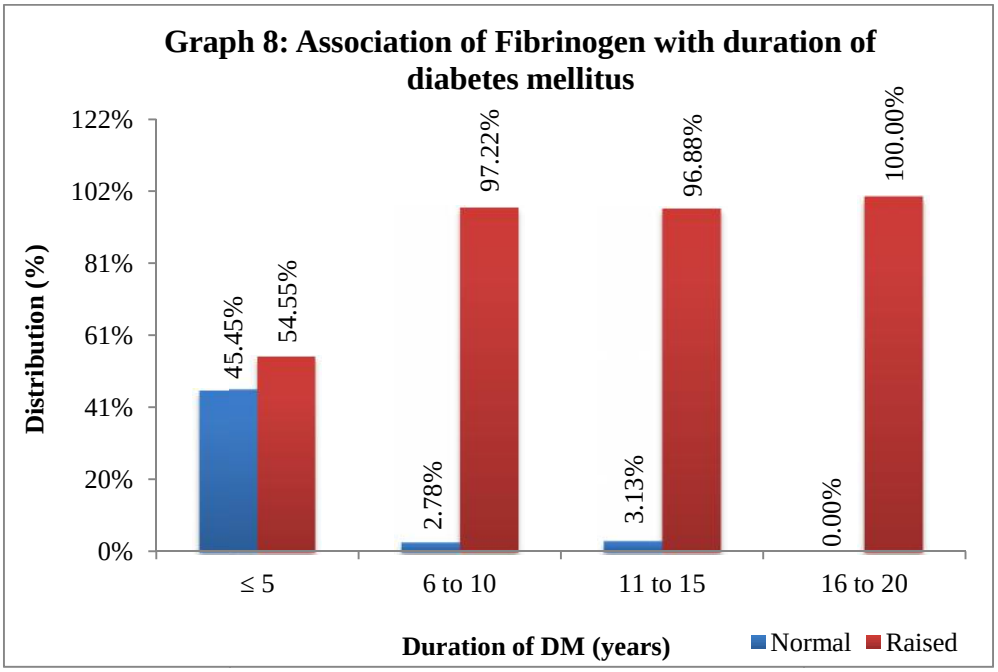
r=0.397; p<0.001

It was observed that, higher the HBA1c, higher was the prevalence of hyperfibrinogenemia.

Table 7: Association Of Fibrinogen With Duration Of Diabetes Mellitus:

Duration of DM (years)	Fibrinogen (mg/dL)				Total	
	Normal (<360)		Raised (≥360)			
	No.	%	No.	%	No.	%
≤ 5	10	45.45	12	54.55	22	22.00
6 to 10	1	2.78	35	97.22	36	36.00
11 to 15	1	3.13	31	96.88	32	32.00
16 to 20	0	0.00	10	100.00	10	10.00
Total	12	12.00	88	88.00	100	100.00

p = <0.001

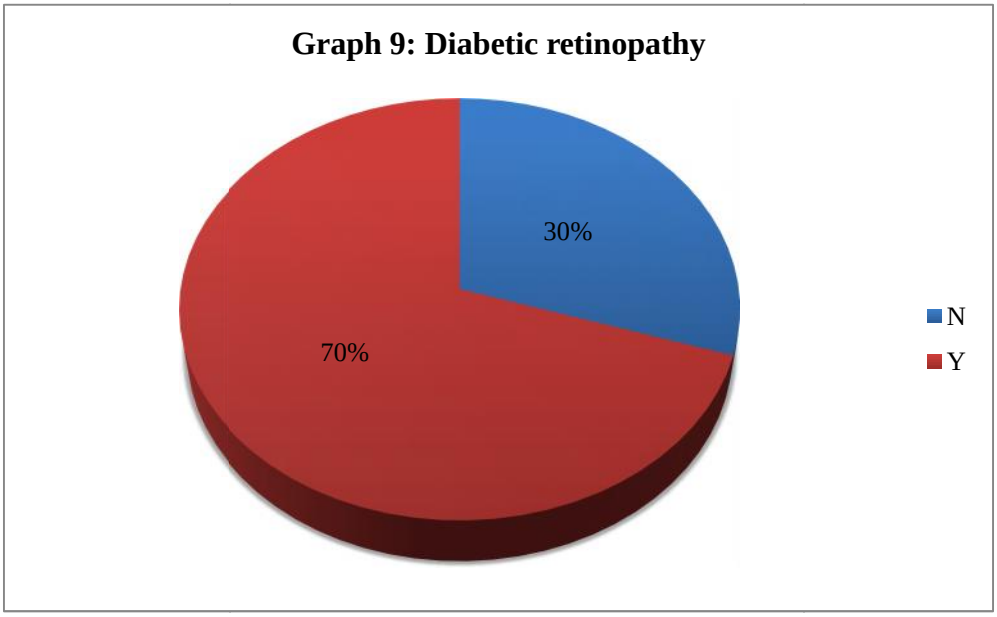


In our study, we found a positive association between the duration of diabetes and the fibrinogen levels, i.e., as the duration of diabetes increased, the prevalence of hyperfibrinogenaemia also increased.

p value is less than 0.001, statistically highly significant.

Table 8: Prevalence Of Diabetic Retinopathy:

Diabetic retinopathy	Distribution (n=100)	
	Number	**Percentage**
Yes	70	70.00
No	30	30.00
Total	**100**	**100.00**

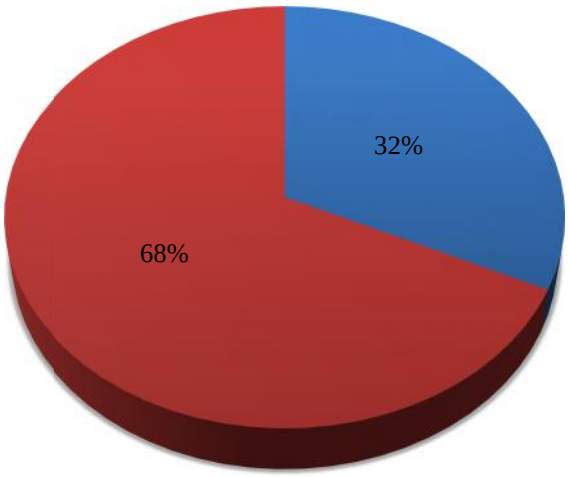


The prevalence of diabetic retinopathy in our study was 70%.

Table 9: Prevalence Of Diabetic Nephropathy:

Nephropathy	Number	Percentage
Yes	68	68%
No	32	32%
Total	100	100%

Graph 10: Diabetic nephropathy

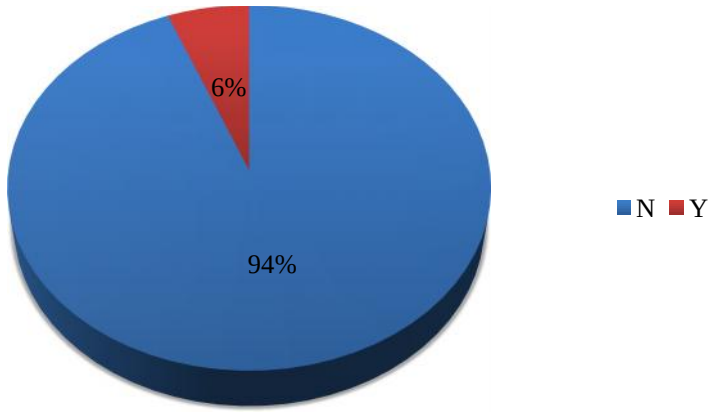


This pie chart shows the prevalence of diabetic nephropathy in our study which was 68%.

Table 10: Prevalence of Diabetic Neuropathy:

Neuropathy	Number	Percentage
No	94	94%
Yes	6	6%
Total	100	100%

Graph 11: Prevalence of diabetic neuropathy

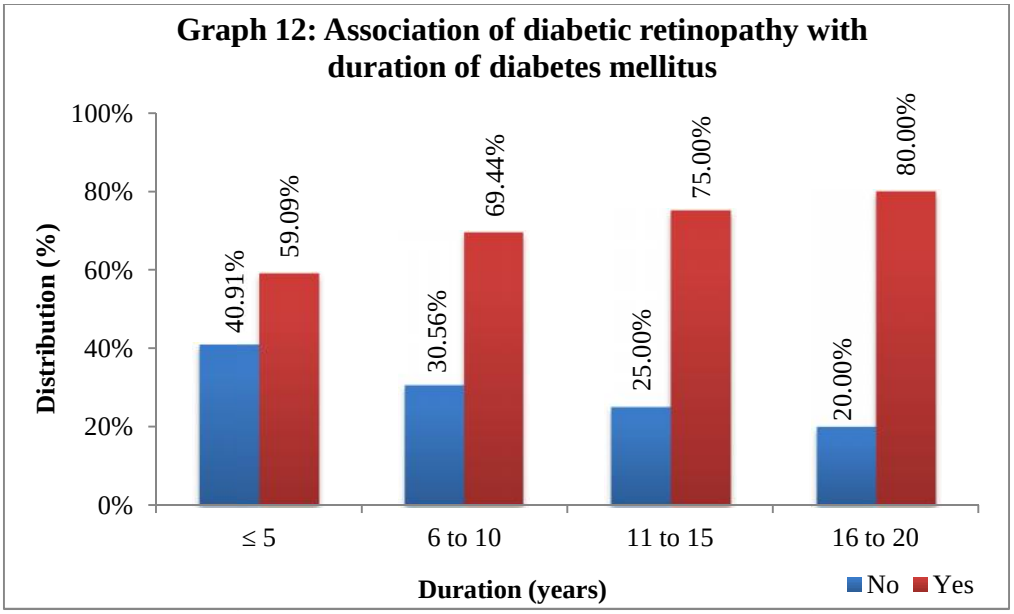


This pie chart shows the prevalence of diabetic neuropathy in our study which was 6%.

Table 11: Association of Diabetic Retinopathy with Duration of Diabetes Mellitus:

Duration (years)	Diabetic retinopathy				Total	
	No		Yes			
	No.	%	No.	%	No.	%
≤ 5	9	40.91	13	59.09	22	22.00
6 to 10	11	30.56	25	69.44	36	36.00
11 to 15	8	25.00	24	75.00	32	32.00
16 to 20	2	20.00	8	80.00	10	10.00
Total	30	30.00	70	70.00	100	100.00

x2=2.109 p=0.586



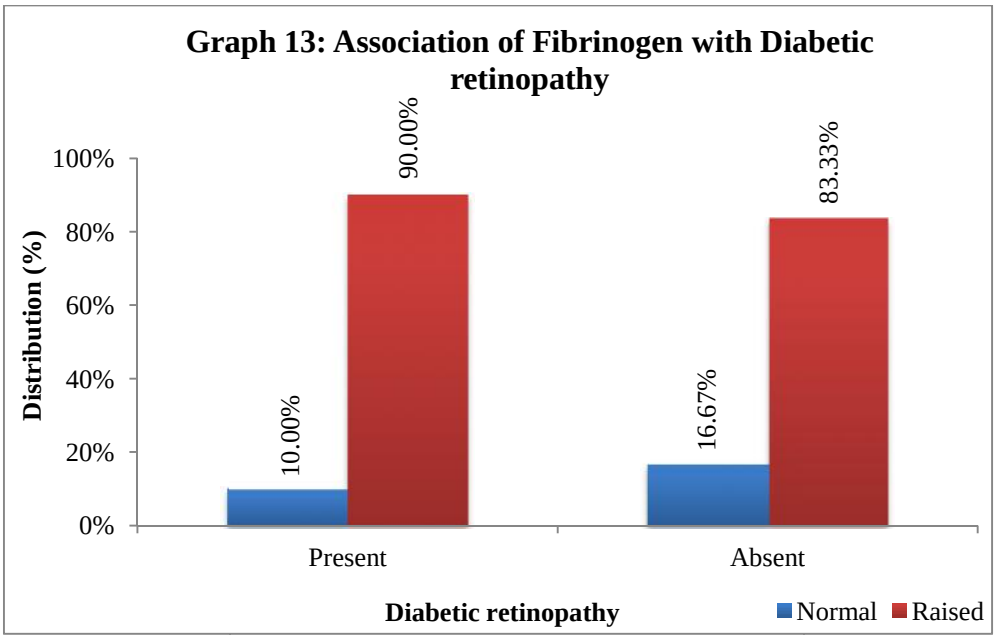
In our study, there was a positive association between diabetic retinopathy and the duration of diabetes, i.e., as the duration increased, the prevalence of diabetic retinopathy increased.

p value = 0.586, statistically not significant.

Table 12: Association of Fibrinogen with Diabetic Retinopathy

Diabetic retinopathy	Fibrinogen (mg/dL)				Total	
	Normal (<360)		Raised (≥360)			
	No.	%	No.	%	No.	%
Present	7	10.00	63	90.00	70	70.00
Absent	5	16.67	25	83.33	30	30.00
Total	12	12.00	88	88.00	100	100.00

p=0.266



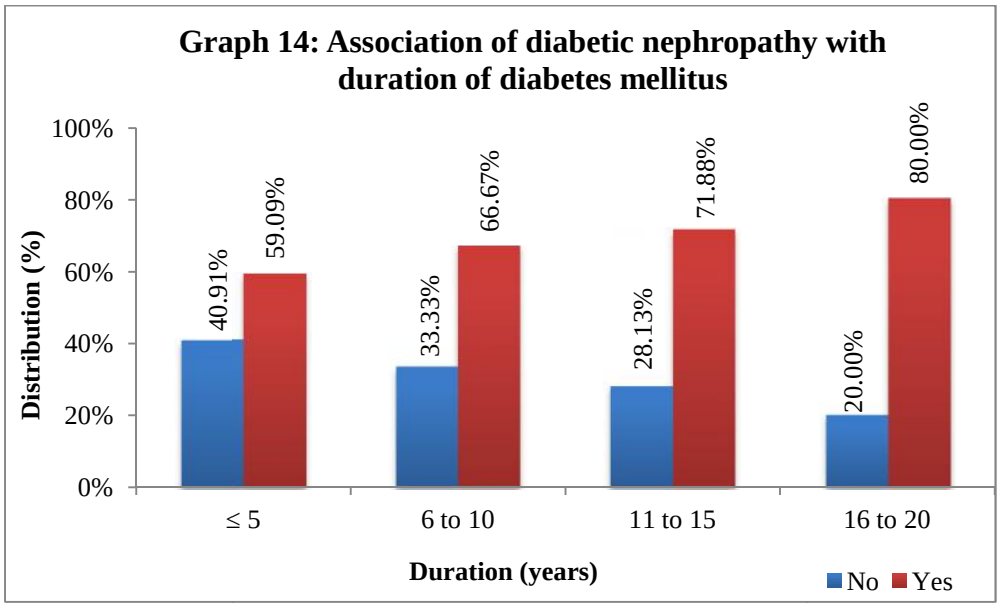
In our study, we found that the prevalence of hyperfibrinogenemia was higher in patients with diabetic retinopathy (90%), when compared to those without diabetic retinopathy(83.33%).

p value = 0.266, statistically not significant.

Table 13: Association of Diabetic Nephropathy with Duration Of Diabetes Mellitus:

Duration (years)	Diabetic Nephropathy				Total	
	No		Yes			
	No.	%	No.	%	No.	%
≤ 5	9	40.91	13	59.09	22	22.00
6 to 10	12	33.33	24	66.67	36	36.00
11 to 15	9	28.13	23	71.88	32	32.00
16 to 20	2	20.00	8	80.00	10	10.00
Total	32	32.00	68	68.00	100	100.00

x2=1.714 p=0.634

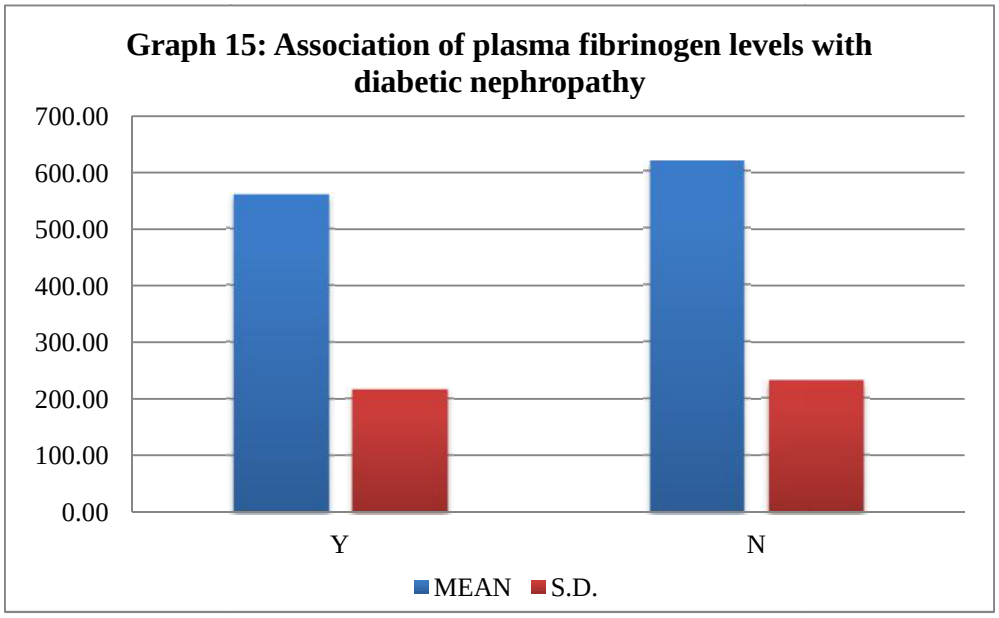


In our study, there was a positive association between diabetic nephropathy and the duration of diabetes, i.e., as the duration of diabetes increased, the prevalence of diabetic nephropathy increased.

p value = 0.643, statistically not significant.

Table 14: Association of Plasma Fibrinogen Levels With Diabetic Nephropathy:

Diabetic Nephropathy				
	Yes	**No**	**P value**	**Inference**
Fibrinogen				
Mean	561.13	618.78	0.2265	NS
S.d	216.14	231.04		



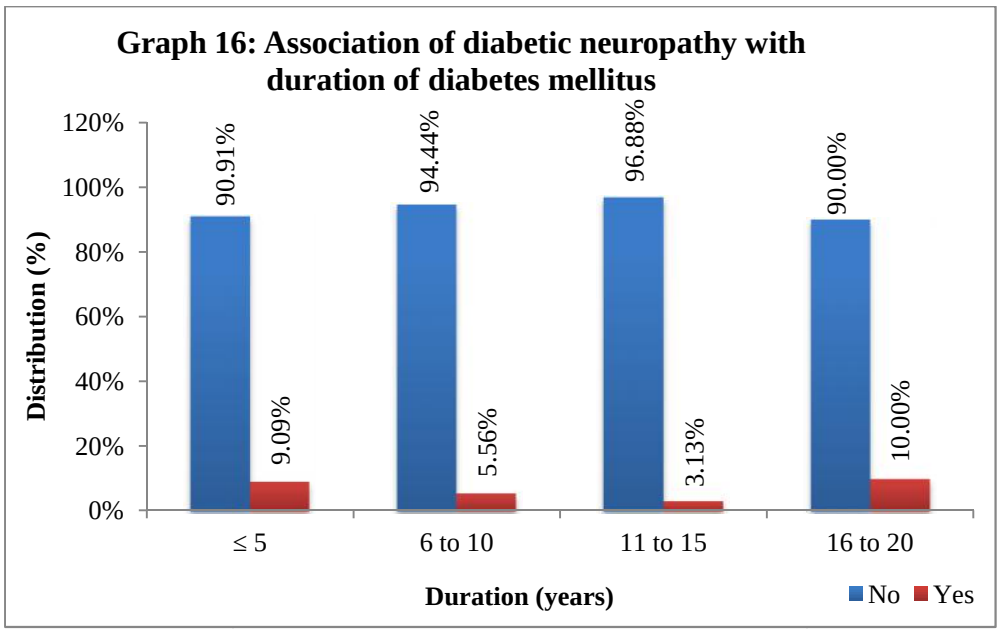
This bar graph shows the correlation of plasma fibrinogen levels with diabetic nephropathy. The mean levels of plasma fibrinogen in patients with diabetic nephropathy were 561.13mg/dl which was lower to that seen in patients without diabetic nephropathy which was 618.78mg/dl.

p value = 0.2265, statistically not significant.

Table 15: Association Of Diabetic Neuropathy With Duration Of Diabetes Mellitus:

Duration (years)	Diabetic Neuropathy				Total	
	No		Yes			
	No.	%	No.	%	No.	%
≤ 5	20	90.91	2	9.09	22	22.00
6 to 10	34	94.44	2	5.56	36	36.00
11 to 15	31	96.88	1	3.13	32	32.00
16 to 20	9	90.00	1	10.00	10	10.00
Total	94	94.00	6	6.00	100	100.00

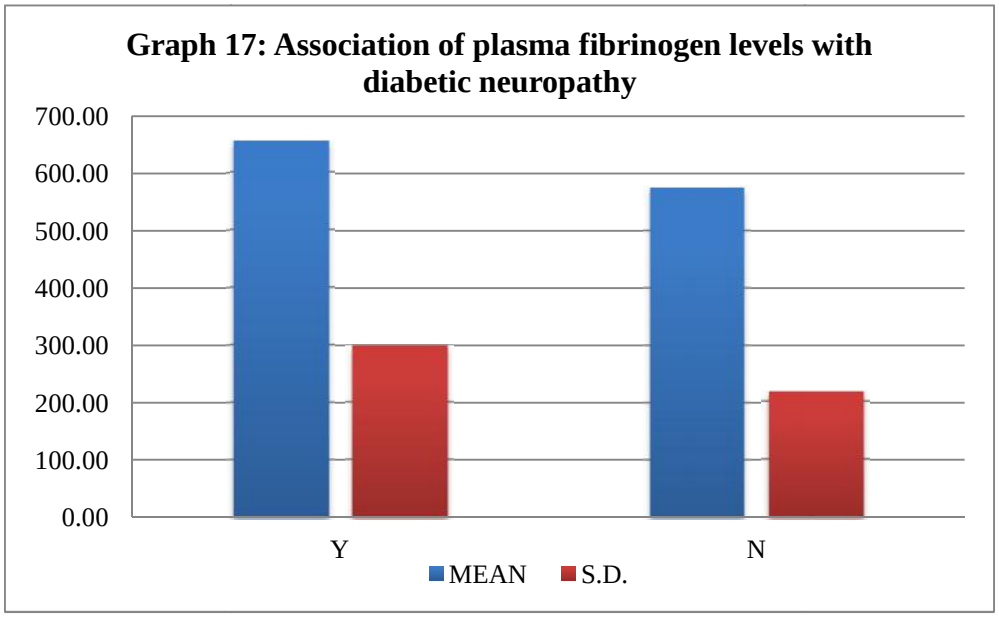
p=0.672



In our study, there was no significant association between diabetic neuropathy and the duration of diabetes.

Table 16: Association of Plasma Fibrinogen Levels With Diabetic Neuropathy:

	Diabetic neuropathy			
	Yes	**No**	**P value**	**Inference**
Hba1c			0.3966	NS
Mean	654.33	574.81		
S.D	298.11	216.94		



This bar graph shows the correlation of plasma fibrinogen levels with diabetic neuropathy. The mean levels of plasma fibrinogen in patients with diabetic nephropathy were 654.33mg/dl which was higher to that seen in patients without diabetic neuropathy which was 574.81mg/dl.

p value = 0.3966, statistically not significant.

DISCUSSION

` This study was conducted in KLEs Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Diabetes mellitus is considered to be associated with a state of hypercoagulability[33,34,35,36].Elevated Plasma Fibrinogen levels are thought to contribute significantly to this hypercoagulability[37]. Fibrinogen studies collaboration and various other studies have found that increased fibrinogen levels are associated with major systemic morbidity like coronary artery disease, stroke etc[38].

Diabetes is associated with low grade inflammation and as a result Interleukin 6 are elevated in these patients. This cytokine stimulates hepatocytes to produce fibrinogen representing an important link between inflammation and hypercoagulation[39].

An association between the levels of fibrinogen and oxidative stress has been observed in diabetics[40]. Fibrinogen synthesis is regulated by a feedback mechanism by thrombin activation[41]. Thrombin formation is stimulated by freeradicals in diabetic patients[42]. Hyperglycemia and insulin resistance and the consequent oxidative stress may give rise to increased thrombin formation.

In our study, we found that the prevalence of hyperfibrinogenemia was 88%.

Hyperfibrinogenemia in diabetes has been reported to be caused by an increased synthesis of fibrinogen which is not compensated by a proportionate increase in the clearance of fibrinogen. This abnormality is associated with insulin

deficiency and have been corrected with insulin[43]suggesting that hyperfibrinogenemia is anindirect indicator of poor glycemic control.

The correlation between glycemic control and fibrinogen levels could be due to (a) glycosylate fibrinogen is less susceptible to degradation by plasmin (b) relative insulin deficiency in diabetic patients results in differential protein synthesis i.e., 29% decrease in albumin synthesis and 50% increase in fibrinogen synthesis[44].

In our study, we found a positive correlation between the levels of plasma fibrinogen and HBA1c, suggesting that higher the HBA1c levels, higher is the plasma fibrinogen levels. Similar results were found in previous studies conducted by Fujii et al and Van Wersch et al respectively[45,46].

In our study, there was no significant association between gender and fibrinogen levels.

In our study, the prevalence of diabetic retinopathy was 94%, diabetic nephropathy was 68% and diabetic neuropathy was 6%. Thus the most common microvascular complication in our study was diabetic retinopathy.

In our study, the levels of HBA1c were higher in patients withdiabetic retinopathy and neuropathy when compared to those without diabetic retinopathy and neuropathy but the association was not statistically significant. The levels of fibrinogen were also higher in patients with diabetic retinopathy and neuropathy as compared to those without diabetic retinopathy or neuropathy but the association was not statistically significant.

In our study, we also found a positive association between the duration of diabetes and fibrinogen levels which was similar to that found in other studies conducted by G Bruno et al[47].

In our study, we also found a positive association between the duration of diabetes mellitus and the prevalence of diabetic retinopathy, but it was not statistically significant. As the duration of diabetes mellitus increased, the prevalence of diabetic retinopathy also increased. This finding was similar to that found in other studies[48,49,50].

We also found a positive association between the duration of diabetes mellitus and diabetic nephropathy but the association was not statistically significant.

CONCLUSION

On the basis of the observations made in our study, we concluded that the prevalence of hyperfibrinogenemia among type 2 diabetes mellitus patients with microvascular complications was 88%.

We also found a positive association between HBA1c levels and fibrinogen levels i.e., the higher the HBA1c the higher was the fibrinogen, indicating that glycaemic control has a significant impact on the fibrinogen levels.

Through our study, we also found a positive association between the duration of diabetes and fibrinogen levels. Longer the duration of diabetes, there was a higher prevalence of hyperfibrinogenemia.

Thus fibrinogen levels can be used as a marker for microvascular complications.

SUMMARY

The present study of 100 patients with type 2 diabetes mellitus studied in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied between January 2016 and December 2016, to find out Association between plasma fibrinogen levels in type 2 diabetes patients with microvascular complications and the association of plasma fibrinogen levels with glycaemic control.

In our study, it was observed that the prevalence of hyperfibrinogenemia among type 2 diabetes patients with microvascular complications was 88%. We also observed that poorer the glycaemic control, higher was the prevalence of hyperfibrinogenemia. There was also a significant association between the duration of diabetes and fibrinogen levels i.e., as the duration of diabetes increased, the prevalence of hyperfibrinogenemia also increased.

The result observed was that, the prevalence of hyperfibrinogenemia among type 2 diabetes patients with microvascular complication was 88%. It was also found that there was a statistically significant association between HBA1c levels and fibrinogen levels. There was also a statistically significant association between duration of diabetes and plasma fibrinogen levels.

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ANNEXURE I

INFORMED CONSENT

Title Of Research Study:

Correlation of Plasma Fibrinogen level in Type 2 Diabetes Mellitus Patients with HbA1c Levels and Microvascular Complications – A One Year Cross sectional Study in a Tertiary Care Hospital.

Principal Investigator:-

Introduction and Purpose:

- The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades and it is projected that the number of individuals with diabetes will continue to increase in near future.
- Impaired glucose tolerance exerts an influence by enhancing thrombogenic factor as well as acute phase reactant such as Fibrinogen.
- Levels of acute phase reactants have been found to be elevated in adult diabetes, but normal in childhood diabetes, suggesting that the increase could be related to the occurrence of microvascular dysfunctions rather than the diabetes per se.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

The study would help highlight the missed etiologies and guide the treating physician in effective management of hyponatremia thus benefitting the patient.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

In the event of injury related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Research Centre, Belagavi. There is no compensation or payment for such medical treatment by law.

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Queries

In case of the queries during study or in future you may contact following persons,

1. **Dr. GANGA S PILLI,**

   Professor of Pathology & Chairman,

   JNMC Institutional Ethics Committee

   on Human Subjects Research,

   J.N.Medical College, Belgaum.

   Phone number: 09480275601

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not be giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____Signature / Thumb print _____

Name of the Witness _____ Signature/ Thumb print _____

Investigator Name: _____Signature :_____

Date:

Place

ANNEXURE II

PROFORMA

Correlation of Plasma Fibrinogen level in Type 2 Diabetes Mellitus Patients with HbA1c Levels and Microvascular Complications – A One Year Cross sectional Study in Tertiary Care Hospital.

NAME:

AGE/SEX:

IP No.

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

DIAGNOSIS:

1)

2)

3)

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Weight-

Height-

BMI-

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Hydration status:

Peripheral pulses:

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N.S.:

INVESTIGATIONS:

CBC

FBS

PPBS

HBA1C

Plasma Fibrinogen Level

Fundoscopy/ Urine Routine/ Monofilament test

PATIENT DEMOGRAPHY								MICROVASCULAR COMPLICATIONS						
CASE NUMBER	INPATIENT\OUTPATIENT NUMB	NAME	AGE(years)	GENDER	ADDRESS	OCCUPATION	DURATION	DIABETIC RETINOPATHY	DIABETIC NEPHROPATHY	DIABETIC NEUROPATHY	FBS	PPBS	HbA1C(%)	FIBRINOGEN(mg/dL)
1	734390	Madhukar	56	M	Belagavi	Farmer	15	Y	N	N	69	180	8.8	202
2	735904	Arathi	45	F	Belagavi	Police Dept	4	N	N	N	182	297	9.1	363
3	739898	Rehamatbi	60	F	Belagavi	Housewife	10	N	N	N	222	523	11.2	533
4	742987	Kempavva	49	F	Akkatangerhal	Housewife	8	N	N	N	190	224	8.9	771
5	747766	Gopal	50	M	Koujalgi	Farmer	8	N	N	N	130	171	10.8	424
6	750837	Mehaboob	48	M	Katkol	Farmer	10	N	N	Y	230	538	10.2	636
7	750728	Bharmani	60	M	Khanapur	Farmer	10	Y	Y	N	130	240	8.1	383
8	761503	Pravin	59	M	Belagavi	Business	10	Y	N	N	136	172	6.4	767
9	763179	Chandrakanth S	52	M	Vengurla	Farmer	15	N	N	N	156	201	6.4	591
10	765230	Prabha	60	F	Belagavi	Housewife	10	N	N	N	227	346	14	670
11	765047	Malutai	45	F	Chikodi	Housewife	5	N	N	N	200	312	13.9	383
12	764838	Rajashekar G	50	M	Belagavi	Business	10	Y	Y	N	191	257	10.5	422
13	765890	Sadashiv	58	M	Raibag	Farmer	12	Y	Y	N	398	416	13.1	890
14	765593	Gulayya	57	M	Jamakhandi	Farmer	15	Y	Y	N	153	296	8.3	934
15	770971	Leelabai	56	F	Gokak	Housewife	4	Y	Y	Y	113	140	5.1	225
16	771057	Shaila	45	F	BasavanKudachi	Housewife	6	Y	Y	N	102	186	5.6	412
17	771908	Karunakar	49	M	Belagavi	Business	5	Y	Y	N	86	120	7.4	307
18	772555	Shakuntala	55	F	Gadinglaj	Housewife	8	N	N	N	138	220	7.8	437
19	774383	Chandravva J	47	F	Saundatti	Farmer	3	N	N	N	223	314	9	244
20	774393	Mahammad D	45	M	Yakkundi	Farmer	2	Y	Y	N	381	400	8.1	175
21	774357	Sanjay	55	M	Belagavi	Business	2	Y	Y	N	117	140	6.2	152
22	775243	Sushiladevi	59	F	Mahadwar Road, Belagavi	Housewife	12	N	N	N	84	133	6.4	459
23	775878	Sumitra	60	F	Belagavi	Housewife	8	Y	Y	N	140	271	7.8	504
24	761503	Praveen	59	M	Belagavi	Retired Off	12	N	N	N	112	136	6.4	767
25	777782	Basangouda	60	M	Urbanhatti, Gokak	Farmer	20	Y	Y	N	55	218	9.6	859
26	781449	Anwar Dange	59	M	Belagavi	Autodriver	12	Y	Y	N	176	247	9.2	547
27	781488	Dundappa. H	60	M	Belagavi	Business	10	Y	Y	N	217	350	8.3	505
28	780360	Nissarahmed Segadi	60	M	Belagavi	Business	12	Y	Y	Y	172	302	8.2	513
29	779379	Annapurna. N	43	F	Belagavi	Housewife	2	Y	Y	N	226	370	13.2	375
30	782811	Kallangouda Patil	48	M	Asundi	Teacher	9	Y	Y	N	182	302	7.8	429
31	786876	Parvatevva	59	F	Vadgaon, Belagavi	Housewife	12	Y	Y	N	88	172	6.8	418
32	787893	Bibi Bepari	60	F	Kudachi, Raibag	Housewife	12	Y	Y	N	130	380	8.3	544
33	768106	Jameel A A Nesari	45	M	R C Nagar, Belagavi	Business	8	Y	Y	N	138	216	10.7	990
34	717557	Basappa S Yadawad	52	M	Bhengeri	Farmer	9	Y	Y	N	190	213	6.9	421
35	719225	Parvati P Dolli	60	F	Kochari, Hukkeri	Housewife	15	N	N	N	272	311	9.8	672
36	718318	Nanasab D Desai	58	M	Mutwad, Soundatti	Farmer	12	N	N	N	130	201	7.2	490
37	725297	Mallanna S Gogi	60	M	Honaga	Farmer	10	N	N	N	136	269	8	572
38	729775	Salim Jamadar	48	M	Hidkaldam, Hukkeri	Business	12	Y	Y	N	149	375	7.1	638
39	733504	Daniel M Hosamani	54	M	T V Centre, Belagavi	Retired Off	15	Y	Y	N	140	211	11.7	989
40	743278	Shankrayya Karadi	60	M	Kanbargi	Business	15	Y	Y	N	90	154	11	720
41	742885	Imtiaz A G Jamkhanwale	60	M	M M Extension, Belagavi	Business	15	Y	Y	N	321	617	10	1080
42	746301	Chinnappa S Ullagaddi	55	M	Shirapurwadi	Farmer	18	Y	Y	Y	143	223	10.7	809
43	779083	Ramesh P Sawant	54	M	Belagavi	Business	8	Y	Y	N	194	282	4.3	415
44	778328	Suhas Mali	59	M	Raibag	Business	17	Y	Y	N	297	401	11.2	901
45	778248	Manohar F Kelgeri	59	M	Bailhongal	Teacher	12	Y	Y	N	201	305	8.5	720
46	778121	Siddlingappa Pattenshetti	45	M	Gokak	Business	6	Y	Y	N	325	430	7.8	608
47	773754	Prabhulingswamiji C	48	M	Belagavi	Priest	8	Y	Y	N	197	261	8.1	540
48	776958	Guruputra Nandennavar	60	M	Gokak	Business	5	Y	Y	N	163	201	6.5	384
49	769530	Basavva B Patil	55	F	Kudachi, Raibag	Housewife	9	Y	Y	N	134	190	7.2	504
50	775630	Irappa Kamate	57	M	Belagavi	Farmer	5	Y	Y	N	150	187	7.4	408
51	775000	Shambuling M Tulasigeri	52	M	Belagavi	Retired Off	18	Y	Y	N	180	219	10.6	802
52	770809	Krishna Patil	59	M	Raibag	Farmer	8	Y	Y	N	154	209	8.2	408
53	769708	Ramappa I Belavi	45	M	Honaga	Farmer	10	Y	Y	N	190	237	12	912
54	771209	Usman Shaikh	60	M	Belagavi	Retd	12	Y	Y	N	117	189	10.1	440
55	768291	Ashok Sadalage	60	M	Belagavi	Business	15	Y	Y	N	173	230	10	750
56	765796	Leo Anthony Soarros	55	M	Vengurla	Housewife	10	Y	Y	N	190	243	9.8	659
57	766101	Subash Honnappagol	46	M	Kakati	Business	8	Y	Y	Y	152	231	9.5	550
58	766372	Shrikant R Masalji	55	M	Belagavi	Business	6	Y	Y	N	110	193	8.5	443
59	761545	Gavisiddappa Methgal	55	M	Bailhongal	Business	15	Y	Y	N	148	789	13	898
60	761188	Vishwas S Shresthi	58	M	Belagavi	Retd	10	N	N	N	150	212	8.9	650
61	761906	Bhimagouda R Patil	50	M	Bailhongal	Business	8	Y	Y	N	89	141	4.8	383
62	760889	Annarao A Ringane	60	M	Chandgad	Farmer	6	Y	Y	N	131	216	9.2	476
63	756622	Shrikanth Hugar	53	M	Belagavi	Business	4	Y	Y	N	147	201	8	450
64	759680	Prabhakar Pattekeri	55	M	Shahunagar, Belagavi	Business	18	Y	Y	N	206	447	13.8	1002
65	754884	Manilal D Patel	60	M	Belagavi	Business	11	Y	Y	N	183	247	10.2	783
66	755464	Priya B Tonannavar	60	F	Chikodi	Housewife	15	Y	Y	N	150	300	12.5	998

PATIENT DEMOGRAPHY								MICROVASCULAR COMPLICATIONS						
CASE NUMBER	INPATIENT\OUTPATIENT NUMB	NAME	AGE(years)	GENDER	ADDRESS	OCCUPATION	DURATION	DIABETIC RETINOPATHY	DIABETIC NEPHROPATHY	DIABETIC NEUROPATHY	FBS	PPBS	HbA1C(%)	FIBRINOGEN(mg/dL)
67	752659	Jayant L Nageshkar	59	M	Sankeshwar	Business	6	Y	Y	N	126	207	5	373
68	752145	Nagaradeppa B	58	M	Honaga	Farmer	14	Y	Y	N	192	264	11	789
69	752134	Appayya G Hiremath	51	M	Belagavi	Business	9	Y	Y	N	150	198	8.5	550
70	749505	Shankar Kawale	54	M	Kakati	Farmer	15	Y	Y	N	169	208	8.7	659
71	747124	Mallappa Kammar	60	M	Belagavi	Business	4	Y	Y	N	96	143	6.2	342
72	742286	Reeta Naidu	51	F	Belagavi	Housewife	10	Y	Y	N	136	189	8.1	602
73	741220	Adiveppa Y Nilajkar	60	M	Chikodi	Retd	5	Y	Y	N	106	140	5.4	313
74	740902	Abdul R Mulla	53	M	Belagavi	Business	4	Y	Y	N	103	150	6.3	416
75	740905	Dilshad Nalband	56	F	Sankeshwar	Housewife	12	Y	Y	N	150	259	10.5	789
76	740839	Moulabee H Khadgal	57	F	Belagavi	Housewife	4	Y	Y	N	152	207	9	455
77	739441	Reeta N	51	F	Goa	Housewife	12	Y	Y	N	136	189	8	605
78	735670	Sahadev V Sayekar	56	M	Honaga	Farmer	12	Y	Y	N	169	190	8.1	652
79	738355	Gadigewwa S Hiremath	60	F	Athani	Housewife	20	Y	Y	N	202	384	10.4	805
80	736198	Paramanand Biradar	52	M	Bijapur	Business	15	Y	Y	N	176	239	9.7	902
81	735385	Shanta V Hiremath	56	F	Kakati	Housewife	17	Y	Y	N	143	209	9	876
82	745818	Harish Naik	60	M	Ramdurg	Farmer	12	N	N	N	150	243	8.9	594
83	751725	Kanta	55	F	Belagavi	Housewife	5	N	N	N	162	280	9	412
84	752030	Satyavva Kasaraddi	60	F	Raibag	Housewife	5	N	N	N	176	300	9.7	459
85	755352	Leelavati V Patil	52	F	Belagavi	Housewife	4	N	N	N	172	243	13.7	348
86	758611	Sangappa P Policepatil	40	M	Chikodi	Farmer	9	N	N	N	153	189	7.5	599
87	758922	Laxmibai V Bhogan	60	F	Chandgad	Housewife	18	N	N	N	121	191	6.6	1051
88	759489	Hanumanthappa N K	53	M	Gokak	Farmer	4	N	N	Y	292	402	15.3	571
89	762290	Shamala P Yalagar	46	F	Belagavi	Housewife	6	N	N	N	150	240	9	353
90	759788	Shakuntala B Patil	58	F	Belagavi	Housewife	12	N	N	N	178	280	8.9	678
91	761883	Dharnendra J Mutagi	58	M	Belagavi	Business	4	N	N	N	180	254	10.3	296
92	761452	Lalitha S Hanagandi	55	F	R C Nagar, Belagavi	Housewife	8	N	N	N	165	314	11.2	475
93	763899	Hasansab G Jamadar	60	M	Belagavi	Business	15	N	N	N	216	311	13.3	758
94	764008	Shankreppa S Itnal	60	M	Dhavaleshwar	Business	20	N	N	N	201	365	7	851
95	789639	Vaman K Hemadri	59	M	Mahantesh Nagar	Business	4	N	N	N	88	300	7.2	210
96	797975	ShabeeraBegum N	59	F	Asad Khan Colony, Belagavi	Housewife	7	Y	Y	N	180	287	9.1	447
97	799314	Mala Hegade	60	F	Belagavi	Housewife	5	Y	Y	N	115	272	9.5	433
98	799137	Guruputra Nandennavar	58	F	Honaga	Farmer	6	Y	Y	N	100	163	6	384
99	799733	Chandrakanth B U	57	M	Sankeshwar	Farmer	12	Y	Y	N	211	354	9.8	600
100	764055	Shantinath B A	58	M	Kakati	Farmer	20	Y	Y	N	201	350	9.3	1005