A CLINICAL STUDY OF MICROVASCULAR COMPLICATIONS IN NEWLY DIAGNOSED DIABETES MELLITUS

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COIMBATORE

CERTIFICATE

This is to certify that this dissertation entitled "**A CLINICAL STUDY OF MICROVASCULAR COMPLICATIONS IN NEWLY DIAGNOSED DIABETES MELLITUS**" submitted by Dr. T.GOMATHI appearing for Part II M.D. Branch I General Medicine Degree examination in April 2012 is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of regulations of The Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India.

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I solemnly declare that the Dissertation titled **"A CLINICAL STUDY OF MICROVASCULAR COMPLICATIONS IN NEWLY DIAGNOSED DIABETES MELLITUS"** was done by me at Coimbatore Medical College & Hospital during the period from September 2010 to August 2011 underthe guidance and supervision of **Prof. Issac Christian Moses M.D**. This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch I) in General Medicine.

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LIST OF ABBREVIATIONS USED

DM	Diabetes Mellitus
WHO	World Health Organization
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non Insulin Dependent Diabetes Mellitus
MODY	Maturity Onset Diabetes of Young
GDM	Gestational Diabetes Mellitus
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
ADA	American Diabetes Association
BMI	Body Mass Index
BP	Blood Pressure
HDL	High Density Lipoprotein
TGL	Triglyceride
LDL	Low Density Lipoprotein
UKPDS	United Kingdom Prospective Diabetes Study
DCCT	Diabetes Control and Complications Trial
AGEs	Advanced Glycosylation End Products

PKC	Protein kinase C
NPDR	Non Proliferative Diabetic Retinopathy
PDR	Proliferative Diabetic Retinopathy
NVD	New vessels on the disc
NVE	New vessels elsewhere
IRMA	Intra Retinal Microvascular Abnormalities
ETDRS	Early Treatment Diabetic Retinopathy Study
ESRD	End-Stage Renal Disease
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
OGTT	Oral Glucose Tolerance Test
CURES	Chennai Urban Rural Epidemiological Study
NO	Nitric Oxide
hsCRP	High sensitivity C Reactive Protein

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INTRODUCTION

Diabetes Mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia. The incidence of Diabetes Mellitus has increased dramatically over the recent decades; predominantly because of changes in life style and an increase in the prevalence of obesity and longevity.

Based on current trends, the International Diabetes Federation projects that 439 million individuals will have diabetes by the year 2030.[1] In terms of clinical progress and the long term complications, Type 2 DM displays heterogeneous picture in each patient. Duration of Diabetes mellitus and degree of hyperglycemia increase the risk of chronic complications of Diabetes. They usually do not become apparent until the second decade of hyperglycemia. Due to a long asymptomatic period of hyperglycemia in Type 2 DM, chronic complications of diabetes may be present at the time of clinical diagnosis itself. [2] Racial and ethnic differences, different combinations of genetic defects of insulin secretion and insulin action, and the associated confounding factors, such as obesity, hypertension, dyslipidemia, and cigarette smoking, could readily provide an explanation of the heterogeneity of Type 2 DM.[3]

Chronic complications are divided into vascular and nonvascular complications. The vascular complications include Microvascular [retinopathy, neuropathy, and nephropathy] and Macrovascular complications [coronary heart disease (CHD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes.

Diabetic Retinopathy

Diabetic retinopathy may be present at the time of clinical diagnosis in most patients. Diabetic retinopathy can be treated effectively if it is detected early, and blindness can be prevented in majority of cases by good glycemic control and timely laser treatment.[4] Therefore, a correct, reliable evaluation of the population prevalence and severity of diabetic retinopathy is important for public health planning and treatment services in the individuals with type 2 diabetes.

Diabetic Neuropathy

Diabetic neuropathies are related to the presence, duration, and severity of hyperglycemia. Diabetic neuropathies have many phenotypes, of which predominantly sensory or sensorimotor distal polyneuropathy is the most common type. In a large population-based epidemiologic study using clinical criteria, there is evidence of neuropathy in 7.5% of patients at the time of diagnosis.

Diabetic Nephropathy

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) and it affects 20% of patients with type 2 DM.[5] However the risk of developing kidney disease does not linearly correlate with the duration of diabetes.

Early intensive hypoglycemic therapy not only reduced the risk of microvascular complications by 21–24%, but also significantly reduced the risk of myocardial infarction and death from any cause by 13–33%.[6] Improved glycemic control can reduce the incidence of microvascular diseases.[7] Reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy.

In India there is an epidemic increase in type 2 diabetes mellitus as reported by the World Health Organization (WHO) .[8] Microvascular complications at the time of diagnosis of diabetes mellitus are showing increasing trend in India. Early detection of micro vascular complications and its treatment at the time of diagnosis can prevent progression of these complications and hence morbidity and mortality. Although many studies have been undertaken in developed countries on the presenting features of newly diagnosed diabetes patients, fewer have been undertaken in low-middle income countries.[9] So this study is done with the aim to highlight the microvascular complications at the time of diagnosis of diabetes in a developing country like ours.

AIM OF THE STUDY

1. To identify the prevalence of microvascular complications at the time of diagnosis of diabetes mellitus.
2. To identify risk factors contributing to the development of microvascular complications.

REVIEW OF LITERATURE

INTRODUCTION

DIABETES MELLITUS (DM) is one of the most common metabolic disorders that share the phenotype of hyperglycaemia. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[10] Globally, type 2 diabetes mellitus (T2 DM) has become one of the most important chronic public health problems.[11] Morbidity and mortality from DM most commonly results from the long-term complications of the disease. Data from several studies suggest that aggressive management of DM and its associated risk factors will lead to a reduction in these long-term complications.[12]

Earlier the criterion for classification of DM was based on the age of onset or type of therapy. Now it is classified on the basis of the pathogenic process that leads to hyperglycemia. The two broad categories of DM are designated as type 1 and type 2. Current classification of diabetes mellitus diverse from previous classifications by the following

1. Elimination of the terms insulin-dependent DM and noninsulin-dependent DM and their acronyms, IDDM and NIDDM.
2. Forms of DM involving pancreatic β-cell destruction, including those cases due to an autoimmune cause and those cases in which an etiology is not known are included under type 1 DM.

3. More precise definition under type 2 DM is insulin resistance with insulin secretory defect.[13]

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

I. Type 1 diabetes (beta cell destruction leading to absolute insulin deficiency)

   A. Immune-mediated

   B. Idiopathic

II. Type 2 diabetes (predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

   A. Genetic defects of beta cell function e.g., MODY 1to 6

   B. Genetic defects in insulin action e.g., Leprechaunism

   C. Diseases of the exocrine pancreas e.g., Pancreatitis, hemochromatosis, Fibrocalculous pancreatopathy, Cystic fibrosis

   D. Endocrinopathies e.g., Acromegaly, Cushing's syndrome

   E. Drug- or chemical-induced e.g., glucocorticoids, pentamidine, diazoxide

   F. Infections e.g., congenital rubella, cytomegalovirus

G. Uncommon forms of immune-mediated diabetes e.g., anti-insulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes e.g., Wolfram's syndrome, Huntington's chorea, porphyria.

IV .Gestational Diabetes Mellitus (GDM)

CLINICAL CLASSIFICATION OF DIABETES MELLITUS

1. PRE DIABETES

Impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT)

2. DIABETES MELLITUS

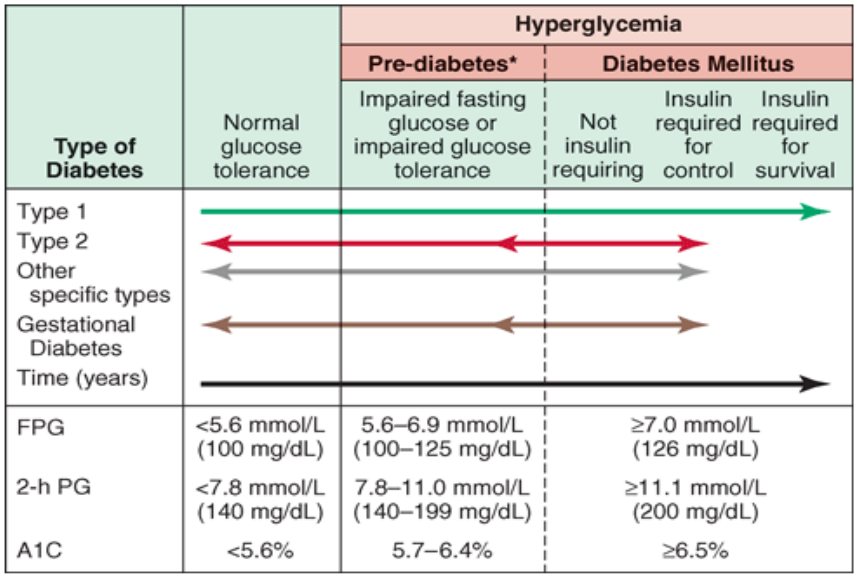

Figure 1: Spectrum of Glucose Homeostasis and Diabetes Mellitus

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dl)[a] (or)
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dl)[b] (or)
- A1C > 6.5%[c] (or)
- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dl) during an oral glucose tolerance test

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

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

c. The test should be performed in laboratory certified according to A1C standards of the Diabetes Control and Complications Trial.

d. The test should be performed using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water, not recommended for routine clinical use.

Source: ADA, 2011.

MAJOR RISK FACTORS FOR TYPE 2 DIABETES includes

- Family history of diabetes
- Obesity (BMI 25 kg/m^2)
- Physical inactivity[14]
- Race/ethnicity
- Previously identified with IFG, IGT (or) an A1C of 5.7–6.4%

- History of GDM or delivery of baby >4 kg (9 lb)
- Hypertension (BP 140/90 mmHg) [15]
- HDL cholesterol level <35 mg/dl and/or triglyceride (TGL) level >250 mg/dl[16]
- Polycystic ovary syndrome or Acanthosis nigricans
- History of cardiovascular disease

SCREENING FOR DIABETES MELLITUS

1. Asymptomatic adults of any age who are overweight or obese (BMI ≥ 25 kg/m2) and who have one or more additional risk factors for diabetes.
2. In those without risk factors for T2 DM, testing should begin at age 30-45 yr.

(If test results are normal, repeat testing should be carried out at 3 to 5-yr intervals)

EPIDEMIOLOGY OF DIABETES MELLITUS

90% of cases of Diabetes mellitus are due to Type 2 DM.[17] The number of people with diabetes is expected to rise from the current estimate of 285 million in 2010 to 438 million in 2030. Genetic and environmental factors precipitate the onset of clinical disease.[18] Age, sex and ethnic background are important in determining the risk of developing T2 DM. Women are more commonly affected than men. In the past T2 DM has been viewed as a disorder of aging and this remains true

today. Due to increasing prevalence of obesity in children, the incidence of Type 2 DM is also increasing.

INDIAN SCENARIO

India leads the world with largest number of diabetic subjects. It is known as "Diabetes Capital of the World". The so called "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians .They are increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. This phenotype makes Asian Indians more prone to diabetes and premature coronary artery disease. At least a part of this is due to genetic factors. 'Fast food culture' and 'Sedentarinism'- The main drivers of diabetes epidemic in India.[19]

PATHOGENESIS OF DIABETES MELLITUS

The pathogenesis of type 2 diabetes involves the interaction of genetic and environmental factors.[20] The clinical presentations are also heterogeneous with a wide range in age of onset, severity of associated hyperglycemia, and degree of obesity. Patients with type 2 diabetes consistently demonstrate three cardinal abnormalities:

(1) Resistance to the action of insulin in peripheral tissues, particularly muscle and fat but also liver.

(2) Defective insulin secretion, particularly in response to a glucose stimulus.

(3) Increased glucose production by the liver.

β-cell dysfunction plays a crucial role in type 2 diabetes.[21, 22] Whether defective insulin secretion and tissue resistance to insulin represent pleiotropic tissue effects of a single defect or multiple abnormalities is unknown. Glucose toxicity refers to the inhibitory effects of chronic hyperglycemia on insulin secretion and action. Hyperglycemia-induced insulin resistance includes down regulation of the glucose transport system by hyperglycemia and a defect in insulin-stimulated glycogen synthesis.

Type 2 diabetes is a progressive disease. Loss of β-cell function, and possibly of β-cell mass, is believed to underlie this progression, highlighting the pivotal role of the β-cell in determining the natural history of this disease.

GLUCOSE HOMEOSTASIS

Glucose homeostasis is dependent on a finely balanced dynamic interaction between tissue sensitivity to insulin and insulin secretion. Insulin that is secreted in response to glucose suppresses the hepatic glucose production and promotes the uptake of glucose in the peripheral tissue to maintain euglycemia.

FASTING GLUCOSE REGULATION

Primary factor determining fasting plasma glucose is hepatic glucose production which depends on

- Fasting (basal) plasma insulin
- Hepatic sensitivity to insulin
- Fasting substrate availability

POSTPRANDIAL GLUCOSE REGULATION

- Clearance of ingested glucose
- Suppression of hepatic glucose production
- Peripheral clearance of glucose

In IGT or DM, these mechanisms are impaired by

i) Delayed and reduced insulin secretion

ii) Lack of suppression of glucagon

iii) Hepatic and peripheral insulin resistance

Both basal insulin secretion and hepatic sensitivity to insulin are impaired in type 2 diabetes mellitus. With decline in insulin sensitivity, the endogenous insulin secretion increases to maintain the normal fasting plasma glucose. As the disease progresses, the compensatory insulin secretion diminishes and the fasting and post meal plasma glucose rises. [23]

MANAGEMENT OF DIABETES MELLITUS

The approach to a chronic disease such as diabetes requires treatment goals that include both the maintenance of the well-being of the affected individual and the prevention of the long-term complications associated with the disease. The relationship of glucose control to the microvascular complications has been validated. To achieve aggressive goals of glycemic control, self-monitoring of blood glucose must be a standard for all patients. The major clinical issue in patients with type 2 diabetes, in addition to that of achieving symptomatic control of hyperglycemia, is the enormous risk of cardiovascular disease and the problems arising from microvascular

complications. Multiple studies on cholesterol lowering,[24] blood pressure control [United Kingdom Prospective Diabetes Study (UKPDS); [25] the use of aspirin[26], and inhibitors of angiotensin-converting enzyme reveal significant benefits in patients with diabetes. The recent data from the Atherosclerosis Risk in Communities (ARIC) Study showed that the risk for diabetes in patients with hypertension is increased by two and a half. For many of these groups, access to good medical care is affected by factors such as socioeconomic status, insurance coverage, cultural background, language barriers, individual and group health beliefs, educational level, and peer behavior. These factors present special problems that will have to be addressed if these patients are to achieve optimal outcomes. Treatment must be individualized, and the relationship of risks to benefits must always be carefully evaluated, but age, per se, is not a reason to alter the target goals for glycemic control. The elderly do not always present with the classical symptoms and signs of hyperglycemia, so the physician must consider this diagnosis, especially in those with neuropathy, non-healing ulcers, and recurrent infections.

Smoking cessation and regular exercise clearly reduce the incidence of micro vascular and cardiovascular complications, There were relative risk reductions of 24% for any diabetes-related end point, 32% for diabetes-related death, 44% for stroke, and 37% for microvascular disease with intensive blood pressure control. On an average, each 10 mm Hg reduction in systolic blood pressure was associated with a 12% decrease in the risk of any end point related to diabetes and a 15% reduction in the risk of death related to diabetes.[27, 28, 29]

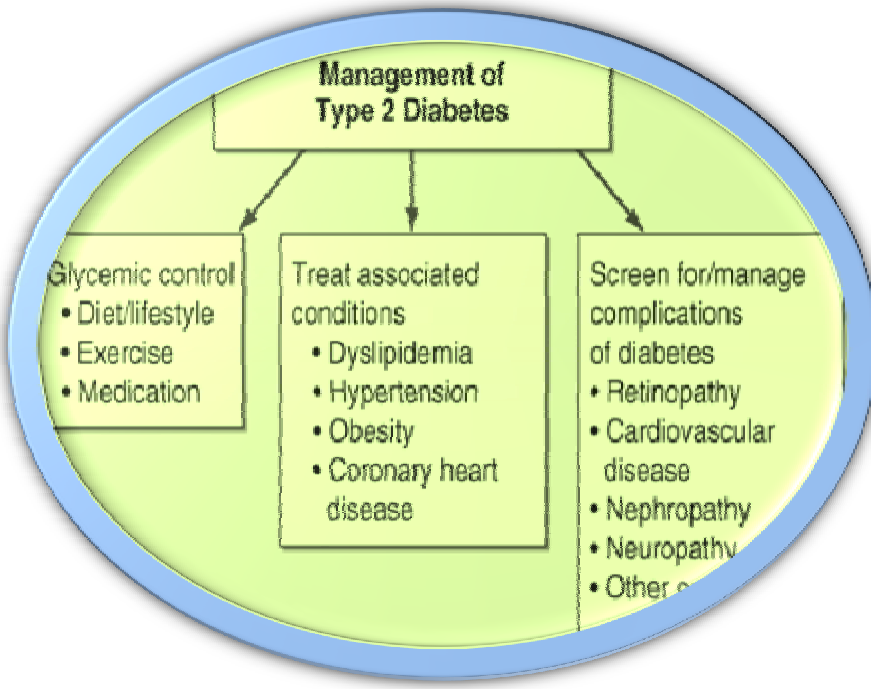

Figure 2 Management of Type 2 Diabetes

The United Kingdom Prospective Diabetes Study with newly diagnosed type 2 diabetes found that an 11% relative decrease in glycated hemoglobin (HbAlc) with intensive versus conventional treatment over a 10-year period was associated with a 25% decrease in microvascular complications. Exercise may improve insulin sensitivity.[30]

COMPLICATIONS OF DIABETES MELLITUS

ACUTE

- Diabetic ketoacidosis (DKA)
- Hyperglycemic hyperosmolar state (HHS)

CHRONIC

- Microvascular complications

  Retinopathy (Nonproliferative/Proliferative)

  Neuropathy

Nephropathy

- Macrovascular complications

  Coronary heart disease

  Peripheral arterial disease

  Cerebrovascular disease

- Others

  Gastrointestinal (gastroparesis, diarrhea), Genitourinary (uropathy/ sexual), Dermatologic, Infectious, Cataracts, Glaucoma, Periodontal disease, Hearing loss.

MICROVASCULAR COMPLICATIONS

The surprisingly high level of HbA1c, mean10.8% at the time of diagnosis emphasises the delay in diagnosis in many patients and explains the common finding of micro vascular complications at presentation of Type 2 diabetes.[31] Hypertension and smoking also have an adverse effect on microvascular outcomes. [32] Sex and racial differences have also been described in the prevalence of microvascular complications.[33] Abnormal NO metabolism is related to advanced diabetic microvascular complications. Increased microvascular permeability and deficient microvascular blood flow are prominent features. In addition there is histological evidence of widespread capillary basement membrane thickening and there is evidence of procoagulant changes in the blood as well as altered rheological properties.[34] Hyperglycemia is known to stimulate the release of inflammatory cytokines and can lead to the induction and secretion of acute-phase reactants by

adipocytes. Several studies evaluated the association between the serum hsCRP level and microvascular complications in type 2 diabetes.[35] Diabetes duration and glycemic control, blood pressure, and lipid control have consistently been shown to correlate with diabetic retinopathy, neuropathy, and nephropathy apart from other known risk factors; there is a possible relationship among the diabetic microvascular complications themselves.[36] Ensuring good glycaemic control remains the most effective therapeutic manoeuvre to reduce the risk of development and / or progression of micro vascular disease.[37,38,39] Landmark trials such as the UKPDS, Kumamoto and the DCCT have proven this to be effective when implemented early in the disease course.[40]

MECHANISMS OF COMPLICATIONS

Four prominent theories have been proposed to explain how hyperglycemia might lead to the chronic complications of DM.

1. **Advanced glycosylation end products** (AGEs) formed due to increased intracellular glucose levels bind to a cell surface receptor, via the non-enzymatic glycosylation of intra and extracellular proteins. AGEs have been shown to cross-link proteins such as collagen, extracellular matrix proteins, promote atherosclerosis, accelerate glomerular dysfunction, induce endothelial dysfunction,[41] reduce synthesis of nitric oxide and alter extracellular matrix composition and structure.

2. Intracellular glucose is metabolized predominantly by phosphorylation and subsequent glycolysis. When levels are increased, the enzyme aldose reductase converts some glucose to sorbitol. Increased sorbitol concentration increases cellular osmolality, alters redox potential, generates reactive oxygen species and leads to cellular dysfunction.
3. Raised glucose level increases the formation of diacylglycerol and activates protein kinase C (PKC). PKC alters the transcription of genes for fibronectin, contractile proteins, type IV collagen, and extracellular matrix proteins in endothelial cells and neurons.
4. Elevated glucose increases the flux through the hexosamine pathway, there by generating fructose-6-phosphate, which is a substrate for proteoglycan production and O-linked glycosylation .This pathway alters function by changes in gene expression of transforming growth factor or plasminogen activator inhibitor-1 or glycosylation of proteins e.g. Endothelial nitric oxide synthase.

DIABETIC RETINOPATHY

Diabetic retinopathy is a well characterized, sight threatening, chronic microvascular complication that eventually affects virtually all patients with diabetes mellitus. Diabetic retinopathy is the leading cause of blindness throughout the world.[42] The prevalence of diabetic retinopathy increases with the duration of diabetes and patient age. Diabetic retinopathy is an independent risk marker for subclinical atherosclerosis in patients with newly diagnosed type 2 diabetes. So diagnosis of diabetic retinopathy may warrant a more careful cardiovascular assessment even in the early stages of diabetes.[43]

EPIDEMIOLOGY OF DIABETIC RETINOPATHY

All patients with type diabetes and more than 60% of those with type 2 diabetes have some degree of retinopathy after 20 years of diabetes. For the past 20 years, diabetic retinopathy has remained the leading cause of new cases of legal blindness between the ages of 20 and 74 years. Because T2 DM accounts for 90% to 95% of the diabetic population, it accounts for a higher fraction of patients with vision loss. The increase in the prevalence of retinopathy complications in the DM group was similar to that of nephropathy.[44]

PATHOPHYSIOLOGY

Exposure to hyperglycemia over an extended period results in a number of biochemical and physiologic changes that ultimately cause endothelial damage. Selective loss of pericytes and basement membrane thickening which favours capillary occlusion and retinal non perfusion. Decompensation of the endothelial barrier function allows serum leakage and retinal edema to occur.[45] Increased platelet adhesiveness, increased erythrocyte aggregation, defective fibrinolysis, abnormal serum lipids, abnormal levels of growth hormone, up regulation of vascular endothelial growth factor and abnormalities in serum and whole blood viscosity have also been correlated with the prevalence and severity of retinopathy. Macular edema (capillary leakage), macular ischemia (capillary occlusion), sequelae from ischemia-induced neovascularization are associated with potential visual loss from diabetic retinopathy.

RISK FACTORS FOR DEVELOPMENT OF DIABETIC RETINOPATHY

- Hypertension
- Poor glycemic control
- Pregnancy
- Smoking
- Obesity
- Nephropathy
- Anaemia
- Hyperlipidemia(especially elevated serum cholesterol and triglyceride levels)
- Alcohol consumption [46]

CLASSIFICATION

- Non proliferative diabetic retinopathy (NPDR)
- Proliferative diabetic retinopathy (PDR)

NON PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

- **Very Mild**
    - Microaneurysm only
- **Mild**
    - Any or all of micro aneurysms, retinal hemorrhages, exudates, cotton wool spots up to the level of moderate NPDR. No IRMA or significant beading.

- **Moderate**
    - Severe retinal hemorrhages in 1-3 quadrants or mild intra retinal microvascular abnormalities
    - Significant venous beading can be present no more than one quadrant.
    - Cotton wool spots commonly present
- **Severe**

    One or more of
    - Severe hemorrhages in all four quadrants
    - Significant venous beading in two or more quadrants
    - Moderate IRMA in one or more quadrants
- **Very Severe**
    - Two or more of the criteria for severe

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

- **Mild to Moderate**
    - New vessels on the disc (NVD) or
    - New vessels elsewhere (NVE)

    (But extent insufficient to meet the high risk criteria)
- **High Risk**
    - New vessels on the disc greater than ETDRS standard photograph 10A (about one third disc area)

- Any NVD with vitreous or pre retinal hemorrhage
- NVE greater than half disc area with vitreous or pre retinal hemorrhage(or hemorrhage with presumed obscured NVD/NVE).[47]

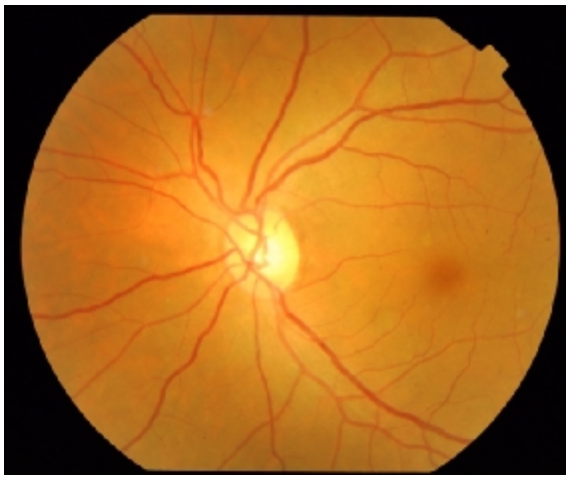

Figure 3: NORMAL FUNDUS

CLINICAL FINDINGS

Clinical findings associated with early and progressing diabetic retinopathy include hemorrhages or microaneurysms, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, and venous caliber abnormalities such as venous loops, venous tortuosity, and venous beading. Venous caliber abnormalities are generally a sign of severe retinal hypoxia.

Vision loss from diabetic retinopathy generally results from persistent non clearing vitreous haemorrhage, traction retinal detachment or diabetic macular edema (DME). The most common cause of vision loss from diabetes is macular disease and

macular edema.[48] Macular edema is more likely to occur in patients with T2 DM, who represent 90% to 95% of the diabetic population.

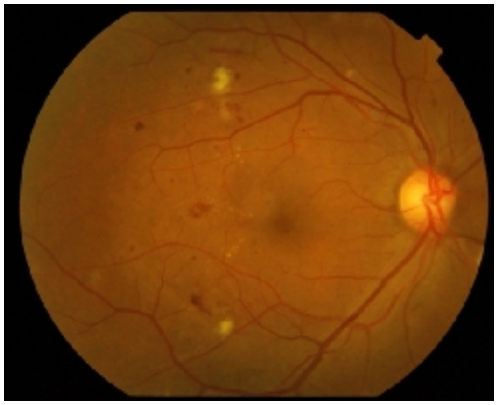

Figure 4: Non Proliferative Diabetic Retinopathy

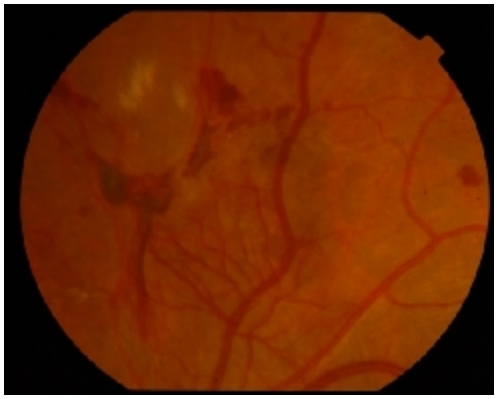

Figure 5: Proliferative Diabetic Retinopathy

MANAGEMENT

Principal goal in the medical management of diabetic retinopathy is the delay and prevention of complications. Intensive glycemic control is associated with a reduced risk of newly diagnosed retinopathy and reduced progression of existing retinopathy in people with diabetes mellitus . Annual retinal evaluation to assess the presence and level of diabetic retinopathy and diabetic macular edema is essential to guide patient care. The UK Prospective Diabetes Study (UKPDS) with type 2 diabetes, showed that intensive glycemic and blood pressure control significantly reduced the incidence and progression of retinopathy and visual loss,[49] that is intensive treatment of both risk factors had an additive effect.[50]

DIABETIC NEPHROPATHY

Worldwide, the leading cause of end-stage renal disease (ESRD) is Diabetic nephropathy. People with diabetes are 17 times more prone to kidney disease, with diabetic nephropathy being the most common complication.[51] Proteinuria is the hallmark of diabetic nephropathy.[52] It is characterized by albuminuria (≥ 300 mg/d) and a reduced glomerular filtration rate and is often present at the time of diagnosis after the kidney has been exposed to chronic hyperglycemia during the prediabetes phase.[53] Diabetic nephropathy is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria, which progresses to microalbuminuria, macroalbuminuria, and eventually to ESRD. Microproteinuria heralds the future development of renal disease and is an independent risk factor for cardiovascular disease. Microangiopathy, especially nephropathy was reported to further increase this cardiovascular risk by approximately 100-fold compared to matched control subjects.[54] The prevalence of microalbuminuria rose gradually across deciles of each glycaemic measure.[55]

PATHOGENESIS

It has been suggested that inflammation and complement activation are involved in the pathogenesis of diabetic microvascular complications.[56] Diabetic nephropathy is histologically characterized by thickening of the glomerular basement membrane,[57] increased fractional mesangial volume, and podocyte abnormalities. Expansion of the glomerular mesangium, which occurs at the expense of the glomerular capillary lumen and filtration surface area, correlates most closely with the

decline in renal function and the development of proteinuria. Mesangial expansion is due to both reduced degradation and increased production of extracellular matrix proteins such as type IV and I collagen, laminin, and fibronectin. Although mesangium has been the major focus of interest, tubulointerstitial injury also play a role in the predictor of renal dysfunction. Pathologic change include thickening of the tubular basement membrane, tubular atrophy, interstitial fibrosis, and arteriosclerosis.[58] Interstitial expansion correlates closely with renal dysfunction, albuminuria, and mesangial expansion. Moreover, the impact of interstitial expansion on renal dysfunction is additive to that of mesangial expansion, suggesting an independent effect. In addition to hyperglycemia-induced abnormalities other insults that either influence the host response to diabetes-induced environmental disturbances, accelerate kidney damage progression. The transgression of albumin into the urine demarcates a disturbance in the barrier function of endothelial glomerular cells (podocytes).

MANAGEMENT

Treatment and prevention strategies depend on stage of disease. Primary prevention includes addressing hyperglycemia,[59] hypertension, and smoking. Secondary prevention adds angiotensin-converting enzyme inhibitors, cholesterol lowering, and perhaps restrictions on dietary protein. Tertiary care, including dialysis or transplantation, is generally managed by nephrologists, but family physicians continue to play an important role in the care of these patients. Long-term, intensified intervention aimed at multiple risk factors in patients with type 2 diabetes and

microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent.[60] Diabetic nephropathy is generally diagnosed based on clinical grounds without a renal biopsy.

DIABETIC NEUROPATHY

EPIDEMIOLOGY.

Diabetic polyneuropathy is the second most common type of polyneuropathy. It typically afflicts persons aged 60 to 70 who have suffered from diabetes for five to 10 years or more and 20 to 40% of diabetics present with neuropathy. In 10% of patients with diabetic neuropathy, it is only the diagnostic evaluation of neuropathy that brings the underlying diabetes to light.[61] About 60-70% of people have mild to severe forms of nervous system damage.[62] Incidence of neuropathy is associated with potentially modifiable cardiovascular risk factors, including a raised triglyceride level, body-mass index, smoking, and hypertension.[63] Neuropathy is usually symptomless and is therefore a hazard to the unwary patient.[64]Patients with newly diagnosed or poorly controlled diabetes[65] may experience uncomfortable dysaesthesiae or pain in the feet and lower legs, which rapidly resolve on establishment of euglycaemia.[66] Duration and degree of hyperglycemia are considered to be risk factors for both autonomic and peripheral neuropathy.[67]

TYPES OF DIABETIC NEUROPATHIES

- **Symmetric neuropathies**

1. Distal sensory neuropathy
2. Large-fiber type of diabetic neuropathy

3. Small-fiber type of diabetic neuropathy
4. Distal small-fiber neuropathy
5. “Insulin” neuritis
6. Proximal diabetic neuropathy (lumbosacral radiculoplexopathy)
7. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

- **Asymmetric neuropathies**

1. Mononeuropathy
2. Mononeuropathy multiplex
3. Radiculopathies
4. Lumbar plexopathy or radiculoplexopathies
5. Proximal diabetic neuropathy (lumbosacral radiculoplexopathy)
6. CIDP

MECHANISM

Diabetic nerves have a several fold increase in nerve energy substrates (glucose, fructose, glycogen). Their energy requirements are sufficiently low to permit them to continue to conduct impulses on adenosine triphosphate (ATP) derived from anaerobic metabolism.

1. Susceptibility to Entrapment/ Compression Neuropathies.

   Three sets of findings are consistently found in chronic diabetic neuropathy: first, a thickening of basal lamina: second, endothelial-cell and smooth-muscle proliferation with increased variance of capillary caliber and the closing of some capillaries; third, the tendency of fiber loss to be multifocal rather than diffuse.

2. Excessive Susceptibility to Ischemic Fiber Degeneration of Diabetic Nerves

3. Insulin-Induced Neuropathy

   Commonly a painful distal sensory polyneuropathy, although it also can be a severe generalized neuropathy. Insulin administration reproducibly causes acute endoneurial hypoxia by increasing nerve arteriovenous flow and reducing nutritive flow of normal nerves. The diabetic state confers resistance to this effect.

PATHOGENESIS OF DIABETIC NEUROPATHY

1. Genetic predisposition
2. Nerve hypoxia/ischemia
3. Oxidative stress
4. Overactivity of polyol pathway
5. Increased advanced glycation end products
6. Deficiency of γ-linolenic acid
7. Protein kinase C, especially increase in β-isoform
8. Growth factor(s) deficiency
9. Dysimmune mechanisms

CONCLUDING THOUGHTS

- First is the validation that glucose is indeed a neurotoxin and that tight glycemic control will prevent target complications.
- Second is the appreciation that pathogenetic mechanisms are likely interactive and linked.
- Third is the evolving improvement in understanding of the targets of glucotoxicity. Major target may be the Dorsal Root Ganglion neurons, Schwann cell and terminals.
- Fourth is a better understanding of molecular pathophysiologic mechanisms, especially in apoptosis.

CLINICAL FEATURES

DIABETIC POLYNEUROPATHY

Initial symptoms are paresthesiae, of burning and unremitting quality.[68] or lancinating pains. Impaired pain and temperature sensations in a stocking distribution. Vibration and joint-position sensations are impaired at the toes, sensory gait ataxia and a positive Romberg's sign. The ankle jerks are usually lost. The combination of pain insensitivity and autonomic denervation predisposes the foot to skin ulceration. Neuropathic joints may develop. Distal muscle weakness and wasting may be present.[69] Nerve-conduction studies generally show diminished or absent sensory-nerve action potentials,[70] with normal or only mildly impaired motor-nerve conduction velocity. Electromyography shows chronic denervation of distal muscles.

DIABETIC AUTONOMIC NEUROPATHY

Usually coexists with a small-fibre sensory peripheral neuropathy. Results from damage to small unmyelinated nerve fibres.[71] The main symptoms are abnormal sweating or diarrhea,[72] postural hypotension, vomiting from gastroparesis, micturition difficulties, and bladder infection due to atony, sexual impotence, and retrograde ejaculation. May reduce awareness of hypoglycaemia due to failure of catecholamine release. Dry, warm feet, miosis, reduced pupil light reflexes, and ptosis may be observed. Bedside tests consist of measuring postural hypotension, which reflects failure of sympathetic fibres, and measuring variability of the heart rate during deep breathing Autonomic neuropathy is associated with a blunted Erythropoietin response to anemia in type 2 diabetic patients without advanced renal failure.[73]

DIABETIC PROXIMAL NEUROPATHY

Acute asymmetrical painful proximal leg muscle weakness to the extreme of symmetrical painless proximal muscle weakness developing over many weeks or months. Diabetic proximal neuropathy has been termed diabetic myelopathy, polyradiculopathy, amyotrophy, lumbar plexopathy, mononeuropathy multiplex, femoral neuropathy, myopathy, or neuropathic cachexia.

DIABETIC MONONEUROPATHY

Painful paraesthesiae in the hands are more commonly due to the carpal tunnel syndrome, to which diabetics are prone.[74] Nerves vulnerable to compression such as the median nerve in the carpal tunnel, the ulnar nerve in the cubital groove, the radial nerve at the humerus, the common peroneal nerve at the fibular head, and the

lateral cutaneous nerve of the thigh at the inguinal ligament. Painful oculomotor nerve palsies, often sparing the pupil, are common.

DIABETIC TRUNCAL NEUROPATHY

Attacks of truncal pain and sensory disturbance occur in diabetic patients. They may be recurrent and affect more than one thoracic nerve root territory.

DIAGNOSTIC TESTS FOR AUTONOMIC NEUROPATHY

1. Resting Heart Rate

   Rate >100 beats/min is abnormal.

2. Beat-to-Beat Heart Rate Variation

   Heart rate variability of >15 beats/min is normal and <10 beats/min is abnormal

3. Heart Rate Response to Standing

4. Heart Rate Response to Valsalva maneuver

5. Systolic Blood Pressure Response to Standing

6. Diastolic Blood Pressure Response to Isometric Exercise

7. Electrocardiographic QT/QTc Intervals

   The QTc should be <440 msec.

8. Spectral Analysis

9. Neurovascular Flow

MANAGEMENT

The only preventive treatment for diabetic neuropathy is the maintenance of blood glucose concentration at close to normal range.[75] The distressing paresthesias of the distal extremities can be managed with amitriptyline or one of the newer generations of antidepressants. Shooting, stabbing pain also responds to some degree to antiepileptic drugs. Gabapentin may give reasonable results. Topical creams with capsaicin, lidocaine or other compounds (including ketorolac, gabapentin, and ketamine) have been found helpful. Nerve blocks and epidural injections have been helpful.

MATERIALS AND METHODS

SETTING

Patients with newly detected Diabetes mellitus those who attended the outpatient department of Diabetology, Coimbatore Medical College Hospital.

COLLABORATING DEPARTMENTS

- Department of Medicine
- Department of Diabetology
- Department of Biochemistry
- Department of Ophthalmology
- Department of Neurology
- Department of Nephrology

DESIGN OF STUDY

Cross sectional study

PERIOD OF STUDY

One year from September 2010 to August 2011

SAMPLE SIZE

100 newly diagnosed type 2 diabetic patients.

ETHICAL COMMITTEE APPROVAL

Ethical committee approval obtained from the Institutional Ethical Committee.

CONSENT

An informed consent was obtained from all participants.

INCLUSION CRITERIA

Newly diagnosed type 2 diabetic adult patients more than 30 years of age were included.

EXCLUSION CRITERIA

- Congestive Cardiac Failure
- Type 1 Diabetes
- Pregnancy
- Known Systemic Hypertension
- Patients on Angiotensin Converting Enzyme(ACE) Inhibitors
- Patients on Angiotensin Receptor Blockers(ARB)
- Patients with urinary tract infections, fever and severely ill patients
- Renal disease

DETAILS OF STUDY SUBJECTS

The age of the patients ranged from 30 to 75 years of age. All the study subjects were interviewed during their first visit to the hospital and their medical

history was obtained using a proforma. Details of the history included age, occupation, family history of diabetes, symptoms of diabetes and its complications, and reason for attending the out-patient department. Laboratory data collected include Fasting plasma glucose, 2 hours post 75 grams plasma glucose(OGTT), Fasting lipid profile – (total cholesterol, HDL, LDL,TGL), Urine microalbumin, Urine culture and sensitivity, Direct Ophthalmoscopic examination, Fundus fluroscein Angiography(FFA),Foot sensitivity by 10-g monofilament, deep tendon reflexes testing by percussion hammer, vibration perception testing by 128HZ tuning fork.

Anthropometric measurements including height, weight and blood pressure measurements were recorded. Assessments of micro vascular complications were done.

SELECTION OF STUDY SUBJECTS

All newly diagnosed Diabetes mellitus (WHO criteria) patients were included in the study.

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

- Fasting plasma glucose >126 mg/dL and
- Two-hour postprandial plasma glucose >200 mg/dL

  Detailed history regarding the symptoms of diabetes like polyuria, polyphagia, polydipsia and weight loss was taken.

HISTORY OF MICROVASCULAR COMPLICATIONS WAS TAKEN IN DETAIL

DIABETIC NEPHROPATHY

History of polyuria, oliguria, facial puffiness, abdominal distension and swelling of legs.

DIABETIC RETINOPATHY

History of blurring of vision, floaters, black spots and sudden visual loss.

PERIPHERAL NEUROPATHY

History of numbness, tingling, paraesthesia, burning sensation over the hands and feet or any sensory loss.

AUTONOMIC NEUROPATHY

Impaired sweating, retention and incontinence of urine, impotence and erectile failure.

ANTHROPOMETRIC MEASUREMENTS

Weighing machine was used to measure weight using spring balance that was kept on firm horizontal surface. Every day the scale was checked and calibration done with known weights. Care was taken that the subjects wore light clothes and the weight was measured to the nearest 0.5 kg.

Height was measured with a tape to the nearest one centimeter. Patients were made to stand upright without shoes and heels together with their back against the wall and eyes directed forward.

BMI was calculated by using the formula Weight /Height^2

Underweight	<18.5	
Healthy weight	18.5–24.9	
Overweight	25.0–29.9	Increased
Obesity	30.0–34.9	I High
	35.0–39.9	II Very high
	40	III Extremely high

Fasting lipid profile was taken after 8hours of overnight fast. The values obtained in the study were compared with the following values.

LDL CHOLESTEROL	
< 70 mg/dl	Therapeutic option for very high risk patients
< 100 mg/dl	Optimal
100- 129 mg/dl	Near optimal/ Above optimal
130- 159 mg/dl	Borderline high
160- 189 mg/dl	High
≥ 190 mg/dl	Very high
TOTAL CHOLESTEROL	
<200 mg/dl	Desirable
200- 239 mg/dl	Borderline high
≥ 240 mg/dl	High

HDL CHOLESTEROL	
< 40 mg/dl	Low
≥ 60 mg/dl	High

BLOOD PRESSURE (BP) MEASUREMENT

It was recorded by using the Sphygmomanometer. BP was recorded after making the patient to rest in the sitting position for ten minutes. Average of two readings taken five minutes apart was taken into consideration. Patients with BP >140/90 mmHg were excluded from the study.

DIABETIC RETINOPATHY

Fundus examination was carried out by Direct Ophthalmoscope after dilatation of pupils. In the absence of direct ophthalmoscopic findings suggestive of Diabetic Retinopathy, Fundus Fluroscein Angiography was done. Presence of atleast one microaneurysm was considered as the minimum criteria for diagnosing diabetic retinopathy. Other changes include haemorrhages, venous calibre abnormalities, intraretinal micro vascular abnormalities, retinal neovascularisation were considered for diagnosis.

DIABETIC NEPHROPATHY

Assessment of nephropathy was done by measuring concentration of albumin in urine (early morning sample). Qualitative (or semiquantitative) tests for microalbuminuria have been proposed for use as screening tests for microalbuminuria. The usual way to do this is to measure the albumin in a 24 hours sample of urine but

the patient compliance is a limiting factor. An alternate method is to measure the concentration of albumin in urine at the initial visit especially in a concentrated morning sample. Hence this method was used in the study.

During the last decade, several longitudinal studies have shown that raised urinary albumin excretion (based on a single measurement) below the level of clinical albuminuria (albustix), so-called microalbuminuria, strongly predicts the development of diabetic nephropathy in both type 1 and type 2 diabetes.

DIABETIC NEUROPATHY

Detection of Diabetic peripheral neuropathy by

a. Foot sensitivity testing by monofilament,

b. Deep tendon reflex testing by percussion hammer,

c. Vibration perception testing by 128HZ tuning fork.

Perkins et al. reported four simple tests includes 10-g Semmes-Weinstein monofilament examination, superficial pain sensation, vibration testing by the on-off method, and vibrations testing by the timed methods have excellent sensitivity and specificity for detecting neuropathy. The timed-vibration method took longer to perform than the others, but each of the other tests took less than 10 seconds.

AUTONOMIC NEUROPATHY

- Resting Heart Rate

  Rate >100 beats/min is abnormal.

- Orthostatic hypotension

  Systolic blood pressure was measured in the supine subject. The systolic blood pressure was again measured after 3 minutes in standing position. Normal response is a fall of <10 mm Hg, borderline is a fall of 10-29 mm Hg, and abnormal is a fall of >30 mm Hg with symptoms.

- Diastolic Blood Pressure Response to Isometric Exercise.
- Electrocardiographic QT/QTc Intervals.

STATISTICAL ANALYSIS

Data collected from the patients were coded and tabulated. Descriptive and inferential statistics were computed using **SPSS** (Statistical Package for Social Sciences) version 17.

Mean significant difference was analyzed and association between two variables was analyzed using Chi-square test.

RESULTS AND OBSERVATIONS

TABLE 1

SEX WISE DISTRIBUTION OF STUDY GROUP

Sex	Number	Percentage
Male	51	51%
Female	49	49%
Total	100	100%

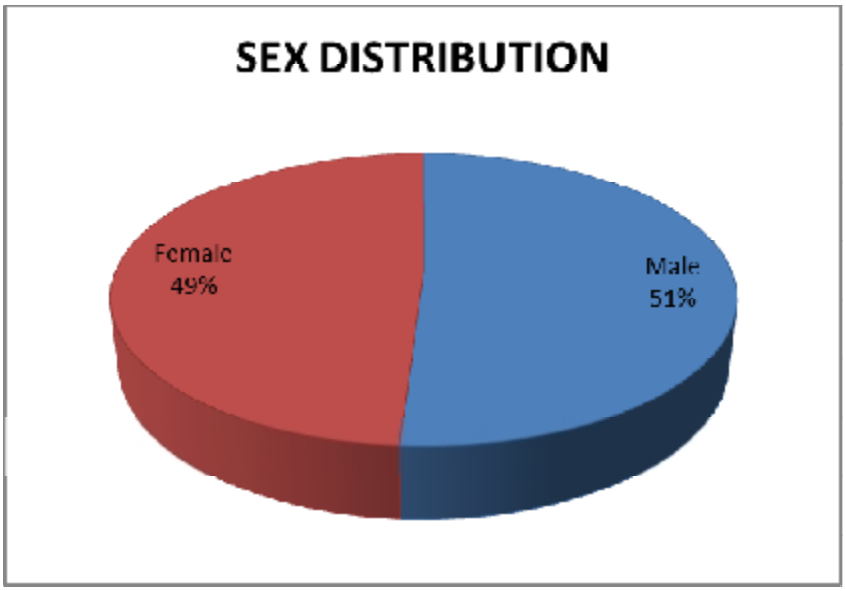

Figure 6: Sex Distribution

Above data suggests that out of the 100 newly diagnosed Diabetes mellitus patients in our study 51% were males (51) and 49% were females (49).

TABLE 2

SHOWING NUMBER OF PATIENTS ACCORDING TO AGE AND SEX DISTRIBUTION

Age	Male	Female	Total
25-35 yrs.	2	1	3(3%)
36-45 yrs.	12	10	22(22%)
46-55 yrs.	18	17	35(35%)
56-65 yrs.	15	16	31(31%)
66-75 yrs.	4	5	9(9%)
	51	49	100

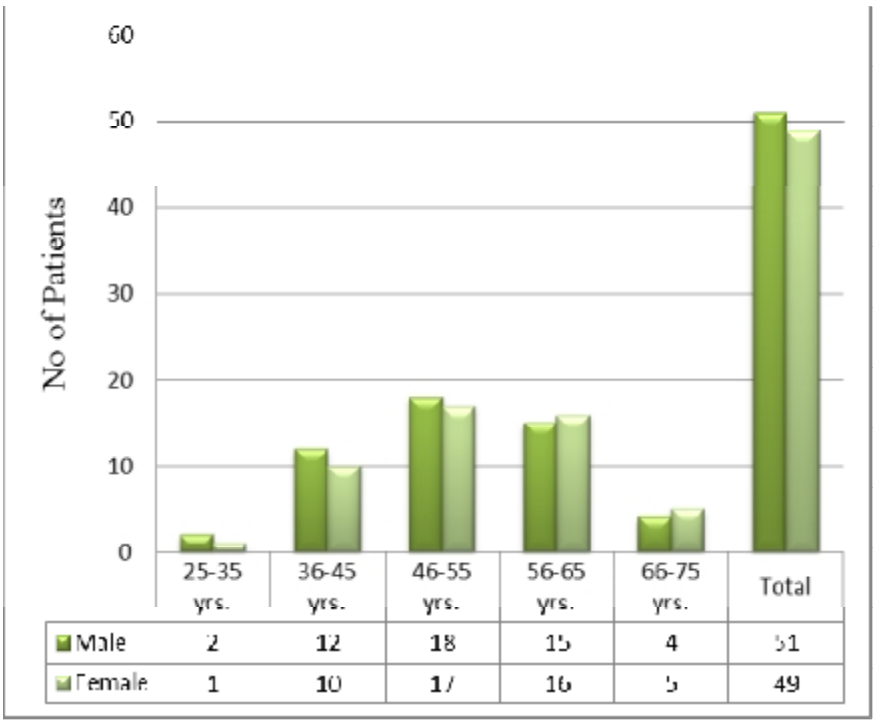

Figure 7: Age and Sex Distribution

Out of 100 study population 35 % of the patients were within the age group of 46-55 yrs, 31% of them were within 56-65 yrs. So the maximum numbers of patients were clustered between 46-65yrs of age. (35%+31%=66%). Mean age was found to be 53.39±9.554.

TABLE 3

FAMILY HISTORY

Family History	Male	Female	Total(n=100)
Positive	14	17	31(31%)
Negative	37	32	69(69%)
	51	49	100(100%)

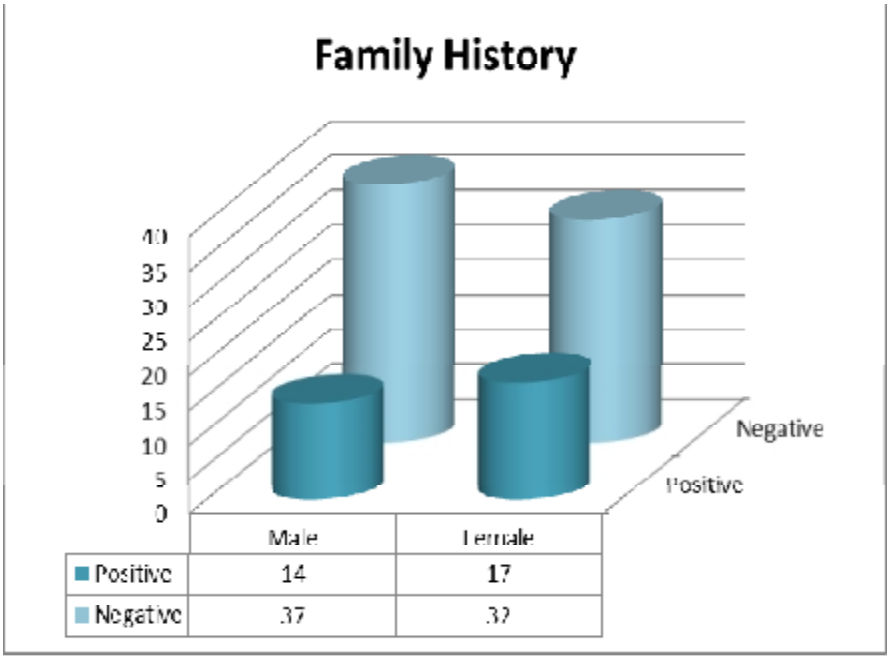

Figure 8: Family History

Of the 100 study population 31% had positive family history of Diabetes mellitus. Out of that 14% were males and 17% were females.

TABLE 4

SHOWING NUMBER OF PATIENTS WITH SYMPTOMATIC NEUROPATHY AND CLINICAL NEUROPATHY

		Clinical Neuropathy		Total
		No	Yes	
Symptom of Neuropathy	No	75	1	76
	Yes	12	12	24
Total		87	13	100

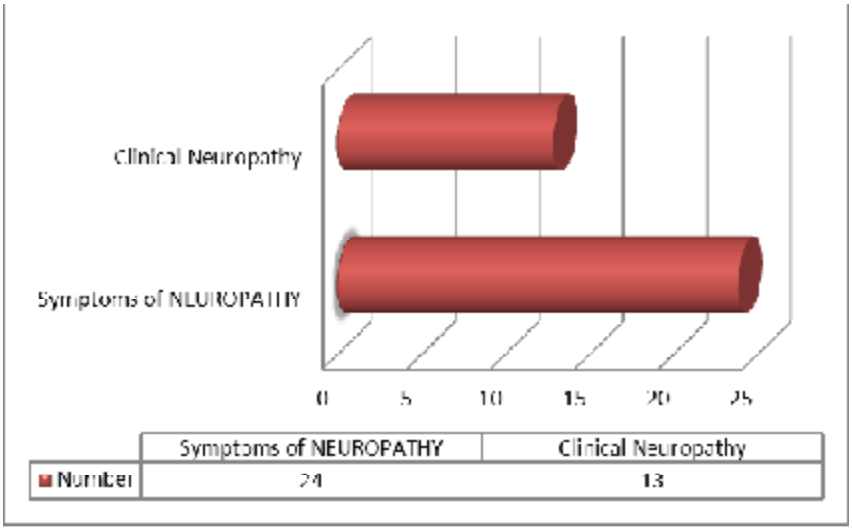

Figure 9: Symptomatic Neuropathy and Clinical Neuropathy

Above table shows that out of the 100 patients, 24 (24%) patients presented with symptomatic neuropathy. Among this 13 patients (13%) were found to have clinical neuropathy.

TABLE 5

SEX AND MICROVASCULAR COMPLICATIONS

		Microvascular Complications		Total	Chi -Square Test	Level of Significance
		No	Yes			
Sex	Male	30	21	51	0.207	0.649
	Female	31	18	49		
Total		61	39	100		

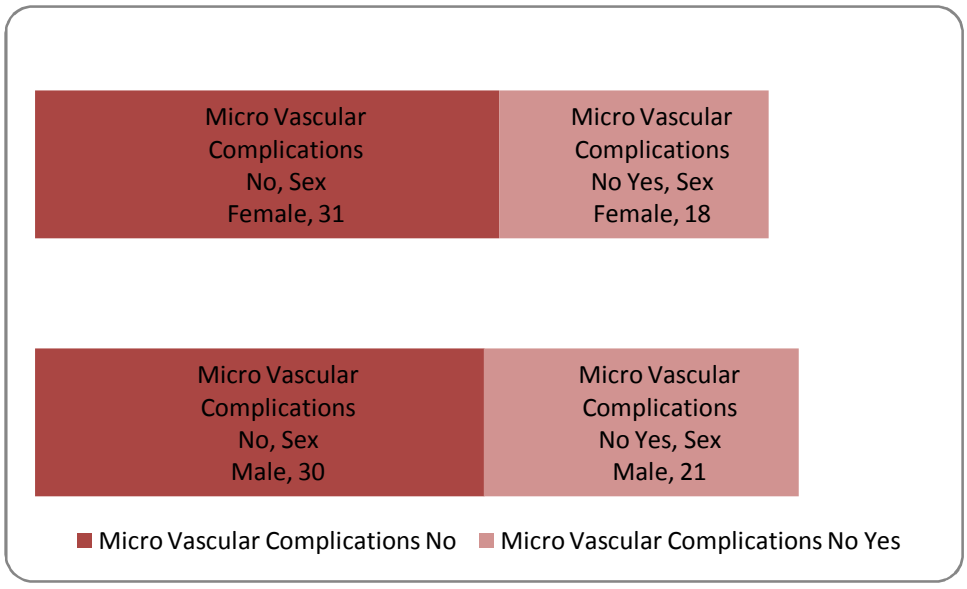

Figure 10: Sex and Microvascular Complications

In the above table the Chi-Square 0.207 for the association between sex and micro vascular complications is not significant (p=0.649). It can be inferred from the above data that there is no association between sex and micro vascular complications of Diabetes mellitus.

TABLE 6

SMOKING AND MICROVASCULAR COMPLICATIONS

		Microvascular complications		Total	Chi-square test	Level of significance
		No	Yes			
Smoking	No	49	19	68	10.924	0.001
	Yes	12	20	32		
Total		61	39	100		

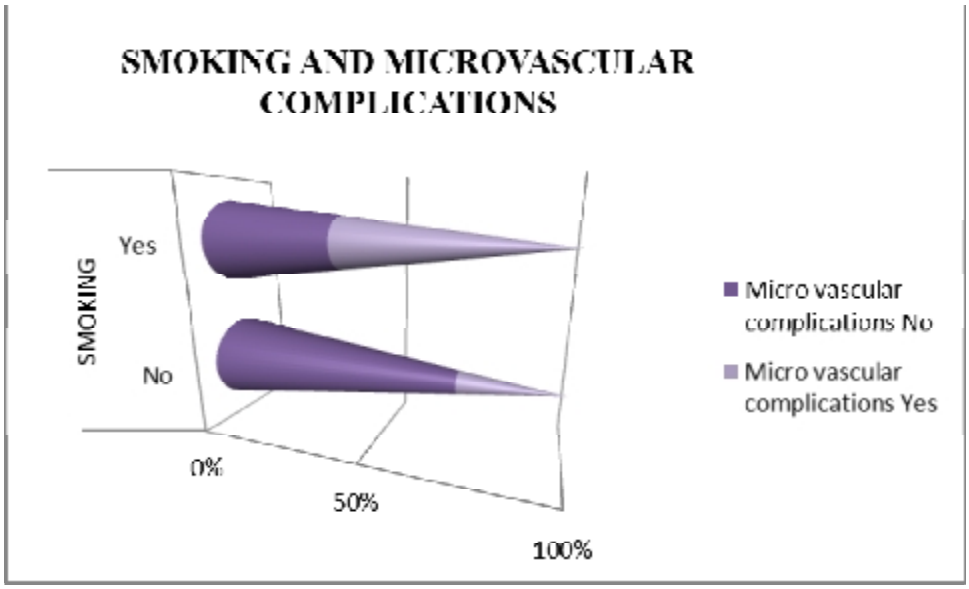

Figure 11 : SMOKING AND MICRO VASCULAR COMPLICATIONS

In the above table the Chi -Square 10.924 for the association between smoking and microvascular complications is significant ($p<0.001$). It can thus be inferred that there is strong association between smoking and development of microvascular complications of Diabetes mellitus.

TABLE 7

ALCOHOL AND MICROVASCULAR COMPLICATIONS

		Microvascular complications		Total	Chi -square test	Level of significance
		No	Yes			
Alcohol	No	46	19	65	7.450	0.010
	Yes	15	20	35		
Total		61	39	100		

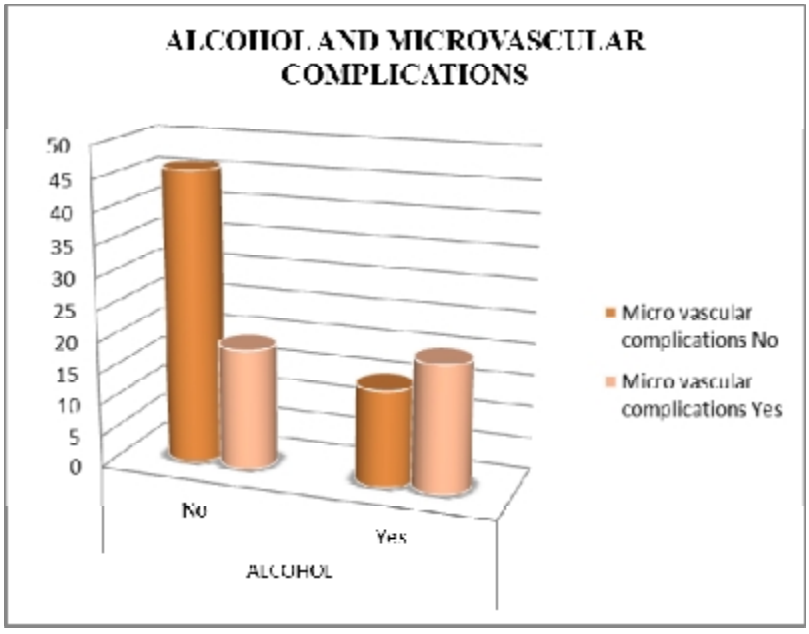

Figure 11: Alcohol and Microvascular Complications

In the above table the Chi -Square 7.450 for the association between Alcohol and microvascular complications is significant ($p<0.01$). It can be inferred that there is strong association between alcohol consumption and development of microvascular complications of diabetes mellitus.

TABLE 8

DISTRIBUTION OF CASES ACCORDING TO BMI

WEIGHT	MALE	FEMALE	TOTAL
Underweight	1	0	1
Normal	12	21	33
Overweight	30	23	53
Obese	8	5	13

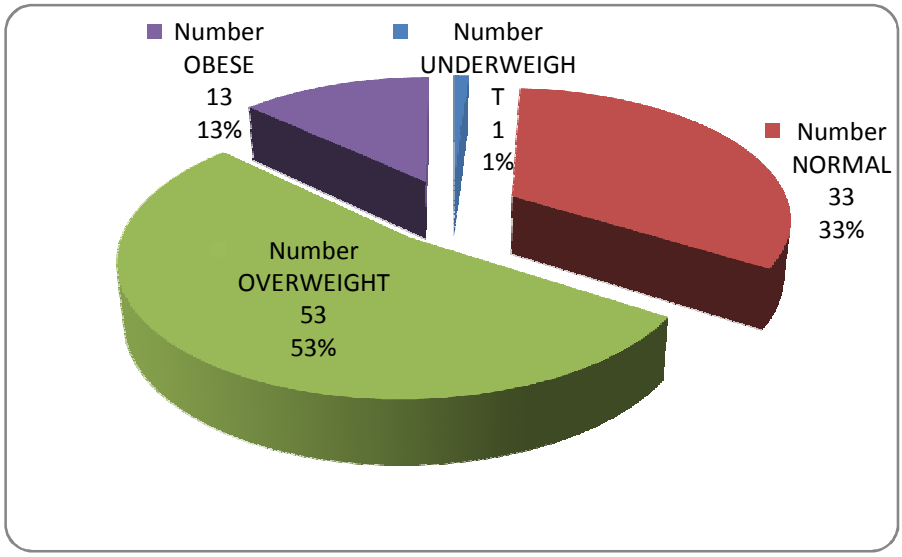

Figure 13: Distribution of Cases According to BMI

Of the study population 33% had normal BMI,1% were underweight,53% were overweight and 13% obese. Out of this 66 patients had high BMI(overweight and obese).

TABLE 9

BMI AND MICROVASCULAR COMPLICATIONS

		Micro vascular complications		Total	Chi-square test	Level of significance
		No	Yes			
BMI	Normal	23	11	34	11.031	0.001
	High	38	28	66		
Total		61	39	100		

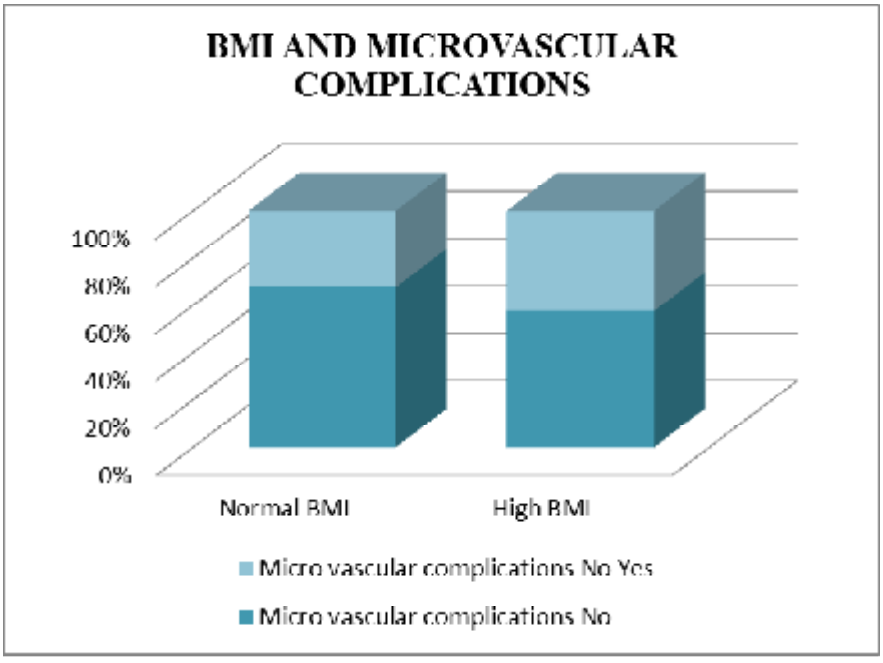

Figure 14: BMI and Microvascular Complications

In the above table the Chi Square 11.031 for the association between high BMI and microvascular complications is significant ($p<0.001$). It can hence be inferred that there is a strong association between BMI and microvascular complications of Diabetes mellitus.

TABLE 10

FASTING PLASMA GLUCOSE AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	217.74	36.811	4.791	0.001
No	61	185.85	29.389		

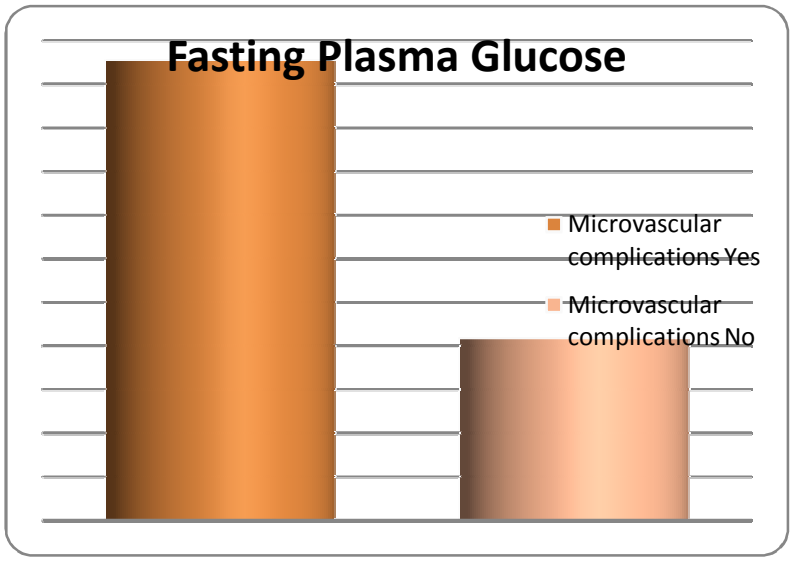

Figure 15: Fasting Plasma Glucose and Microvascular Complications

In the above table the z value 3.449 for the mean difference in the fasting plasma glucose level is significant($p<0.001$) .The mean fasting blood glucose of patient with microvascular complications and patient without microvascular complications were 217.74 and 185.85 respectively. It can be inferred from the above data that patients with high fasting glucose level are more prone for the development of microvascular complications.

TABLE 11

POSTPRANDIAL PLASMA GLUCOSE AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	315.85	59.642	5.642	0.001
No	61	256.18	45.752		

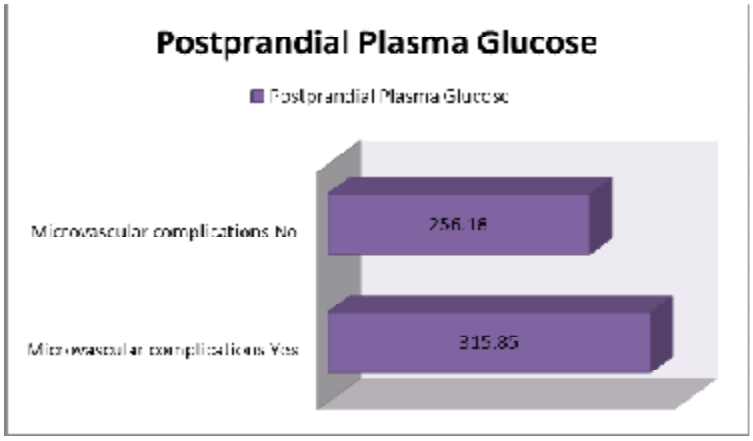

Figure 16: Postprandial Plasma Glucose and Microvascular Complications

In the above table the z value 5.642 for the mean difference in the postprandial plasma glucose level is significant (p<0.001). The mean postprandial plasma glucose of patient with microvascular complications and patient without microvascular complications were 315.85and 256.18 respectively. It can be inferred that patient with high postprandial glucose level are more prone for microvascular complications.

TABLE 12

TOTAL CHOLESTROL AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	233.21	26.514	3.707	0.001
No	61	213.57	25.393		

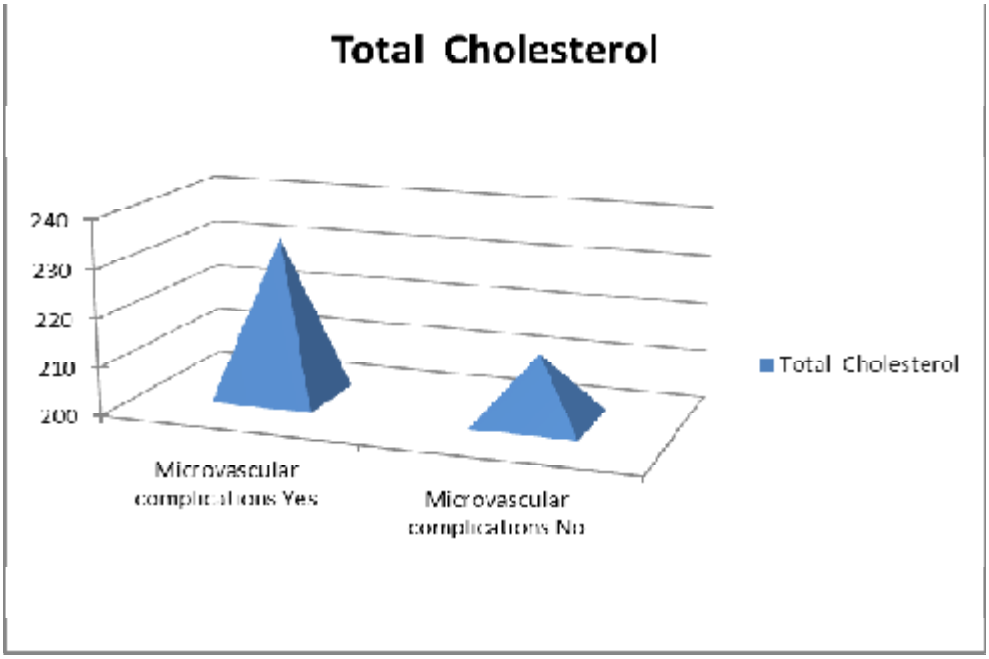

Figure 17: Total Cholesterol and Microvascular Complications

In the above table z value 3.707 for the mean difference in the Total Cholesterol between patients with and without microvascular complications is significant ($p<0.001$). The mean Total Cholesterol for patients with and without microvascular complications were 233.21 and 213.57 respectively. So it can be inferred that patients with microvascular complications had elevated Total Cholesterol when compared to patients without micro vascular complications.

TABLE 13

LDL CHOLESTROL AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	132.41	16.880	5.198	0.001
No	61	116.08	14.248		

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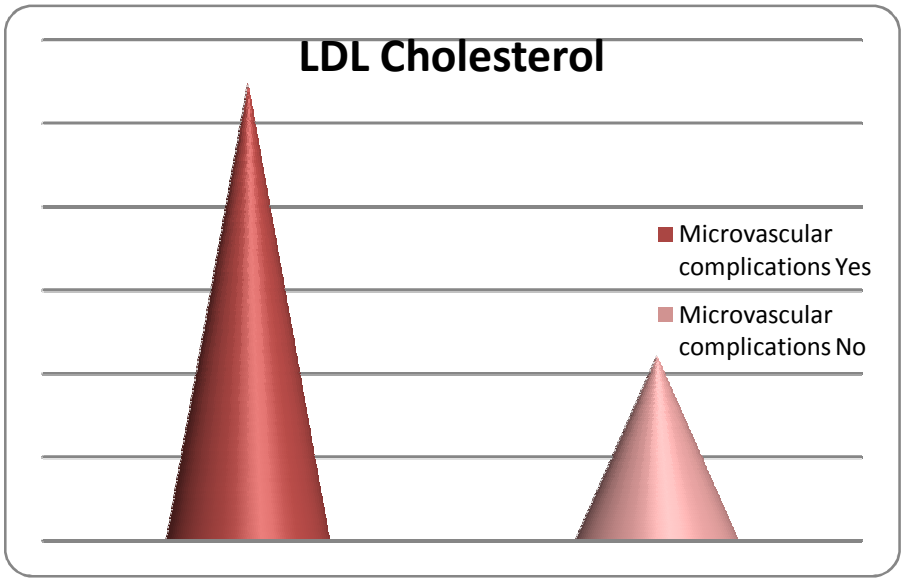

Figure 18: LDL Cholesterol and Microvascular Complications

In the above table z value 5.198 for the mean difference in the LDL Cholesterol between patients with and without micro vascular complications is significant ($p<0.001$).The mean LDL Cholesterol for patients with and without microvascular complications were 132.41 and 116.08 respectively. So it can inferred that patients with microvascular complications had high LDL Cholesterol when compared to patients without microvascular complications. In our study the mean LDL Cholesterol for patients with microvascular complications was 132.41±16.880.

TABLE 14

TGL CHOLESTROL AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	159.8462	36.65812	5.373	0.001
No	61	126.8361	24.80671		

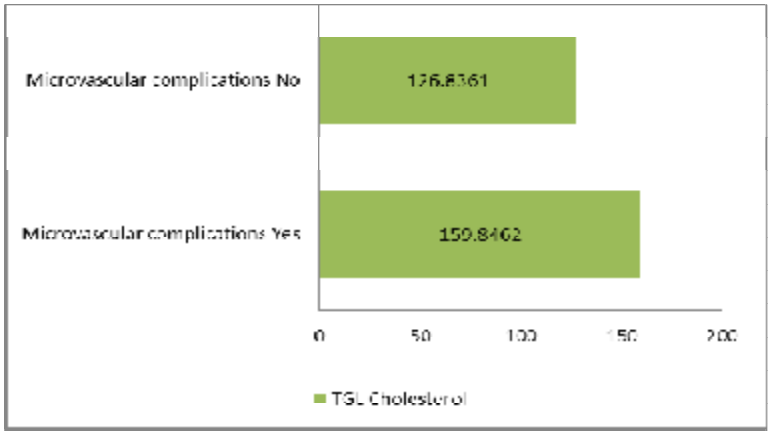

Figure 19: TGL Cholesterol and Microvascular Complications

In the above table z value 5.373 for the mean difference in the TGL Cholesterol between patients with and without microvascular complications is significant ($p<0.001$). The mean TGL Cholesterol for patients with and without microvascular complications were 159.8462 and 126.8361 respectively. So it can inferred that patients without microvascular complications had low TGL Cholesterol when compared to patients with microvascular complications.

TABLE 15

HDL CHOLESTROL AND MICROVASCULAR COMPLICATIONS

Microvascular complications	Number	Mean	Standard deviation	Z	Level of significance
Yes	39	45.51	3.170	3.266	0.002
No	61	47.90	3.798		

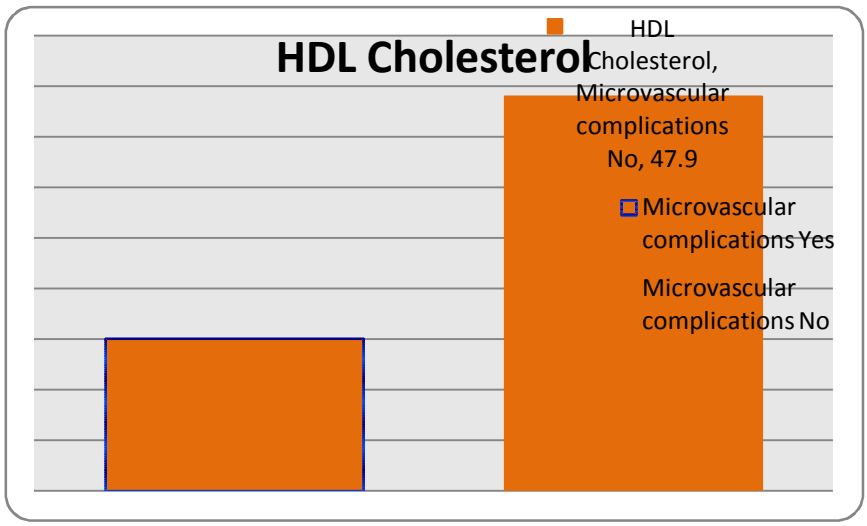

Figure 20: HDL Cholesterol and Microvascular Complications

In the above table z value 3.266 for the mean difference in the HDL Cholesterol between patients with and without microvascular complications is significant (p<0.002).The mean HDL Cholesterol for patients with and without microvascular complications were 45.51 and 47.90 respectively. So it can be inferred that patients without microvascular complications had high HDL Cholesterol when compared to patients with microvascular complications.

TABLE 16

RETINOPATHY AND MICROALBUMINURIA

	Nephropathy		Total	Chi square test	Level of significance
	No	Yes			
Normal	67	13	80	13.172	0.001
NPDR	9	11	20		
Total	76	24	100		

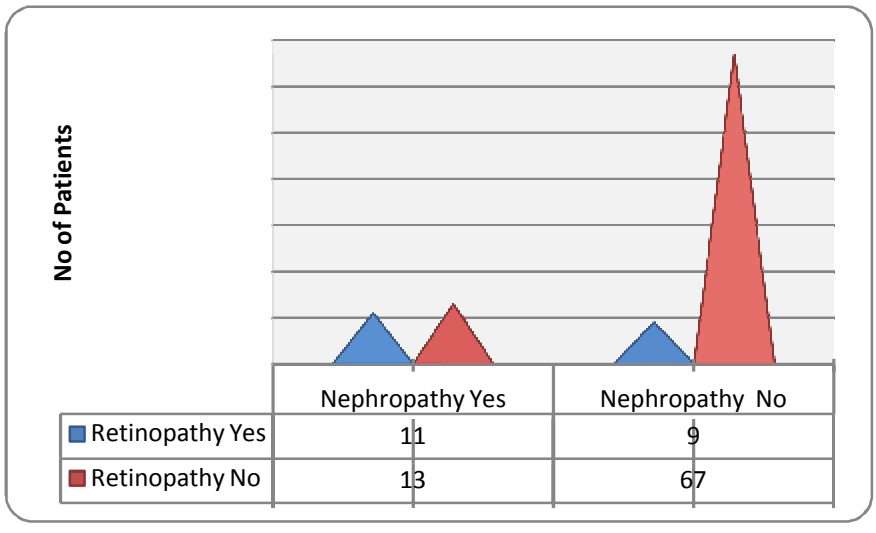

Figure 21: Retinopathy and Microalbuminuria

In the above table the Chi-Square 13.172 for the association between Nephropathy and Retinopathy is significant ($p<0.001$). It can be inferred from the table that there is strong association between nephropathy and retinopathy.

TABLE 17

RETINOPATHY AND NEUROPATHY

	Neuropathy		Total	Chi-square test	Level of significance
	No	Yes			
Normal	70	10	80	0.088	0.766
NPDR	17	3	20		
Total	87	13	100		

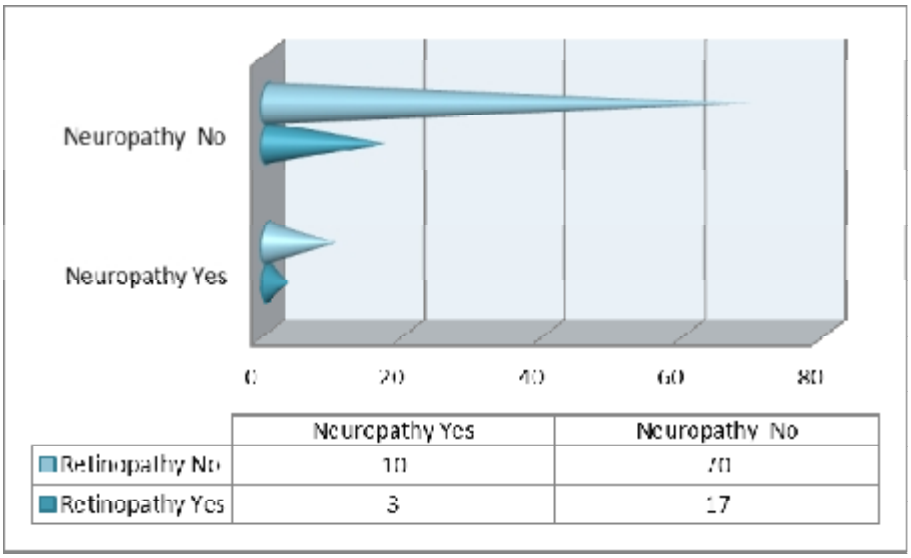

Figure 22: Retinopathy and Neuropathy

In the above table the Chi-Square 0.088 for the association between Neuropathy and Retinopathy is not significant(p=0.766).It can be inferred that there is no association between development of neuropathy and retinopathy.

TABLE 18

NEUROPATHY AND NEPHROPATHY

	Neuropathy		Total	Chi-square test	Level of significance
	No	Yes			
Normal	68	19	87	1.713	0.191
Yes	8	5	13		
Total	76	24	100		

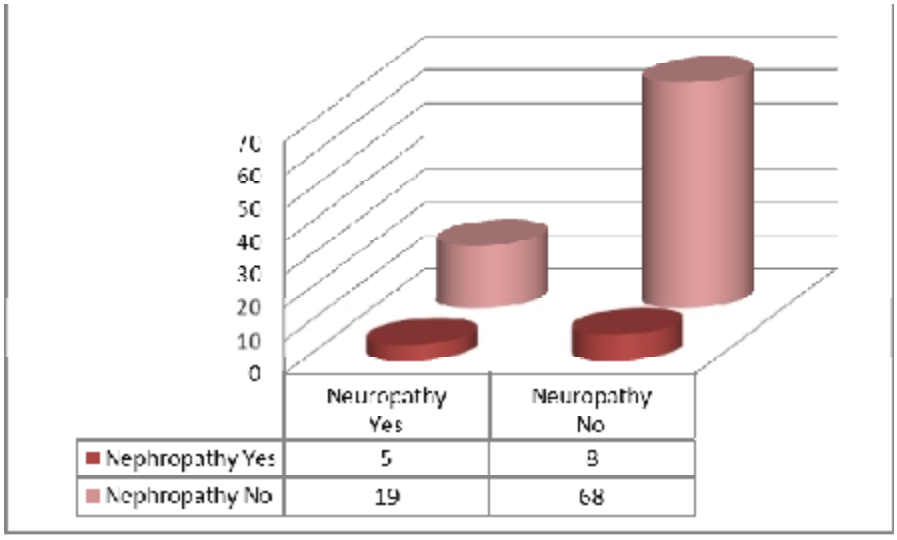

Figure 23: Neuropathy and Nephropathy

In the above table the Chi Square 1.713 for the association between Neuropathy and Nephropathy is not significant (p = 0.191). It can be inferred that there is no association between development of Neuropathy and Nephropathy.

TABLE 19

DISTRIBUTION OF MICROVASCULAR COMPLICATIONS

Microvascular complications	Number
Yes	39
No	61
Total	100

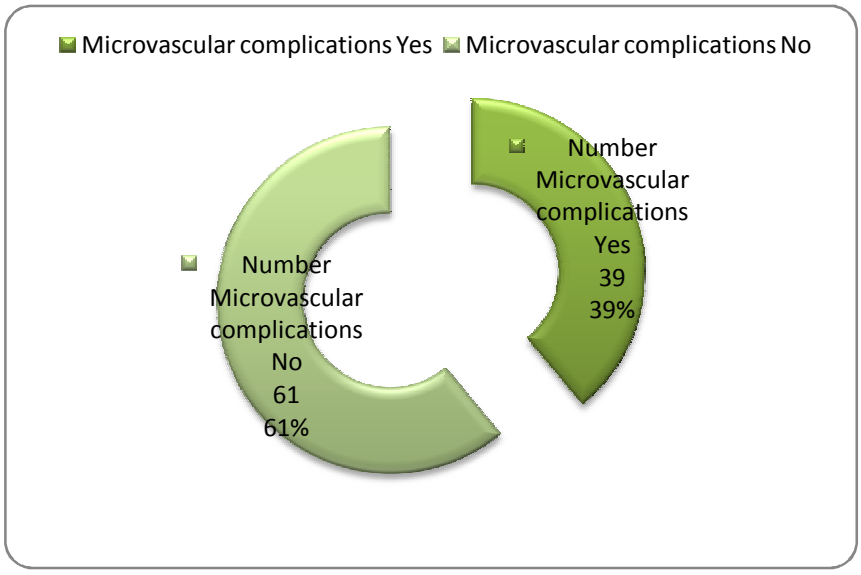

Figure 23: Distribution of Microvascular Complications

Out of the 100 study population 39% presented with microvascular complications at the time of diagnosis of diabetes mellitus.

TABLE 20

MEAN AND STANDARD DEVIATION

Characteristics	Mean	Mean± SD
Age(yrs)	53.39	53.39±9.554
BMI(kg/$m^{2)}$	25.79	25.79±2.812
Fasting Plasma Glucose(mg/dl)	198.29	198.29±35.888
Postprandial Plasma Glucose(mg/dl)	279.45	279.45±59.072
Blood Urea(mg/dl)	28.21	28.21±3.875
Serum Creatinine(mg/dl)	0.974	0.974±0.2065
Total Cholesterol(mg/dl)	221.23	221.23±27.445
LDL Cholesterol (mg/dl)	122.45	122.45±17.218
HDL Cholesterol(mg/dl)	46.97	46.97±3.737
TGL Cholesterol (mg/dl)	139.71	139.71±33.92067

Among the 100 study group the mean age was 53.39±9.554. The mean BMI was 25.79±2.812. The mean Fasting and Postprandial Plasma Glucose was 198.29±35.888 and 279.45±59.072 respectively. The mean blood Urea and serum Creatinine was 28.21±3.875 and 0.974±0.2065 respectively. The mean Total Cholesterol, LDL Cholesterol, HDL Cholesterol and TGL Cholesterol were 221.23±27.445, 122.45±17.218, 46.97 ±3.737 and 139.71±33.92067 respectively.

DISCUSSION

SEX DISTRIBUTION

In this study 100 newly diagnosed diabetic patients were taken. Out of which 51% were males and 49% were females. In Iraj Heydari et al[2] study 52% were males which correlates with our study.

AGE

The mean age of our study was 53.39 ±9.554 which closely relates to the studies done by F Harzallah et al [9] ,Fang Li et al [6], Kyung-Soo Kim et al[76], Hillier and Pedula et al. [77]

	Present study	Harzallah et al[9]	Fang Li et al[6]	Kyung-Soo Kim et al[76]	Hillier and Pedula et al[77]
Mean age in years	53.39±9.554	54.1±14	51.2±10.8	54.6±9.3	60±10.1

With increasing age, prevalence of diabetes also increases.. In our study 66% of the populations were around 46-65 years of age.

RISK FACTORS

FAMILY HISTORY

In our study population out of 100 patients 31% had positive family history which was slightly lower than the study by Kyung-Soo Kim et al,[76] which showed family history of 43%.

SMOKING

Among our study population 32% had history of smoking which was comparable with the study by Annemieke M.W. Spijkerman et al[78] et al which showed history of smoking in 31.7% of study population.

ALCOHOL

In this study, out of the 100 patients 35 of them were alcoholics. According to the study done by R J Young et al,[46] alcohol is a risk factor for the development of diabetic retinopathy.

BMI

Obesity is one of the independent risk factor for Diabetes mellitus and its complications. Weight loss can make cells more sensitive to the effects of insulin, thereby helping to reduce blood sugar.[79] The increasing trend of obesity among children coincides with a rise in the incidence of early-onset diabetes.[80]

In our study the mean BMI was 25.79±2.812, which correlated best with the studies done by Kyung-Soo Kim et al[76] and Fang Li et al[6] in which the BMI means were 25.0±3.1 and 25±2.8 respectively. The percentage of overweight patients in our study was 53% which correlated well with the study done by A P Nambuya et al[81] in which the percentage was 53.

	BMI
Present Study	25.79±2.812
Kyung-Soo Kim et al[76]	25.0±3.1
Fang Li et al[6]	25±2.8

FASTING PLASMA GLUCOSE

In our study, patients showed mean fasting plasma glucose of 198.29±35.884 which correlated with the study by Fang Li et al[6] ,in which mean fasting plasma glucose was 226.8±52.2. In the Kyung-Soo Kim et al[76] study the mean fasting plasma glucose was 185.3±67. Our study populations, patients with microvascular complications had high mean fasting glucose of 217.74±36.811.

POSTPRANDIAL PLASMA GLUCOSE

In our study, patients showed mean postprandial plasma glucose of 279.45±59.072, which was comparable to the study by Kyung-Soo Kim et al,[76] in which mean postprandial plasma glucose was 298.5±105.1. In Among our study patients with microvascular complications had high mean postprandial glucose of 315.85±59.642.

HYPERCHOLESTEROLEMIA

Our study showed a mean total cholesterol of 221.23±27.445 which correlates with the study by B Nazimek-Siewniakn et al[82] in which the mean total cholesterol was 222.912±46.403 and also with the study done by S D Pietro et al[83] where the mean value was 221±46. In our study the mean Total Cholesterol for patients with microvascular complications was 233.21±26.514.

LDL CHOLESTEROL

In our study the mean LDL cholesterol of patients was 122.45±17.218, which correlated best with the study done by Annemieke M.W. Spijkerman et al[78] which was 135.34416. The mean LDL in Fang Li et al[6], Chien-Yu Lin et al,[84] Kyung-Soo Kim et al[76] was 116.±37.89, 90.5±41.6 and 117.±38.1 respectively.

The most comparable mean of 126.83681 was done in the study by N N Jisieike-Onuigbo et al.[86]

	Low Density Lipoprotein (Mean)
Present study	122.45±17.218
N N Jisieike-Onuigbo et al[86]	126.83681
Kyung-Soo Kim et al[76]	117.0±38.1
Annemieke M.W. Spijkerman et al[78]	135.34416
Fang Li et al[6]	116.0±37.89
Chien-Yu Lin et al[84]	90.5±41.6

TRIGLYCERIDES

The mean TGL level in our study is 139.71±33.92 which is comparable with the values in the study done by Annemieke M.W. Spijkerman et al[78] where the mean triglyceride level was 159.48. In our study the mean TGL Cholesterol for patients with microvascular complications was 159.8462±36.65812.

	Present Study	Annemieke M.W. Spijkerman et al[78]
Triglycerides (Mean)	139.71±33.92	159.48

HDL CHOLESTEROL

In our study the mean HDL cholesterol of patients was 46.97±3.737 which correlated best with the study done by Kyung-Soo Kim et al[76] with a mean of 45.5±1.9. The mean HDL in Annemieke M.W. Spijkerman et al[78], Fang Li et al[6],

Chien-Yu Lin et al[84] was 42.53, 44.85±11.21 and 40.4±5.1 respectively. However the closest correlation was with the study done by Katherine J Craig et al[85] where the mean was 46.40371. Our study the mean HDL Cholesterol for patients with microvascular complications was 45.51±3.170.

	High Density Lipoprotein (Mean)
Present Study	46.97±3.737
Fang Li et al[6]	44.85692±11.21
Annemieke M.W. Spijkerman et al[78]	42.53674
Kyung-Soo Kim et al[76]	45.5±11.9
Kathrine J. Craig et al[85]	46.40371

DIABETIC NEPHROPATHY

Micro proteinuria predicts the development of early renal disease. It is also an important independent risk factor for development of cardiovascular disease in diabetes. Microalbuminuria in Type 2 Diabetes is a reliable maker for Diabetic Retinopathy also. Microalbuminuria in patients with Type 2 diabetes is predictive of clinical proteinuria and increased mortality.[87] In our study 24% of population had diabetic nephropathy which correlates with the study done by N. Weerasuriya et al[88] in the Srilankan population of which 29% had nephropathy, the Ranjit Unnikrishnan et al[89] study showed nephropathy in 23.8% of patients. F Harzallah et al[9] study showed nephropathy in 13% of patients.

	Our Study	N Weerasuriya et al[87]	Ranjit Unnikrishnan et al[88]	Harzallah et al[9]
Nephropathy %	24	29	23.8	13

DIABETIC RETINOPATHY

Diabetic retinopathy, the major ocular complication of diabetes, is the leading cause of visual impairment and blindness. [90] In our study, out of 100 patients, 20% had diabetic retinopathy (Non proliferative diabetic retinopathy), by presence of atleast one micro aneurysm, using either fundus direct ophthalmoscope or fundus fluroscein angiography. Study by N. Weerasuriya et al[88] showed retinopathy in 15% of the population. The study by Wang Y et al[91] demonstrated retinopathy in 19.6% of patients. F Harzallah et al[9] study showed 8% retinopathy. The discrepancy in the prevalence can be attributed to the differences in the race and ethnicity.[92]

	Retinopathy %
Our Study	20
N Weerasuriya et al[87]	15
Wang Y et al[90]	19.6
F Harzallah et al[9]	8

DIABETIC NEUROPATHY

Among our study population 24% had symptomatic neuropathy. After complete examination it was found that 13% had clinical neuropathy. Among this 13% it was found that 5% of them had autonomic neuropathy. The study done by

Zhaolan Liu et al[11] showed a percentage of 17.8. The F Harzallah et al[9] study showed neuropathy in 24% of patients.

	Clinical Neuropathy %
Present Study	13
Zhaolan Liu et al[11]	17.8
F Harzallah et al[9]	24
Weerasuriya et al[87]	25.1

CONCLUSION

- Out of 100 newly diagnosed Diabetes mellitus 39 patients were presented with microvascular complications.
- Diabetic nephropathy was found to be the commonest microvascular complication followed by Diabetic retinopathy and Neuropathy.
- Risk factors like Smoking, Alcohol, BMI and Hyperlipidemia were associated with microvascular complications significantly.
- Incidence of microvascular complications was associated with high fasting and postprandial plasma glucose.

SUMMARY

Type 2 diabetes mellitus is a silent asymptomatic disease for over a decade before it is diagnosed. This delay in diagnosis is why micro vascular complications are present at the time of diagnosis itself. There are a lot studies in newly diagnosed type 2 diabetes in the developed countries; very few studies have highlighted on the complications of diabetes in the low-mid income countries. This study is aimed at portraying the trend of newly detected type 2 diabetes and its microvascular complications in such countries.

The disparity in the values obtained in this study when compared to the other studies is mainly because of the ethnic and racial differences of various regions. The differences in values can also be attributed to the different methods and materials used in assessing the patient.

All the patients included in the study presented with high fasting and post prandial plasma glucose levels. On analysing, patients with microvascular complications had very high plasma glucose levels. This highlights on the fact that patients present to the physician very late in course of the disease. Early routine screening in the population and strict glycemic control can alone reduce the incidence of micro and macrovascular complications of diabetes.

In most patients the development of complications in diabetes is not because of only the elevated plasma glucose levels. There are various other factors contributing to the development of complications early in diabetics. The risk factors that have definite association as proved in our study are hypercholesterolemia, high

TGL, high LDL, low HDL, obesity, smoking, alcohol. Thus management of diabetes not only includes a strict glycemic control but also treatment and control of the associated risk factors at the same time.

In this study the most common microvascular complication was diabetic nephropathy. Microalbuminuria is an important predictor of progression to renal failure and is an important independent risk factor for development of cardiovascular disease. Though some patients presented with microalbuminuria in our study, none of them had overt renal failure. Thus early screening and timely management can retard the progression of the disease and reduce the cardiovascular complications.

The development of diabetic retinopathy at the time of diagnosis is on the increasing side. In our study of all the patients who presented with diabetic retinopathy, everyone had NPDR. This is a comforting sign since patients presenting at an earlier stage of retinopathy can be treated to prevent the progression of the disease and life threatening visual loss. Thus early screening for retinopathy becomes mandatory for all newly detected diabetics.

Diabetic neuropathy is a major complication that affects both the sensory and autonomic nervous system. A significant number of patients presented with neuropathy in our study. Hence a thorough examination by the physician is required in all newly detected diabetics for early identification and treatment of neuropathy. Only early intervention can reduce the morbidity and improve the quality of life of the patients.

In this era the rising trend of the number of diabetics is becoming a global burden. India which is the “Diabetic Capital of World” should take steps at the primary level itself to screen the target and at risk population. The management of diabetes is an integrated multidisciplinary approach that includes the combined participation of the patient, their family members, physician, specialists, nutritionist and others. Tight glycemic control, regular follow up, early screening and simultaneous treatment of other risk factors forms the basis in the treatment of diabetes.

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PROFORMA

NAME **AGE** **SEX**

OP.NO **OCCUPATION**

ADDRESS

PRESENTING COMPLAINTS

H/O Increased frequency of micturition	Yes	☐	No	☐
H/O Increased thirst	Yes	☐	No	☐
H/O Burning sensation in extremities	Yes	☐	No	☐
H/O Numbness/parasthesia in feet	Yes	☐	No	☐
H/O Numbness/parasthesia in hands	Yes	☐	No	☐
H/O Cold sensation in extremities	Yes	☐	No	☐
H/O Muscle cramps	Yes	☐	NO	☐

H/O Urinary urgency/frequency/nocturia Yes ☐ No ☐

H/O Blurring of vision Yes ☐ No ☐

PAST HISTORY

Previous H/o illness

TREATMENT HISTORY

PERSONAL HISTORY

H/O alcohol intake Yes ☐ No ☐

Duration

Quantity

H/O Smoking Yes ☐ No ☐

Duration

Quantity

H/O Weight loss Yes ☐ No ☐

FAMILY HISTORY

Diabetes Yes ☐ No ☐

Hypertension Yes ☐ No ☐

GENERAL PHYSICAL EXAMINATION

Height	Cm
Weight	Kg
B.M.I	(Kg/m^2)

Pallor	Yes	☐	No	☐
Icterus	Yes	☐	No	☐
Clubbing	Yes	☐	No	☐
Cyanosis	Yes	☐	No	☐
Lymphadenopathy	Yes	☐	No	☐

VITAL PARAMETERS

Pulse Blood pressure

Respiratory Rate Temperature

SYSTEMIC EXAMINATION

Higher mental function

Cranial nerves

Fundoscopy Examination

Fundus fluroscein Angiography

MOTOR SYSTEM

	Right		Left	
	UL	LL	UL	LL
Nutrition				
Power				
Tone				
Coordination				
Involuntary Movements				
Gait				

Superficial reflexes

Corneal Reflex

Abdominal Reflex

Cremastric Reflex

Plantar Reflex

Deep Tendon Reflexes

	Biceps jerk	**Triceps jerk**	**Supinator jerk**	**Knee jerk**	**Ankle jerk**
Right					
Left					

SENSORY SYSTEM

- Touch
- Temperature
- Cortical
- Pain sensation by Semmes Weinstein Monofilament Test
- Vibration sensation by 128HZ Tuning fork

AUTONOMIC FUNCTION

Resting Heart Rate

Postural Hypotension

CARDIOVASCULAR SYSTEM

RESPIRATORY SYSTEM

PROVISIONAL DIAGNOSIS

INVESTIGATIONS

- Fasting plasma glucose (mg %)
- Postprandial plasma glucose (mg %)
- Urine complete analysis

  Microalbumin

  Sugar

  Deposits
- Urine culture &sensitivity
- Blood urea (mg %)
- Serum creatinine (mg %)

- Serum Electrolytes (mEq/l)
- ECG
- **LIPID PROFILE**

    Total cholesterol

    LDL

    HDL

    VLDL
- **Fundus Fluroscein Angiography**

MASTER CHART

			SYMPTOMS					BLOOD PRESSURE (mmHg)		URINE		BLOOD SUGAR (mgs)				LIPID PROFILE (mgs)						
SI No	**Age**	**Sex**	**H/O Retinopathy**	**H/O Nephropathy**	**H/O Neuropathy**	**Family history**	**Smoking**	**Supine**	**Standing**	**Albumin**	**Culture Sensitivity**	**Fasting**	**Post prandial**	**Blood Urea**	**Sr.Creatinine**	**Total Cholestrol**	**LDL**	**TGL**	**HDL**	**Fundus/FFA**	**NEUROPATHY**	**ECG**
1	50	F	N	Y	N	Y	N	124/70	120/70	Y	-	206	340	28	0.8	208	128	201	40	NPDR	-	-
2	51	M	N	Y	N	N	Y	130/70	124/7O	Y	-	184	307	30	1.2	238	110	160	48	NPDR	-	-
3	43	F	N	N	N	Y	N	124/70	120/70	-	-	269	430	25	1	184	130	118	40	-	-	-
4	42	M	N	N	N	N	Y	120/80	120/80	Y	-	194	307	31	0.8	190	110	149	42	-	-	RAE
5	55	F	N	N	N	N	N	130/80	126/80	-	-	154	276	30	0.8	210	124	210	42	-	-	-
6	70	M	Y	N	N	N	Y	118/70	114/70	Y	-	225	272	28	1.2	240	140	157	43	NPDR	-	RAE
7	55	F	N	Y	N	N	N	126/80	124/80	-	-	142	276	30	1	202	140	156	44	-	-	-
8	45	F	N	Y	N	Y	N	120/80	120/80	Y	-	163	309	22	0.9	220	100	135	52	-	-	-
9	40	F	Y	Y	Y	Y	N	128/80	126/80	-	-	236	403	30	1.2	213	170	143	50	NPDR	-	-
10	49	M	N	Y	Y	N	Y	120/80	120/80	Y	-	160	257	24	0.13	270	145	179	45	-	Y	-
11	49	F	Y	N	N	N	N	130/70	126/70	Y	-	286	403	30	1.2	260	120	160	48	NPDR	-	-
12	50	M	Y	Y	Y	N	Y	128/80	116/78	Y	-	279	420	28	0.8	250	118	230	46	NPDR	Y	ST RAE
13	48	F	N	Y	N	N	N	130/90	126/88	-	-	186	252	30	0.8	210	100	200	50	-	-	-

14	52	F	N	N	N	Y	N	130/78	128/78	-	-	218	296	28	1.2	200	104	143	48	-	-	-
15	60	F	N	Y	Y	N	N	120/80	120/80	Y	-	204	296	30	0.9	240	126	130	45	-	-	-
16	42	M	N	N	N	N	N	110/80	110/80	-	-	203	245	26	0.8	200	100	123	49	-	-	-
17	65	M	N	N	N	Y	N	120/80	120/80	-	-	196	265	30	0.8	208	130	134	45	-	-	-
18	45	F	N	N	N	N	N	116/80	116/80	-	-	210	224	26	0.9	190	110	114	43	-	-	-
19	52	F	N	Y	N	Y	N	126/80	120/80	-	-	202	298	30	0.8	180	100	139	45	-	-	-
20	38	M	Y	N	N	N	Y	110/80	110/80	-	-	159	210	25	1	185	102	123	48	-	-	-
21	54	M	N	N	N	N	N	120/70	`116/70	-	-	208	269	24	1.2	197	110	110	47	-	-	-
22	67	F	N	Y	N	N	N	128/88	124/88	-	-	220	300	30	1.2	218	100	125	43	-	-	-
23	67	F	Y	Y	Y	Y	N	130/80	118/78	Y	-	280	406	30	1.2	230	136	152	45	-	Y	ST
24	60	F	N	Y	N	Y	N	116/80	114/80	-	-	210	309	28	1.2	230	118	150	45	-	-	-
25	65	F	N	N	N	N	N	126/80	126/76	-	-	200	260	28	1.2	222	130	138	40	-	-	-
26	63	F	N	N	N	Y	N	128/80	128/80	-	-	186	229	32	1.2	240	112	117	43	-	-	-
27	55	M	N	N	N	Y	N	110/80	110/78	-	-	178	202	28	1.2	200	100	127	45	-	-	-
28	55	F	N	Y	N	N	N	120/80	120/80	-	-	198	259	28	1.2	199	99	100	44	-	-	-
29	75	F	Y	Y	Y	N	N	130/80	126/80	Y	-	269	389	30	1.2	240	134	150	41	-	-	-
30	47	F	N	N	N	N	N	110/80	110/80	-	-	180	258	28	1.2	235	124	97	51	-	-	-
31	65	F	N	Y	N	N	N	126/80	124/80	-	-	165	212	30	0.8	207	113	132	43	-	-	-
32	45	M	N	Y	N	Y	Y	120/80	120/80	-	-	156	218	23	1.3	130	111	110	42	-	-	-
33	48	M	Y	Y	Y	Y	Y	130/80	130/80	Y	-	216	355	30	1.2	207	123	145	44	-	Y	-
34	65	M	N	N	N	N	N	126/80	126/80	-	-	145	203	28	0.8	206	100	140	52	-	-	-
35	35	F	N	Y	N	N	N	100/70	100/70	Y	-	206	307	28	0.8	208	112	150	48	NPDR	-	-
36	54	F	N	N	Y	N	N	120/80	120/80	-	-	187	298	28	1.1	180	99	200	50	-	Y	-
37	40	M	N	Y	N	N	Y	120/80	120/80	-	-	180	256	30	1.2	200	108	103	45	-	-	-
38	60	F	N	N	Y	N	N	126/80	110/80	-	-	204	281	28	1	258	150	126	45	-	Y	-

39	54	F	Y	Y	N	N	N	120/70	120/70	Y	-	279	380	30	0.6	184	130	200	44	-	-	-
40	70	M	N	Y	N	N	Y	120/70	120/70	Y	-	286	453	34	1.2	210	140	178	40	-	-	-
41	63	F	N	N	N	N	N	130/70	130/70	-	-	200	283	22	0.9	248	120	147	45	-	-	-
42	60	F	Y	Y	Y	Y	N	126/80	124/80	-	-	154	283	28	0.8	228	110	123	45	-	-	-
43	50	F	N	Y	N	N	N	110/80	110/80	Y	-	252	343	29	1	247	170	129	49	-	-	-
44	45	F	Y	Y	N	N	N	120/70	116/70	Y	-	255	442	24	0.6	204	132	100	45	-	-	-
45	60	F	Y	Y	Y	Y	N	120/80	120/80	Y	-	134	242	38	0.9	180	110	220	40	NPDR	Y	-
46	42	F	N	Y	N	Y	N	120/78	120/78	-	-	184	375	22	0.7	226	112	104	45	-	-	-
47	55	F	N	N	N	N	N	120/70	120/70	-	-	150	226	25	0.8	178	100	128	45	-	-	-
48	51	M	N	N	N	N	N	116/80	114/80	-	-	130	213	24	0.8	186	89	90	53	-	-	-
49	56	M	N	N	N	N	N	128/70	120/70	Y	-	170	235	28	1.1	175	111	100	50		-	-
50	50	M	N	N	N	N	N	118/80	116/80	-	-	198	260	30	0.6	210	100	105	50	-	-	-
51	56	M	N	N	N	N	N	126/80	126/78	-	-	145	218	29	0.8	200	110	145	48	-	-	-
52	60	F	N	Y	N	N	N	130/70	126/70	-	-	186	254	32	1	223	126	112	49	-	-	-
53	52	M	N	Y	Y	Y	Y	128/80	126/80	Y	-	210	305	22	1.2	255	140	229	40	NPDR	-	-
54	45	M	Y	N	N	Y	Y	110/80	110/80	-	-	204	267	27	0.9	207	110	128	50	-	-	-
55	46	M	N	N	N	N	N	116/80	110/80	-	-	199	277	26	0.7	210	100	145	53	-	-	-

56	48	F	N	N	N	N	N	124/80	124/80	-	-	226	268	29	0.8	228	123	134	49	-	-	-
57	60	M	N	N	N	Y	Y	130/80	128/80	-	-	247	310	30	0.8	260	134	178	42	NPDR	-	-
58	60	M	Y	Y	N	N	N	130/70	128/70	-	-	203	256	31	1.2	234	142	147	49	-	-	-
59	62	M	N	N	Y	Y	Y	130/80	110/70	-	-	204	260	36	1.2	250	140	137	46	-	Y	ST
59	62	M	N	N	Y	Y	Y	130/80	110/70	-	-	204	260	36	1.2	250	140	137	46	-	Y	ST
60	40	M	N	Y	N	N	Y	110/70	110/70	Y	-	193	240	33	1.2	268	136	144	46	-	-	-
61	60	F	N	N	Y	N	N	128/80	126/80	-	-	164	202	28	0.9	203	112	106	53	-	-	-
62	42	M	N	N	N	N	N	110/80	110/80	-	-	178	210	27	0.7	200	100	97	54	-	-	-
63	50	M	N	Y	N	Y	Y	124/80	120/80	-	-	224	297	28	0.8	250	130	145	48	NPDR	-	-
64	28	M	N	N	N	Y	N	110/80	110/80	-	-	183	251	29	0.9	189	99	126	54	-	-	-
65	70	M	N	Y	Y	Y	Y	130/80	116/80	-	-	210	278	26	1	224	126	156	49	NPDR	Y	ST
66	57	F	N	N	N	N	N	126/80	126/80	-	-	184	209	30	1.1	234	130	145	48	-	-	-
67	72	M	N	N	Y	N	Y	132/80	130/80	-	-	169	207	32	1.2	260	140	117	45	-	-	-
68	63	M	N	N	N	N	N	130/90	128/88	-	-	145	221	33	1.1	256	137	129	46	-	-	-
69	56	M	N	N	Y	N	Y	120/80	120/80	-	-	213	268	26	0.8	250	119	167	45	-	Y	-
70	52	F	Y	Y	N	Y	N	116/80	116/80	Y	-	167	231	35	0.9	280	145	160	41	NPDR	-	-
71	60	M	N	N	N	Y	Y	130/80	126/80	-	-	197	254	33	0.8	256	135	116	48	-	-	-

72	50	M	Y	N	N	N	Y	120/80	120/80	-	-	156	267	28	0.7	213	113	99	50	-	-	-
73	65	M	Y	N	N	N	Y	130/78	128/78	-	-	204	278	26	0.9	238	143	150	46	NPDR	-	-
74	58	F	N	Y	N	N	N	120/80	120/80	-	-	178	227	24	1	226	126	136	48	-	-	-
75	45	M	Y	N	N	Y	Y	108/70	108/70	-	-	199	296	28	1	240	103	143	52	-	-	-
76	47	M	N	N	Y	N	Y	116/70	116/70	-	-	205	313	31	1.2	216	100	116	51	-	-	-
77	42	F	N	N	N	N	N	120/80	120/80	-	-	157	294	30	1.1	219	118	125	53	-	-	-
78	35	M	N	N	N	N	N	110/80	110/80	-	-	188	285	29	1.2	183	120	96	55	-	-	-
79	40	F	N	Y	N	Y	N	116/0	116/80	Y	-	233	256	28	1.2	240	140	218	45	NPDR	-	-
80	39	M	N	N	N	N	Y	100/70	100/70	-	-	173	312	27	1.1	170	112	113	53	-	-	-
81	44	M	N	N	N	N	N	120/70	120/70	-	-	198	300	29	0.8	189	121	134	55	-	-	-
82	54	F	Y	N	Y	Y	N	110/80	110/80	-	-	207	287	28	0.8	218	140	145	49	-	Y	-
83	62	M	Y	N	N	Y	Y	130/70	126/70	-	-	256	298	28	0.9	250	150	158	47	NPDR	-	-
84	60	F	N	Y	N	N	N	126/80	126/80	-	-	212	234	25	1	245	136	110	47	-	-	-
85	51	M	N	N	N	N	N	110/80	110/80	-	-	165	226	29	1.1	254	134	100	48	-	-	-
86	42	F	N	N	N	N	N	110/80	110/80	-	-	187	211	26	1	201	112	98	52	-	-	-
87	62	F	N	N	N	N	N	132/70	130/70	-	-	235	244	32	1.2	243	140	128	48	-	-	-
88	62	F	N	N	Y	N	N	134/80	120/80	-	-	224	273	32	0.8	260	145	140	45	-	Y	ST

89	65	M	Y	N	N	N	Y	126/80	126/80	-	-	180	201	3	0.9	226	118	143	50	-	-	-
90	58	M	Y	N	N	N	Y	116/80	116/80	-	-	260	400	31	0.8	248	146	187	47	NPDR	-	-
91	70	F	N	Y	Y	Y	N	136/80	134/80	-	-	153	217	30	0.9	244	150	100	45	-	-	-
92	60	M	N	N	N	N	Y	130/70	130/70	-	-	230	237	28	0.7	225	120	96	49	-	-	-
93	41	M	N	N	N	N	N	110/70	110/70	-	-	175	210	25	0.8	211	111	123	52	-	-	-
94	54	M	Y	N	Y	N	Y	126/80	126/80	-	-	241	312	28	0.9	247	143	98	44	NPDR	-	-
95	68	F	N	N	N	N	N	13O/78	130/78	-	-	164	237	26	1	254	123	160	47	-	-	-
96	54	M	N	N	N	N	N	120/80	120/80	-	-	199	243	29	1.2	256	134	114	49	-	-	-
97	48	F	Y	N	N	Y	Y	100/70	100/70	-	-	215	296	27	1.1	240	148	100	45	NPDR	-	-
98	50	M	N	N	N	N	N	124/80	112/78	-	-	186	299	30	1.2	201	111	178	49	-	Y	-
99	43	F	N	N	Y	N	N	110/70	110/70	-	-	140	212	28	1.2	200	100	150	51	-	-	-
100	54	M	Y	Y	Y	N	Y	130/80	128/80	Y	-	202	365	28	1.3	248	144	250	45	NPDR	-	-

KEY TO MASTERCHART

M	MALE
F	FEMALE
Y	YES
N	NO
LDL	LOW DENSITY LIPOPROTEIN
TGL	TRIGLYCERIDE
HDL	HIGH DENSITY LIPOPROTEIN
FFA	FUNDUS FLUROSCEIN ANGIOGRAPHY
NPDR	NON PROLIFERATIVE DIABETIC RETINOPATHY
ECG	ELECTROCARDIOGRAPHY
ST	SINUS TACHYCARDIA
RAE	RIGHT ATRIAL ENLARGEMENT

SYMPTOMS OF NEPHROPATHY

Polyuria, oliguria, puffiness of face, leg swelling and abdominal

Distension.

SYMPTOMS OF NEUROPATHY

Tingling, numbness, paraesthesia, impotence, erectile dysfunction, impaired sweating, retention and incontinence of urine.

SYMPTOMS OF RETINOPATHY

Blurring of vision, black spots, floaters and sudden visual loss.