DIABETES MELLITUS TYPE 2
EVALUATION OF MICROVASCULAR & MACROVASCULAR COMPLICATIONS

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CERTIFICATE

This is to certify that the dissertation titled **"DIABETES MELLITUS TYPE 2 – EVALUATION OF MICROVASCULAR & MACROVASCULAR COMPLICATIONS"** is the bona fide original work of **DR.T. B. UMA DEVI** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamil Nadu DR. M.G.R Medical University to be held in MARCH 2007. The Period of study was from August 2005 to May 2006.

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DECLARATION

I, **DR. T. B. UMA DEVI** hereby solemnly declare that the dissertation titled **"DIABETES MELLITUS TYPE 2 – EVALUATION OF MICROVASCULAR & MACROVASCULAR COMPLICATIONS"** was done by me at Govt. Stanley Medical College and Hospital from August 2005 to May 2006 under the Supervision and Guidance of my Unit Chief **and Head of Department PROF. S. NATARAJAN, M.D.,** Professor of Medicine.

This dissertation is submitted to Tamil Nadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine.**

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INDEX

INTRODUCTION

Diabetes Mellitus comprises a group of common metabolic disorder that shares the phenotype of hyperglycemia. Several distinct type of DM exists and is caused by complex interaction of genetic, environmental factors and lifestyle choices.

The two broad categories of DM are designated as Type 1 and Type 2 Diabetes.

Type 1 Diabetes occurs due to auto-immune Beta cell destruction.

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production.

The chronic complication of DM affects many organ systems and is responsible for the majority of morbidity and mortality associated with the disease. The vascular complication of DM are further subdivided into Micro-vascular (Retinopathy, neuropathy, nephropathy) and Macro-vascular (coronary artery disease, peripheral arterial disease and cerebro-vascular disease).

The micro-vascular complications of both Type 1 and Type 2 DM result from chronic hyperglycemia. Since type 2 DM often has a long asymptomatic period of

hyperglycemia, many individuals with Type 2 DM have complications at the time of diagnosis.

The evidence implicating a causative role of chronic hyperglycemia in macrovascular complications is less conclusive. Moreover coronary heart disease events and mortality are two to four times greater in patients with Type 2 DM. Other factors like dyslipidaemia and Hypertension play an important role in macro vascular complications.

PRESENT STUDY

The present study was done on the patients with age more than 35 years with DM Type 2 attending the out-patient department of Diabetology at Government Stanley Medical College & Hospital, Chennai. These patients primarily belong to Lower socio-economic strata of the Society.

AIM OF THE STUDY

(1) To evaluate the microvascular and macrovascular complications of Type 2 Diabetes Mellitus, attending the Diabetology Out-Patient Department at Government Stanley Hospital, Chennai. The Patients were categorised according to the duration of diabetes for the purpose of study into

(a) Newly diagnosed DM.

(b) DM of < 5 years.

(c) DM for 5 – 10 years.

(d) DM > 10 years.

(2) To evaluate the Risk factors such as hypertension, obesity, hypercholesterolemia and smoking.

REVIEW OF LITERATURE

DIABETES MELLITUS

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by chronic hyperglycemia associated with disturbances of carbohydrate, fat and protein metabolism due to absolute or relative deficiency in insulin secretion and/or action. Diabetes causes long term damage, dysfunction and failure of various organs; especially the eyes, kidneys, nerves, heart and blood vessels. In a nutshell diabetes is appropriately described as a "Metabolic cum Vascular disorder" [1].

Recently the World Health Organization in consultation with an expert committee of the American Diabetes Association has reported a new classification and diagnostic criteria[2]. The term insulin dependent diabetes mellitus and non-insulin dependent diabetes mellitus and their acronyms, IDDM and NIDDM are eliminated. These terms have been confusing and have frequently resulted in classifying the patient based on treatment rather than etiology.

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

Type 1

Auto immune
Idiopathic

Type 2

Predominantly insulin Resistance
Predominantly insulin secretory defects

Other Specific Types

Genetic defects of beta cell dysfunction e.g., MODY 1 to 4
Genetic defects in insulin action e.g., Type A insulin resistence
Diseases of Exocrine pancreas, e.g., Fibro calculus pancreatopathy
Endocrinopathies, e.g., Acromegaly, Cushings, etc.,
Drugs or chemical induced, e.g., glucocorticoids
Infections, e.g., congenital rubella
Uncommon forms of immune mediated diabetes, e.g., Stiff Man Syndrome
Other Genetic syndromes.

Gestational Diabetes

STAGES OF DIABETES

Stages of diabetes range from normal glucose tolerance, through IGT and IFG (impaired fasting glucose), into frank diabetes mellitus, which may be non-insulin requiring, insulin requiring for control and insulin requiring for survival. Type 1 DM can be found across the whole spectrum. In the early stages of treatment there can be a period of non-insulin requirement, but later followed by insulin

requirement for survival. In type 2 DM, insulin may be required during a period of ketoacidosis precipitated by severe stress or infection.

DIAGNOSIS of DM

a. Diabetes is diagnosed if the fasting value ≥126mg or a 2-hour plasma glucose ≥ 200mg.
b. Impaired Glucose Tolerance is present when the fasting level is ≤126 mg and two-hour value is in the range of 140-200mg/dl
c. Impaired fasting glucose is present when the fasting level is ≥100 and ≤ and two hour value is ≤ 140mg/dl.
d. Glucose Tolerance is normal when the fasting and the 2-hour values are less than 100mg and 140 mg respectively.
e. Diagnostic criteria for gestational diabetes is different.

AETIOPATHOGENESIS OF TYPE 2 DM

The role of genetic factors in the etiology of type 2 DM has been appreciated ever since the recognition of the disease. Studies of identical twins revealing 10% concordance for type 2 DM have highlighted the single dominant influence of genetic factors in the etiology of type 2 DM. This concordance was recorded independent of obesity and even when the index twin and co twin lived in different environment. Earlier attempts to invoke a simple Mendalian type of inheritance,

viz., autosomal dominant, autosomal recessive and sex-linked inheritance met variable results. It was only subsequently recognized that the diabetic genotype might be modified by other factors, which ultimately influence the phenotypic expression. Similarly, attempts to quantify the risk in the inheritance of diabetes mellitus met with variable results. Diabetic genotype is influenced by various other factors the predominant one being central obesity. Even though obesity per se does not produce diabetes mellitus, it nevertheless precipitates the disease in susceptible individual. Epidemiological studies have established the significant contribution by other factors such as physical indolence, dietary habits (independent of obesity), viz., consumption of refined carbohydrates and reduced intake of fiber, urbanization with associated affluence and the stress of life, in the etiology of type 2 DM.

The current understanding type2 DM is that it involves triple abnormalities in the genesis of hyperglycemia, 1) impaired pancreatic insulin secretion, 2) peripheral resistance to insulin action occurring primarily in liver muscle, and 3) excessive hepatic glucose output. The classical glycemic profile of type 2 DM consists of elevated basal or fasting levels upon which postprandial glycemic excursions are superimposed. The hepatic glucose output is the principal factor for fasting hyperglycemia and the post prandial hyperglycemia in large part is determined by the peripheral glucose utilization (Insulin resistance)[3].

1.Impaired Panreatic Insulin Secretion*:* The beta cell dysfunction in diabetics fall into two distinct types. a) the pulsatile insulin delivery is lost even when the glucose tolerance is normal and b) the loss of compensatory mechanism, which include increase beta cell mass, quantitative insulin output and maximum secretary capacity.

a) ***Insulin Secretion in type 2 DM:*** The normal fasting insulin level is between 5 and 15μU/ml. It may be low (<5μU/ml) in subjects with high insulin sensitivity and elevated (>15μU/ml) in insulin resistant subjects. Normally insulin is secreted in a pulsatile fashion and also secreted in response to meals and or secretagogues. The pulsatile secretion is called ultradian oscillations. The ultradian pulse of insulin secretion occur 90 to 120 minutes and are exaggerated after the ingestion of food. Besides the ultradian pulsations, rapid oscillations of insulin level occur every 8 to 16 minutes in the beta cell. These rapid oscillatory insulin pulses are effective in inhibiting hepatic glucose output.

   The insulin secretion following a glucose load shows a biphasic response. The first phase acute insulin response (AIR) is due to release of insulin stored in the granules, which suppresses the hepatic glucose output. This occurs within 4 to 5 minutes and returns to normal within 10 minutes. The second phase is in response to the ambient raise in the

glucose level, which promotes disposal of glucose in peripheral tissue (Muscle and adipose tissue).

b) ***Beta cell dysfunction:*** The beta cell mass is mildly reduced especially when obesity is taken into account. Amyloid deposits are frequently observed in the islets. Morphologically islets appear normal and insulitis is never present. Amylin or the islet Amyloid polypeptide is a 37 amino acid protein normally produced by the beta cells and co-packaged with insulin in the secretary granules and co-secreted in the sinusoidal space. For reasons unknown this material tends to get accumulated extracellularly in close contact with beta cells and forms fibrils. Amylin has been reported to lower basal and insulin stimulated glycogen synthatase in the muscles and to inhibit glucose stimulated insulin secretion. These abnormalities of deficient insulin secretion and insulin action are similar to the pathogenic factors of type 2 DM.

There are evidences of impaired beta cell response to glucose (blindness of beta cells to glucose) but acute insulin response to non-glucose stimulus like arginine, neurotransmitters and hormones persist.

Insulin Secretory Abnormalities in Type 2 Diabetes Mellitus

- Decreased glucose sensing
  - Impaired ability to respond to elevations and reductions in glucose during glucose infusion.
  - Reduced or absent first-phase insulin secretion in response to intravenous glucose administration.
- Reduced or absent early insulin secretory response to oral glucose
- Alterations in the rapid oscillations of insulin secretion
- Reduced effect of gastrointestinal hormones in potentiating glucose mediated insulin secretion.
- Inadequate insulin secretion for the magnitude of hyperglycemia.

2. Peripheral Resistance to Insulin: Numerous longitudinal and cross sectional studies have provided evidences that hyperinsulinemia antedates the development of type 2 DM. This insulin resistance can occur in various tissues, liver, muscle, splanchnic, etc. After glucose ingestion insulin is released into the portal vein and is carried to the liver where it binds to its specific receptors on the hepatocytes and suppresses the hepatic glucose output. Failure of the liver to perceive this signal results in the increased hepatic glucose output and is manifested as raised blood glucose levels in type 2 DM.

In muscles the defects in action are

1) impaired insulin receptor tyrosinekinase activity,
2) diminished glucose transporters and
3) Diminished glycogen synthatase and pyruvate dehydrogenase.

These defect results in disturbances in major intracellular pathways of glucose disposal namely glycogen synthesis and glucose oxidation.

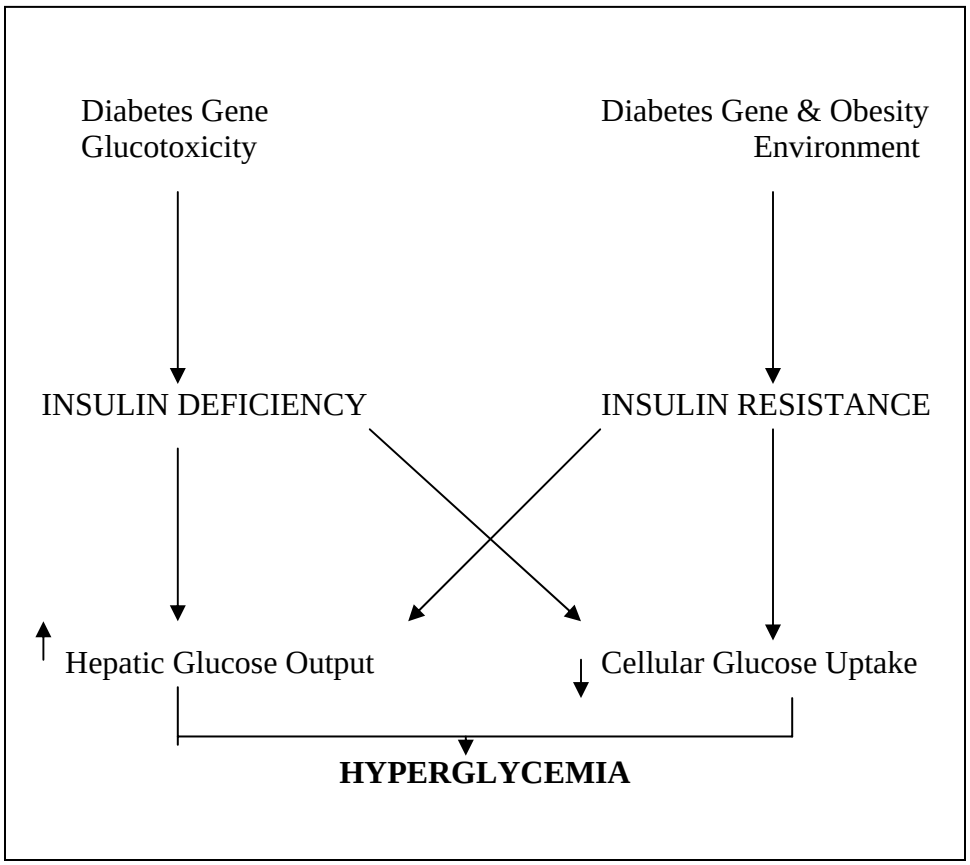
In type 2 DM subjects both receptor and post receptor defects have been shown to contribute to insulin resistance. Post binding defects are of three types a) impaired generation of insulin's second messenger b) diminished glucose transport into the cell and c) a post glucose transport abnormality in some critical step involved in glucose utilization. In diabetic subjects with moderate to severe hyperglycemia post binding defects in insulin action are responsible for the insulin resistance. In subjects with impaired glucose tolerance the defect may be at insulin binding to its receptor.

NATURAL HISTORY OF TYPE 2 DM

Normal glucose homeostasis is dependent on a finely balanced dynamic interaction between tissue sensitivity to insulin and insulin secretion. This evolution of the disease process in type 2 DM requires the defects in both insulin secretion and insulin action.

With the decline in insulin sensitivity, the endogenous insulin secretion increases to maintain normal fasting plasma glucose. As the disease progresses, the compensatory insulin secretion diminishes and the fasting plasma glucose rises.

PATHOGENESIS OF HYPERGLYCEMIA IN TYPE 2 DM



CHRONIC COMPLICATIONS

INTRODUCTION

The quality and expectancy of life of people with Diabetes, whether Type 1 or Type 2 is profoundly influenced by the development of complications and by how far and how fast they progress.

Complications may be diabetes specific mainly affecting the microvasculature (the triad of retinopathy, nephropathy and neuropathy) or they may be macrovascular in nature and present as coronary artery disease, cerebro vascular disease or peripheral vascular disease for which the incidence is 3 to 6 fold greater than normal with diabetes.

The Diabetic control and complication trial[4] provided definite proof that reduction in chronic hyperglycemia can prevent many of the early complication of Type 1 DM.

The ***United Kingdom Prospective Diabetes Study*** *(UKPDS)*[5] studied the course of about 5000 individuals with Type 2 DM for more than 10 years. The UKPDS demonstrated that there was a continuous relationship between glycemia control and development of complication. One major finding in *UKPDS* was that strict blood pressure control significantly reduced both macro and micro vascular complications.

Similar reduction in the risk of retinopathy and nephropathy ware demonstrated with intensive glycemia control in ***Kumamoto study***[3].

The findings of *DCCT, UKPDS* and *Kumamoto* studies supports the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetes microvascular complications.

These landmark studies prove the value of metabolic control and emphases the importance of

(1) intensive glycemic control in all forms of DM.

(2) Early diagnosis and strict blood pressure control in Type 2 DM.

MICROVASCULAR COMPLICATIONS

DIABETIC RETINOPATHY

DM is a leading cause of blindness between the age of 20 and 74. The risk of blindness is 25 times greater in diabetes than in non-diabetics[3]. The incidence of Diabetic Retinopathy is related more to the duration of Diabetes than any other factor. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular oedema.

PATHOPHYSIOLOGY: Diabetic Retinopathy is a micro-angiopathy affecting retinal precapillary arterioles, the capillary and venules. There are basically two factors responsible for Diabetic Retinopathy. They are

(1) Microvascular occlusion due to changes in capillary endothelium.

(2) Microvascular leakages due to pericyte drop out.

Classification of Diabetic Retinopathy

ETDRS Classification – (Early Treatment of Diabetic Retinopathy Study)[6]

I. Non Proliferative Diabetic Retinopathy.

(a) Mild

Atleast 1 Micro aneurysm.

(b) Moderate

Soft exudate, venous beading and intra retinal microvascular abnormalities (IRMA).

(c) Severe

Haemorrhages/ microaneurysm in all 4 quadrants of Retina.

(d) Very Severe

Any 2 or more of (c).

II. Proliferative Diabetic Retinopathy

Composed of new vessels on Disc (NVD) or New Vessels Elsewhere (NVE), preretinal or vitreous haemorrhages, Fibrous tissue proliferation.

III. Clinically Significant Macular Edema (CSME)

Other complications of Diabetes in the eye are

- Cataract – Diabetic cataracts are seen at an earlier age and they also mature faster.
- Glaucoma - Open angle Glaucoma is more common in the diabetic population.
- Optic neuritis/Anterior Ischemic Optic Neuropathy
- Extraocular Muscle Palsies – causing sudden onset of Diplopia.

DIABETIC NEPHROPATHY

Diabetic Nephropathy is clinically defined by the presence of persistent proteinuria of more than 500 mg/day in a diabetic patient who has concomitant diabetic retinopathy and hypertension and in the absence of clinical or laboratory evidence of other kidney or renal tract disease. The presence of diabetic

retinopathy is an important pre-requisite because in its absence albuminuria in a Type 2 Diabetic patient may be due to diabetic or non diabetic glomerulosclerosis and the chances for both are equal[7].

Diabetic Nephropathy is the leading cause of chronic renal failure worldwide. It is also one of the most significant long-term complication in terms of morbidity and mortality for individual patients with diabetes. The mortality rate from all causes in diabetic patients with nephropathy is 20 to 40 times higher than that of patients without nephropathy.

Increased Prevalence of Diabetic Nephropathy in South Asians: Racial differences in the prevalence of diabetic renal disease between the people of Asian ethnic origin and white Caucasians have been reported in the UK. ***Samanta et al***[8] had studied the prevalence of diabetic complications among Indo-Asians and white Caucasians. It was found in this study that renal diseases are more common among the Indo Asian people with diabetes when compared to white Caucasians and this difference remained significant after adjusting for age, sex, duration of diabetes, age at diagnosis, hypertension, smoking and treatment with or without insulin.

Natural Course of Diabetes Nephropathy

According to ***Mogensen***[9], the course of diabetic nephropathy is mainly characterized by changes in urinary albumin excretion and GFR while in Type 1 Diabetic patients the course is well defined and progresses through fine stages**.**

In Type 2 Diabetes, the course of diabetes nephropathy is less well characterized due to the often unknown date of onset of disease or other factors influencing progression of nephropathy, such as hypertension, age and other components of the metabolic syndrome. Patients with diabetic nephropathy especially with Type 2 diabetes have a high cardiovascular risk. ***Vijay et al***[10] showed that the risk of cardiovascular disease was three fold higher in South Indian Nephropathic subjects when compared with their non-nephropathic counterparts. Thus in Type 2 diabetes, many patients may not reach end stage renal disease due to premature death from CVD.

Pathophysiology: The pathogenesis of diabetic nephropathy is multifunctional genetic susceptibility has been proposed to be an important factor in the development and progression of diabetic nephropathy.

The key change in diabetic glomerulopathy is augmentation of extracellular material. The earliest morphologic abnormality in diabetic nephropathy is the

thickening of the GBM and expansion of the mesangium due to accumulation of extracellular matrix. Three major histologic changes occur in the glomeruli in diabetic nephropathy. They are:

(1) Mesangial expansion is directly induced by hyperglycemia via increased matrix production.

(2) Glomerular basement membrane thickening and

(3) Glomerular sclerosis is caused by intraglomerular hypertension.

Causes of Diabetic Nephropathy: The exact cause of Diabetic Nephropathy is still unknown but the mechanism postulated are

- Hyperglycemia causing hyperfiltration and renal injury.
- Advanced glycation products (AGE)
- Activation of cytokines

In addition to renal haemodynamic alteration, patients with overt diabetic nephropathy (dipstick positive proteinuria and decreasing GFR) generally develop systemic hypertension. Hypertension in an adverse factor in all progressive renal diseases and seems especially so in diabetic nephropathy.

DIABETIC *NEUROPATHY*

Diabetic Neuropathy occurs in approximately 50% of individuals with long standing Type 1 and Type 2 Diabetes[11]. It may manifest as polyneuropathy, mononeuropathy and autonomic neuropathy. As with the complications of DM,

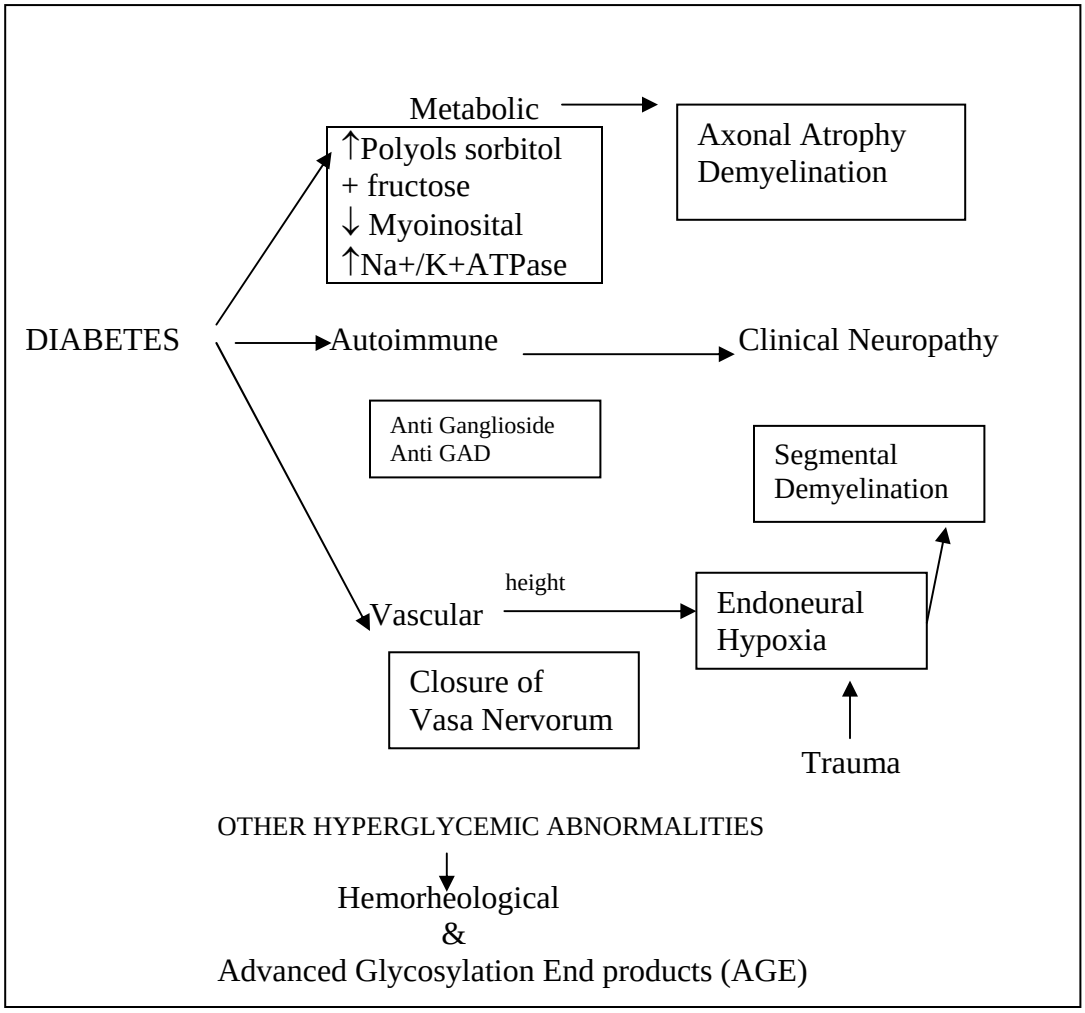
the development of neuropathy correlates with the duration of diabetic and glycemic control; both newer myelinated and unmyelinated nerve fibers are lost.

CLASSIFICATION OF DIABETIC NEUROPATHIES [12]

CLINICAL	
POLYNEUROPATHY	*MONONEUROPATHY*
Sensory	Cranial Isolated peripheral
Chronic sensorimotor	
Acute sensory	Mononeuritis multiplex
Autonomic	Truncal
Cardiovascular	
Gastrointestinal	
Genitourinary	
Miscellaneous	
Proximal motor(amyotrophy)	
Truncal	

Pathology & Pathogenesis: Two major features contributing to the pathology of human diabetic neuropathy are nerve fiber degeneration and gross diseases of the blood vessels supplying them. Microangiopathy is probably one of the main causes underlying the pathogenesis of diabetic neuropathy[13].

PATHOGENESIS OF DIABETIC NEUROPATHY[14]



CLINICAL FEATURES & DIAGNOSIS

1. ***Somatic Neuropathy:*** The most common presentation is chronic symmetrical neuropathy often referred in clinical practice by the phrase diabetic neuropathy and it predisposes to significant morbidity through foot ulceration. Sensory loss predominates although the motor and autonomic system is usually sub clinically affected. ***Dyck and his team from the Mayo Clinic*** [15] have staged Somatic Neuropathy.

STAGING OF DIABETIC NEUROPATHY

Stage 0

No neuropathy (no symptoms and fewer than two abnormalities on formal testing)

Stage 1

Asymptomatic neuropathy (two or more abnormalities on formal testing with no symptoms)

Stage 2

Symptomatic neuropathy (two or more abnormalities on formal testing with minor symptoms)

Stage 3

Disabling neuropathy (two or more abnormalities on formal testing with severe symptoms)

Other important manifestation of Diabetic Neuropathy includes chronic distal symmetric neuropathy. There is length dependent pattern of nerve damage with sensory loss starting in the toes and spreading in the feet and legs in a stocking distribution. The hands tend to get involved after the neuropathy has extended above mid-calf. Sensory ataxia due to impairment of proprioception can occur in later stages of the disease and can be particularly disabling factor that increase risk of ulceration along with

severity of neuropathy include callus, deformity vascular disease and/or poor skin blood flow.

2. ***Cranial Nerve Palsies:*** third and sixth cranial nerves are most commonly affected by diabetes. The onset of cranial nerve palsies is acute and they tend to occur in older patient[16]. Recovery is usual and complete within 3 months. The typical opthalmoplegia of third nerve palsy is often preceded by pain and associated with pupillary sparing due to peripheral nature of pupillomotor fibers with the third nerve.

Peripheral nerves in diabetes are prone to entrapment palsies examples, carpal tunnel syndrome, foot drop, meralgia parasthetica.

AUTONOMIC NEUROPATHY: Diabetic autonomic neuropathy may involve any system of the body

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ORGANISATION OF DIABETIC AUTONOMIC NEUROPATHY

A. Cardiovascular

- Heart rate abnormalities
- Blood Pressure
- Abnormalities –Postural hypotension

- Diabetic cardiomyopathy
- Silent myocardial ischaemia
- Sudden cardiac death

B. Gastrointestinal

- Constipation – Colonic atony
- Diabetic diarrhoea – small intestinal dysfunction
- Gastroparesis diabeticorum chronic or acute (Gastric and Duodenal atony)
- Dyspepsia, Dysphagia and oesophageal ulcerations (Oesophageal atony)
- Faecal incontinence (Anal sphincter weakness)
- High incidence of cholesterol stones (Gall bladder atony)

C. Urinary

- Impaired Bladder sensation
- Hesitancy, weak stream
- Dribbling, incomplete bladder emptying
- Increased past void residual urine
- Bladder over distension
- Urinary retention

D. Genital

- Erectile dysfunction
- Ejaculation failure/ retrograde ejaculation

- Female sexual dysfunction

E. Sudomotor and thermo regulatory disorders

- Distal anhidrosis
- Gustatory sweating
- Abnormal vasomotor responses

F. Pupillary and Lacrimal gland dysfunction

- Miosis
- Impaired light reflexes

G. Other consequences of Diabetic Autonomic Neuropathy

- Disturbances of respiratory control
- Contribution to pathogenesis of diabetic foot
- Aggravation of diabetic state and other neuro endocrine abnormalities
- Unawareness of hypoglycemia
- Worsening of diabetic retinopathy

Autonomic neuropathy in diabetes is a principal cause of foot ulceration.

MACROVASCULAR COMPLICATIONS

Cardiovascular disease is increased in individuals with Type 1 or Type 2 DM. *The Framingham Heart Study*[17] revealed a marked increase in peripheral arterial disease, congestive heart failure, CAD, MI and sudden death in DM.

The American Heart Association recently designed DM as a major risk factor for cardiovascular disease (same category as smoking hypertension and hyperlipidaemia). Type 2 diabetic patient without a prior M1 have a similar risk for coronary artery related events as non-diabetic individuals who have had a prior myocardial infraction.

The main factor that contribute to the increased incidence of cardiovascular disease in diabetic patients are

1. The acceleration of atherosclerotic process leading to macrovascular disease.
2. Development of specific cardiomyopathy.
3. Progressive microvascular disease.
4. Development of autonomic neuropathy.

Heart disease in diabetic patients include

(a) coronary artery disease

(b) small vessel disease

(c) Diabetic Cardiomyopathy

(d) Heart failure

(e) Cardiac autonomic neuropathy

Coronary Artery Disease*:* Coronary Artery Disease is twice as frequent in diabetic men and four times as frequent in diabetic women after menopause compared to the respective non diabetics[1]. Besides the increased prevalence, CAD in diabetic subjects is also characterized by premature onset and disproportionately enhanced susceptibility of female diabetics. Coronary Artery Disease in diabetics is characterized by greater prevalence of triple vessel disease. The distribution of fatty streaks, fibrous plaques and coronary stenosis are relatively more.

An abnormal resting ECG (ST-T wave changes, conduction abnormalities, chamber hypertrophy and rhythm disturbance and pattern of old myocardial infraction has been documented in 40% normotensive ambulant diabetic subjects.

Pathogenesis: There are many potential risk factors and increased likelihood of coronary heart disease.

1. **Hyperglycemia** is an independent risk factor for CAD and is associated with increased mortality.
2. **Lipid Abnormalities:** The most common pattern of dyslipidaemia in Type 2 DM patient is elevated triglyceride level and decreased HDL levels.
3. **Insulin Resistance** (hyper insulinaemia)

   Insulin resistance cluster with elevated Blood Pressure, Obesity, and elevated levels of total triglycerides and low levels of HDL. Cholestrol and haemostatic abnormalities.

   This clustering of cardiovascular risk factors - the insulin resistance syndrome – predicts coronary artery disease in non-diabetic individuals and in patients with Type 2 DM.
4. **Obesity:** The measurement of BMI reflects the risk of mortality with variation in weight. The explanation is that the intra-peritoneal adipose tissue is predominantly responsible for the development of insulin resistance, because of the higher lipolytic activity and direct drainage to the liver through the portal circulation.

   In addition to coronary artery disease, cerebrovascular disease is increased in individuals with DM (threefold increase in stroke).

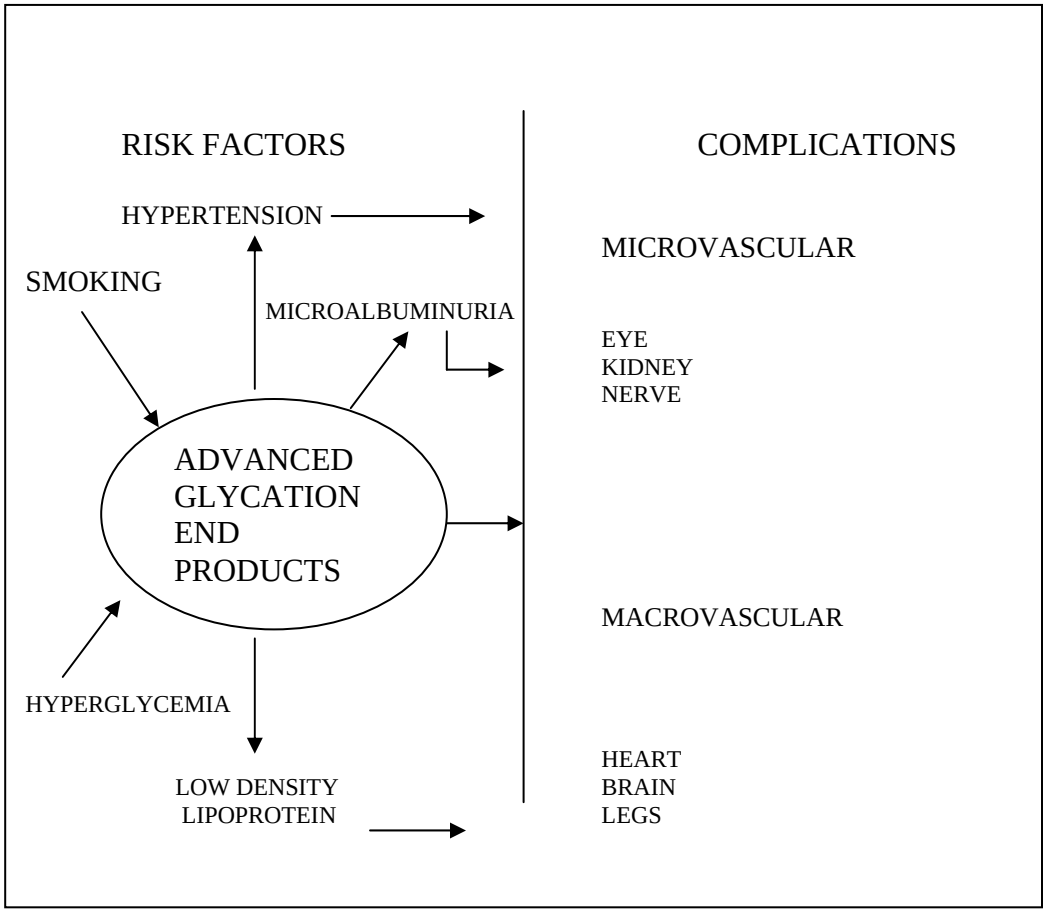
Individuals with DM have an increased incidence of congestive heart failure (diabetic cardiomyopathy). The etiology of this abnormality is probably multi factorial and includes factors such as myocardial ischaemia from atherosclerosis, hypertension and myocardial dysfunction secondary to chronic hyperglycemia.

DIABETES AND HYPERTENSION: Hypertension is a common, important and modifiable risk factor for both the micro and macro vascular complications of diabetes. Hypertension is present in 50 – 80% of patients with Type 2 diabetes according to modern definition (i.e., above 140/90 mm/Hg). Hypertension is clearly associated with insulin resistance in Type 2 DM patient, but the strength and nature of the association is still unclear. Microalbuminuria is the best prediction of progression of diabetic nephropathy towards the end stage renal failure. The blood glucose level correlates with Blood Pressure and may independently relate to albuminuria. Obesity magnifies the prevalence and incidence of both DM and hypertension [18].

Types of Hypertension in Diabetes[19].

1. Essential Hypertension
2. Hypertension subsequent to nephropathy
3. Isolated systolic Hypertension
4. Supine Hypertension with orthostatic fall.

PATHOGENESIS OF COMPLICATIONS [20]



METHODOLOGY

Selection of Cases:

Patients with type 2 DM aged more than 35 years attending the Diabetology Out-Patient Department, Government Stanley Hospital were evaluated for

(A) Risk factors - Hypertension, Obesity, Smoking & Hypercholesterolemia.

(B) Microvascular Complications – Retinopathy, Nephropathy & Neuropathy.

(C) Macrovascular Complications – CAD, Cerebrovascular Disease, Peripheral Vascular Disease.

(D) For evaluation of complications they were categorised according to the duration of diabetes

1. Newly Diagnosed
2. DM < 5 Years
3. DM 5 – 10 Years.
4. DM > 10 Years.

A detailed history was recorded in respect of all the subject patients, particularly the duration of DM, Smoking, Complications, Family History of DM, etc.

The following criteria was taken

(1) Diagnosis of Diabetes

Fasting Plasma Glucose > 126mg%

2 Hrs Plasma glucose > 200mg%

Criteria for Risk factors:

(1) Diagnosis of Hypertension[21]

Stages	Systolic	Diastolic
Pre Hypertension	120 – 139	80 - 89
Hypertension Stage 1	140 - 159	90 – 99
Hypertension Stage 2	> 160	> 100

(2) Obesity

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

Over weight 25 – 30

Obese > 30

(b) Waist circumference[22]

Male > 90 cms

Female > 80 cms.

(3) Total Cholesterol[23]

< 200 Normal

200 – 239 Borderline High

> 240 High

Criteria For Microvascular Complications

1. Diabetic Retinopathy: Ocular Fundus examination by opthalmoscope after dilatation of pupils.

   (a) Non proliferating Diabetic Retinopathy:

   Microaneurysm, Haemorrhage, hard exudates

   (b) Proliferative Retinopathy

   New vessels on disc (NVD)

   New vessels elsewhere (NVE)

   (c) Clinically significant macular oedema (CSME)

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

2. Diabetic Nephropathy

   (a) Macroproteinuria - Protein excretion of >500 mg/day out of which 50% is albumin. Macroalbuminuria was tested. Microlbuminuria was not tested.

(b) Serum Creatinine

Calculation of GFR done based on Cockcroft Gault Formula [24].

Estimated creatinine clearance (ml/min) =

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

Multiply by 0.85 for Women.

3. Diabetic Neuropathy

Symptoms of sensory and motor signs on physical examination were done.

Criteria for Macrovascular Complications

1. Cardiovascular Disease

History : Symptoms of Angina – Chest pain

ECG:

- LVH
- Ischaemic Heart Disease – ST – T were checked for changes
- Features of Old M1

Echo: (Taken where necessary as follows)

- Diastolic dysfunction in HT
- Regional wall motion abnormalities
- Ejection Fraction

2. Peripheral Vascular Disease

Clinical examination of Peripheral palpable Arteries done. Doppler study was done in relevant cases.

3. Stroke

History and Clinical examination for stroke was done.

OBSERVATIONS & DATA ANALYSIS

Total Number of Patients – 122

Male - 65 (53%)
Female - 57 (47%)

TABLE 1

AGE AND SEX DISTRIBUTION

Mean Age of Patients = 54 Years

Mean Age of Newly Diagnosed Diabetes = 50 Years.

MAXIMUM PATIENTS WITH DIABETES ARE BETWEEN 41 - 60 YEARS.

AGE (Years)	MALE	FEMALE	TOTAL N = 122
34 - 40	3	2	5 (4%)
41 - 50	19	19	38 (31%)
51 - 60	27	22	49 (40%)
61 - 70	14	11	25 (20%)
> 70	2	3	5 (4%)

TABLE - 2

DURATION OF DM

85% of Patients have duration of Diabetes of < 5 Years .

DURATION OF DM	MALE	FEMALE	TOTAL (n = 122)
NEW CASE	22	19	41 (34%)
< 5	24	20	44 (36%)
5-10	12	12	24 (20%)
> 10	7	6	13 (11%)

TABLE - 3

POSITIVE FAMILY HISTORY WITH DM

Positive Family History of DM in 31% of Patients.

FAMILY HISTORY OF DM	TOTAL (n = 122)
POSITIVE	38 (31%)
NEGATIVE	84 (69%)

DATA ON RISK FACTORS

TABLE - 4

CATEGORY OF HYPERTENSION AND DM

Total Number of Patients with Hypertension in Diabetes is 88 (72%)

52% of Patients are in Stage –1 of Hypertension.

Newly Diagnosed Patients with Hypertension are 60%.

CATEGORY	NEWLY DIAGNOSED (n = 41)	< 5 YEARS (n = 44)	5 – 10 YEARS (n = 24)	10 YEARS (n = 13)	TOTAL (n = 88)
PRE HT 120 – 139 80 – 89	6	15	4	2	27 (30%)
STAGE 1 140 – 159 90 – 99	12	19	10	6	47 (53%)
STAGE 2 160/100 AND ABOVE	7	2	1	4	14 (15%)
TOTAL	25 (61%)	36 (89%)	15 (62%)	12 (92%)	88 (72%)

TABLE - 5

OBESITY AND DURATION OF DM

51% of Newly Diagnosed Patients are Obese/Overweight.

OBESITY BMI	NEWLY DIAGNOSED (n = 41)	< 5 YEARS (n = 44)	5 – 10 YEARS (n = 24)	10 YEARS (n = 13)	TOTAL (n = 70)
OVERWEIGHT 25 – 30	17	22	13	6	58 (83%)
OBESE > 30	4	4	2	2	12 (17%)
TOTAL	21 (51%)	26 (59%)	15 (62%)	9 (69%)	70 (57%)

TABLE - 6

DM AND ABDOMINAL OBESITY

69% of Patients have Abdominal Obesity based on Waist Circumference.

SEX	TOTAL (n = 122)
MALE	43 (66%)
FEMALE	41 (72%)
TOTAL	84 (69%)

TABLE - 7

DM AND HYPER CHOLESTEROLEMIA

25 (61%) of Newly Diagnosed Patients have Hyper Cholesterolemia.

TOTAL CHOLESTROL Mg/dL	NEWLY DIAGNOSED (n = 41)	< 5 YEARS (n = 44)	5 – 10 YEARS (n = 24)	10 YEARS (n = 13)
200 – 239	10	18	9	7
240 & ABOVE	15	17	11	4
TOTAL (n = 99)	25 (61%)	35 (79%)	20 (83%)	11 (85%)

TABLE – 8

RISK FACTOR AND DM

Most common Risk Factor with DM is Hypercholesterolemia - 91(74%).

Next Common Risk factor is Hypertension - 88(72%).

RISK FACTOR	MALE	FEMALE	TOTAL n = 122
HYPERTENSION	46	30	76 (62%)
OBESITY	31	39	70(57%)
SMOKING	24	NIL	24(20%)
HYPERCHOLESTROLEMIA	48	43	91(74%)

DATA ON MICROVASCULAR COMPLICATION

TABLE - 9

MICROVASCULAR COMPLICATION AND DURATION OF DM

Retinopathy is the most common Microvascular Complication.

Retinopathy (34%), Neuropathy (24%) and Nephropathy (24%) present at the time of Diagnosis of DM.

MICROVASCULAR COMPLICATION	NEWLY DIAGNOSED (n = 41)	< 5 YEARS (n = 44)	5 – 10 YEARS (n = 24)	10 YEARS (n = 13)	TOTAL (n = 122)
RETINOPATHY	14 (34%)	12 (27%)	9(37%)	6(46%)	41(34%)
NEUROPATHY	10(24%)	8(18%)	5(20%)	2(15%)	25(20%)
NEPHROPATHY	10(24%)	12(27%)	11(46%)	6(46%)	39(32%)

TABLE - 10

TYPES OF DIABETIC RETINOPATHY

Non-Proliferative Retinopathy is the most common complication in Retinopathy.

TYPES	TOTAL (n = 41)
NON PROLIFERATIVE RETINOPATHY	36 (88%)
PROLIFERATIVE RETINOPATHY	3 (9%)
MACULOPATHY	2 (5%)

TABLE - 11

STAGES OF CKD IN DIABETES

43% of DM Patients with CKD are in Stage 2. No Patients with DM were found in Stages 4 & 5 in this study.

GFR	STAGES OF CKD	TOTAL n = 39
90 – 120	STAGE 1	9 (23%)
60 – 89	STAGE 2	17 (43%)
30 – 59	STAGE 3	13 (33%)
< 30	STAGES 4 & 5	NIL

TABLE - 12

RENAL FAILURE AND DM

11% of DM Patients had Renal Failure.

SERUM CREATININE	TOTAL n = 122
< 1.5 mg/dL	109 (89%)
1.5 - 3 mg/dL	13 (11%)

DATA ON MACROVASCULAR COMPLICATION

TABLE - 13

CAD AND DM

32 (72%) of CAD presented in Patients with DM with Duration of < 5 Yrs

DURATION	TOTAL n = 44
NEWLY DIAGNOSED	13 (29%)
< 5 YEARS	19 (43%)
5-10 YEARS	6 (14%)
>10 YEARS	6 (14%)

TABLE - 14

MANIFESTATION OF CAD

45% of Patients with CAD are Asymptomatic.

MANIFESTATION	TOTAL
SYMPTOMATIC	24 (54%)
ASYMPTOMATIC	20 (45%)

TABLE - 15

MACROVASCULAR COMPLICATIONS AND DM

The most common Macrovascular complication is CAD (36%)

COMPLICATION	TOTAL n = 122
CAD	44(36%)
PERIPHERAL VASC. DISEASE	7(6%)
CVA	12(10%)

TABLE -- 16

FASTING BLOOD SUGAR LEVEL AND DM

Mean fasting Blood sugar = 195mg/dL.

75% Patients had poor sugar control.

FASTING BLOOD SUGAR Mg/dL	NEWLY DIAGNOSED	< 5 YEARS	5 – 10 YEARS	10 YEARS	TOTAL n = 122
126 - 200	16	23	13	4	56 (46%)
201 – 300	9	9	2	1	21 (21%)
> 300	4	8	3	-	15 (12%)

DISCUSSION

The total number of patients analysed were 122, out of which 53% were Male and 47% were Female patients. The mean age of patients found in the study was 54 years. These findings correlate with studies done by ***Raheja et al*** *(2001)* [25] which showed the mean age of 53.3 years and another stud by National Rural Diabetic Survey of 1989-91 which showed mean age of subjects with diabetes with 52.3 years [26]. In the present study, the mean age of newly diagnosed diabetes is found to be 50 years.

The prevalence of diabetes increases with age. The prevalence of diabetes in elderly patients in the study is 24% with maximum cases in elderly being 61 – 70 years age group. This finding correlate with study done by ***Ahuja MMS*** *(1996)* [27] Epidemological Studies of DM in India showed prevalence of diabetes in elderly patients (Age > 60 yrs) in urban population as 23.4% and maximum prevalence was in age group of 61 – 69 years.

Out of 122 patients 31% cases had positive family history of Diabetes. Many Indian studies show strong association of positive family history in DM type 2. These findings correlate with study of ***Shah et al*** *(1999)*[28] which showed positive family history of 24.9% and ***Ramachandran et al*** (1999)[29] which showed strong correlation of positive family history with DM type 2.

RISK FACTORS

HYPERTENSION

The prevalence of hypertension in diabetes in the present study is 72%. Out of the total 88 patients with hypertension, 61% patients had hypertension at the time of diagnosis. The studies done by ***Banerjee et al*** (2001)[30] found 50% with hypertension. ***CDC's National Diabetes Survillance System 2005***, USA[31] shows 62.5% of patients have hypertension in diabetes. Among the stages of hypertension according to JNC VII report, maximum patients 53% were in Stage 1. Various Indian studies show prevalence of hypertension in DM to be around 50 – 80%.

OBESITY

This study shows that 57% patients were over weight and obese according to BMI. But when waist circumference was taken 68% patients had abdominal obesity. This correlates with a study done by ***Channaraya et al*** (2002)[32] which showed trunkal obesity based on waist circumference was 69%. Many of Indian studies showed strong correlation between obesity and DM Type 2.

SMOKING

20% of patients in the present study were smokers and all of them were males. A study by ***SV Madhu et al*** (2002)[33] showed smokers to be 15% and an International study by ***CDC – National Diabetes Surveillance System, 2005***, USA[31] shows smokers at 17.7% among diabetic patients.

HYPERCHOLESTEROLEMIA

Out of 122 patients 74% patients had hypercholesterolemia. 61% of patients had hypercholesterolemia at the time of diagnosis. This study correlates with a study done by ***S.Shafiq et al*** (2001)[34] which showed hypercholesterolemia of 78% and ***CDC – National Diabetes Surveillance System, 2005***, USA[31] which showed the hypercholesterolemia at 60%.

The most common risk factor in Diabetes is hypercholesterolemia which is 74%. Next common risk factor is hypertension. All these risk factors play a significant rolein the pathogenesis of Macrovascular complications. The risk factor – Hypertension - 61%, Obesity – 51% and hypercholesterolemia – 61% were present at the time of diagnosis.

MICROVASCULAR COMPLICATIONS

Diabetic Retinopathy 34% is the most common microvascular complication. Out of the patients with retinopathy, 88% had non-proliferative retinopathy. The prevalence of retinopathy increases according to the duration of diabetes. This study correlates with the studies done by ***G. Premalatha, V Mohan et al*** (2002)[35] in Urban South Indian Population which showed that Retinopathy was 34.1% and ***M.Ranka et al*** (2004)[36] found it to be 28.9% in a North Indian study.

CKD in Diabetes was seen in 32% of patients in the study. Out of the patients with CKD, maximum patients i.e., 43% were in Stage 1. 18% of them had Proteinuria. Microalbuminuria was not done in this study. The finding however correlates with the study done by ***Ramachandra et al*** (1999)[29] which showed prevalence of Proteinuria at 19.7%.

Diabetic Neuropathy was prevalent in 20% of patients. This finding correlates with study done by ***G.Premalatha, V.Mohan et al*** (2002)[35] which had 19.1% patients with Neuropathy.

A significant finding in the study was Retinopathy 34%, Neuropathy 24% and Nephropathy 24% were present at the time of diagnosis.

MACROVASCULAR COMPLICATIONS

Coronary Artery Disease – 36% is the most common Macrovascular complication in the study. 45% of patients with CAD were asymptomatic in the study. 72% of patients with CAD had duration of DM of < 5 years.

Peripheral Vascular Disease was present in 6% of patients in the study. This correlates with the study by ***G.Premalatha, V.Mohan et al*** (2002)[35] which showed 4%.

Cerebrovascular disease was found in 10% of patients in the study. This correlates with the International Study ***CDC – National Diabetes Surveillance System, 2005, USA***[31] which showed 9% prevalence of stroke in DM type 2.

CONCLUSION

1. In this study 53% of patients were males and 47% were females, all of them being above 35 years of age. The mean age of the Patients was 54 years.

2. The highest number of patients with diabetes was in the age group of 41 – 60 years.

3. 85% of Patients had duration of diabetes < 5 years.

4. Hypertension was found in 62% of patients.

5. Obesity was found in 57% of patients.

6. Smoking was found in 20% of patients.

7. Hypercholestrolemia was found in 74% of patients.

8. The highest risk factor was Hypercholestrolemia followed by Hypertension.

9. Retinopathy was found in 34% of the Patients.

10. Neuropathy was found in 20% of the Patients.

11. Nephropathy was found in 32% of the DM patients.

12. The most common Microvascular Complication was Retinopathy.

13. Newly diagnosed DM patients presented with Retinopathy in 34%, Neuropathy in 24% and Nephropathy in 24%.

14. Coronary artery disease was found in 36% of Patients.

15. Peripheral Vascular Disease was found in 6% of patients.

16. Cerebrovascular Disease was found in 10% of patients.

17. The most common Macrovascular Complication is coronary artery disease.

18. Significant number of patients with coronary artery disease presented by patients with < 5 Years duration of DM.

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PROFORMA

DIABETES MELLITUS TYPE 2 – EVALUATION OF MICROVASCULAR AND MACROVASCULAR COMPLICATIONS

Name: Age: Sex:

OPNo. Diabetology OP No:

HISTORY TAKING

Type of Diabetes Melitus:

Duration of Diabetes Melitus:

History & Duration of Hypertension:

H/o Anginal Chest Pain:

H/o Previous treatment for M1:

H/o Smoking:

H/o taking treatment for complications-

H/o Stroke

H/o TIA

Family H/o Diabetes Mellitus

GENERAL EXAMINATION

Height:

Weight:

Waist Circumference:

VITALS

Pulse: Rate, Rhythm, Felt in all peripheral palpable vessels.

B.P.:

EXAMINATION OF SYSTEM:

CARDIOVASCULAR SYSTEM

APICAL IMPULSE:

HEART SOUNDS:

ADDED SOUNDS:

RESPIRATORY SYSTEM:

BREATH SOUNDS:

ADDED SOUNDS:

ABDOMEN:

ORGANOMECIALY:

FREE FLUID

CENTRAL NERVOUS SYSTEM

Higher Fuction:

Cranial Nerves:

Motor System:

Sensory System:

Spine & Cranium:

OPTHALMOLOGICAL EXAMINATION OF FUNDUS

INVESTIGATION

Blood Sugar - Fasting:

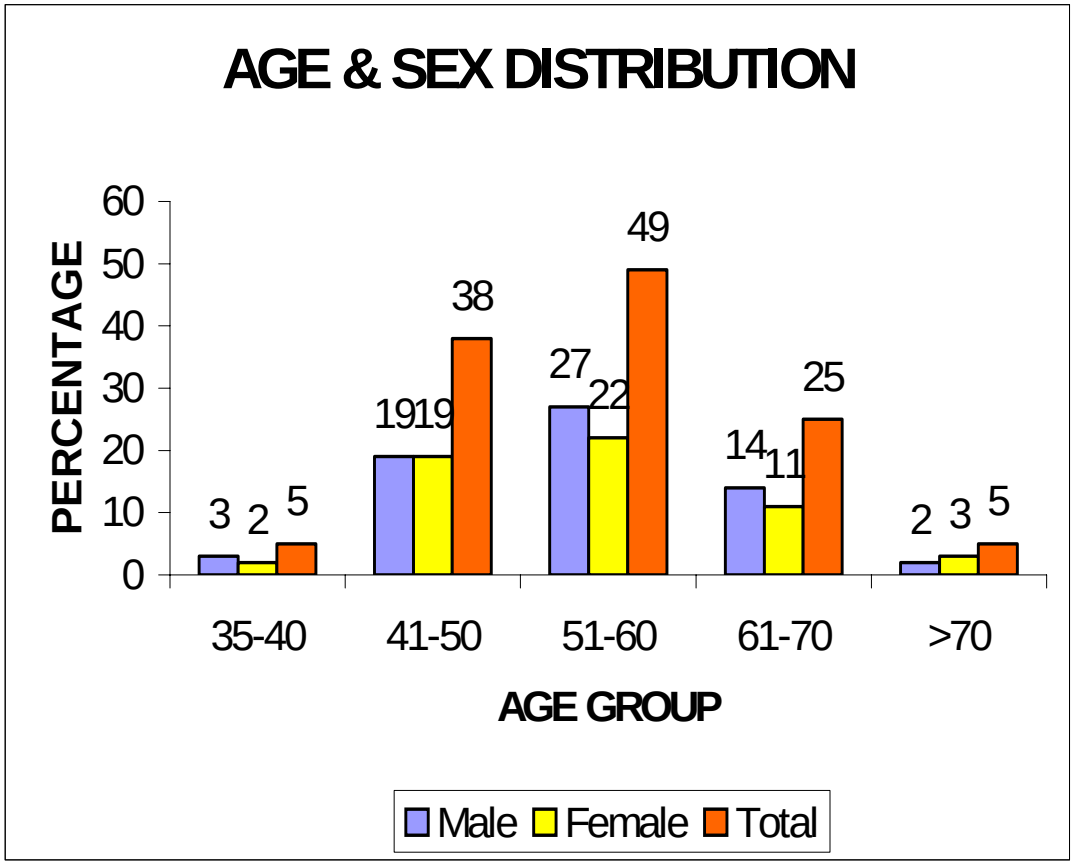
- PP (2Hrs) :

Blood Urea:
Serum Creatinine:
Total Cholesterol:
Urine Albumin:
24Hrs Urine Protein:

ECG

ECHO

Doppler Study


AGE & SEX DISTRIBUTION
PERCENTAGE
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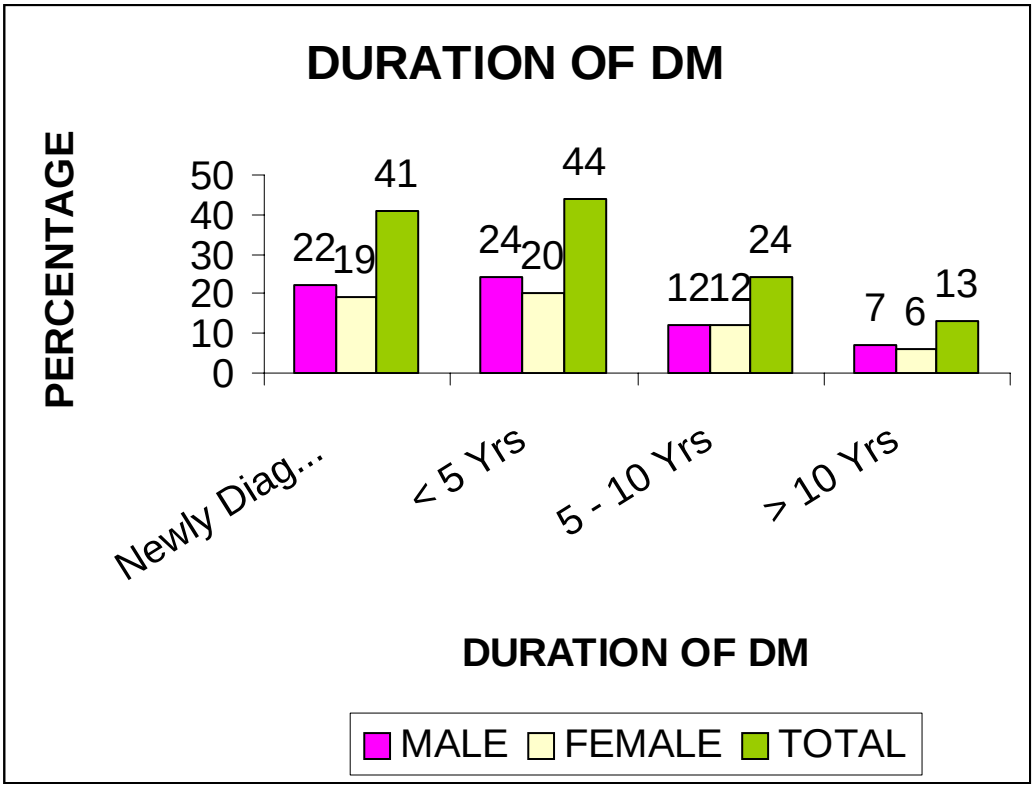
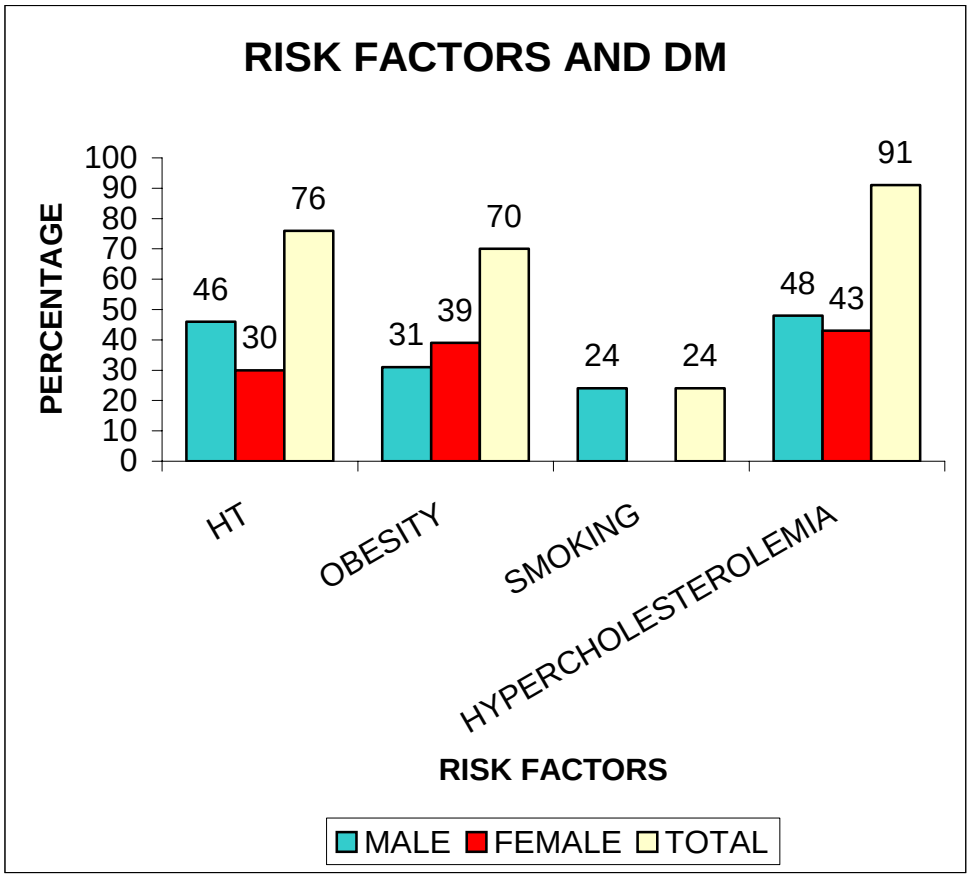
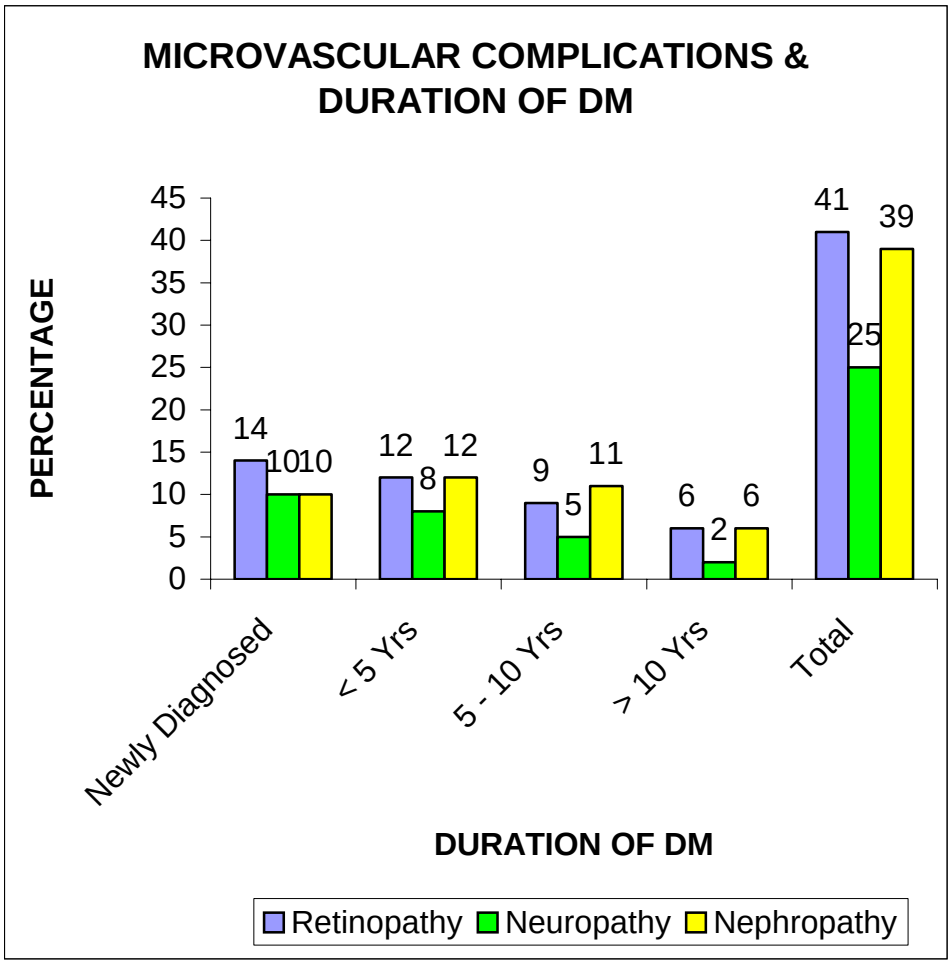
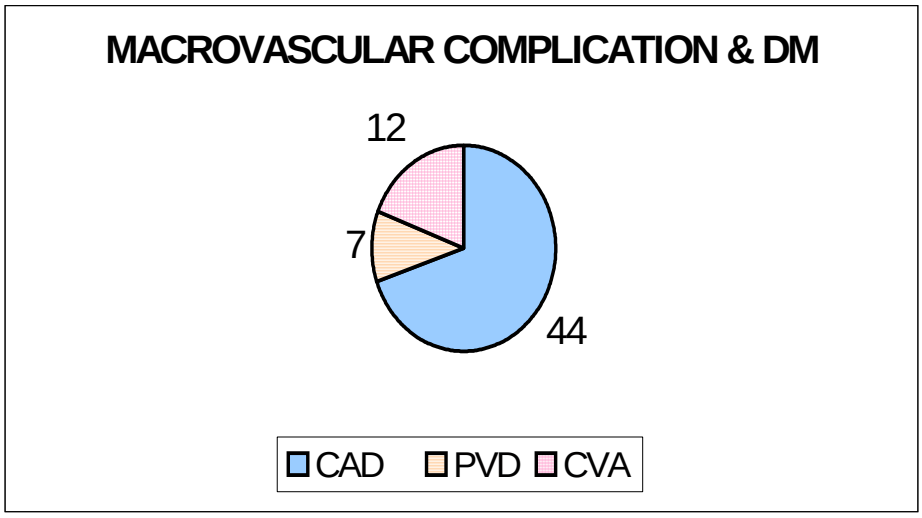
50
40
30
20
10
0
3
2
5
19
19
38
27
22
49
14
11
25
2
3
5
35-40
41-50
51-60
61-70
>70
AGE GROUP
Male
Female
Total


DURATION OF DM
PERCENTAGE
50
40
30
20
10
0
22
19
41
24
20
44
12
12
24
7
6
13
Newly Diag...
< 5 Yrs
5 - 10 Yrs
> 10 Yrs
DURATION OF DM
MALE
FEMALE
TOTAL


RISK FACTORS AND DM
PERCENTAGE
100
90
80
70
60
50
40
30
20
10
0
46
30
76
31
39
70
24
24
48
43
91
HT
OBESITY
SMOKING
HYPERCHOLESTEROLEMIA
RISK FACTORS
MALE
FEMALE
TOTAL


MICROVASCULAR COMPLICATIONS & DURATION OF DM
PERCENTAGE
45
40
35
30
25
20
15
10
5
0
14
10
10
12
8
12
9
5
11
6
2
6
41
25
39
Newly Diagnosed
< 5 Yrs
5 - 10 Yrs
> 10 Yrs
Total
DURATION OF DM
Retinopathy
Neuropathy
Nephropathy


MACROVASCULAR COMPLICATION & DM
12
7
44
CAD
PVD
CVA

MASTER CHART

S.No.	Age	Sex	Duration of DM	HTN	H/o Smoking	H/o CAD	H/o Retinopathy	H/o Nephropathy	H/o Neuropathy	F H/o DM	Ht.cms	Wt Kg	Waist Circum Cms	BP	Fundus	Blood Sug/F	Blood Sug/PP	Bl.Urea	Creatinine	Tot. Chol	Urinea Alb	Urine Protein	ECG	Echo
1	61	M	Nu	-	-	-	-	-	-	-	170	58	90	110/70	-	262	300	26	0.6	251	Nil	-	N	-
2	45	F	Nu	-	-	-	-	-	-	-	156	85	96	150/100	NPR	195	281	19	0.3	351	Nil	-	N	-
3	60	F	6Yr	3Yr	-	-	-	-	-	-	145	55	97	120/70	-	326	385	33	0.5	329	Nil		N	-
4	68	M	5Yr	-	√	√	-	-	√	-	154	60	100	140/90	-	340	339	23	0.6	189	Nil	-	N	-
5	65	F	5Yr	-	-	-	-	-	-	-	150	65	100	130/80	-	106	310	32	0.8	186	Nil		N	-
6	55	F	Nu	Nu	-	-	-	-	-	-	149	60	87	150/90	-	99	237	62	1.5	173	Nil		N	-
7	72	F	6Yr	2Yr	-	-	-	-	-	-	152	64	88	140/100	-	121	224	28	0.7	215	Nil		N	-
8	48	M	Nu	-	√	-	-	-	-	-	175	80	106	110/80	-	256	277	31	0.7	158	Nil		N	-
9	44	M	Nu	Nu	√	-	-	-	-	√	169	63	86	140/100	NPR	271	394	32	0.5	262	Nil		N	-
10	70	F	Nu	1Yr	-	-	-	-	-	-	149	73	103	170/100	-	128	200	34	0.8	239	Nil		IHD	N
11	60	F	4Yr	4Yr	-	-	-	-	-	-	153	48	82	140/80	-	250	397	29	0.5	123	1 +		N	-
12	38	M	9Yr	9Yr	√	-	-	-		√	163	44	68	110/70	NPR	250	309	33	0.6	222	Nil		N	-
13	45	M	Nu	Nu	√	-	-	-	-	-	160	65	98	130/90	-	89	242	47	0.8	317	Nil		N	-
14	55	M	2Yr	-	√	√	-	-	-	-	165	65	96	130/80	-	220	280	30	1.0	331	Nil		B	N
15	45	F	2Yr	2Yr	-	-	-	-	-	-	157	48	90	170/90	-	284	300	20	0.6	284	2 +	Y	N	-
16	62	F	Nu	-	-	-	-	-	-	-	145	55	104	120/80	-	164	294	21	0.4	267	Nil		IHD	H

17	57	M	Nu	Nu		√	-	-	-	-	162	58	82	150/80	-	96	215	18	0.6	95	1+		IHD	DD
18	60	F	Nu	-		-	-	-	-	√	145	65	97	130/80	-	260	340	27	1.1	305	1+	Y	IHD	N
19	70	M	Nu	N		-	-	-	-	-	166	55	84	160/90		174	223	44	1.1	221	Nil		IHD	-
20	40	F	Nu	Nu/10m	-	-	-	-	-	√	157	56	96	150/90	-	250	302	29	0.9	368	Nil		IHD	-
21	50	F	Nu	Nu	-		-	-	√F		153	60	98	130/80	-	147	264	18	0.9	197	1+	Y	N	-
22	45	F	2Yr	N	-	-	-	-	-		154	65	106	140/100	-	154	301	20	0.8	325	Nil		N	-
23	40	M	Nu	2Yr	-	-	-	-	√		164	65	98	150/100	-	112	237	26	0.9	177	Nil		IHD	DD
24	53	F	15Yr	15Yr	-	√	-	-	-		143	56	93	160/100	-	221	319	14	0.6	327	Nil		OMI	H
25	42	F	8 Yr	-	-	-	-	-	-		153	53	85	130/90	NPR	208	264	44	1.1	306	1+	Y	N	-
26	50	F	2Yr	N	-	-	-	-	-		154	46	85	160/90	-	248	234	45	0.9	230	1+	Y	B	N
27	47	F	15Yr	6Yr	-	-	-	-	√		155	55	92	140/90	-	104	216	18	0.6	458	1+	Y	N	-
28	70	F	Nu	N	-	-	-	-	-		150	56	104	160/100	M	123	249	21	0.9	203	1+	Y	N	-
29	48	M	8Yr	-	-	-	-	-	√	√	157	56	97	110/70		250	300	21	1.1	313	2+	Y	N	-
30	62	M	Nu	-	-	-	-	-	-	-	156	55	90	120 80	-	156	250	16	0.7	271	1+	Y	N	-
31	43	M	1Yr	3Yr		-				√	173	64	91	136/90	-	248	267	21	0.8	264	Nil		IHD	N
32	37	M	Nu	-	-	-	-	-	-	-	167	75	101	110/70	-	91	269	20	1.1	407	Nil		N	-
33	70	M	Nu	-	-	√	-	-	-		170	70	106	140/90	-	176	247	27	0.9	256	Nil		B	-
34	45	F	Nu	-	-	-	-	√	-	--	157	65	95	110 70	-	200	327	28	0.6	193	Nil		N	-
35	52	M	Nu	-	√	√	-	-	-	√	165	68	104	120/80	-	126	259	32	0.9	197	Nil		OMI	H
36	35	F	Nu	-	-	-	-	-	-	-	155	56	90	110/70	-	257	304	18	0.6	134	Nil		IHD	N

37	45	F	5Yr	5Yr		√	-	-	-	√	162	62	95	130/90	-	264	274	26	0.6	242	Nil		IHD	DD
38	35	F	Nu	-	-	-				√	160	54	79	120/80	-	193	282	17	0.6	169	Nil		IHD	N
39	54	M	1½Yr		√	-	-	-	-	--	175	66	97	120/70	NPR	96	301	54	1.0	215	Nil		N	-
40	59	M	5Yr	N	-	-	-	-	-	-	165	80	112	170/100	-	116	249	26	0.7	232	Nil		N	-
41	47	M	2Yr	N	√	-	-	-	-	-	165	60	90	150/100	NPR	196	236	25	0.9	303	Nil		IHD	N
42	60	M	Nu	-	-	-	-	-	√	√	163	48	80	110/60	-	124	309	20	0.8	134	Nil		N	-
43	57	M	3Yr	N	√	-	-	-	-	√	165	57	88	150/90	-	248	279	25	0.9	173	Nil		N	-
44	43	M	7Yr	√						√	180	67	89	130/90	NPR	160	180	18	0.6	287	Nil		N	-
45	40	M	3Yr	4Yr		-	-	-	-	√	155	55	87	140/90	NPR	119	301	22	0.6	179	Nil		N	-
46	78	M	5Yr	1Yr	√	-	-	-	-	-	167	67	100	130/90	-	114	309	23	0.6	250	Nil		N	-
47	43	M	4Yr	1Yr	-	-	-	-	-	-	180	56	78	130/80	-	299	339	19	0.6	195	Nil		N	-
48	60	M	Nu	Nu	-	-	-	-	-	-	162	66	101	210/100	-	99	209	36	1.2	227	1+	Y	N	-
49	45	F	Nu	1Yr	-	-	-	-	-	-	157	77	106	130/80	-	129	210	21	0.7	210	Nil		N	-
50	65	M	Nu		√	-	-	-	√	-	165	54	86	140/90	NPR	287	311	45	1.0	200	Nil		N	-
51	37	M	7Yr	-	√	-	-	-	-	√	164	57	80	120/70	NPR	267	310	27	0.7	339	Nil		N	-
52	55	M	Nu	-	√	-	-	-	√	-	165	54	86	140/90	NPR	81	247	25	0.6	308	Nil		N	-
53	35	M	1Yr	-						√	171	83	108	120/90	-	163	324	28	0.6	301	Nil		N	-
54	58	M	2Yr	2Yr	-	-	-	-	-		173	75	102	150/90	-	123	142	34	0.9	149	Nil		N	-
55	54	F	3Yr	3Yr	-	-	-		√	√	157	60	94	130/90	-	309	392	15	0.6	360	Nil		N	-
56	54	M	3Yr	-	-	-	-	-	-	-	160	49	82	130/90		274	301	23	0.7	164	Nil		N	-

57	40	F	Nu	-	-	-	-	-	√	-	159	75	114	110/70		215	264	28	0.9	233	Nil		N	-
58	69	M	15Yr	N	√					√	165	57	89	170/90	-	143	269	19	0.6	179	Nil		N	-
59	50	F	4Yr		√	-	-	-	√	-	155	50	83	110/70	-	235	314	27	0.7	271	Nil		IHD	N
60	44	F	Nu	-	-	-	-	-	√	-	155	69	101	120/80	-	163	208	25	0.7	234	Nil		N	-
61	40	M	5Yr	-	-	-	-	-	√	-	169	92	115	130/70	-	183	324	21	0.4	264	Nil		N	-
62	75	M	4Yr	-	-	-	-	-	-		163	55	92	140/90	NPR	276	394	26	0.5	163	1+	Y	N	-
63	45	M	5Yr	5Yr	√	√	-	-	-	√	160	69	97	140/90	NPR	243	300	27	0.6	227	2+	Y	N	-
64	45	M	10Yr	6 Mo	-	√					167	70	96	150/90	M	238	301	35	1.0	156	2+	Y	IHD	H
65	69	M	Nu	-	√	√	-	-	-	-	170	65	94	120/70	-	130	227	18	0.6	236	Nil		OMI	H
66	65	F	10Yr	-	-	-	-	-	-	√	142	43	81	120/70	-	124	324	26	0.6	303	Nil		IHD	DD
67	43	F	Nu	-	√		-	-	-	√	147	69	99	150/100	NPR	127	241	51	0.9	199	1+	Y	IHD	N
68	70	M	Nu	-	-	-	-	-	-	-	173	55	87	120/70	M	168	200	13	0.6	309	Nil		N	-
69	60	M	Nu	-	√	-	-	-	-	-	170	70	96	140/86	NPR	177	223	25	1.0	175	Nil		B	N
70	45	F	Nu	-	-	-	-	-	√	-	145	44	73	100/70	NPR	92	262	23	0.7	130	Nil		N	-
71	40	F	1½Yr	-	-	-	-	-	-	-	150	57	84	130/70	-	135	246	75	0.8	168	Nil		N	-
72	57	F	6 Mo	N	-	-	-	-	√	-	150	65	100	150/100	-	87	197	24	0.7	211	Nil		N	-
73	40	M	Nu	-	-	-	-	-	-	-	160	56	85	100/70	-	134	262	28	1.0	218	Nil		N	-
74	47	M	10 Yr	-	-	-	-	-	-	√	155	55	86	120/70	NPR	160	244	24	0.8	220	Trace		N	-
75	38	F	1 Yr	-	-	-	-	-	-	-	150	50	82	120/70	NPR	180	277	13	0.6	260	Nil		N	-
76	63	M	3Yr	Nu	√	√	-	-	-	√	155	54	87	130/70	-	240	339	26	0.6	190	Nil		IHD	N

77	60	F	1Yr	-	-	-	-	-	-	-	152	80	97	120/70	-	196	296	24	0.8	197	1+	Y	N	-
78	76	M	5 Yr	3 Yr	-	-	-	-	-	-	170	85	115	140/80	-	198	264	25	0.6	220	Nil		N	-
79	39	M	Nu	-	√	√	-	-	-	√	165	60	86	130/70	-	200	267	26	0.9	218	Nil		IHD	N
80	59	M	10Yr	5 Yr		-		-	-	-	172	80	100	140/100	-	156	210	24	0.7	211	1+	Y	N	-
81	65	F	12Yr	4 Yr	-	√	-	-	√	√	147	67	96	150/100	-	172	201	28	0.6	210	Nil		IHD	DD
82	51	M	4 Yr	2 Yr	-	-	-	-		-	158	76	100	140/90	-	156	210	27	0.8	220	Nil		N	-
83	54	M	5Yr	-	√	-	-	-	-	-	162	70	96	140/80	-	140	201	24	0.6	211	Nil		N	-
84	69	M	20Yr	-	√	-	-	-	-	√	168	72	94	130/70	NPR	156	200	23	0.8	240	Nil		N	-
85	44	M	5Yr	√	-	-	-	-	√	√	157	68	90	130/70	-	130	201	28	1.0	303	Nil		N	-
86	45	F	3Yr	-	-	-	-	-	-	√	149	65	89	130/70	-	152	324	23	0.6	236	1+	Y	N	-
87	50	F	Nu	Nu	-	-	-	-	-	-	148	64	87	150/100	NPR	177	241	18	0.4	197	Nil		N	-
88	67	M	3Yr	2Yr	-	-	-	-	√	√	162	70	100	150/100	-	160	200	29	0.6	200	Nil		N	-
89	61	M	10Yr	5 Yr	√	-	-	-	-	-	160	52	86	154/100	-	172	217	27	0.8	210	Nil		N	-
90	50	M	Nu	Nu	-	-	-	-	√	√	157	68	105	160/100	-	140	203	24	0.6	250	Nil		N	-
91	48	M	5Yr	5Yr	√	√	-	-	-	-	160	72	102	150/100	NPR	156	198	22	0.7	196	Nil		IHD	N
92	58	F	3 Yr	5Yr	-	-	-	-	-	√	152	66	96	130/90	-	96	140	28	1.0	220	Nil		N	-
93	50	F	5Yr	5Yr	-	-	-	-	√	-	150	60	100	100/70	NPR	110	186	45	1.0	236	Nil		N	-
94	45	F	3Yr	-	-	-	-	-	-	√	155	45	85	140/90	NPR	112	176	28	0.6	303	3+	Y	N	-
95	60	F	4yr	4yr	-	√	-	-	-	-	153	62	95	170/100	NPR	156	200	27	0.8	256	3+	Y	OMI	H
96	54	F	1Yr	1Yr	-	√	-	-	-	√	156	64	96	150/100	-	125	201	24	0.9	224	Nil		IHD	N

97	57	F	11Yr	5Yr	-	√	-	-	-	-	152	60	106	150/90	NPR	156	174	30	1.2	210	1+	Y	IHD	-
98	60	M	15Yr	5Yr		√	-	-	-	√	160	70	92	160/100	-	172	196	40	1.5	200	1+	Y	OMI	H
99	56	M	12Yr	2Yr	√	√	-	-	-	-	158	68	104	140/90	NPR	146	206	28	1.6	240	Nil		IHD	DD
100	55	F	9Yr	1Yr	-	√	-		√	-	148	62	90	140/90	-	172	252	32	1.6	460	Nil		OMI	H
101	56	F	14Yr	14Yr	-	-	-	-	-	-	149	64	96	140 90	NPR	154	264	42	1.5	196	Nil		N	-
102	58	F	10Yr	2Yr						√	152	60	92	130/100	-	162	276	20	1.0	198	Nil		N	-
103	48	F	10Yr	5Yr	-	√	-	-	√	-	154	62	94	150/100	NPR	200	282	29	1.5	220	Nil		OMI	H
104	49	M	8Yr	2Yr	-	-	-	-	-	-	164	65	102	146/90	NPR	148	256	30	1.6	260	Nil		N	-
105	52	M	12Yr	6Yr	√	-	-	-	-	-	166	80	104	130/90	-	260	290	32	1.4	220	1+	Y	N	-
106	62	M	15Yr	15Ye	√	√	-	-	√	-	158	76	106	180/100	NPR	156	200	40	1.6	224	Nil		IHD	N
107	60	M	10Ye	4Yr	-	-	-	-	-	-	156	72	108	140/90	-	162	202	42	1.6	226	Nil		N	-
108	56	M	Nu	Nu	-	√	-	-	-	√	162	70	98	180/100	NPR	156	204	28	0.9	198	Nil		N	-
109	52	M	5Yr	-	-	-	-	-	-	-	164	86	106	140/90	NPR	178	260	40	1.7	240	Nil		N	-
110	65	F	13Yr	3Yr	-	-	-	-	√	-	152	56	98	150/90	NPR	142	196	28	1.2	226	Nil		N	-
111	56	F	6Yr	-	-	-	-	-		-	156	70	96	140/90	-	156	242	26	0.9	210	Nil		N	-
112	54	M	9Yr	4Yr		√	-	-	-	√	160	72	100	130/90	--	178	256	30	1.2	202	1+	Y	OMI	-
113	56	F	5Yr	5Yr	--	-	-	-		-	149	56	96	150/100	NPR	156	200	20	0.9	200	Nil		IHD	-
114	58	F	6Yr	-	-	-	-	-	-	-	152	60	98	140/92	-	172	206	20	0.8	260	Nil		N	-
115	57	F	Nu	Nu	-	--	-	-	-	√	154	62	96	160/100		182	208	28	0.9	192	Nil		OMI	H
116	58	M	8Yr	5Yr		√	-	-	-	-	158	58	94	156/100	NPR	167	210	40	1.8	252	2+		OMI	H

117	52	F	4Yr	-	-	-	-	-	-	-	146	58	96	130/ 90	-	156	196	26	1.0	220	Nil		N	-
118	50	F	Nu	Nu	-	-	-	-	-	-	148	60	100	150/ 100	PR	162	211	28	1.1	240	Nil		N	-
119	62	F	10Y r	2Yr	-	-	-	-	√	√	152	60	92	180/ 100	PR	172	256	28	1.2	226	Nil		N	-
120	64	F	12Y r	10Y r	-	-	-	-	-	-	151	62	94	150/ 90	-	174	300	26	1.3	230	Nil		N	-
121	60	F	8Yr	2Yr	-	-	-	-	-	-	150	56	86	156/ 90	-	176	272	28	1.6	236	Nil		N	-
122	54	F	5Yr	-	-	-	-	-	-	-	149	65	96	140/ 90	-	178	296	26	1.5	240	Nil		N	-

Abbreviations Used: Nu – New; NPR - Non Proliferative Retinopathy; PR - Proliferative Retinopathy; M – Maculopathy; N – Normal; B – Block; IHD - Ischaemic Heart Disease; OMI – Old Myocardinal Infraction; DD – Diastolic Dysfunction; H – Hypokinetic Wall Motion Abnormalities.