DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS

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CERTIFICATE

This is to certify that the dissertation entitled "**DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS"** is a bonafide work done by **Dr.VIJAY SHEKAR P**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2010 -2013.

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DECLARATION

I solemnly declare that this dissertation entitled "**DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2010-2013 under the guidance and supervision of**, Prof.K.SIVASUBRAMANIAN, M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

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INTRODUCTION

Type 2 diabetes mellitus is an established risk factor for cardiovascular events and the development of congestive cardiac failure, through its association with hypertension and coronary artery disease. The existence of myocardial dysfunction in diabetic subjects even in the absence of ischemic, valvular and hypertensive heart disease was proposed by Rubler *et al*. in 1972 and subsequently abnormalities in both systolic and diastolic functions have been demonstrated.

Diastolic dysfunction has been described as an early sign of diabetic heart muscle disease preceding the systolic damage. Diastolic abnormalities in normotensive type 2 diabetic patients without coronary artery disease and clinical evidence of heart failure was demonstrated by Regan *et al*. using cardiac catheterization and subsequently by noninvasive techniques such as Doppler echocardiography.

Diastolic dysfunction is independently associated with increased all-cause mortality as well as cardiovascular mortality in a population based sample of middle aged and elderly adults. The impact of isolated diastolic dysfunction in diabetes concerns exercise tolerability. It influences maximal treadmill performance and explains lower maximal performance observed in patients with type 2 diabetes.

Diabetic complications can be classified broadly as microvascular and macrovascular complications. The influence of diabetic complications on diastolic dysfunction has been investigated in several studies. Abnormalities have been observed especially in population of diabetic patients with severe microvascular complications as evidenced by marked proteinuria and proliferative retinopathy.

Studies (Takenaka*et al*.(1988), Hiramatsu*et al*.(1992),Annonu*et al*(2001)) performed in diabetic patients free of coronary artery disease, have demonstrated that patients with mild to severe retinopathy exhibited LV diastolic dysfunction. This relation with retinopathy, was however constantly not found.

Sampson *et al*(1990) found a significantly higher proportion of abnormal diastolic dysfunction in the group of diabetes with proteinuria. Watschinger *et al*.(1993) and Guglielmi *et al.*(1995) demonstrated LV diastolic dysfunction, whereas controls without microalbuminuria showed no diastolic impairment.

The pathogenesis of diastolic dysfunction in type 2 diabetic patients is not completely elucidated. The relation of microvascular complications with diastolic dysfunction in type 2 diabetics suggests that diabetic microangiopathy is a background factor.

AIM OF THE STUDY

Primary Objectives

To assess the diastolic dysfunction in type 2 diabetic patients using Doppler echocardiography.

Secondary Objectives

To find out the correlation between diastolic dysfunction and microvascular complications (nephropathy and retinopathy).

REVIEW OF LITERATURE

Diabetes mellitus has been a disease known to the society from time immemorial. Descriptions of patients presenting with folliculitis, weight loss, polyuria and urine that attracted ants have been found in writings from earliest civilizations of Asian and Indian origin[1]. Since then, descriptions and our understanding of this disorder have kept growing as evidenced from reports all across the globe.

What started in 17th century as tasting human urine to detect blood sugar levels has now grown into sophisticated laboratory diagnostic testing. And it does not stop here. With growing technology, our insight into the disease, its complications and the possible pathogenesis keeps growing. This development is essential, as supported by the growing pandemic of diabetes. It has been estimated that nearly 285 million people are affected by diabetes mellitus by the year 2010 and it shows no signs of regression in the near future. The estimates continue to increase with atleast 438 million people to be affected by the year 2030[2]. Diabetes mellitus being the most common cause of end stage renal disease (ESRD), non-traumatic lower limb amputations and blindness in the United States, is an indication of how much health burden the disorder can cause. It lays emphasis on treating the complications aggressively but more important would be to detect the complications at the earliest and prevent their progression.

UNDERSTANDING DIABETES MELLITUS:

Diabetes mellitus is a group of metabolic disorders resulting in hyperglycemia with disturbances in carbohydrate, fat and protein metabolism. Hyperglycemia may result from a defect in insulin secretion, insulin action or both. Hyperglycemia when present for a long period of time leads to a host of metabolic abnormalities and also results in end organ damage.

With previous classifications of diabetes being based upon the age of onset and requirement for insulin, presently the emphasis is on the underlying pathogenic process. Diabetes mellitus is classified broadly as Type 1 and Type 2 although other subtypes do exist. Type 1 diabetes mellitus results from complete or near total insulin deficiency whereas type 2 diabetes mellitus is a result of combination of insulin resistance, impaired insulin secretion and increased glucose production.

The etiologic classification of diabetes as recommended by the WHO and ADA extends beyond type 1 and type 2 diabetes and is as follow

Type 1 diabetes mellitus
Type 2 diabetes mellitus
Other specific types of diabetes: 1. Genetic defects of beta cell function 2. Genetic defects of insulin secretion 3. Diseases of exocrine pancreas 4. Endocrinopathies 5. Drugs/chemical induced 6. Infections
Gestational diabetes

Since our study is limited to the population of type 2 diabetes, further discussion is restricted to type 2 diabetes, its pathogenesis and complications.

TYPE 2 DIABETES MELLITUS

EPIDEMIOLOGY AND RISK FACTORS:

Type 2 diabetes is the most common form of diabetes. Previously termed as non-insulin dependent diabetes, type 2 diabetes occurs as a result of a combination of insulin resistance, impaired insulin secretion and increased glucose production.

Although the incidence of both type 1 and type 2 diabetes is increasing, type 2 diabetes has become a rapidly growing pandemic attributed to factors like increased prevalence of obesity and increased aging. Type 2 diabetes though present worldwide, the highest prevalence is in the Pacific islands and Middle East. Not only does the prevalence rate vary in different geographic regions, but the pattern of presentation also varies. Patients from Asian ethnicity have an intermediate prevalence pattern (7-9% of the total population) and phenotypically differ from the rest of the world by having a lower BMI, younger age at onset, presence of greater visceral adiposity and a decreased insulin secretory capacity.

These patients may not require insulin at the time of diagnosis, but may require insulin later in the disease course for glycemic control. Type 2 diabetes patients usually have a gradual onset of hyperglycemia and hence do not present with the classic symptoms of polyuria, polydipsia and

polyphagia. Although type 2 diabetes is undiagnosed in many due to lack of symptoms, the risk of developing complications remain the same. So there is a need to screen people at a higher risk of developing diabetes.

Risk factors for developing type 2 diabetes include

1. Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
2. Obesity (BMI >25 kg/m^2)
3. Physical inactivity
4. Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
5. Previously identified with IFG, IGT, or an HbA_1C of 5.7–6.4%
6. History of GDM or delivery of baby >4 kg (9 lb)
7. Hypertension (blood pressure 140/90 mmHg)
8. HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
9. Polycystic ovary syndrome or acanthosis nigricans
10. History of cardiovascular disease[3]

PATHOGENESIS

The two important pathogenic mechanisms implicated in type 2 diabetes are insulin resistance and decreased insulin secretion, which is due to genetic

factors, environmental factors and obesity either in single or in combination.Insulin resistance may result from mutations in the insulin receptor or polymorphisms of insulin signaling pathways. The genetic basis for type 2 diabetes is supported by the fact that the concordance of type 2 diabetes among identical twins is more than 70%. Individuals with both parents having diabetes carry a risk of 40% of developing diabetes. Variation of transcriptor factor 7 gene has been associated with impaired glucose tolerance and diabetes mellitus.

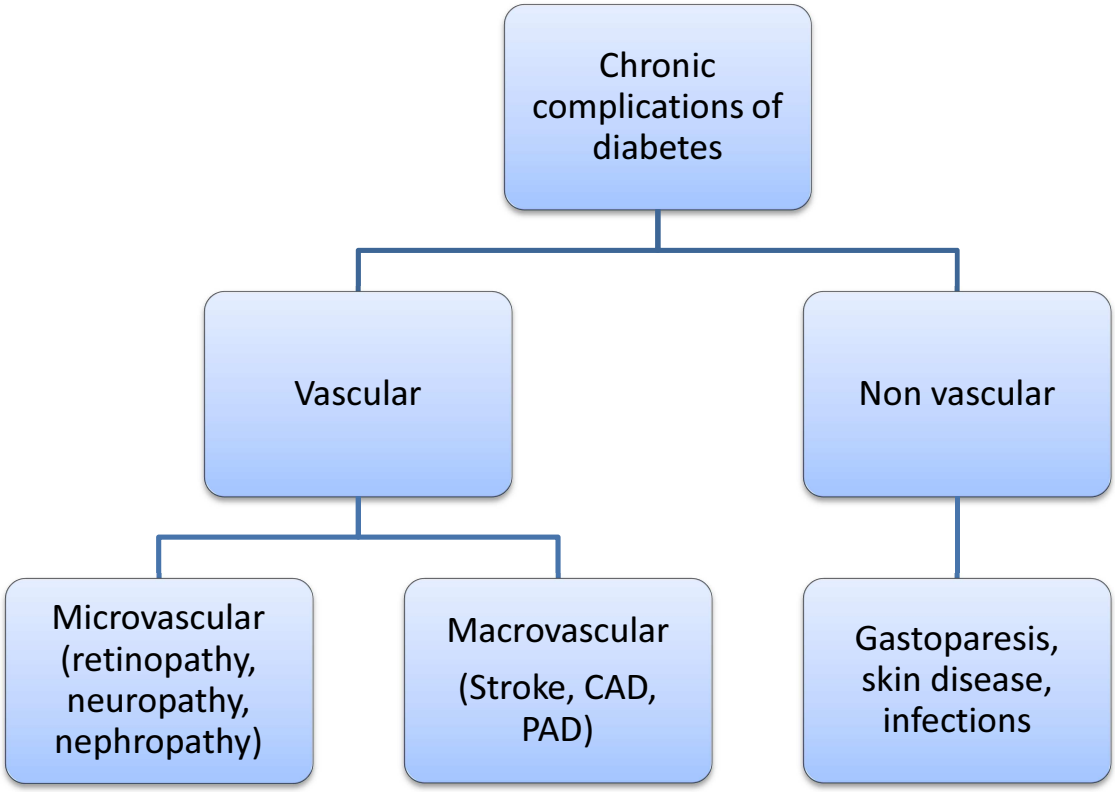
Data suggest that inflammation and diabetes are closely related. Adipose tissue besides being a principal storage site of energy, also acts as an endocrine organ. Obesity mediates insulin resistance by elaborating inflammatory cytokines (adipokines). Adipocyte cell size highly correlates with insulin resistance and the risk of developing type 2 diabetes[4]. Visceral obesity, which includes both mesenteric and omental fat deposits correlates better than overall obesity[5]. Proposed mechanisms include an unrestrained lipolysis with an increased delivery of free fatty acids (FFA) to the portal circulation.

Another contributory pathogenic mechanism is the decrease in insulin secretion due to a beta cell dysfunction. During the early phase, beta cells increase insulin release in an attempt to compensate for insulin resistance. As the disease progresses, there is a progressive decline in beta cell

function. To start with, the insulin secretory defect is limited to the glucose stimulated insulin secretion. Eventually, there is decrease in overall insulin secretory capacity. There is also a reduction in the mass of the beta cells. Type 2 diabetes is also associated with amyloid deposition in the islet cells. Whether amyloid deposition is a cause or effect remains a controversy.

Any given patient with type 2 diabetes, at the time of diagnosis, will have both insulin resistance and beta cell dysfunction in varying degrees.

COMPLICATIONS



The complications of type 2 diabetes can be acute or chronic. Chronic complications are primarily responsible for morbidity and mortality of diabetes. Chronic complications may be vascular or nonvascular in nature. Vascular complications of diabetes can be classified into microvascular and macrovascular complications.

Macrovascular complications include coronary artery disease, peripheral arterial disease and cerebrovascular accidents (stroke).Traditionally microvascular complications have been described under the headings of neuropathy, nephropathy and retinopathy.

PATHOGENESIS OF MICROVASCULAR COMPLICATIONS:

There is a need to understand the molecular and cellular mechanisms of microvascular complications in order to device strategies that will aim at treatment and prevention of these complications. Chronic hyperglycemia and associated metabolic abnormalities due to a insulin secretory defect or insulin resistance have profound influences on the cellular function, extracellular matrix and organ function. The important mechanisms that contribute to microvascular complications are

a) Sympathetic nervous system: Overactivity of sympathetic nervous system contributes to the development of hypertension.[6] During late

stages of diabetes, sympathetic denervation occur leading to altered vascular responses.[7]

b) Renin angiotensin aldosterone system (RAAS): RAAS plays an important role in the development of hypertension, cardiovascular disease and diabetic nephropathy. Various studies have demonstrated the role of angiotensin II (AT II) in the pathology of vascular complications of diabetes. Both the tissue RAAS and local RAAS play an important role. Local RAAS present in the pancreas and adipocytes also contributes to the pathogenesis.

c) Advanced glycation end(AGE) products: AGE products are formed by nonenzymatic reactions between glucose and proteins. The most common AGE product is carboxymethyl lysine.[8] These compounds react with specific receptors (RAGE) and interfere with vascular signaling, alters the properties of extracellular matrix and alters matrix cell interactions of the endothelial cells. AGEs also induce the elaboration of growth factors and increase the production of reactive oxygen species.[9]

d) Oxidative stress: It is an imbalance between reactive oxygen species and cellular antioxidant mechanisms. Patients with diabetes have a decreased levels of intracellular glutathione, which correlates with the severity of nephropathy and retinopathy.[10] Hyperglycemia promotes

oxidative stress through inhibition of pentose phosphate pathway(primary source of NADPH), generation of super oxides from mitochondria, increasing the activity of vascular NADPH oxidase and inhibiting NO mediated endothelial function.

e) Hexosamine pathway and O-linked glycosylation: Diabetes increases the activity of hexosamine pathway and post translational glycosylation of proteins resulting in elaboration of growth factors.[11]

f) Activation of protein kinase C (PKC) pathway: Although 12 different isoforms of PKC exist, beta 2 isoform of PKC is activated in particular especially in the retina and renal glomeruli. Activation of vascular PKC results in an impaired endothelium mediated vasodilation thus contributing to a pathological microvascular change.[12]

g) Growth factors: The following growth factors may act separately or in concert to produce microvascular changes. The important growth factors implicated are vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor beta (TGF beta), connective tissue growth factors and growth hormone/insulin like growth factor.

h) Endothelium derived factors: There occurs an imbalance between the vasodilator and vasoconstrictor molecules derived from the

endothelium. In diabetes there is an increased production of endothelin (a powerful vasoconstrictor) and decreased production of nitric oxide and prostacyclins.[13] A widespread endothelial dysfunction is a prominent feature of diabetes.

Although our knowledge on the sequence of these pathways is incomplete, drugs that target these signaling pathways can reduce microvascular complications, in addition to glycemic control which is of prime importance.

DIABETIC NEPHROPATHY

Diabetic nephropathy occurs in 30- 50% of patients with type 2 diabetes.[14] Although the natural history of diabetic nephropathy is less well understood in type 2 diabetes, it is estimated that nephropathy develops only after 5 -10 years of the disease. The incidence of diabetic nephropathy is increasing rapidly due to growing pandemic of diabetes. And more patients with diabetic nephropathy reach ESRD because the longevity of diabetic patients is increased due to availability of better drugs for control of cardiovascular risk factors.

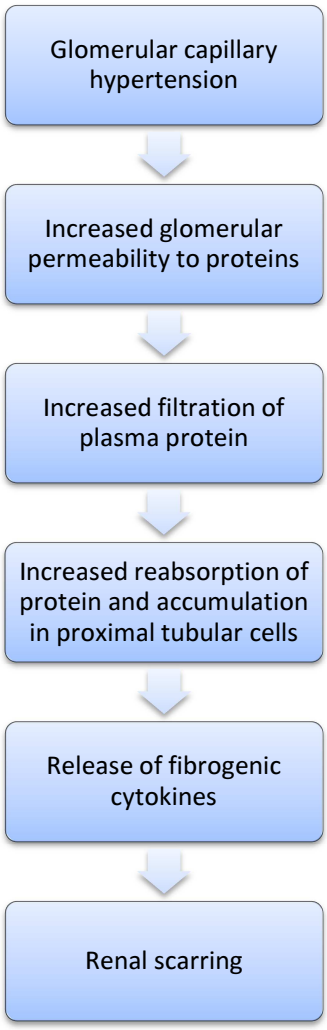
Risk factors for nephropathy

1. Genetic factors: Familial clustering of diabetic nephropathy and ACE polymorphisms suggest the role of genetics.

2. Duration of diabetes
3. Hypertension
4. Hyperglycemia
5. Smoking: Smoking causes vasoconstriction, platelet dysfunction and coagulation abnormalities which accelerates vascular damage.

Though the cellular and molecular mechanism of nephropathy has already been briefed, two factors which are responsible for progression of a diabetic nephropathy require special mention- hypertension and proteinuria.

Hypertension is not only a consequence of renal damage, but it plays an important role in the genesis and progression of nephropathy. There is a significant correlation between blood pressure levels and drop in glomerular filtration rate. Proteinuria is an independent and strong predictor of decline in renal function. Excessive protein load leads to tubulointerstitial damage and contribute to disease progression. A model of how hypertension and proteinuria contribute to renal damage is depicted below:[15]



The natural history of type 2 diabetes has a predictable course of events. In the initial stages of diabetes, there is glomerular hyperfiltration stage characterized by an increase in GFR.

After a period of 5-10 years, patient starts excreting small amounts of protein termed as microalbuminuria. This stage is known as the stage of incipient nephropathy.[16] Microalbuminuria is defined as excretion of 30-

299 mg/24 hour urine sample or 30-299 μg/mg of creatinine in a spot sample. Microalbuminuria is the earliest marker of diabetic nephropathy.

Once microalbuminuria sets in, the patient develops hypertension and progresses over a period of 5- 10 years to macroalbuminuria. 50% of individuals with microalbuminuria progress to macroalbuminuria. This stage is the stage of overt nephropathy Macroalbuminuria is defined by albumin excretion of >300 mg/day or > 300 μg/mg of creatinine.

Patients who develop macroalbuminuria develop ESRD over a period of 5-7 years. Although a variety of genetic and physiological markers are available to determine which group of patient will progress to overt nephropathy and ESRD, till date there is no standard to ascertain this.

Microalbuminuria in diabetes

Microalbuminuria is defined as excretion of 30 – 299 mg albumin per 24 hour in atleast two out of three consecutive non ketotic sterile samples. It refers to the amount of albumin which cannot be detected by the conventional dipstick methods.[43] Under normal circumstances the amount of albumin excreted in 24 hours is less than 30 mg.

The pathogenic mechanism of microalbuminuria in diabetes needs to be revisited here. Albumin is a negatively charged particle and has a physical radius of 3.6 nm. The glomerular basement membrane has pores of the size

of 4 nm, but the negative charge of the glomerular basement membrane repels the albumin.

During the early stages of diabetes, the negative charge in the glomerular basement membrane is lost due to a loss of heparin sulphate. As a consequence, albumin is freely filtered across the basement membrane which appears in the urine. As the disease progresses the basement membrane architecture is distorted resulting in loss of large molecular weight proteins as well.[43]

The presence of microalbuminuria not only is an early marker of diabetic nephropathy but also carries much more significance. Microalbuminuria is also a marker of cardiovascular disease and is a predictor of mortality in diabetic nephropathy patients.[44] What is more important is that microalbuminuria identifies nephropathy at a stage when it is potentially treatable and reversible. Hence estimation of microalbuminuria is of prime importance.

NATURAL HISTORY OF DIABETIC NEPHROPATHY[43]

Stage of nephropathy	Glomerular filtration rate(GFR)	Urine protein excretion	Histopathological changes in the kidney
Stage of hyperfiltration	Increases	Normal	Hypertrophy/increased kidney volume
Incipient nephropathy	Normal/increased	30- 299 mg/day	Basement membrane thickening
Overt nephropathy	Decreased	>300 mg/day	Glomerular occlusion and mesangial expansion
End stage renal disease(ESRD)	GFR<15 ml/min	Present	Scarring and fibrosis

It is important to understand the natural history to device treatment strategies and prevent the progression of the disease. Once macroalbuminuria develops the pathological changes are irreversible. Hence, it is important to identify nephropathy at an earlier stage i.e. the stage of incipient nephropathy. Once microalbuminuria is identified, it should not only be monitored but also aggressively treated.

DIABETIC RETINOPATHY

Diabetic retinopathy is a highly specific vascular complication of type 2 diabetes. Diabetes is the leading cause of blindness. The duration of diabetes is an important risk factor for the development of retinopathy. More than 60 % of diabetic patients will have some changes of retinopathy after a period of 20 years.[17]

Diabetic retinopathy is classified into two stages: non proliferative diabetic retinopathy and proliferative retinopathy. Clinically significant macular edema and vitreous hemorrhage are important causes of blindness in a patient with diabetic retinopathy.

The various retinal lesions that are found in a case of diabetic retinopathy are:

a) Micro aneurysms: Micro aneurysms are one of the earliest findings in diabetic retinopathy. They are saccular outpouchings of the retinal vasculature and occur as a result of endothelial dysfunction. Ruptured micro aneurysms lead to intra retinal haemorrhages[18]
b) Hemorrhages: Hemorrhages may differ in their appearance depending on the retinal layer involved. The “dot/blot” hemorrhages are small intraretinal hemorrhages which are characteristic of diabetic retinopathy. These hemorrhages occur in the deeper layers of the

retina. Hemorrhages in the nerve fibre layer result in flame shaped hemorrhage.

c) Intra retinal microvascular abnormalities(IRMA): IRMA s are pre existing vessels with new endothelial cell proliferation that act as "shunts" through areas of non perfusion. Presence of IRMAs usually indicate a severe form of non proliferative retinopathy and carries an increased risk of neovascularization.

d) Venous caliber abnormalities: These include venous beading, dilatation and loop formation and indicate early stage of diabetic retinopathy.

e) Retinal neovascularization: Development of new and abnormal vessels is a feature of proliferative retinopathy. Neovascularization may occur at the disc (NVD) or elsewhere at the retina (NVE).

Diabetic retinopathy may present as non proliferative retinopathy, proliferative retinopathy or macular edema.

Non proliferative diabetic retinopathy is classified according to the severity as:[45]

a) Mild NPDR: Presence of micro aneurysm

b) Moderate NPDR: Presence of micro aneurysm or hemorrhage, venous beading and IRMA

c) Severe NPDR: Hemorrhages or microaneurysms in all 4 quadrants or venous beading in atleast 2 quadrants or IRMA in atleast in one quadrant.

d) Very severe NPDR: Presence of 2 or more of the lesions categorized as severe NPDR.

As the severity of the NPDR increases, risk of patient developing proliferative retinopathy increases.

Proliferative diabetic retinopathy (PDR) includes neovascularization (NVD or NVE), preretinal or vitreous hemorrhage. Presence of high risk PDR is an immediate indication for laser photocoagulation and hence identifying these lesions is crucial in saving vision of the patient.

Clinically significant macular edema (CSME) which is defined as retinal thickening within two disc diameters from the centre of macula is a potentially treatable lesion. Presence of macular edema indicates there is a 25% chance of moderate visual loss in the next 3 years.

DIABETIC NEUROPATHY

Diabetic neuropathy occurs in about 50% of patients with type 2 diabetes. The classification of diabetic neuropathy is primarily based on the clinical manifestations. Although several classification systems are available, the

simplest and widely used classification divides diabetic neuropathy into diffuse or symmetric neuropathies and focal neuropathies.[46]

Diffuse or symmetric neuropathies include

1. Distal symmetric sensorimotor polyneuropathy
2. Autonomic neuropathy
3. Acute painful neuropathy
4. Hyperglycemia induced neuropathy
5. Treatment induced neuropathy
6. Symmetric proximal lower extremity neuropathy
7. Chronic inflammatory demyelinating polyneuropathy(CIDP)

Of these, distal symmetric sensorimotor polyneuropathy is the most common type. Foot ulcers and diabetic arthopathy are dreaded complications of diabetic neuropathy and hence remain as issues of prime interest.

Autonomic neuropathy can affect cardiovascular system resulting in resting tachycardia, orthostatic hypotension and arrhythmias, gastrointestinal system resulting in gastroparesis and genitourinary system resulting in erectile dysfunction and bladder emptying abnormalities.

Focal/multifocal neuropathies include:

1. Cranial neuropathy

2. Thoracoabdominal neuropathy

3. Focal limb neuropathy

4. Diabetic amyotrophy

Mononeuropathy represents symptoms along the distribution of a single nerve. Mononeuritis multiplex is common among diabetics and refers to simultaneous involvement of multiple peripheral nerves. Cranial mononeuropathy occurs in diabetic patients with the most commonly involved nerve being the third cranial nerve. Diabetic amyotrophy occurs as a result of involvement of the lumbar plexus or the femoral nerve and presents as severe pain in the hip and thigh associated with weakness of hip flexors and extensors

Having discussed the macrovascular and microvascular complications with special emphasis on the pathogenic mechanism of microvascular complications, the relationship between the cardiovascular system and diabetes is the topic of prime interest.

DIABETES AND CARDIOVASCULAR SYSTEM

The prevalence of cardiovascular disease is higher among type 2 diabetes patients. There is a marked increase in the occurrence of myocardial infarctions, coronary artery disease, congestive heart failure and peripheral arterial disease, which is attributed to the increase in atherosclerosis. The incidence of sudden cardiac death is increased by two to three fold in diabetic patients. Such is the strength of association between cardiovascular disease and diabetes, that American Heart Association has designated diabetes as "coronary artery disease equivalent".

Diabetes is the seventh leading cause of mortality, with majority of mortality occurring due to cardiovascular complications.[19]Overall cardiovascular disease which include both coronary artery disease and cerebrovascular accidents account for about 65% of the mortality in diabetic patients.[20] Although there has been a decline in the deaths due to cardiovascular disease in the past three decades, the effect of cardiovascular mortality in diabetics lags well behind the general population. Identification and treating of cardiovascular risk factors gains top priority in improving the outcome of type 2 diabetes patients.

CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETES

The traditional risk factors which promote atherosclerosis and are associated with type 2 diabetes include:

1. Female sex
2. Smoking
3. Reduced physical activity
4. Hypertension
5. Abdominal obesity
6. Dyslipidemia

Although the traditional risk factors play an important role in the development of atherosclerosis in diabetic patients, the cardiovascular mortality rate exceeds by 50% the rate predicted by these factors. This suggests that nontraditional risk factors such as hyperglycemia, insulin resistance and insulin play a pivotal role in contribution to cardiovascular disease.[47]

A few risk factors of prime importance are discussed below

Hypertension:

Hypertension is a common comorbid condition and accounts for nearly 85% of excess cardiac risk. Hypertension increases the risk of coronary artery disease, stroke, nephropathy and retinopathy. When hypertension coexists

with diabetes, the risk of stroke or CVD is increased two fold and the risk for developing ESRD is increased five fold[21]. Hypertension in individuals with diabetes has characteristic features which include volume expansion, increased salt sensitivity, isolated systolic hypertension, loss of the nocturnal dipping of blood pressure and pulse, and increased propensity towards orthostatic hypotension.[22]

Dyslipidemia:

Dyslipidemia is an important risk factor for development of atherosclerosis in diabetic patients. The important lipid abnormalities in diabetic patients are as follows:

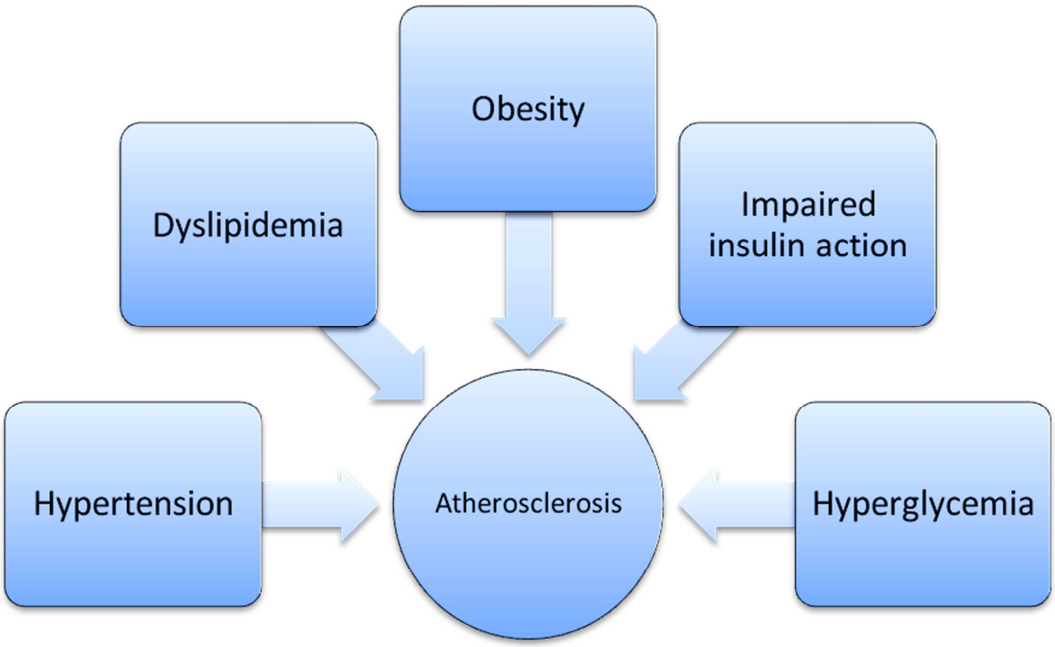
1. Increased levels of VLDL due to increased hepatic production
2. Increase in triglycerides due to increased VLDL production and decreased catabolism. Lipoprotein lipase activity is reduced in diabetics which plays an important role in metabolism of triglycerides.
3. Decreased HDL levels[23]
4. LDL levels remain unchanged. But diabetes patients have a tendency to form smaller, denser LDL particles, which undergo oxidation easily and promote atherosclerosis.[24]

The growing pandemic of obesity has led to the development of a new entity "metabolic syndrome", which includes dyslipidemia, hypertension, diabetes and obesity and threatens to increase the cardiovascular mortality.

Insulin resistance and hyperglycemia

Insulin resistance is associated with atherogenic factors and procoagulant state and thus promotes atherosclerosis even before overt hyperglycemia develops.[25] Insulin resistance is associated with an increase in plasminogen activator inhibitor 1(PAI 1) and fibrinogen, both of which favour thrombus formation. The duration of insulin resistance is also a critical factor in promoting atherosclerosis. Thus insulin sensitivity and atherosclerosis are inversely related.

Serum glucose level is another important risk factor for cardiovascular events. The level of chronic hyperglycemia as measured by glycosylated hemoglobin (HbA1C) is an independent risk factor for coronary artery disease. A 1% increase in HbA1C levels doubles the risk of cardiovascular disease.[26]



Risk factors for cardiovascular disease in type 2 diabetes

DIABETES AND CARDIAC DISEASE

With enough evidence suggesting an increased number of cardiovascular events and their risk factors, we take a closer look of how diabetes specifically affects the heart. Diabetes contributes to the following events in heart, which are responsible for the increased cardiovascular morbidity and mortality.

1. Coronary artery disease
2. Congestive cardiac failure
3. Diabetic cardiomyopathy
4. Cardiac autonomic neuropathy(CAN)

CORONARY ARTERY DISEASE AND DIABETES

As already mentioned the risk of coronary artery disease is increased two to three fold in diabetic patients. Multivessel disease is more common among diabetic population than in the general population. Angiographic studies performed in diabetic patients either in a setting of acute myocardial infarction or an elective angioplasty have confirmed a higher proportion of diabetic patients to have a multivessel disease i.e. involvement of two or more vessels with more than 75% stenosis[27]. Not only is the number of vessels involved in diabetes increased, the distribution of atherosclerotic plaques is diffuse and more severe. Various autopsy studies also confirm the same.[28]

Acute coronary syndromes represent a major cause of death in diabetic patients. Diabetic patients who develop myocardial infarction have a higher mortality both in the acute phase as well as during the long term follow up. In hospital mortality rates are two fold higher in diabetic patients, the predominant factor being development of cardiogenic shock and congestive cardiac failure.[29,30] The mechanisms that result in a higher incidence of cardiogenic shock following an acute coronary event will be discussed later. Other possible mechanisms for a poor outcome include increase in the

incidence of re-infarction, infarct extension, and recurrent ischemia. Diabetic patients tend to have a decreased propensity to form collaterals and so re-infarctions and recurrent ischemia are common.[31] Long term outcome following myocardial infarction is also poor in diabetes patients and is related to recurrent MI and development of new onset congestive cardiac failure.

Diabetes may also influence treatment outcomes in patients with coronary artery disease. Although it is widely believed that thrombolysis may increase the risk of ocular bleeding in a diabetic patient with proliferative retinopathy, many studies have failed to show an association. Hence, thrombolysis should not be deferred even in a setting of proliferative retinopathy. Although coronary artery by pass graft (CABG) offers no difference in treatment outcomes between diabetics and non diabetics, the scenario is not the same with stenting procedures. There is an increased risk of restenosis following placement of coronary stents in diabetic population. The major mechanism of restenosis is the increased proliferation of smooth muscle cells in diabetic population.[32]

Another important feature of coronary artery disease in diabetic patients is its propensity to cause an unrecognized myocardial infarction often referred to as “silent ischemia”. Patients may present without any symptoms or may present with atypical symptoms. The probable mechanism for a silent

ischemia is presence of autonomic neuropathy in diabetics which involves sensory supply to the heart.[33] The hypothesis is supported by the fact that angina perceptual threshold i.e. the time interval between onset of ischemic changes to onset of pain during exercise testing is prolonged in diabetic patients.[34]

CONGESTIVE CARDIAC FAILURE AND DIABETES

It is well established that the prevalence of heart failure is higher among diabetic patients. Observations from the Framingham Study suggest that diabetes increases the risk of developing heart failure by 2 fold in men and 5 fold in women. This increase in the prevalence usually parallels the prevalence of coronary artery disease. Coronary artery disease remains the most common cause of heart failure in the general population and also in diabetics. Hypertension remains a major contributor to heart failure second only to CAD. It accounts for 24% of cases.[35]

CARDIAC AUTONOMIC NEUROPATHY (CAN)

Cardiac autonomic neuropathy refers to the dysfunction of the autonomic system related to the heart.[48] Cardiac autonomic neuropathy can manifest as orthostatic hypotension, resting tachycardia or painless myocardial infarction, which has been highlighted earlier.

Initially the parasympathetic fibres are affected, resulting in an increased sympathetic tone resulting in resting tachycardia. There is also blunting of hemodynamic responses to exercise. As a result of the decreased parasympathetic tone, coronary vasoconstriction occurs, which results in ischemia.

CAN significantly contributes to cardiovascular morbidity and mortality. The possible mechanisms are

1. Increased risk of ventricular arrhythmias due to perturbations in the rhythm. As a consequence, diabetic patients with CAN are at an increased risk of sudden cardiac death.
2. Increased resting heart which increases the myocardial oxygen demand.
3. Silent myocardial ischemia.
4. Impaired vasomotor regulation.

Presence of CAN indicates a poor prognosis to the underlying cardiac disorder. CAN is detected by measuring the heart rate variability over a 24 hour period, QT interval and QT dispersion.[36]

DIABETIC CARDIOMYOPATHY

Whether factors other than coronary artery disease and hypertension can result in heart failure in diabetics remain a controversial subject and an area of potential research.

Diabetic cardiomyopathy refers to presence of dilated cardiomyopathy in diabetic patients in the absence of coronary artery disease, hypertension and valvular heart disease.[44]

The concept of diabetic cardiomyopathy was first proposed by Rubler et al in 1972[49]. Later Regan et al[50] demonstrated increased left ventricular filling pressures in normotensive diabetic patients free of symptoms of heart failure. Abnormalities in diastolic function with an intact systolic function were demonstrated by Raev et al. Various studies on clinical subjects and postmortem studies suggested the possibility of existence of idiopathic cardiomyopathy associated with diabetes.

Diabetic cardiomyopathy may not present with florid symptoms of failure but its presence can be assessed by subtle changes in imaging. Although most studies were performed on type 1 diabetics, data is available for type 2 diabetes patients also.

The existence of diabetic cardiomyopathy remains controversial. To confirm its presence and its potential role in worsening cardiovascular outcome in

diabetic patients, a thorough understanding of heart failure, methods of detection and underlying pathogenic mechanisms is needed.

HEART FAILURE AND ITS TYPES

Heart failure, in simple terms, is the inability of the heart to meet with the metabolic needs of the tissues. Although there are several ways to classify heart failure, the most scientific classification relevant to this topic would be to divide it into systolic heart failure and diastolic heart failure. This classification is purely based on echocardiographic parameters.

An important parameter is assessment of heart failure while performing an echocardiography is ejection fraction. Ejection fraction is defined as fraction of blood pumped out of the ventricle during each cardiac cycle.

Ejection fraction = (End diastolic volume – end systolic volume)/end diastolic volume

Normal ejection fraction ranges between 55-70%.

Systolic failure is defined as heart failure with reduced ejection fraction (< 40%) i.e. failure of contraction of ventricles, in which case there is decreased amount of blood available to carry adequate oxygen and nutrients to the tissues. Diastolic heart failure is defined as heart failure with preserved ejection fraction (40-50%).i.e. failure of ventricles to relax.

DIASTOLIC HEART FAILURE[51]

Diastole or the relaxation phase of the ventricle, begins with the aortic closure and ends with mitral closure.

The diastole, like the systole is an active process and comprises of four phases:[52]

1. Isovolumetric relaxation time: In this phase, both aortic and mitral valves remain closed and there is no flow of blood from atrium to ventricle in this phase.
2. Early filling period: The mitral valve opens and the left atrium empties into the left ventricle, which represents about 80% of the diastolic flow. The early filling period velocity is denoted by E.
3. Diastasis: The pressures on the left atrium and ventricle are equilibrated and there is very little flow during this phase.
4. Atrial contraction: The atrium contracts resulting in flow of blood into the ventricle representing 15% of diastolic flow. The velocity in this phase is denoted by A.

Under normal conditions, E velocity is larger than A velocity and hence E/A ratio is more than 1. In pathological states associated with abnormal relaxation of the ventricle, there is an increase of flow during the atrial contraction phase to about 25-30%, producing reversal of E/A ratio.

Diastolic heart failure is a clinical syndrome, whereas diastolic dysfunction is a mechanical abnormality of diastole of the heart with or without clinical symptoms. Diastolic dysfunction can occur is isolation or in combination with systolic dysfunction.

Any abnormality in the left ventricular relaxation or its compliance alters the onset, rate and extent of left ventricular pressure decline. These abnormalities disrupt the normal relationship between left ventricular pressure and volume. As a consequence, the filling pressures increase in order to maintain a normal left ventricular end diastolic volume.[51]

During exercise and tachycardia, these filling pressures are increased further resulting in exertional dyspnea and fatigue.

The various causes of diastolic dysfunction are:

1. Cardiac conditions: Cardiomyopathies of restrictive and hypertrophic type result in diastolic dysfunction. Constrictive pericarditis also results in diastolic failure
2. Hypertension: Hypertension results in a left ventricular hypertrophy which interferes with normal relaxation.
3. Ischemic heart disease: It is usually associated with systolic dysfunction.

4. Old age: As the age increases, the myocardium loses its elastic properties and results in impaired relaxation
5. Obesity
6. Diabetes

Assessment of diastolic function and grading

As the symptoms produced by systolic and diastolic do not differ much except for the frequency of occurrence, it is difficult to differentiate between them on clinical grounds. Hence, invasive or non invasive methods are employed to assess the diastolic function.

Cardiac catheterization is the gold standard for assessing diastolic dysfunction. Because of its invasive nature, it cannot be performed in all individuals and hence its utility is limited in terms of assessing diastolic dysfunction.

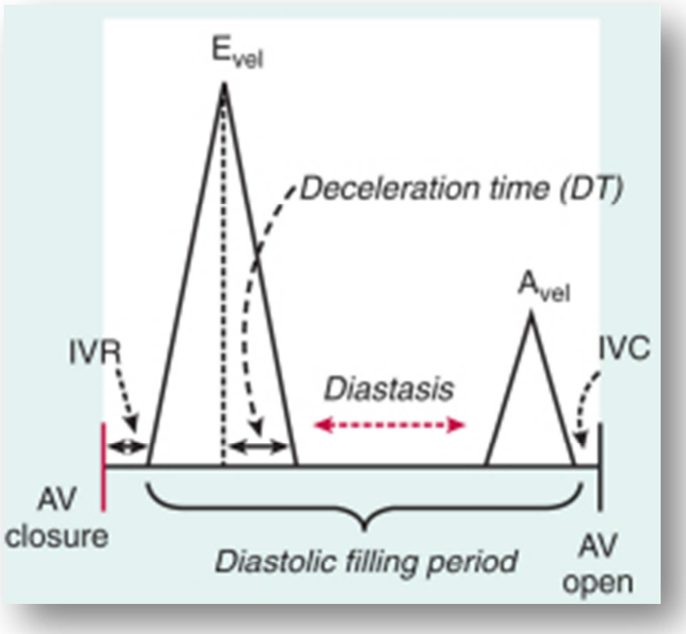
Echocardiography is the most widely used imaging modality to assess the diastolic function. It is a non invasive technique and easily available tool. Doppler echocardiography is commonly employed to assess and grade the diastolic dysfunction.

Various parameters like:

1. E wave velocity (velocity of flow during early filling phase),
2. A wave velocity (velocity of flow during atrial contraction),
3. E wave deceleration time (EDT)(time interval between the peak of E wave to zero)
4. Isovolumetric relaxation time (IVRT) are measured

Doppler study of the pulmonary vasculature yields additional paramaters like S wave velocity, D wave velocity, S/D ratio and atrial reversal (AR). These parameters are used either in single or in combination to assess and grade diastolic dysfunction.[53]

Echocardiographic parameters to assess diastolic function



Diastolic dysfunction presents in four patterns:[52]

Grade I: (Abnormal relaxation pattern)

Characterized by a decreased E wave velocity and increased A wave velocity. E/A ratio < 1; Increased IVRT (>100ms); Increased EDT (>240 ms); S/D ratio>1; AR < 35 cm/s. Patients with grade I diastolic dysfunction have no symptoms at rest but have mild exercise limitation.

Grade II (Pseudonormal pattern):

The normal LV filling pattern is maintained i.e. E/A ratio >1. But LV filling pressures are increased, evidenced by increased AR velocity. Abnormal relaxation pattern is observed during Valsalva maneuver. Patients have exertional dyspnea and moderate functional impairment

Grade III (Reversible restriction):

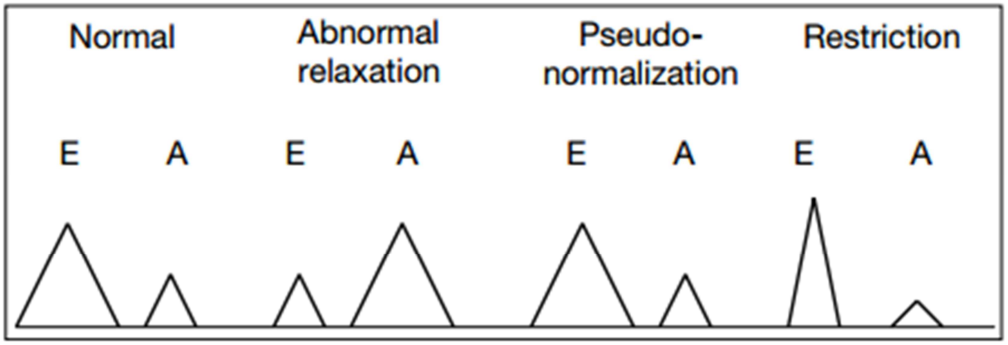
Characterized by E/A ratio>2.5; decreased EDT (< 150 ms); decreased IVRT (<70 ms); S/D ratio < 1; AR >35 cm/s. These findings are reversible with Valsalva. Patients have dyspnea with mild exertion and marked functional impairment.

Grade IV (Irreversible restriction):

Features of restrictive pattern which are not reversed by Valsalva are present.

Other techniques like ventriculography and cardiac catheterization may be used to assess the diastolic dysfunction.

Schematic diagram of diastolic dysfunction(in echocardiography)



Grade of diastolic dysfunction	Pathological abnormality	Echocardiographic parameters
Grade I	Impaired relaxation	E/A ratio < 1
Grade II	Impaired relaxation and compliance	E/A ratio>1 with increased left atrial pressures
Grade III	Restrictive filling(reversible)	E/A ratio > 2.5 and elevated ventricular filling pressures
Grade IV	Restrictive filling (irreversible)	Same as grade III with irreversible changes

DIASTOLIC DYSFUNCTION IN DIABETES

Diastolic dysfunction is a pre runner of heart failure in diabetic patients.[54] It is also an independent risk factor for all-cause mortality. The cardiovascular outcome worsens with increasing severity of diastolic dysfunction. Diastolic dysfunction can occur in isolation without co existent systolic function.

The importance of diastolic dysfunction is emphasized by the fact that diabetic patients are associated with increased risk of heart failure and cardiogenic shock following a myocardial infarction. Observations from various studies highlight the following facts:

1. Studies using serial estimations of cardiac enzymes and echocardiography have found no evidence that patients with diabetes sustain more extensive infarctions than their nondiabetic counterparts.[37]
2. Cardiogenic shock and heart failure are out of proportion to the index infarct size in diabetic patients.
3. Clinical manifestations of heart failure occur in patients with diabetes despite a modest drop in the ejection fraction (EF).[38]

These observations suggest the possibility of preexisting diastolic dysfunction as a major contributor to the adverse outcomes. Subclinical

diabetic cardiomyopathy, which is characterized by diastolic dysfunction, is a likely possibility.[39]

Diastolic dysfunction in diabetic patients may also influence exercise capacity as evidenced by a reduced maximal capacity during treadmill.[63,64]

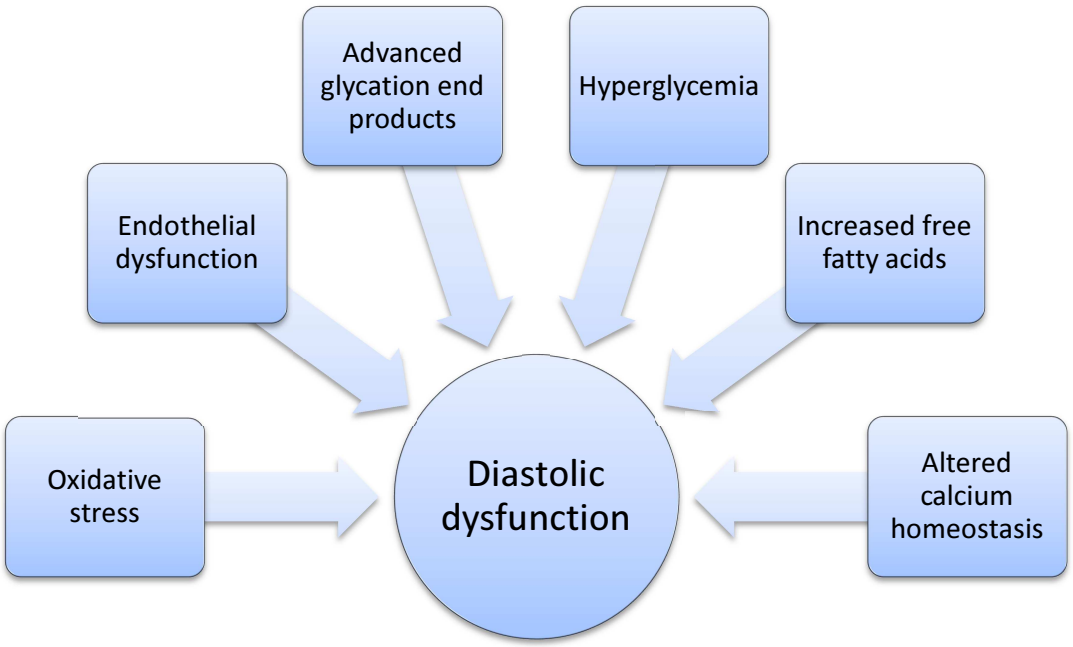
The presence of diastolic dysfunction was confirmed later by variety of observations. Framingham study reported increased incidence of heart failure among diabetic patients even after adjustment for confounding variables.[40] Washington cardiomyopathy study also confirmed the association between diabetes and idiopathic cardiomyopathy. Echocardiographic studies performed later also confirmed the existence of diastolic filling abnormalities in diabetic patients.[41,42] All these data suggest that diabetes could be a cause for diastolic dysfunction even in the absence of systolic dysfunction.

Studies (Takenaka *et al*.(1988), Hiramatsu *et al*.(1992),Annonu *et al*(2001)) performed in diabetic patients free of coronary artery disease and hypertension, have demonstrated that patients exhibited LV diastolic dysfunction.

Mechanisms of diastolic dysfunction in diabetes:[43]

Although the exact pathogenesis of diastolic dysfunction remains unknown, various molecular mechanisms have been proposed. The most important mechanisms being:

1) Metabolic disturbances: Diabetic hearts have a blunted response to the uptake of insulin mediated uptake of glucose. There is an increased utilization of free fatty acids, which can result in cardiac dysfunction. Ketoacids, the production of which is increased in diabetes is taken by the cardiac myocytes, which in turn reduces coenzyme A and citric acid cycle and produces myocardial dysfunction. Abnormalities in calcium homeostasis results in activation of the PKC signaling pathways and result in cardiac dysfunction. Insulin resistance may also mediate cardiac dysfunction.
2) Myocardial fibrosis: Diabetic hearts have demonstrated myocyte hypertrophy, perivascular fibrosis and increased quantities of matrix collagen. It is attributed to the accumulation of advance glycation end products (AGE).
3) Small vessel disease: Endothelial dysfunction, oxidative stress and impaired coronary reserve contribute to a small vessel disease.
4) Cardiac autonomic neuropathy



Factors contributing to diastolic dysfunction

When observed carefully, there is a considerable overlap between the mechanisms proposed for microvascular complications and diastolic dysfunction. It is also postulated that the severity of diastolic dysfunction parallels the severity of microvascular complications.

Heart disease in diabetes is primarily due to macrovascular disease, but growing evidence from different observations suggesting the possibility of a microvascular diabetic heart is gaining more importance. With diabetic therapies being targeted at molecular and cellular levels, cardiac dysfunction in diabetics can be curtailed if not prevented.

MATERIALS AND METHODS:

STUDY DESIGN

Cross sectional study

SAMPLE

Diabetic patients from Institute of Internal Medicine and Institute of Diabetology, Rajiv Gandhi Government General Hospital were enrolled in the study. Around 60 patients were enrolled for the study after informed consent from all patients. Institutional ethical clearance was obtained. Patients were selected based upon the following inclusion and exclusion criteria.

INCLUSION CRITERIA:

- Known case of type 2 diabetes mellitus patients
- Newly diagnosed type 2 diabetes mellitus patients
- Age group >30 years.

Patients who were already on drugs for diabetes either in the form of insulin or OHAs were included. Newly diagnosed patients (patients who had symptoms of diabetes along with a random blood sugar >200mg/dl or fasting plasma glucose >126 mg/dl) were also included in the study. Age group of more than 30 years was used to avoid overlap of type 1 and other forms of diabetes mellitus.

EXCLUSION CRITERIA:

- Pregnant women
- Hypertensive patients
- Known coronary artery disease patients
- Known valvular heart disease, arrhythmias
- Other co morbidities(COPD, pre-existing renal disease, thyroid disorders)

METHODOLOGY

After informed consent from the enrolled patients, a questionnaire was prepared to obtain details of the patient's address, sex, age, occupation and symptoms if any. History of diabetes, its duration, drug history and potential complications were given special importance. The patient's vital parameters were recorded. Patient's height and weight were measured to estimate the body mass index (BMI). The body mass index was calculated using the formula.

Body mass index (BMI) = Weight of the patient (in kg)/ $(\text{height})^2$ (in m^2)

Routine examination of the patient was done. Ophthalmoscopic evaluation was done using the direct ophthalmoscope. Diabetic retinopathy if present was identified and classified non proliferative retinopathy (NPDR) and proliferative retinopathy (PDR).

Patients were subject to laboratory investigations like complete blood counts, renal function tests, fasting and postprandial blood sugar levels and fasting lipid profile.

Diabetic nephropathy was assessed in the patient by measuring the renal parameters (blood urea and serum creatinine). Urine routine and cultures were done to exclude a urinary tract infection. Proteinuria was assessed in all patients. Ultrasonogram of kidneys was done when required.

MEASUREMENT OF MICROALBUMINURIA:[45]

Microalbuminuria is estimated by a 24 hour urine collection or a spot urine sample. While collecting the sample, following precautions are taken: the patient should be at rest; patient should be free of ketosis; and glycemic status should be fairly under control.

When 24 hour urine samples are used for estimation, excretion of 30- 299 mg/day is considered as microalbuminuria.

Alternatively, estimation of urine albumin excretion rate(AER) or spot urine estimation of albumin to creatinine ratio(ACR) is used. The spot sample is preferred as it is the convenient method in clinical practice. Urine albumin excretion rate (AER) of 20- 200 micro g/min signifies microalbuminuria. Normal values are less than 20 micro g/min. Urine albumin to creatinine ratio (ACR) of less than 30 micro g/mg of creatinine is normal.

30 – 299 micro g/ mg signifies microalbuminuria. Values more than 300 indicate overt nephropathy or macroalbuminuria.

The various methods by which microalbuminuria can be estimated are:

1. Microalbumin urine test strips: Employs immunochemical strips which are specific for albumin.
2. Radio immunoassay: This technique is highly sensitive and has good accuracy but carries the disadvantage of radioactivity.
3. Radio immunodiffusion: This method requires long incubation period and hence is not widely accepted.
4. ELISA: Competitive and sandwich ELISA techniques are employed for quantification of albumin.
5. Immunoturbidometry: Quantifies the amount of albumin based on spectrophotometric analysis and is suitable for analyzing large number of samples at a faster rate.

Causes for false positive tests:

Transient increases in urine albumin excretion may occur in a setting of

1. Short term hyperglycemia
2. Fever
3. Urinary tract infections
4. Marked hypertension
5. Cardiac failure

6. Contamination with seminal or menstrual fluid
7. Following exercise

In our patients, microalbuminuria was estimated in a spot urine sample using photometric techniques by the method of fully automated immunoturbidometry. The above mentioned causes were excluded in the patient before estimating urine albumin excretion. Urine creatinine was also estimated and urine albumin to creatinine ratio was calculated to reduce errors due to intraindividual variability in albumin excretion

The following reference values were used:

Urine creatinine **:** In males: 39-259 mg/dl

In females: 28-217 mg/dl

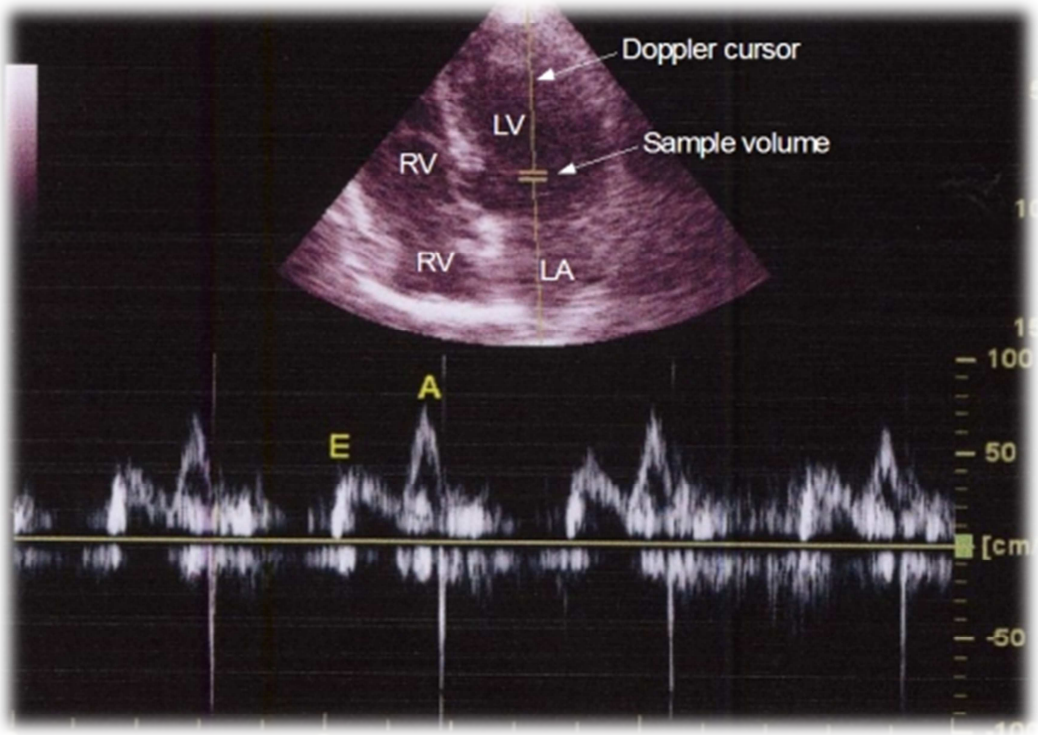
Normal ACR **:** < 30 microgram /mg of creatinine.

ASSESSMENT OF DIASTOLIC DYSFUNCTION:

All the patients enrolled in the study were subjected to Echocardiography. Transthoracic echocardiography was done after clinical evaluation.

2D echocardiography was done to assess the ventricular dimensions, presence of regional wall motion abnormalities and left ventricular ejection fraction. The parasternal long axis and short axis views were used. The ejection fraction was obtained using Simpson's approach.

Doppler echocardiography was done and using the apical four chamber view. The transmitral velocities were obtained by positioning the sample volume at the level of the tips of mitral leaflets. The early mitral inflow velocity (E) and late inflow velocity (A) was obtained and E/A ratio was calculated.



Doppler ECHO: Measurement of E velocity and A velocity

E/A ratio of less than 1 was considered grade 1 diastolic dysfunction. When E/A ratio was more than 1, additional parameters like the velocity propagation, E wave deceleration time were considered to differentiate Grade II diastolic dysfunction from a normal pattern. The velocity

propagation of the early mitral inflow was assessed using a colour M mode echocardiography.

Data obtained by above methods was analysed statistically using

1. SPSS 15
2. Chi square test

OBSERVATIONS AND RESULTS

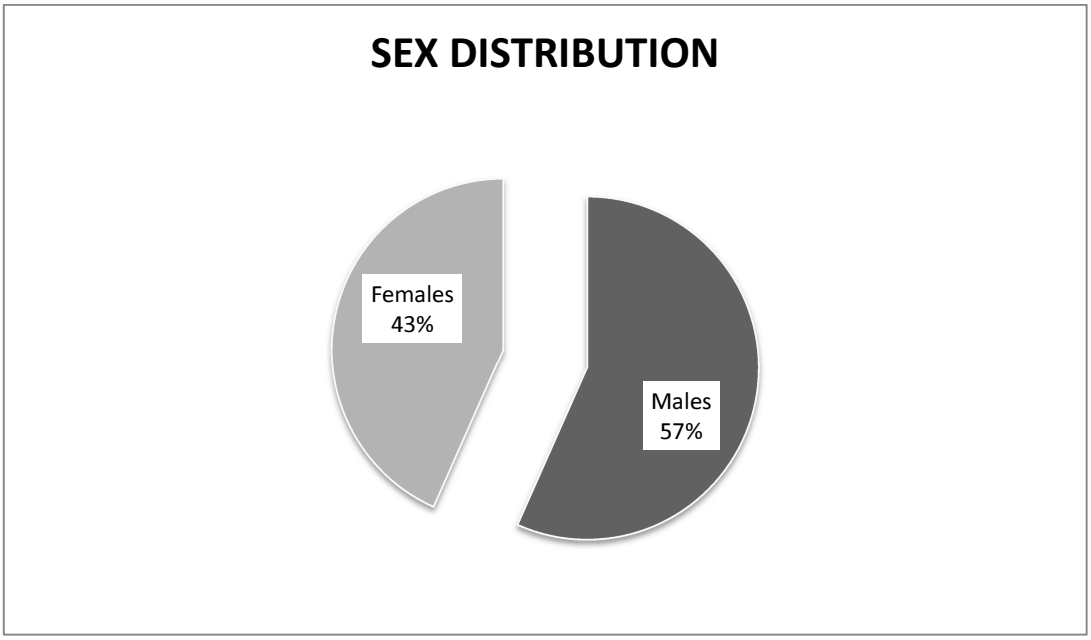
PATIENT CHARACTERISTICS:

Sex Distribution:

Among the 60 patients enrolled in the study, 34 were male patients and 26 were female patients.

Table 1: Sex distribution

Sex	No. of patients (n=60)	Percentage
Males	**34**	**56.67%**
Females	**26**	**43.33%**

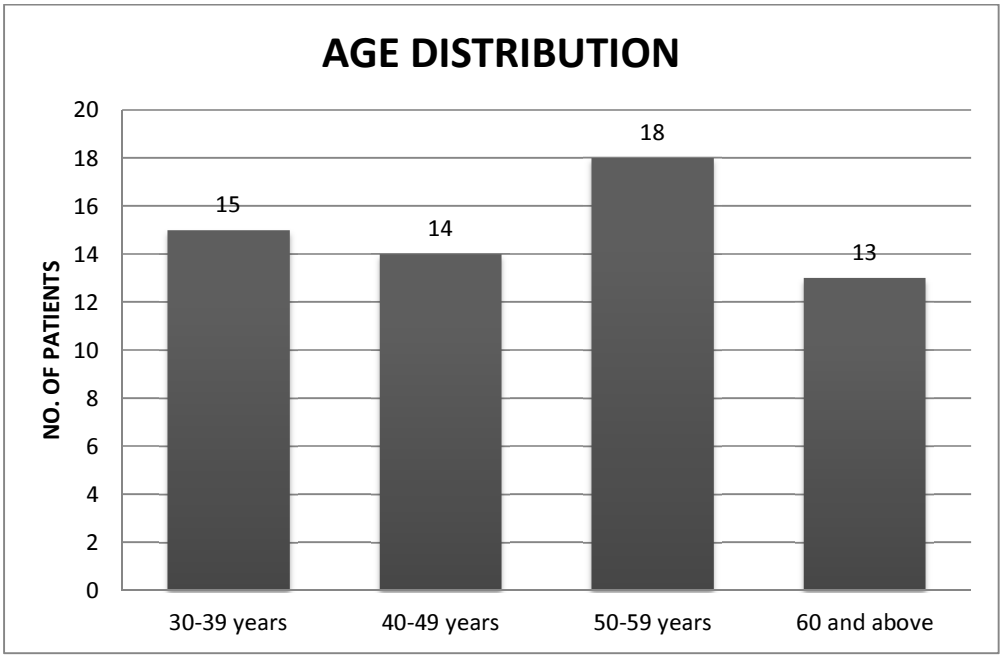


Age distribution

Only patients above the age of 30 years were included in the study. Patients were evenly distributed with respect to age characteristics. Maximum number of patients was in the age group 50 -59 years (18 patients). 13 patients were above the age of 60 years. The mean age in our study was 49.3±10.4.

Table 2: Age distribution

Age distribution	No. of patients(n=60)
30-39 years	**15**
40-49 years	**14**
50-59 years	**18**
60 and above	**13**



Duration of diabetes

With respect to duration of diabetes, patients were evenly distributed. Maximum number of patients was in the subcategory of 0-4 years duration (23 patients out of 60). Mean duration of diabetes in our study was 6.07 years ±4.9.

Table 3: Duration of diabetes

Duration of diabetes	No. of patients (n=60)
0-4 years	23
5-9 years	20
10 years and above	17

Treatment modality of diabetes

Among the 60 patients, 34 were on oral hypoglycemic agents, 11were receiving insulin and 6 of them received both forms of therapy. 9 patients were newly diagnosed and yet to be started on treatment.

Table 4: Treatment of diabetes

Treatment modality	No of patients (n=60)
Oral hypoglycemic agents(OHA)	34
Insulin	11
OHA and insulin	6

Distribution of BMI (body mass index)

Patients were stratified on the basis of their BMI. Most patients (35 patients out of 60) had a BMI value between 25 and 29.9. 10 patients were obese (BMI > 30 kg/m^2). None of the patients in our study had morbid obesity. The mean BMI value in our study was 26.58±2.78.

Table 5: Body mass index

BMI Values(in kg/m^2)	No. of patients (n=60)
< 24.9	**15**
25- 29.9	**35**
>30	**10**

Triglyceride levels

54 out of 60 patients had triglyceride levels more than 150 mg/dl, out of which 13 of them had values above 250mg/dl. The mean triglyceride level value in our study was 210.43±60.09.

Table 6: Triglyceride level distribution

Triglyceride level (mg/dl)	No. of patients (n=60)
<150	**6**
150- 200	**27**
200-249	**14**
>250	**13**

Retinopathy in diabetes

Among the 60 patients, 31 patients (51.67%) had retinopathy of which 26 of them had non proliferative retinopathy and 5 patients had proliferative retinopathy.

Table 7: Retinopathy in diabetes

Type of retinopathy	No. of patients (n = 31)
Non proliferative diabetic retinopathy	26
Proliferative retinopathy	5

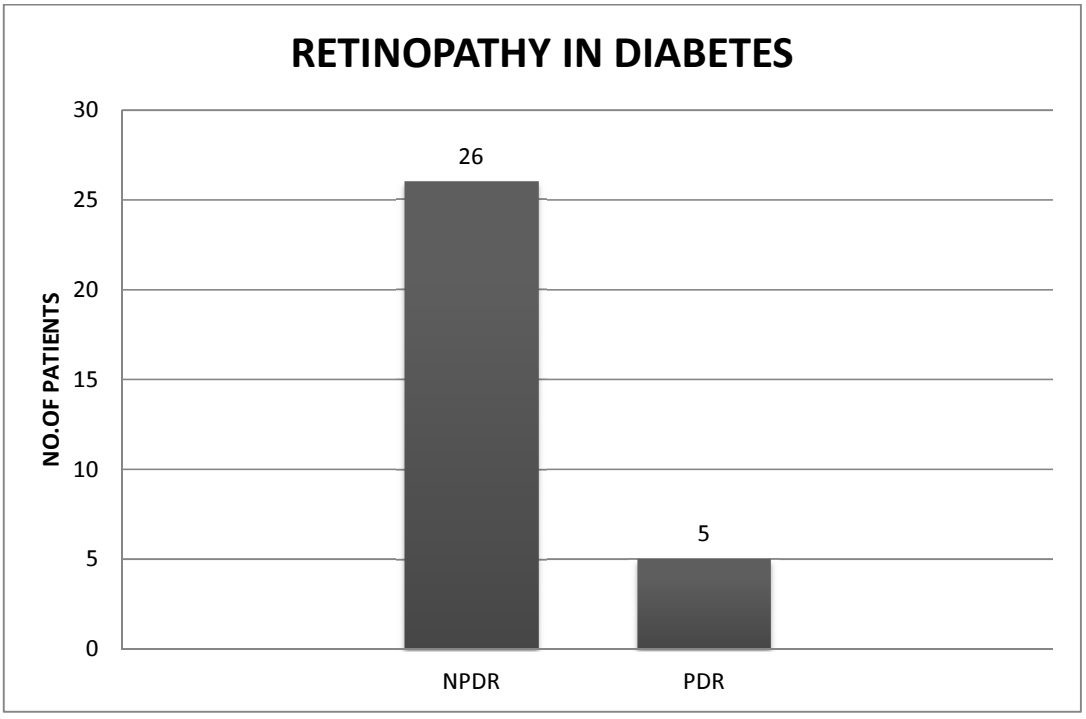
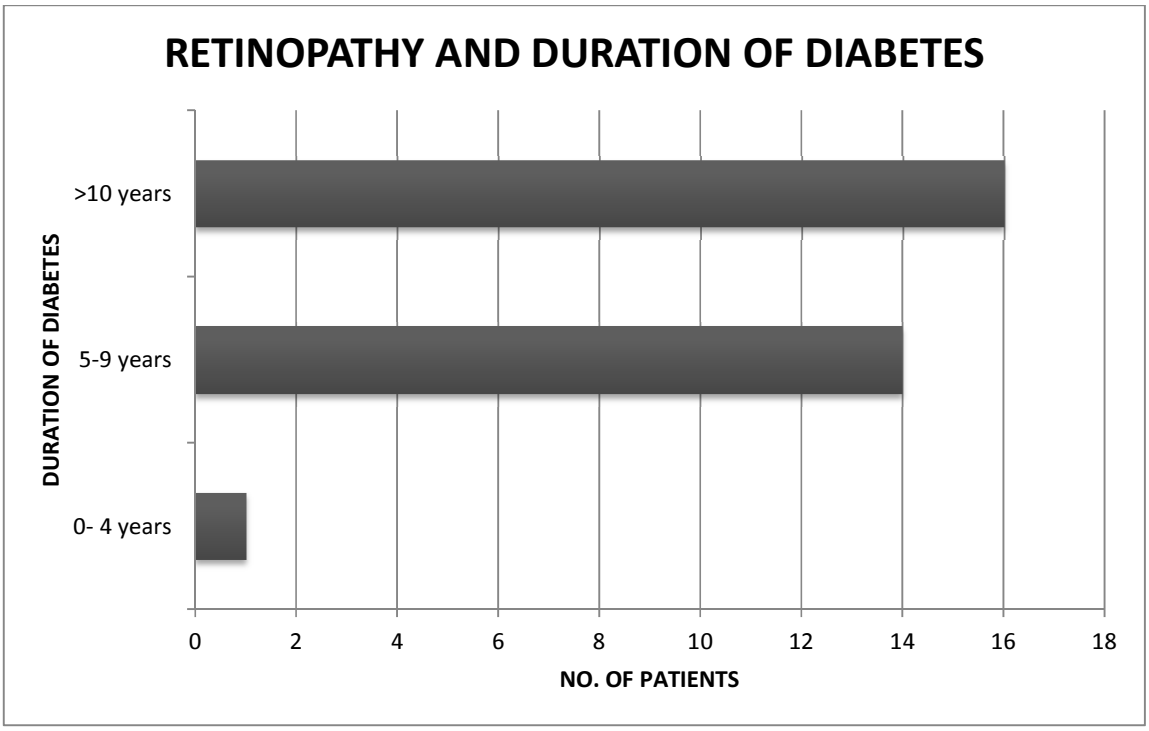


Table 8: Retinopathy distribution with respect to duration

Duration of diabetes	No. of patients with retinopathy (n=31)	
	NPDR	PDR
0-4 years	1	0
5-9 years	13	1
10 years and above	12	4

Out of the 31 patients with retinopathy, 16 patients had diabetes for 10 years or more. The prevalence was very low when the duration of diabetes was less than 5 years.

Out of 5 patients with proliferative retinopathy, 4 of them had diabetes for 10 years or longer.



Nephropathy in diabetes

40 patients out of 60 had evidence of nephropathy in the form of proteinuria. Microalbuminuria was present in 34 patients and overt nephropathy (macroalbuminuria) was present in 6 patients.

Table 9: Nephropathy in diabetes

Nephropathy	No. of patients (n=40)
Microalbuminuria	**34**
Macroalbuminuria	**6**

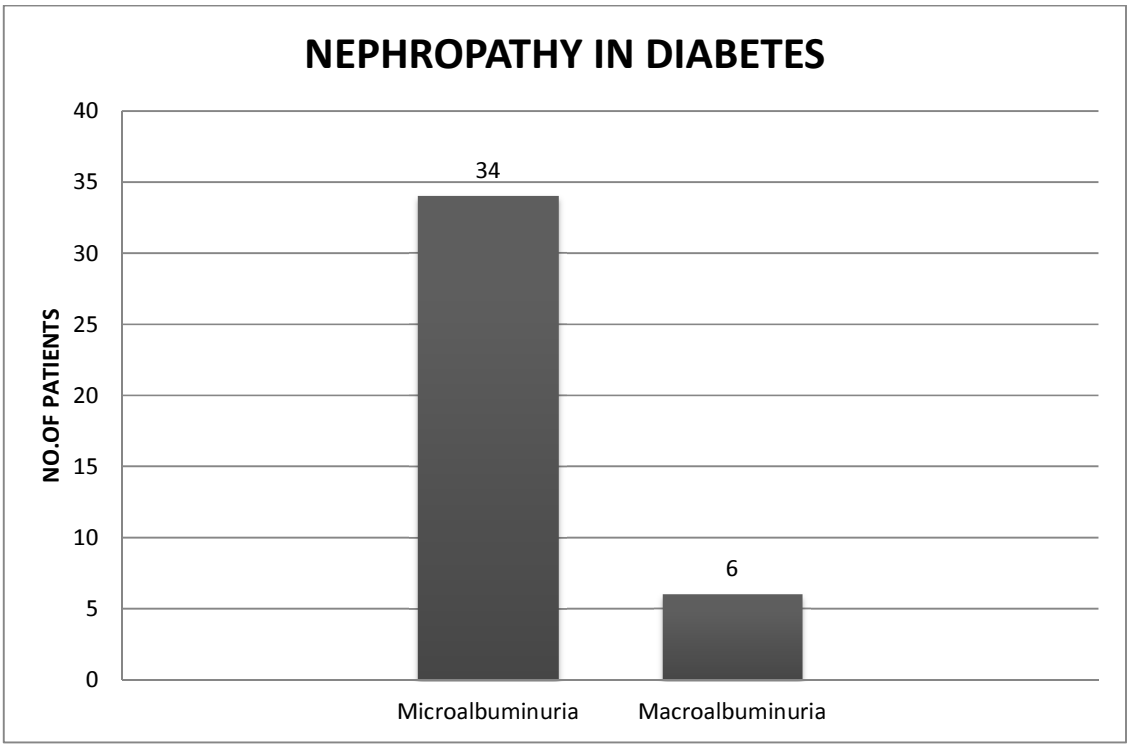
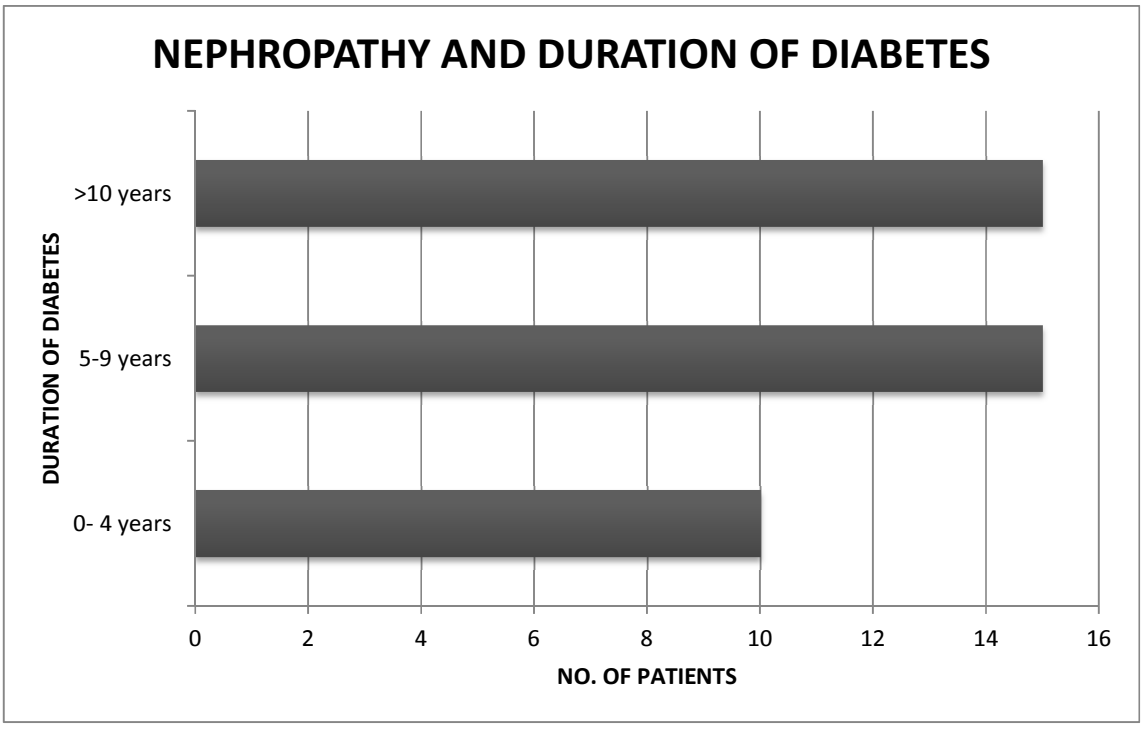


Table 10: Diabetes duration and nephropathy

Duration of diabetes	No. of patients with nephropathy (n=40)	
	Microalbuminuria	Macroalbuminuria
0-4 years	10	0
5-9 years	13	2
10 years and above	11	4

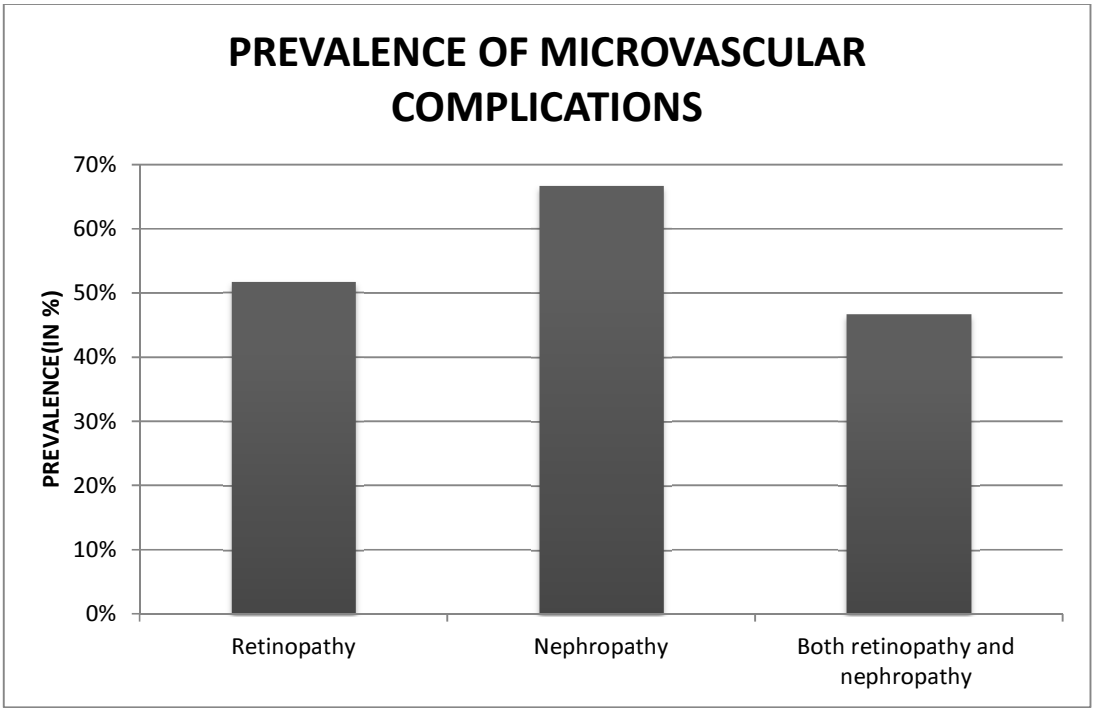
The prevalence of nephropathy was considerably higher when the duration of diabetes was more than 5 years. Nearly 62.5% of patients with proteinuria had diabetes for more than 5 years.



Microvascular complications

The overall prevalence of retinopathy in our study was 51.6% and that of nephropathy was 66.67%.

Microalbuminuria was present in 56.6% of cases.



Prevalence of diastolic dysfunction

Among the 60 patients of type 2 diabetes, 34 of them had evidence for diastolic dysfunction. 32 of these patients had Grade I diastolic dysfunction and 2 of them had Grade II diastolic dysfunction. Grade III and Grade IV dysfunction were not observed in our study.

The mean E/A ratio in our study was 1.047±0.356. In patients with diastolic dysfunction the E/A ratio was much lower (0.7701±0.09) than patients with normal function (1.326±0.24) ($p<0.001$**).

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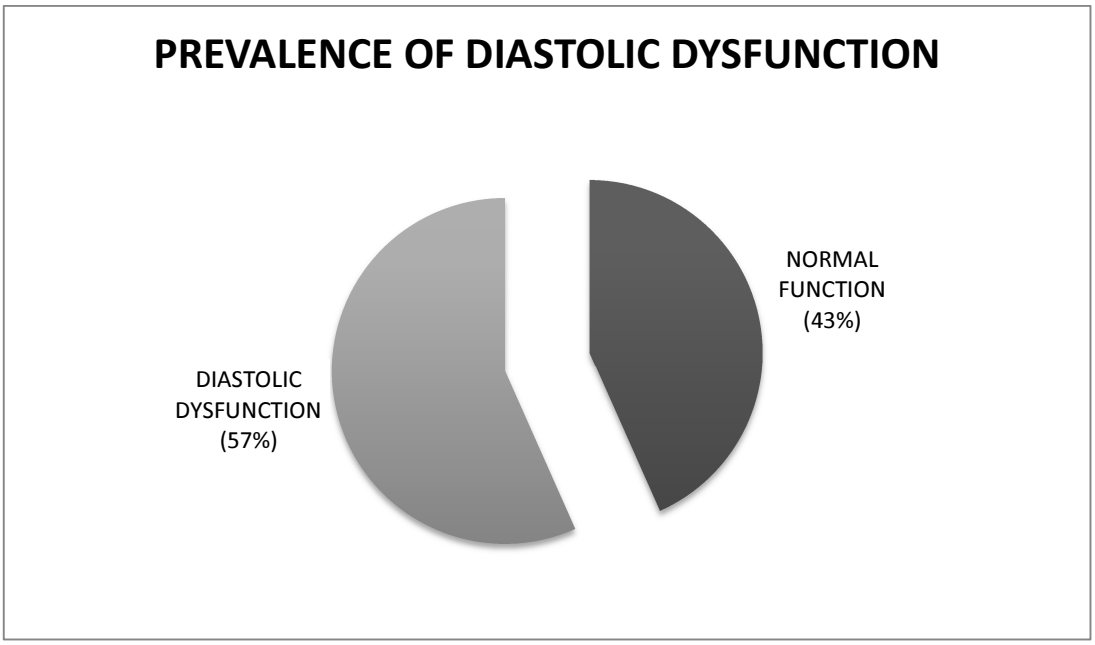


The above mentioned patients had isolated diastolic dysfunction. Patients having associated systolic dysfunction were excluded from the study population. None of these patients had clinical evidence for heart failure.

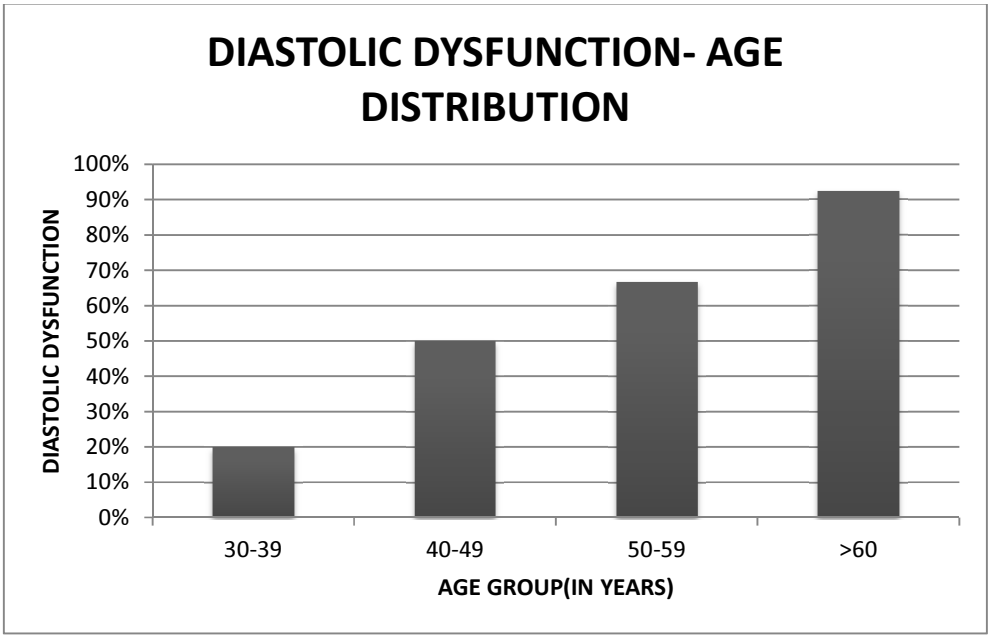
Age distribution

The prevalence of diastolic dysfunction increases with age. The highest percentage of patients having isolated diastolic dysfunction was in the 60 and above age group. (12 out 13 patients)

Table 11: Diastolic dysfunction and age distribution

Age group (n=60)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
30-39 years (n= 15)	3	0	20%
40-49 years(n= 14)	7	0	50%
50 -59 years(n= 18)	11	1	66.7%
60 years and above(n= 13)	11	1	92.3%

By Pearson Chi square test, for the above values **p value = 0.010**,** significant at 1% level.



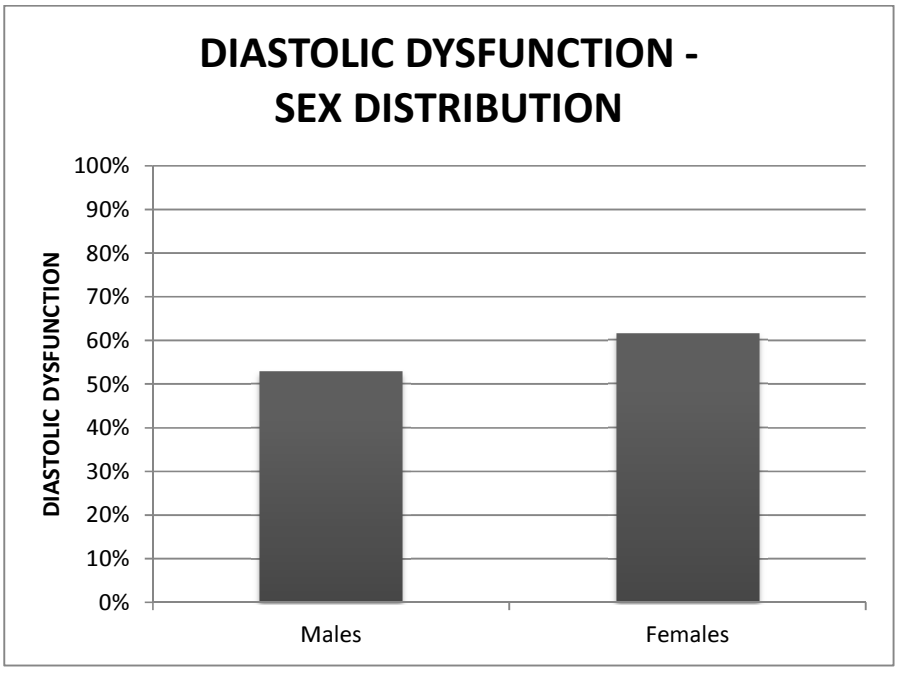
Diastolic dysfunction and sex

Out of 34 male patients, 18(52.9%) had diastolic dysfunction and among 26 females, 16 (62.5%) had diastolic dysfunction.

Table 11: Diastolic dysfunction and sex

Sex (n=60)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
Male (n=34)	16	2	52.9%
Female (n= 26)	16	0	62.5%

By Pearson Chi square test P value =**0.307**, statistically not significant



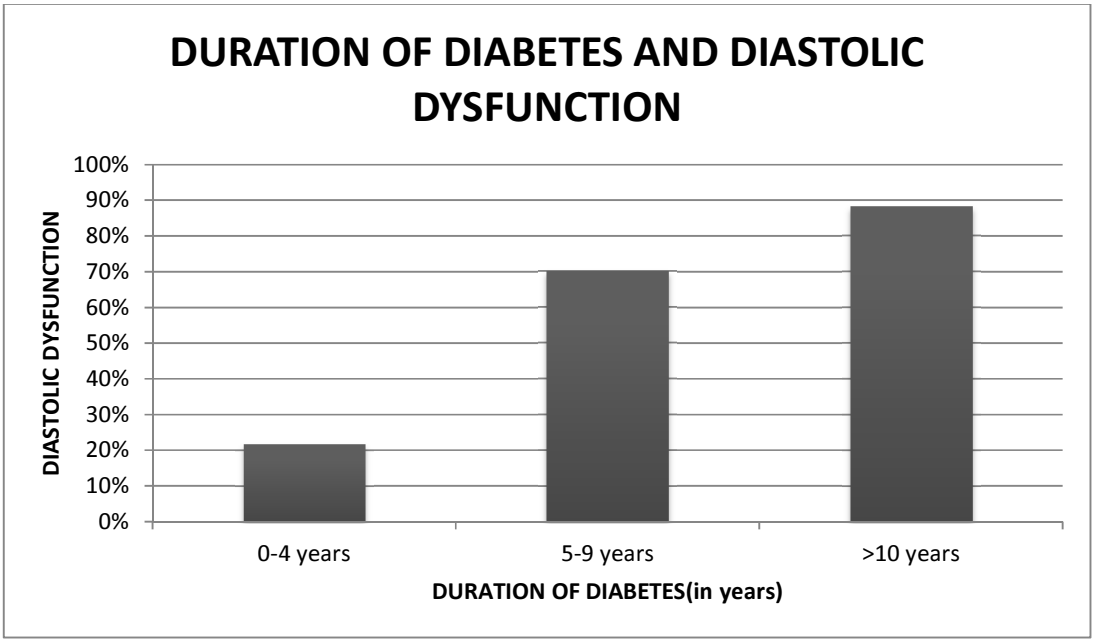
Diastolic dysfunction and duration of diabetes

In our study, the prevalence was 88.3%, when the duration of diabetes was more than 10 years. The prevalence of diabetes increased steadily with increasing duration. Our study did not compare the diastolic dysfunction with respect to severity of diabetes.

Table 12: Diastolic dysfunction and duration of diabetes

Duration of diabetes(n=60)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
0 – 4 years (n= 23)	5	0	21.7%
5- 9 years(n= 20)	13	1	70.0%
10 years and above(n=17)	14	1	88.3%

By Chi square test, **p value = 0.001**,** significant at 1 % level.



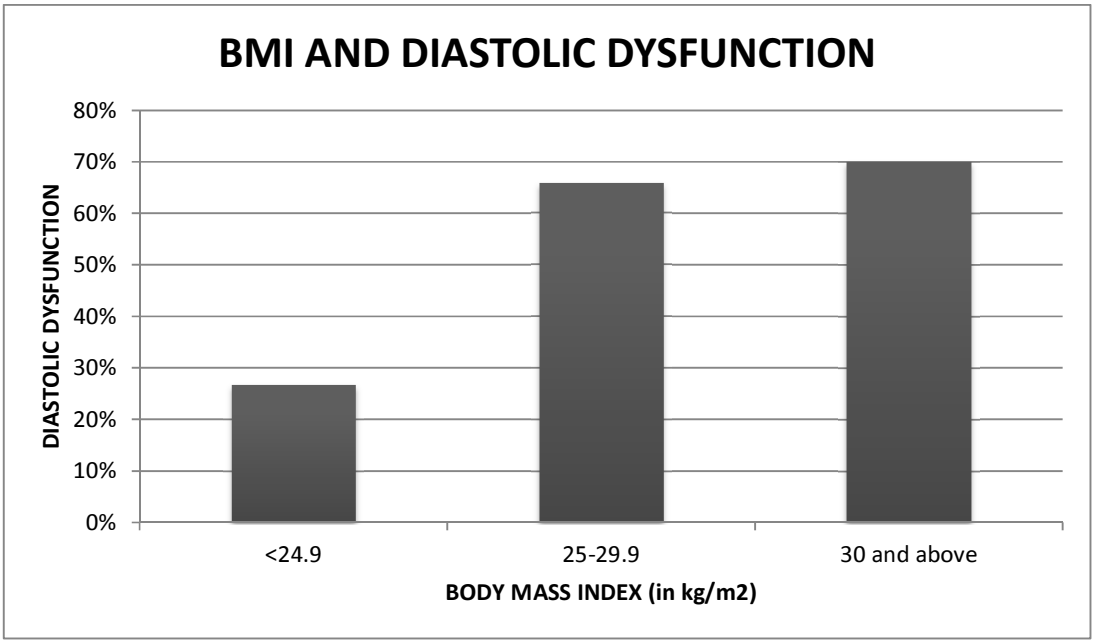
Diastolic dysfunction and obesity

In our study, positive correlation for obesity is as high as 70%, when the BMI value is more than 30, suggesting a very strong association between obesity and diastolic dysfunction.

Table 13: Diastolic dysfunction and obesity

Body mass index(n=60)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
< 25(n= 15)	4	0	26.7%
25- 29.9(n= 35)	23	0	65.7%
30 and above(n=10)	5	2	70%

By Pearson Chi square test, **p value = 0.002****, significant at 1% level.



Diastolic dysfunction and triglyceride levels:

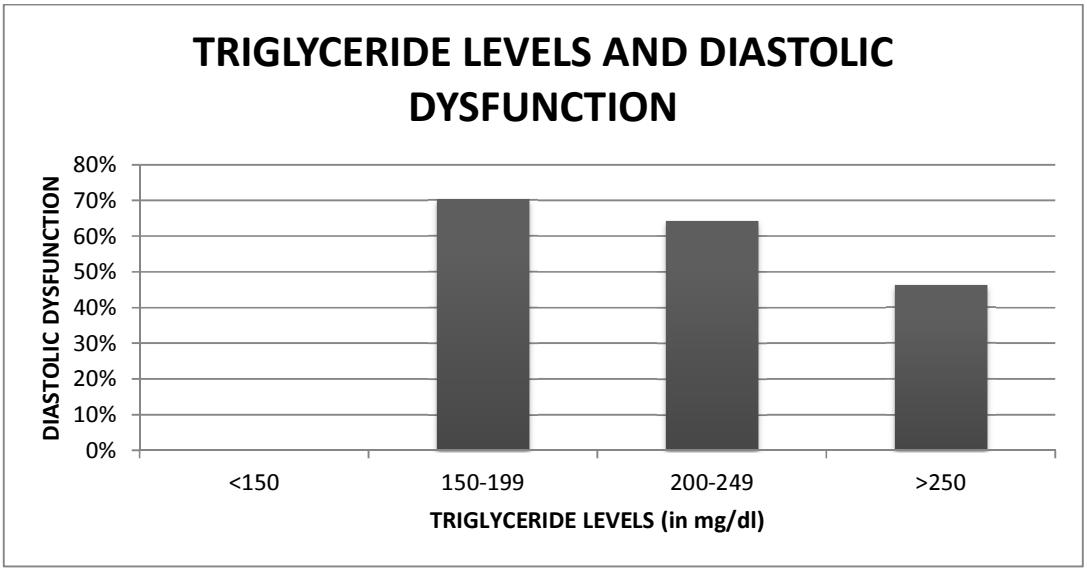
Since the most common abnormality in lipid profile in a diabetic patient is triglyceride increase, we tried to find out the correlation between triglyceride level and diastolic dysfunction.

Table 14: Diastolic dysfunction and triglyceride levels

Triglyceride levels(n=60)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
< 150 mg/dl (n= 6)	0	0	0%
150- 199 mg/dl(n= 27)	19	0	70.4%
200-249 mg/dl(n= 14)	8	1	64.2%
>250 mg dl(n= 13)	5	1	46.2%

By Pearson chi square test, **p= 0.032*,** significant at 5% level.

In our study, highest percentage of diastolic dysfunction was observed in the 150 -199 mg/ dl age group around 70%. Patients with triglyceride levels less than 150 mg/dl showed no diastolic abnormalities.



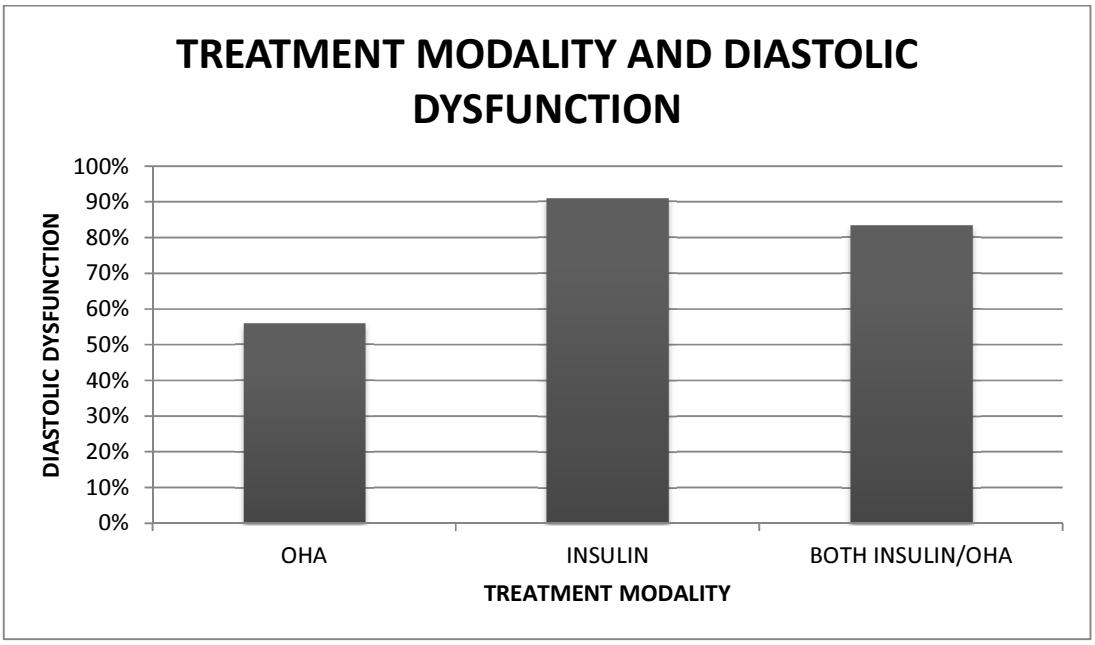
Diastolic dysfunction and treatment modality

As per our study, patients receiving insulin alone or in combination with a oral hypoglycemic agents had a higher prevalence of diastolic dysfunction.

Table 15: Diastolic dysfunction and treatment modality

Treatment modality(n=51)	No. of patients with diastolic dysfunction (n=34)		% of patients of diastolic dysfunction
	Grade I	Grade II	
OHAs (n= 34)	17	2	55.9%
Insulin (n= 11)	10	0	90.9%
OHAs/Insulin(n= 6)	5	0	83.3%

By Pearson chi square test, **p= 0.121**, statistically not significant.



Diastolic dysfunction and retinopathy

Out of 31 patients with retinopathy, 26(83.8%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for proliferative retinopathy. All 5 patients with proliferative retinopathy had diastolic dysfunction.

Table 16: Diastolic dysfunction and retinopathy

Retinopathy	No. of patients with diastolic dysfunction (n=26)		% of patients of diastolic dysfunction
	Grade I	Grade II	
Non proliferative retinopathy(n= 26)	19	2	80.8%
Proliferative retinopathy(n = 5)	5	0	100%
Total (n=31)	24	2	83.8%

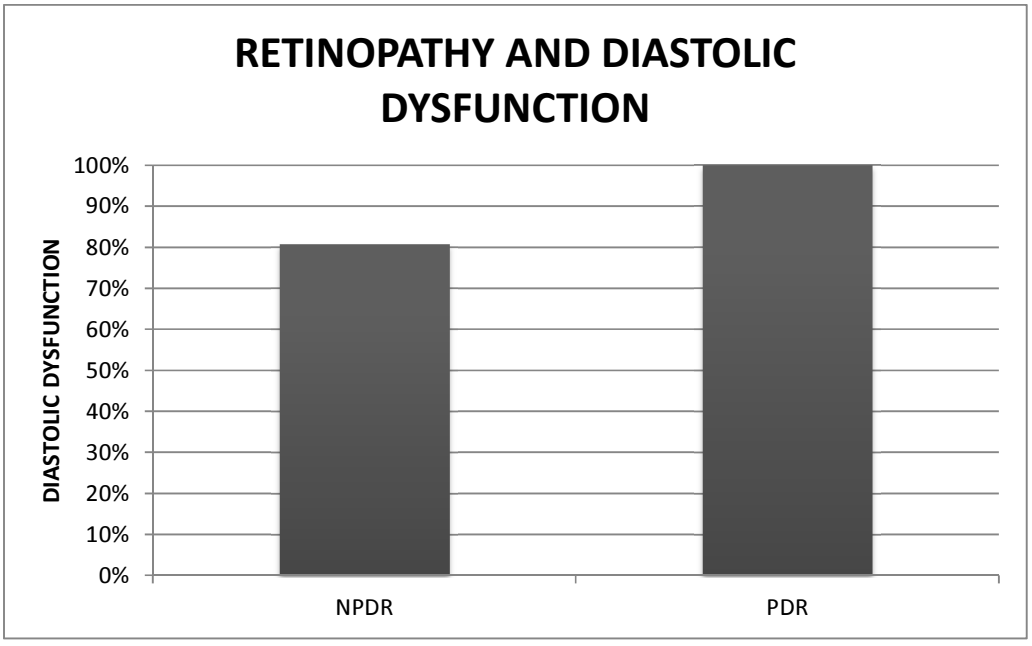
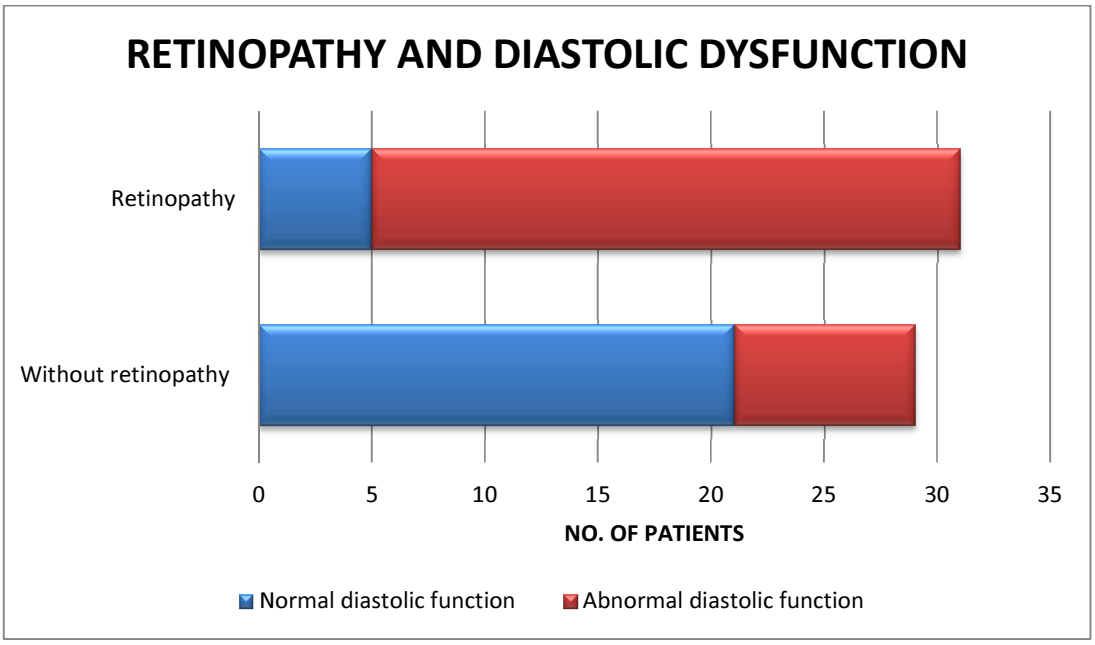


Table 17: Retinopathy and Diastolic Dysfunction

Retinopathy	No. of patients(n=60)		Total no. of patients
	Normal diastolic function	Diastolic dysfunction	
No retinopathy	21	8	29
Retinopathy	5	26	31

Chi square test values for the above data: p value<0.001**



Diastolic dysfunction and nephropathy

Among 40 patients with nephropathy, 32 of them had diastolic dysfunction accounting for 80%. The association with macroalbuminuria was significantly higher with all 6 patients developing diastolic dysfunction.

Table 18 : Diastolic dysfunction and nephropathy

Nephropathy	No. of patients with diastolic dysfunction (n=26)		% of patients of diastolic dysfunction
	Grade I	Grade II	
Microalbuminuria (n= 34)	25	1	76.5%
Macroalbumuria (n = 6)	5	1	100%
Total (n=40)	30	2	80.0%

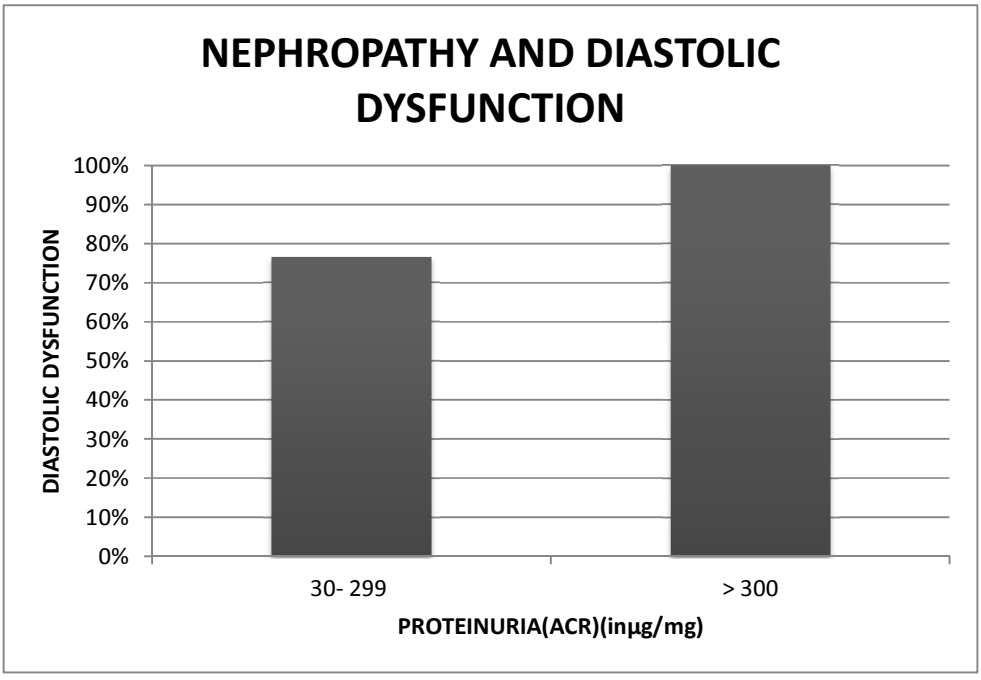
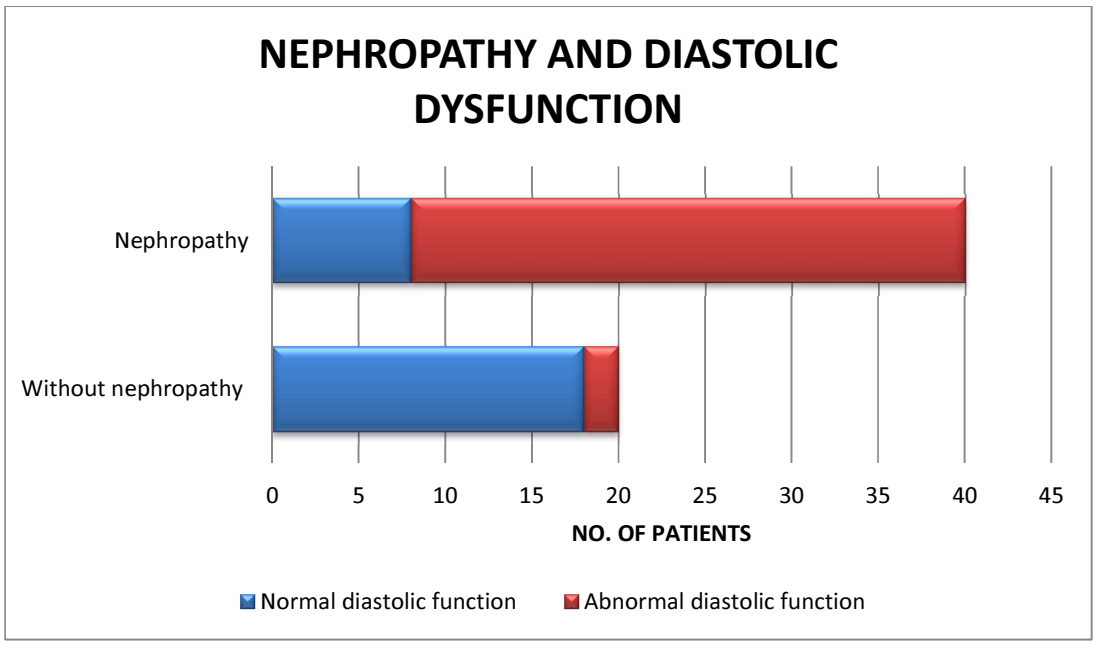


Table 19: Diastolic dysfunction and nephropathy

Nephropathy	No. of patients (n=60)		Total no. of patients
	Normal diastolic function	Diastolic dysfunction	
No nephropathy	18	2	20
Nephropathy	8	32	40

By Chi square test value: p <0.001**



DISCUSSION

Diastolic dysfunction in diabetes:

As per our study, 57 % of type 2 diabetes had diastolic dysfunction. Khalil S I et al. (2007)[56] estimated that about 58% of diabetic patients had diastolic dysfunction of which majority of them were Grade I diastolic dysfunction.

Cosson et al (2003)[44] demonstrated 69% of diabetics have abnormalities in diastolic filling.

However, the prevalence may vary among different population and study groups because of the different parameters employed in Doppler echocardiography is assessing the diastolic function. Although E/A ratio is the commonly employed parameter, higher grades of diastolic dysfunction tend to be missed out if additional parameters or specific maneuvres are employed. Cosson et al (2003) [44] reported around 20% increase in the prevalence if additional parameters are employed. In our study we have employed propagation velocity and E wave decelaration time in identifying the pseudonormal pattern (Grade II dysfunction).

Freire et al. (2007)[52] estimated the prevalence of asymptomatic isolate diastolic dysfunction in the general population to be 27%.

Diastolic dysfunction and age:

As per our study, increasing age is a risk factor in diabetes for diastolic dysfunction. With almost 70% patients with diastolic dysfunction above the age of 50 years, it is quite clear that age is directly proportional to the prevalence of diastolic dysfunction.

Srivastava et al.(2006) [57] confirmed that increasing age is an independent predictor for both cardiac dysfunction and diastolic dysfunction in type 2 diabetic patients. The mean age of patients in the study was 60 ± 1.

Khalil S I et al (2007) [56] also demonstrated that age is an important risk factor for diastolic dysfunction in type 2 diabetes. In the study, prevalence of diastolic dysfunction in the age group 41-50 years was around 80% compared to 12.5% in the 21- 30 year age group. The mean age of the study group was 40.79± 7.65 years.

Diastolic dysfunction and sex:

Although our study demonstrates a higher prevalence among females, it was statistically not significant and underlying causes or mechanisms are not available to substantiate the discrepancy.

R. Wachter et al (2007)[55] shows that the presence of diabetes mellitus has an influence on diastolic function in males but there was no difference in females between the diabetic and non- diabetic population. Non diabetic males showed a lower prevalence (58.9%) of impaired relaxation compared

to those with diabetes (69.7%). The presence of coexisting coronary artery disease did not change the outcome.

Diastolic dysfunction and duration of diabetes:

High statistical significance (p = 0.001**) was observed for the association between duration of diabetes and diastolic dysfunction

Data from Khalil S I et al (2007) [56] show that the prevalence of diastolic dysfunction increases with duration of diabetes. The study demonstrates a 100% prevalence of diastolic dysfunction when the duration of diabetes was more than 10 years. In our study, the prevalence was 88.3% in the same age group. In a study by Raev et al.[59], diastolic dysfunction started at 8 years after the onset of diabetes.

R. Wachter et al (2007)[55] failed to demonstrate a positive correlation between duration of diabetes and diastolic dysfunction, but showed a significant difference when analysed with respect to severity of diabetes. According to the study, patients with HbA1C >8 % had a higher prevalence of diastolic dysfunction (92.9%). Freire et al (2007)[52] also confirmed the presence of diastolic dysfunction in patients with HbA1C more than 8%. For every 1% increase in HbA1C, there is 8% increase in the risk of developing heart failure.

Diastolic dysfunction and obesity:

Obesity as defined by BMI > 30 kg/m^2 was present in 16.6% of patients. Srivastava et al (2006) [57] showed data that a little over 50 % of the study population was obese. Obesity in the above study was defined by value of BMI > 30 kg/m^2. Patients with a BMI > 30 kg/m^2 had a significant increase in cardiac dysfunction and diastolic dysfunction as per the study. Although, the prevalence of obesity was comparatively lower in our study, the risk of diastolic dysfunction in obese individuals had comparable results.

Diastolic dysfunction and treatment modality:

Though our study demonstrated a higher prevalence of diastolic dysfunction in patients receiving insulin, it was statistically not significant.

However, hyperinsulinemia is a potential pathogenic mechanism implicated in diabetic cardiomyopathy. But it remains unclear whether exogenous insulin have the same effect as that of endogenous insulins. There are also other confounding factors like hyperglycemia, which would have necessitated the use of insulin.

Hence these results should be interpreted with caution and it does not preclude the use of insulin. Further studies on a larger scale are required for its confirmation.

Diastolic dysfunction and lipid profile:

Diastolic dysfunction was highest in the 150-199 mg/ dl group. But isolated measurement of triglyceride alone is not recommended. A complete lipid profile is needed to contemplate further results.

Khalil S I et al (2007)[56] showed no association between lipid profile and diastolic dysfunction.

Diastolic dysfunction and retinopathy:

It is known that 60% of patients with type 2 diabetics develop retinopathy at the end of 20 years. In our study, nearly 50% of patients showed evidence for retinopathy, the mean duration of diabetes in our study being 6.07 years.

The association between retinopathy and diastolic dysfunction had strong correlation in our study ($p<0.001$**). Patients with proliferative retinopathy had a stronger association.

Takenaka et al (1988)[58] demonstrated an association between retinopathy and type 2 diabetic patients free from coronary artery disease and hypertension. Annonu et al (2001)[60] demonstrated that E/A ratio < 1 in 49 % of patients with retinopathy.

Diastolic dysfunction and nephropathy:

The prevalence of microalbuminuria in our study was 56.6%, compared to other Indian data, which report a prevalence of around 30%. A considerable number of patients with diabetic duration < 5 years had microalbuminuria (10 patients). End stage renal disease was not observed in our study because hypertensive patients were excluded from the study and most ESRD patients would have associated hypertension. Though all possible causes of false elevation of microalbuminuria were excluded, it requires confirmation with serial measurements.

However, the association between nephropathy and diastolic dysfunction is strong in our study ($p<0.001$**).

Although various studies done in type 1diabetes suggest an association between albuminuria and diastolic dysfunction, study done in type 2 diabetes by Annonu et al (2001)[60] failed to demonstrate a significant association.

The association of diastolic dysfunction with microvascular complications strongly suggests the possibility of a background microangiopathy. Since microalbuminuria is also marker of endothelial dysfunction, diastolic dysfunction indicates a widespread endothelial dysfunction. Zoneraich et al demonstrated small vessel disease in 72% of diabetic patients[61]. Microvascular changes include formation of microaneurysms and capillary membrane thickening.[62]

Deposition of advanced-glycated end products (AGEs), which include collagen, elastin and other connective tissue proteins in the interstitial spaces, as well as fibrosis in the myocardium have been reported in biopsy specimens of human diabetic hearts.[65]

Thus with available data from our study and supporting data, the existence of diastolic dysfunction in diabetics, who are normotensive and free from coronary artery disease is confirmed. More importantly diastolic dysfunction exists in isolated form and is asymptomatic. The possible pathogenic mechanism for diastolic dysfunction has been proposed due its strong association with microvascular complications.

Newer modalities of diabetic treatment targeting the pathogenic mechanisms like aldose reductase inhibitors, PKC pathway inhibitors, ACE inhibitors can reverse diastolic dysfunction and improve cardiovascular mortality.

CONCLUSION

As per our study performed on 60 patients with type 2 diabetes free of coronary artery disease and hypertension,

- Diastolic dysfunction is common in individuals with type 2 diabetes. Grade I diastolic dysfunction is more commonly encountered. Grade III and Grade IV diastolic dysfunction were not encountered. Diastolic dysfunction in our study was isolated and asymptomatic.
- Increasing age in diabetic patients is a risk factor for diastolic dysfunction. The risk is substantially increased above the age of 60.
- Sex does not influence diastolic dysfunction in diabetes. Our study did not document a statistical significance.
- Duration of type 2 diabetes positively correlates with diastolic dysfunction. Longer the duration of diabetes, greater is the prevalence of diastolic dysfunction.
- Modality of treatment does not influence the outcome of diabetes with respect to diastolic dysfunction.
- Triglyceride levels though statistically significant in our study, require further confirmation. Patients with triglyceride levels < 150 mg/dl did not develop diastolic dysfunction.
- Obesity has a positive correlation with diastolic dysfunction. The association is strong when BMI values > 30 kg/m^2.

- Microvascular complications like retinopathy and nephropathy strongly correlates with diastolic dysfunction. The association is greater for proliferative retinopathy and macroalbuminuria.
- Cardiac disease in diabetes is no longer only a macrovascular disease, but microvascular changes do play a role.
- Our study recommends screening of diabetic patients for diastolic dysfunction, especially those with duration of diabetes > 5 years, obese individuals, old age and patients with microvascular complications even if they are asymptomatic.

A Doppler echocardiography is an easily available tool that can be used for screening purposes.

BIBLIOGRAPHY

1. C. Savona-Ventura; The History of Diabetes Mellitus A Maltese perspective Malta 2002.
2. Chan JC et al: Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. *JAMA* 301:2129, 2009.
3. James H. Warram, Andrzej S. Krolewski Epidemiology of Diabetes Mellitus; Joslin's diabetes mellitus 14th edition
4. Schneider BS, Faust IM, Hemmes R, et al. Effects of altered adipose tissue morphology on plasma insulin levels in the rat. *Am J Physiol* 1981;240:E358–E362
5. Abate N, Garg A, Peshock RM, et al. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 1996;45:1684–1693.
6. Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes, and hypertension. *Clin Exp Hypertens* 2001;23:45–55.
7. Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. *Circulation* 1997;96: 4104–4113.

8. Schleicher ED, Wagner E, Nerlich AG. Increased accumulation of the glycoxidation product N(epsilon)-(carboxymethyl)lysine in human tissues in diabetes and aging. *J Clin Invest* 1997;99:457–468.
9. Rojas A, Romay S, Gonzalez D, et al. Regulation of endothelial nitric oxide synthase expression by albumin-derived advanced glycosylation end products. *Circ Res* 2000;86:E50–E54.
10. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care* 1996;19:257–267.
11. Schleicher ED, Weigert C. Role of the hexosamine biosynthetic pathway in diabetic nephropathy. *Kidney Int Suppl* 2000;77: S13–S18.
12. Tesfamariam B, Brown ML, Cohen RA. Elevated glucose impairs endothelium-dependent relaxation by activating protein kinase C. *J Clin Invest* 1991; 87:1643–1648.
13. Cosentino F, Eto M, De Paolis P, et al. High glucose causes upregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: role of protein kinase C and reactive oxygen species. *Circulation* 2003;107: 1017–1023.
14. American Diabetes Association. Diabetic nephropathy. *Diabetes Care* 2003;26 [Suppl 1]:S94–S98.
15. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med* 1998;12:1448–1456.

16. Schwab SJ, Dunn, FL, Feinglos, MN. Screening for microalbuminuria. A comparison of single sample methods of collection and techniques of albumin analysis. *Diabetes Care* 1992;15:1581–1584.

17. Rand LI, Krolewski AS, Aiello LM, et al. Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 1985;313:1433–1438.

18. The Early Treatment Diabetic Retinopathy Study Research Group. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: Early Treatment Diabetic Retinopathy Study report No.3. *Int Ophthalmol Clin* 1987;27:254–264.

19. Trends in diabetes mortality. MMWR Morb Mortal Wkly Rep 1988;37:769–773.

20. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971–1993. *Diabetes Care* 1998;21: 1138–1145.

21. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 2001;37:1053–1059.

22. Gress TW, Nieto J, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000;342:905–912.

23. Gowri MS, van der Westhuyzen DR, Bridges SR, et al. Decreased protection by HDL from poorly controlled type 2 diabetic subjects

against LDL oxidation may be due to the abnormal composition of HDL. *Arterioscler Thromb Vasc Biol* 1999;19:2226–2233.

24. Tsai EC, Hirsch IB, Brunzell JD, et al. Reduced plasma peroxyl radical trapping capacity and increased susceptibility of LDL to oxidation in poorly controlled IDDM. *Diabetes* 1994;43:1010–1014

25. Reaven GM, Laws A. Insulin resistance, compensatory hyperinsulinaemia, and coronary heart disease. *Diabetologia* 1994;37:948–952.

26. Singer DE, Nathan DM, Anderson KM, et al. Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. *Diabetes* 1992;41:202–208.

27. Silva JA, Escobar A, Collins TJ, et al. Unstable angina. A comparison of angioscopic findings between diabetic and nondiabetic patients. *Circulation* 1995;92:1731–1736.

28. Waller BF, Palumbo PJ, Lie JT, et al. Status of the coronary arteries at necropsy in diabetes mellitus with onset after age 30 years. Analysis of 229 diabetic patients with and without clinical evidence of coronary heart disease and comparison to 183 control subjects. *Am J Med* 1980;69:498–506.

29. Savage MP, Krolewski AS, Kenien GG, et al. Acute myocardial infarction in diabetes mellitus and significance of congestive heart

failure as a prognostic factor. *Am J Cardiol* 1988;62(10 Pt 1): 665–669

30. Malmberg K, Ryden L. Myocardial infarction in patients with diabetes mellitus. *Eur Heart J* 1988;9:259–264.

31. Abaci A, Oguzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999;99:2239–2242.

32. Carrozza J, Kuntz RE, Fishman RF, et al. Restenosis after arterial injury caused by coronary stenting in patients with diabetes mellitus. *Ann Intern Med* 1993;118:344–349.

33. Faerman I, Faccio E, Milei J, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients. Histologic evidence of their relationship. *Diabetes* 1977;26:1147–1158.

34. Ambepityia G, Kopelman PG, Ingram D, et al. Exertional myocardial ischemia in diabetes: a quantitative analysis of anginal perceptual threshold and the influence of autonomic function. *J Am Coll Cardiol* 1990;15:72–77.

35. Hypertension in Diabetes Study (HDS): II. Increased risk of cardiovascular complications in hypertensive type 2 diabetic patients. *J Hypertens* 1993;11: 319–325.

36. Kahn JK, Sisson JC, Vinik AI. QT interval prolongation and sudden cardiac death in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 1987;64:751–754.

37. Lehto S, Pyorala K, Miettinen H, et al. Myocardial infarct size and mortality in patients with non-insulin-dependent diabetes mellitus. *J Intern Med* 1994; 236:291–297.

38. Iwasaka T, Takahashi N, Nakamura S, et al. Residual left ventricular pump function after acute myocardial infarction in NIDDM patients. *Diabetes Care* 1992;15:1522–1526.

39. Zarich SW, Arbuckle BB, Cohen LR, et al. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. *J Am Coll Cardiol* 1988;12:114–120.

40. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham Study. *Am J Cardiol* 1974;34:29–34.

41. Shapiro LM, Howat AP, Calter MM, et al. Left ventricular function in diabetes mellitus. II: Relation between clinical features and left ventricular function. *Br Heart J* 1981;45:129–132.

42. Arvan S, Singal K, Knapp R, et al. Subclinical left ventricular abnormalities in young diabetics. *Chest* 1988;93:1031–1034.

43. Ching Ye Hong, KeeSeng Chia. Markers of diabetic nephropathy. *J diabetes Complications* 1988;12:43-60.

44. Cosson S, Kevorkian JP. Left ventricular diastolic dysfunction: an early sign of diabetic cardiomyopathy? *Diabetes Metab* 2003,29, 455-66

45. Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms: ETDRS report no. 11. *Ophthalmology* 1991;98 [Suppl 5]:807–822, with permission.

46. Thomas PK, Tomlinson DR. Diabetic and hypoglycemic neuropathy. In: Dyck PJ, Thomas EH, Lambert RB, eds. Peripheral neuropathy Philadelphia: WB Saunders, 1993:1219–1250

47. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. *Circulation* 1996;93:1809–1817

48. Toyry JP, Niskanen LK, Mantysaari MJ, et al. Occurrence, predictors, and clinical significance of autonomic neuropathy in NIDDM. Ten-year follow-up from the diagnosis. *Diabetes* 1996;45:308–315

49. Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972, 30, 595-602.

50. Regan TJ, Weisse AB. Diabetic cardiomyopathy. *J Am Coll Cardiol* 1992, 19, 1165-6.

51. Michel D Astous. Diastolic heart failure. Perspectives in Cardiology, 2002,30-37

52. Freire et al. Diastolic Dysfunction in Diabetes. *Arq Bras Endocrinol Metab* 2007;51:168-175

53. Govind S, Saha S, Brodin LA, Ramesh SS, Arvind SR, Quintana M. Impaired myocardial functional reserve in hypertension and diabetes mellitus without coronary artery disease: Searching for the possible link with congestive heart failure in the myocardial Doppler in diabetes (MYDID) study II. *Am J Hypertens*. 2006;19(8):851-857.

54. Schannwell CM, Schneppenheim N, Perings S, Plen G, Strauer BE. Left ventricular diastolic dysfunction as an early manifestation of diabetic cardiomyopathy. *Cardiology* 2002;98:33-9.

55. R. Wachter et al. impact of left ventricular diastolic function in patients with arterial hypertension. European Journal of Heart Failure 2007;9:469-476

56. Khalil S I et al. Study of left ventricular diastolic function in patients with Diabetes Mellitus. *Sudan JMS* 2007;2:85-90.

57. Srivastava PM, Thomas MC, Calafiore P, Isaac RJM, Jerums G, Burrell LM. Diastolic dysfunction is associated with anaemia in patients with type II diabetes. *Clinical science* 2006:109-116.

58. Takenaka K, Sakamoto T, Amano K, et al. LV filling determined by Doppler echocardiography in diabetes mellitus. *Am J Cardiol* 1988,61, 1140-3.

59. Raev DC. Which LV function is impaired earlier in the evolution of diabetic cardiomyopathy? An echocardiographic study of young type I diabetic patients. *Diabetes Care* 1994, 17, 633-9.

60. Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. LV systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. *J Am Soc Echocardiogr* 2001, 14, 885-91.

61. Zoneraich S, Silverman G, Zoneraich O. Primary myocardial disease,diabetes mellitus, and small vessel disease. *Am Heart J*, 1980, 100,754-5.

62. Factor SM, Okun EM, Minase T. Capillary microaneurysms in the human diabetic heart. *N Engl J Med*, 1980, 302, 384-8.

63. Irace L, Iarussi D, Guadagno I, et al. LV function and exercise tolerance in patients with type II diabetes mellitus. *Clin Cardiol*, 1998, 21,567-71.

64. Poirier P, Garneau C, Bogaty P, et al. Impact of LV diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. *Am J Cardiol*, 2000, 85, 473-7.

65. Das AK, Das JP, Chandrasekar S. Specific heart muscle disease in diabetes mellitus--a functional structural correlation. *Int J Cardiol*, 1987, 17, 299-302.

ABBREVIATIONS

ADA	American Diabetes Association
AGE	Advanced Glycation End products
AT II	Angiotensin II
BMI	Body Mass Index
CAN	Cardiac Autonomic Neuropathy
CSME	Clinically Significant Macular Edema
ESRD	End Stage Renal Disease
FFA	Free fatty acids
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
Hb A1C	Glycosylated haemoglobin
HDL	High Density Lipoprotein
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
LDL	Low density lipoprotein
NPDR	Non proliferative diabetic retinopathy
NVD	Neovascularisaction at disc
NVE	Neovascularisation elsewhere
PDR	Proliferative diabetic retinopathy
PDGF	Platelet derived growth factor
PKC	Protein Kinase C
RAAS	Renin Angiotensin Aldosterone System
VLDL	Very low density lipoprotein
VEGF	Vascular endothelial growth factor

PROFORMA

Name : Age : Sex :

Address : Occupation :

SYMPTOMS

Dyspnea	:	Yes	☐	No	☐
Orthopnea	:	Yes	☐	No	☐
PND	:	Yes	☐	No	☐
Chest pain	:	Yes	☐	No	☐
Oliguria	:	Yes	☐	No	☐
Abdominal distension	:	Yes	☐	No	☐
Swelling of legs	:	Yes	☐	No	☐
Puffiness of Face	:	Yes	☐	No	☐
Burning micturition	:	Yes	☐	No	☐
Numbness/Parasthesias	:	Yes	☐	No	☐
Blurring of vision	:	Yes	☐	No	☐

PAST HISTORY

Diabetes Mellitus	:	Yes	☐	No	☐

- Duration :
- Treatment : OHA / Insulin
- Compliance of treatment :
- Other co-morbid illnesses

PERSONAL HISTORY

Smoking	:	Yes	☐	No	☐
Alcoholism	:	Yes	☐	No	☐

GENERAL EXAMINATION

Authropometry

Height (in m): Weight (in kg) : BMI :

Pulse

Blood Pressure

SYSTEMIC EXAMINATION

CVS : RS : ABDOMEN : CNS :

FUNDUS EXAMINATION

INVESTIGATIONS

Hemogram

TC	:	cells/mm^3	DC	:	
ESR	:	mm/hr	Hb	:	g/dl
PCV	:	%	Platelets	:	lakhs/mm^3
RBCs	:	million/mm^3			

Renal Function Test

Glucose (F)	:	mg/dl	Glucose (PP)	:	mg/dl
Urea	:	mg/dl	Creatinie	:	mg/dl
Na^+	:	mEq/l	K+	:	mEq/l

Lipid Profile

Total cholesterol	:	mg/dl
LDL	:	mgs/dl
HDL	:	mg/dl
Triglycerides	:	mg/dl

Urinanalysis

Sugar

Deposits

Albumin

Creatinine

Albumin to Creatinine Ratio (ACR)

Culture

Ultra sonogram of Kidneys

ECG

ECHO CARDIOGRAM:

Left ventricular dimensions/ejection fraction

Diastolic dysfunction

Sl.No	Name	Sex	Age	Past History			Personal History		Body mass Index(BMI)	Fundus Examination	Investigations						Echo Cardiogram			
				Diabetes Mellitus							Hemogram (Hb)	Blood Sugar	Lipid Profile		Microalbumin	Albumin / Creatinine Ratio	E velocity	A velocity	E/A ratio	Grade of Diastolic Dysfunction
				Duration	Treatment OHA / Insulin	Compliance of treatment	Smoking	Alcoholism				Glucose (F) (mg/dl)	Total cholesterol (mgs/dl)	TGL (mgs/dl)						
1	Nagammal	F	55	8	OHA	R	Nil	N	27	NPDR	8.9	112	264	167	**160**	**256.5**	**0.64**	**1.1**	**0.58182**	I
2	Mani	M	62	12	OHA	R	N	Y	27	NPDR	9.1	116	212	187	**156**	**243**	**0.435**	**0.604**	**0.7202**	I
3	Kirubakaran	M	35	0			Y	Y	24	Normal	10.4	185	351	213	**7.7**	**16.8**	**1.07**	**0.53**	**2.01887**	N
4	Rajeswari	F	45	7	I	R	N	N	32	NPDR	10.5	242	207	150	**22**	**13.6**	**0.54**	**0.764**	**0.70681**	I
5	Samuel	M	38	0			N	N	25	Normal	14	234	180	500	**160**	**98.6**	**0.61**	**0.54**	**1.12963**	N
6	James Paul	M	45	5	I	R	N	Y	23	Normal	7.8	312	360	340	**2.5**	**18.6**	**0.864**	**0.54**	**1.6**	N
7	Lakshmipathy	M	47	5	OHA	R	N	N	24	Normal	11.2	123	186	164	**2.2**	**16.4**	**0.613**	**0.41**	**1.49512**	N
8	Gnanam	F	60	10	OHA/I	R	N	N	26	PDR	10.9	298	181	176	**160**	**256.5**	**0.64**	**1.1**	**0.58182**	I
9	Maniammal	F	32	0			N	N	28	Normal	7.8	246	212	135	**4.4**	24.7	0.763	0.546	1.39744	N
10	Saroja	F	50	10	OHA	R	N	N	26	Normal	10.7	106	160	265	**2.5**	25	0.604	**0.41**	1.47317	N
11	Vasanthin	F	50	12	OHA	R	N	N	28	NPDR	9.2	65	147	235	**160**	467.7	0.81	**1.1**	0.73636	I

12	Ellammal	F	58	15	OHA	R	N	N	31	NPDR	12.4	163	220	147	**54**	133.2	0.78	0.542	**1.43911**	N
13	Beenabevi	F	59	20	OHA	R	N	N	26	NPDR	7.1	102	232	246	**46**	148.3	0.81	1.07	**0.75701**	I
14	Vadivel	M	58	1	OHA	I	Y	Y	28	Normal	10.1	160	246	160	**2.5**	6.7	0.604	0.435	**1.38851**	N
15	Bharathi	F	31	0			N	N	24	Normal	7.5	206	211	157	**22**	114.1	1.07	0.53	**2.01887**	N
16	Arumugam	M	58	10	OHA	R	Y	Y	32	NPDR	9.4	185	234	207	**81.4**	109.9	1.46	0.88	**1.65909**	II
17	Irudhayaraj	M	42	5	OHA	R	N	Y	25	Normal	9.8	247	217	118	**3.3**	19.3	0.9	0.73	**1.23288**	N
18	Job	M	57	10	OHA	R	N	N	26	NPDR	13.7	160	143	340	**2.5**	17.7	0.94	1.02	**0.92157**	I
19	Paneerselvam	M	53	5	OHA	R	Y	Y	24	NPDR	11.2	169	164	169	**16.1**	45.6	0.954	0.84	**1.13571**	N
20	Sriramulu	M	62	2	OHA	I	N	Y	21	NPDR	7.8	144	195	115	**18.1**	33.5	1.07	0.93	**1.15054**	N
21	Sundari	F	56	6	OHA/I	R	N	N	31	NPDR	10.4	151	195	280	**2.5**	16.8	0.735	0.61	**1.20492**	N
22	Arul doss	M	60	7	OHA	R	Y	N	30	NPDR	4.4	134	205	279	**92.3**	522.7	0.98	0.5	**1.96**	II
23	Mathammal	F	52	7	I	R	N	N	26	NPDR	11.9	214	176	220	**7.9**	68.6	0.611	0.742	**0.82345**	I
24	Shanthi	F	38	15	I	R	N	N	27	PDR	9.1	183	201	322	**160**	344.6	0.845	1.02	**0.82843**	I
25	Muthuraman	M	42	0			N	N	26	Normal	8.6	232	213	312	**160**	291.2	Jan-00	1.02	**1.18627**	N
26	Solomon	M	33	0			Y	Y	23	Normal	10.3	210	191	206	**2.2**	21.6	0.76	0.62	**1.22581**	N
27	Krishnaiah	M	46	5	OHA	R	Y	Y	31	NPDR	9.6	110	210	200	**17.4**	56.1	0.763	0.543	**1.40516**	N
28	Dhanalakshmi	F	56	11	I	R	N	N	25	NPDR	11.6	142	246	178	**78.2**	106.3	0.845	1.14	**0.74123**	I

29	Chakravarthi	M	64	13	I	R	Y	Y	28	PDR	7.8	110	213	256	**91.4**	526.4	0.78	0.984	**0.79268**	I
30	Raja	M	66	6	OHA	R	Y	Y	30	NPDR	12.4	86	165	196	**19.4**	56.77	0.912	1.04	**0.87692**	I
31	Pushpavalli	F	36	1	OHA	R	N	N	29	Normal	11.5	95	190	145	**3.2**	23.4	1.03	0.87	**1.18391**	N
32	lalitha	F	55	2	OHA	R	N	N	25	Normal	12.1	102	184	220	2.6	16.4	0.98	0.76	**1.28947**	N
33	Ranjitham	F	38	5	OHA	R	N	N	28	Normal	10.6	206	194	196	**8.4**	59.5	0.703	0.912	**0.77083**	I
34	Kanikaanan	M	43	7	OHA/I	R	Y	Y	26	NPDR	9.7	213	186	156	**49**	151.2	0.56	0.864	**0.64815**	I
35	Selvaraj	M	47	1	OHA	R	Y	N	26	Normal	10.7	145	240	165	**8.4**	26.2	1.12	0.92	**1.21739**	N
36	Manickam	M	67	16	OHA/I	I	Y	Y	28	NPDR	12.2	186	165	256	**19.3**	48.2	0.98	1.1	**0.89091**	I
37	Jothi	F	42	4	OHA	R	N	N	26	Normal	12.3	145	142	220	**34.1**	121	0.67	0.832	**0.80529**	I
38	Mallika	F	36	1	OHA	I	N	N	27	Normal	14.2	125	163	175	**6.5**	25.4	0.765	0.645	**1.18605**	N
39	Vnayagam	M	46	3	OHA	R	Y	Y	32	Normal	10.1	154	207	310	**54.2**	151.2	0.95	1.13	**0.84071**	I
40	Kanakkammal	F	62	9	I	R	N	N	26	NPDR	13.1	98	190	186	**46.1**	143.3	0.546	0.765	**0.71373**	I
41	Madhaiyyan	M	61	10	OHA	R	Y	Y	34	NPDR	7.9	133	174	165	**68.7**	213.5	0.653	0.812	**0.80419**	I
42	Kala	F	48	4	OHA	R	N	N	24	Normal	8.7	210	208	354	**54.2**	151.2	0.985	0.862	**1.14269**	N
43	Kumerasan	F	43	9	I	R	N	N	25	PDR	12.1	190	218	165	**160**	421.8	0.64	0.85	**0.75294**	I
44	Vendammal	F	39	0			N	N	24	Normal	10.4	176	173	145	**2.2**	12.1	0.675	0.563	**1.19893**	N
45	Subramanian	M	36	1	OHA	I	Y	Y	24	Normal	13.3	120	194	205	**18.6**	36	0.765	1.12	**0.68304**	I

46	Murugan	M	63	13	OHA	R	N	Y	24	NPDR	12.2	230	157	185	**154**	321.1	0.859	1.14	**0.75351**	I
47	Naseer	M	43	2	OHA	I	Y	Y	21	Normal	11.1	187	200	247	**19.3**	43.4	0.654	0.985	**0.66396**	I
48	Govindasamy	M	64	13	OHA/I	R	N	Y	28	PDR	8.1	134	185	184	**20.7**	67	0.876	0.953	**0.9192**	I
49	Isaac	M	34	1	OHA	R	Y	Y	24	Normal	10.4	125	173	173	**2.5**	12.4	0.78	0.64	**1.21875**	N
50	Vembuli	M	55	5	OHA	I	Y	Y	26	NPDR	12.3	136	197	165	**153**	265.3	0.715	0.965	**0.74093**	I
51	Mohammad Mooran	M	43	6	I	R	N	N	27	NPDR	12.8	174	208	195	**54.6**	212.3	0.87	1.2	**0.725**	I
52	Napinnai	F	56	4	OHA	R	N	N	25	Normal	10.8	138	254	202	**34.3**	135.2	0.65	0.931	**0.69817**	I
53	Sundaravadivu	F	65	7	OHA	I	N	N	25	NPDR	11.3	198	167	156	**44.5**	200.6	1.03	1.12	**0.91964**	I
54	Aleem basha	M	34	0			Y	Y	29	Normal	12.6	102	183	182	**2.2**	8.6	0.7	0.54	**1.2963**	N
55	Rajendran	M	52	6	I	R	N	Y	30	Normal	11	96	221	173	**36.5**	126.4	0.87	0.972	**0.89506**	I
56	Thangamani	F	58	10	I	R	N	N	25	NPDR	11.6	94	228	165	**31.1**	132	0.53	0.821	**0.64555**	I
57	Sekar	M	34	1	OHA	R	Y	Y	26	Normal	12.2	126	146	214	**4.2**	24.2	0.602	0.54	**1.11481**	N
58	Ezhil	M	39	0			N	Y	24	Normal	11.8	198	165	312	2.5	16.4	0.813	0.653	**1.24502**	N
59	Ramasamy	M	60	6	OHA	R	N	Y	24	Normal	10.9	184	178	156	36.3	167	1.07	1.23	**0.86992**	I
60	Murugalakshmi	F	51	10	OHA/I	I	N	N	29	NPDR	10.8	242	154	214	34.2	146	0.78	0.934	**0.83512**	I

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

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CERTIFICATE OF APPROVAL

To
Dr. P. Vijay Shekar
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. P. Vijay Shekar

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Diastolic dysfunction in type 2 diabetes and its correlation with microvascular complications" No.18042012.

The following members of Ethics Committee were present in the meeting held on 19.04.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member Secretary
3.	Prof. B. Kalaiselvi MD Prof. of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. Md. Ali. MD.DM Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof.P.Karkuzhali MD Director i/c, Prof., Inst. of Pathology, MMC, Ch-3	-- Member
7.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
8.	Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. S. Govindsamy. BABL	-- Lawyer
10.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS

Dissertation submitted in partial fulfillment of requirements for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH I

Of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,
CHENNAI, INDIA.

MADRAS MEDICAL COLLEGE,
CHENNAI 600003

APRIL 2013

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DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES AND ITS CORRELATION WITH MICROVASCULAR COMPLICATIONS Dissertation submitted in partial fulfillment of requirements for M.D. DEGREE IN GENERAL MEDICINE BRANCH I Of THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, INDIA. MADRAS MEDICAL COLLEGE, CHENNAI 600003 APRIL 2013 1 INTRODUCTION Type 2 diabetes mellitus is an established risk factor for cardiovascular events and the development of congestive cardiac failure, through its association with hypertension and coronary artery disease. The existence of myocardial dysfunction in diabetic subjects even in the absence of ischemic, valvular and hypertensive heart disease was proposed by Rubler et al. in...