"CORRELATION OF SERUM HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS"

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CERTIFICATE

This is to certify that the dissertation entitled **"CORRELATION OF SERUM HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS "** is a bonafide work done **by DR. SANDEEP SRINIVAS**, Post graduate student, Institute of Internal Medicine, Madras Medical College, Chennai -03, in partial fulfilment of the University Rules and Regulations for the award of MD Branch – I Internal Medicine, under our guidance and supervision, during the academic year 2013 – 2016.

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I solemnly declare that the dissertation entitled **"CORRELATION OF SERUM HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS"** is done by me at Madras Medical College, Chennai – 03 during April 2015 to September 2015 under the guidance and supervision of **Prof. Dr. R. PENCHALAIAH**, to be submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfilment of requirements for the award of M.D. DEGREE IN GENERAL MEDICINE BRANCH-I

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CONTENTS

KEY WORDS

- Diabetes Mellitus
- Hypertension
- Dyslipidemia
- Diastolic dysfunction
- Cardiovascular disease
- Diabetic Cardiomyopathy
- Glycated hemoglobin

INTRODUCTION

Type 2 diabetes mellitus is the most common endocrinopathy commonly encountered in clinical practice. It is a group of diseases characterized by absolute or relative lack of insulin ultimately resulting in increased blood glucose or simply hyperglycemia.

Cardiovascular disease is frequently encountered in patients with type 2 diabetes mellitus. In fact, it contributes to significant morbidity and mortality in such patients upto the tune of 80 %. The economic burden in managing type 2 diabetic patients with co existent cardiovascular disease is very high. Various cardiovascular manifestations can occur in patients with type 2 diabetics notably coronary artery disease. Also, on a comparative viewpoint patients with diabetes have increased risk for development and also of dying from coronary artery disease than non diabetics. In addition, they have increased risk for developing macrovascular complications like peripheral vascular disease and stroke besides other microvascular complications.

Sustained hyperglycemia can influence the development and progression of atherosclerosis. This has been attributed to vascular perturbations linked to diabetes which include – endothelial dysfunction, effects of advanced glycation end products , effects of circulating free fatty acids and increased systemic inflammation. Besides, hypertension and

dyslipidemia influence and accelerate the progression of atherosclerosis in patients with type 2 diabetes mellitus.

Diabetes is an independent risk factor for heart failure which can be both systolic and/ or diastolic heart failure; and patients have the worst outcomes once heart failure has developed.

Diabetics and non diabetics- can both have various common features such as ischemic heart disease, hypertension, left ventricular hypertrophy, atrial fibrillation and valvular disease; however there is increased myocardial vulnerability to the effects of the aforementioned factors which may act in a synergistic fashion to increase risk for morbidity and mortality in patients with diabetes mellitus.

Diabetic cardiomyopathy is not an old concept, it is fairly new and a distinct entity. It was in 1972 that for the first time in the history of medicine fascinating observations were made. 4 patients were found to have diabetes and heart failure without any evidence of systemic hypertension or coronary artery disease. The dissection of the heart revealed startling facts. There was evidence of LV hypertrophy and fibrosis without atheroma of coronary blood vessels or another substrate responsible for the above mentioned finding. This clinical entity was baptized with the terminology “Diabetic Cardiomyopathy”.

Thus, the condition is defined as myocardial dysfunction in patients with diabetes mellitus in the absence of hypertension, coronary artery disease or other known cardiac disease. This concept was brought to light through various experimental, epidemiological, pathological and clinical studies. The studies highlighted the presence of various myocardial changes - both structural and functional in patients with diabetes with no other co morbid illnesses. These include myocardial damage, hypertrophy of left ventricle, myocardial small vessel changes, cardiac autonomic neuropathy, etc.

The etiology and pathogenic mechanisms implicated in diabetes are multifactorial. Sustained hyperglycemia has been found to cause disturbances in ionic channels like sodium – potassium ionic channel, generation of reactive oxygen species, deposition of advanced glycation end products, inflammatory reaction, myocardial fibrosis etc., all of which play a crucial role in the genesis and maintainence of diabetic cardiomyopathy.

With regard to heart failure, in diabetics without any co morbidities diastolic dysfunction dominates the early course with relatively preserved ejection fraction before they proceed to develop systolic dysfunction by which time patient has overt symptoms of heart failure and various other complications of diabetes both macrovascular like stroke, peripheral vascular disease and microvascular like retinopathy, neuropathy and nephropathy. The development of systolic dysfunction portends a poor prognosis.

Diastolic dysfunction which is an early feature in diabetes can be assessed using non invasive methods like echocardiography which uses parameters like transmitral inflow velocity, tissue Doppler lateral annulus velocity, deceleration time etc. These parameters show the presence of impaired relaxation time with normal systolic function early in the course of diabetes.

AIMS

AND

OBJECTIVES

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1. To study the correlation between HbA1C levels with grades of diastolic dysfunction in asymptomatic type 2 diabetic individuals.

2. To study the prevalence of diastolic dysfunction in asymptomatic type 2 diabetic individuals in relation to duration of diabetes, differences in sex.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

HISTORICAL REVIEW

The term “diabetes” was used first by Apollonius of Memphis around the year 230 B.C. which in Greek means “to pass through”. The words describe a siphon that described polyuria.

In India, at around the same time, physicians observed that the urine from people with diabetes attracted flies and ants. They also noted that such patients had extreme thirst and foul smelling breath. They named the condition – ‘madhumeha’ or ‘honey urine’ [1]. It was only later in the 5th century that two renowned physicians namely Sushruta and Charaka differentiated between the two types of diabetes mellitus. They noticed that lean individuals who developed diabetes did so at an earlier age rather than heavier individuals who developed diabetes at a later age.

Aulus Cornelius Celsus gave the first complete clinical description of diabetes in his exemplary work comprising of eight volumes entitled – De medicine [2].

Aretaeus of Cappadocia was the first to distinguish between diabetes mellitus and diabetes insipidus [3].Together with Galen, who was a roman physician, he observed that the condition was a rare one. In fact, Galen mentioned that he had noticed only two such cases in his entire career!

Frederick Banting, an orthopaedic surgeon and Charles Best, a physiology student finally identified the substance in the year 1920 whose deficiency was postulated to be responsible for the development of diabetes[4] for which they were awarded the noble prize. Banting initially named the antidiabetic substance as “isletin” and later, MacLeod christened it as “insulin” as we know it today [5]. The discovery of insulin was revolutionary in the field of medicine and over the years several purification methods were used and newer insulin formulations have been tried.

INSULIN AND GLUCOSE METABOLISM:

The effects of insulin on glucose metabolism is myriad. Insulin and various other “counter regulatory hormones” as we call them serve to maintain normoglycemia. The arterial glucose values averages around 90 mg/dl with a maximum of 165 mg/dl after ingestion of a meal [6]and remains above 55 mg/dl even after exercise[7] or a moderate fast[8]. A decrease in even 20 mg/dl (90 – 70mg/dl) will suppress the release of insulin and stimulate the production of counter regulatory hormones like cortisol, growth hormone, glucagon and catecholamines which ultimately serve to maintain a state of euglycemia[9].

Glucose is considered to be obligate fuel for the brain and only after a considerable period of fasting ketone bodies are used by the brain to a significant extent [10].

ROLE OF INSULIN :

Insulin regulates the metabolism of glucose by both direct and indirect mechanisms. The effects are as described below:

- Suppression of release of glucose from kidney and liver[11]
- Increased glucose uptake in muscle and adipose tissue[12]
- Suppression of hormone sensitive lipase resulting in inhibition of release of free fatty acids and enhancing their clearance[13]
- Promotes glycogen accumulation by inhibiting glucose 6 phosphatase and phosphorylase and stimulating glycogen synthase[14]

Chief regulator of insulin secretion is plasma glucose. Increased glucose such as after a meal stimulates insulin secretion which tends to lower the sugar values. On the other hand, during fasting there is a surge of counter regulatory hormones which tends to increase blood sugar values. Also, after consumption of a meal, there is release of certain intestinal factors called " incretins " which augment insulin secretion.

ROLE OF GLUCAGON:

Glucagon is secreted by the alpha cells of the pancreas and the main factors which influence its secretion are insulin and glucose. Its secretion is inhibited by increased blood sugar levels and stimulated by decreased blood sugar levels. It acts mainly on the hepatic cells and its immediate action is to increase blood glucose levels mainly by a process called glycogenolysis. This means that the stored glucose in the hepatic cells is released at the time of fasting. Only later is the process of gluconeogenesis activated where glucose is synthesized from many sources like - amino acids, lactate etc., for the purpose of energy generation.

ROLE OF CATECHOLAMINES:

Catecholamines mainly act through beta adrenergic receptors to increase blood glucose levels – i.e., the net effect is hyperglycemia and this take place in response to stress and hypoglycaemia. In the kidney, they stimulate gluconeogenesis and in skeletal muscles they stimulate glycogenolysis resulting in formation of lactate, a chief precursor for gluconeogenesis. In a similar fashion they stimulate lipolysis in adipose tissue resulting in release of FFA and also glycerol , again key precursors for gluconeogenesis.

ROLE OF GROWTH HORMONE AND CORTISOL:

The actions of the above two hormones takes time to become evident. The hormones are antagonistic to insulin – meaning that they enhance gluconeogenesis and reduce glucose transport. Cortisol is also found to impair insulin secretion. That is why treatment with immunosuppressive glucocorticoids cause glucose intolerance over a period of time because they result in insulin resistance and prevent an appropriate rise in compensatory insulin secretion.

ROLE OF FREE FATTY ACIDS:

Except brain, blood cells and the renal medulla, most tissues in our body use free fatty acids as their metabolic fuel. Their presence has numerous metabolic consequences. They are regulated by insulin (decrease the levels of FFA), growth hormone and sympathetic nervous system (increase FFA levels) and hyperglycemia.

Therefore, understanding the various hormones involved in glucose metabolism is vital.

Diabetes mellitus is thus a disorder of glucose metabolism which results from either absolute or relative insulin deficiency resulting in hyperglycemia with a range of effects on various organ systems in the body.

The mechanisms may be genetic, acquired or environmental.

Diabetes mellitus is classified as:[15]

(A) Type 1 DM

(B) Type 2 DM

(C) Gestational DM and

(D) Other types of DM which include those due to genetic defects, drugs like corticosteroids, infections, etc.

DIAGNOSING DM:

A patient can be suspected to have diabetes mellitus if he / she presents with the classical clinical features of increased thirst, increased urination, recent weight loss and has a random blood glucose value of ≥ 200 mg/dl.

Various other criteria have been proposed based on the risk of developing microvascular complications like retinopathy and observed association between glucose levels.

A fasting plasma glucose value of ≥ 126 mg/dl, glycated haemoglobin of ≥ 6 .5% and the two hour post oral glucose tolerance test value of ≥ 200 mg/dl[16] are associated with increased risk of developing microvascular complications like retinopathy, nephropathy and neuropathy.

Of the said criteria, glycated haemoglobin deserves special mention. Initially, the use of glycated haemoglobin was not approved as there were no uniformity in assays worldwide[17]. However in June 2009, American Diabetes Association recommended that glycated haemoglobin can be used with accuracy to diagnose diabetes in both children and in adults but the same could not be used in pregnant women.

A HbA1c value of ≥ 6.5 % was used as cut off to make a diagnosis of diabetes mellitus and studies have shown that HbA1c level is an excellent marker for cardiovascular morbidity and mortality , and is gold standard in monitoring therapy[18].

ADA criteria to define population at high risk for diabetes:

Patient's age more than 45 years.

Patient's age less than 45 years with the following:

a. Obesity
b. Family history with diabetes mellitus (parents or siblings)
c. Previous history of GDM or delivered a baby weighing more than 4 kgs.
d. Presence of hypertension.
e. Presence of hyperlipidemia.
f. Previous evidence of IGT or IFG.

g. Member of a minority population.

h. History of vascular disease

i. Habitual physical inactivity

j. Polycystic ovarian disease.

DIABETES AND THE HEART:

Cardiovascular disease is the principal cause of death in patients with type 2 diabetes mellitus. Diabetics are at increased risk of myocardial infarction compared with the general population[19]. To make matters worse, even if patients with diabetes develop coronary artery disease, their survival outcomes are poor and not satisfactory compared to non diabetics.

Patients often have a ‘ silent myocardial infarction ’ in the setting of diabetes [20] indicating that such patients are detected to have myocardial ischemia (due to coronary atherosclerosis) only on investigations like the electrocardiograph and echocardiography as they don’t have any symptoms. This is presumably because of cardiac autonomic neuropathy which affects both sympathetic and parasympathetic systems.

Such patients are also likely to die of myocardial infarction even before they reach the hospital than non diabetics[21]. This can be due to probable co existing diabetic heart muscle disease which results in myocardial

contractility and this occurs independent of coronary artery disease. This has been termed diabetic cardiomyopathy which will be described in detail later.

This concept was derived from a landmark trial conducted during the 1970's. 73 patients with idiopathic form of primary myocardial disease were chosen out of which only 16 patients were found to have diabetes mellitus. They were compared to matched patients who did not have cardiomyopathy. 57 of them were excluded as they had history of chronic alcoholism and other causes associated with cardiomyopathy. The chosen 16 were diagnosed with diabetes earlier itself, even before the patients could enter into the study. The patients were subjected to detailed physical examination and investigations and the results were tabulated.

Autopsy conducted in 3 of 4 dead diabetic persons showed intramural small vessel changes in the absence of any large vessel changes. On the other hand, autopsy conducted in 28 non diabetic individuals showed only one person having small vessel changes and that patient was found to have PAN.

Thus, it was concluded from the study that the idiopathic cardiomyopathic changes in diabetic patients with poorly controlled blood could possibly be due to intramural small vessel changes.[22]

RISK FACTORS FOR CARDIOVASCULAR DISEASES IN TYPE 2 DIABETICS:

In addition to diabetes mellitus, cardiovascular disease in diabetics can also be accelerated by co existing risk factors which can be divided into modifiable and non modifiable risk factors.

Non modifiable risk factors are:

(A) Old Age

(B) Male Gender

(C) Type A personality

(D) Familial hypercholesterolemia

(E) Hyperhomocystenemia

Modifiable risk factors are:

(A) Obesity

(B) Sedentary lifestyle

(C) Smoking

(D) Excessive alcohol consumption

(E) Consumption of diet lacking in vegetables or antioxidants

(F) Increased consumption of saturated fat, red meat etc.

The aforementioned factors play a synergestic role in increasing cardiovascular mortality and morbidity in patients with diabetes mellitus.

Type 2 diabetes is now considered to be a vascular disorder – otherwise " vasculopathy". Various vascular disturbances are known to occur in diabetics with a wide spectrum of consequences including predisposition and promotion of thrombosis and vasospasm.

Cardiovascular disease risk in diabetics was studied in various trials. The WHO multinational trial [23] which enrolled about 3,583 patients established that neither the degree of hyperglycemia or the duration of diabetes was related to the amount of cardiovascular deaths. The Framingham study [24] which enrolled 239 subjects also did not establish any relationship between hyperglycemia and incidence of cardiovascular deaths. A similar outcome was derived in the Whitehall study [25] which enrolled 178 subjects.

However, the Wisconsin Epidemiological study of Diabetic Retinopathy [26] which enrolled around 10,135 diabetic subjects revealed that a 1% decrease in HbA1c level predicted a 10% fall in CVD events but 50% reduction in occurrence and progression of retinopathy without adjustment for other CVD risk factors.

Therefore, optimal glucose control is necessary to retard the progression of myocardial disease.

Mechanisms of diabetic cardiomyopathy:

The mechanisms proposed to cause diabetic cardiomyopathy can be discussed under the following headings:

(a) Metabolic disturbances

(b) Small vessel disease

(c) Myocardial fibrosis

(d) Insulin resistance

(e) Autonomic dysfunction

Metabolic disturbances in diabetics:

1. Disturbances in substrate supply and utilization -

Diabetic individuals have a defect in stimulation of glycolysis and oxidation of glucose[27] primarily because of the following reasons:

- Slow rate of transport of glucose into myocardium basically due to depletion in the number of glucose transporters like GLUT 1 and GLUT 4 resulting in reduced myocardial glucose supply and its utilization[28].
- High levels of free fatty acid – contributes to inhibitory effect of fatty acid oxidation on pyruvate dehydrogenase complex, a crucial enzyme in glucose metabolism[29].

The above two mechanisms have an influence on the diabetic myocardium resulting in reduced myocardial ATP availability, particularly in type 2 diabetic individuals.

Recent studies also indicate that as a consequence of oxidative stress resulting from deranged glucose metabolism, there is alteration in the function of the so called “cardiac progenitor cells”. This results in a defective cardiac progenitor cell growth and consequent myocyte dysfunction. The above derangements lead ultimately to myocardial aging/ apoptosis and heart failure [30].

Substrate metabolism affecting the myocardial contractility was clearly demonstrated in genetically determined mice. This contractile dysfunction was clearly evident in the form of increases LV end diastolic pressure, reduced LV pressure and cardiac output.

2. **Free fatty acid metabolism:**

There is increased free fatty acid levels in type 2 diabetic individuals. This is a result of enhanced lipolysis of adipose tissue and reduced levels of a key molecule called carnitine which is important in the clearance of free fatty acids.

The above problems lead to:

- Abnormally high requirements of oxygen in the metabolism of free fatty acids.
- Intracellular accumulation of potentially toxic substances
- Impairment of glucose oxidation

These ultimately result in reduced myocardial performance and morphological changes which tends to become better with metabolic improvement[31].

Role of carnitine deficiency was found in streptozotocin induce diabetic rats without any evidence of coronary occlusion and normal cholesterol levels which correlated well with decreased serum and myocardial carnitine levels and also abnormally visualized mitochondria[32].

3. **Disturbances in calcium homeostasis regulation**:

The accumulation of toxic molecules, free radicals and abnormal lipid molecules in cell membrane result in alteration in key proteins - both regulatory and contractile, calcium ATPase and sodium - calcium exchanger function.

There is altered calcium sensitivity of the so called 'regulatory proteins' involved in myocardial actin – myosin regulation. Impaired left ventricular function in such a situation can be attributed to:

- Diminished calcium sensitivity[33]
- Decreased cardiac pump protein
- Decreased sarcoplasmic reticulum calcium ATPase[34]

The above factors result in both - abnormal systolic and abnormal diastolic dysfunction.

In diabetic without a known cause of myocardial dysfunction or cardiac disease the disturbances of LV function primarily reflect diastolic dysfunction which can be attributed positively to factors such as interstitial collagen deposition which can be reversed with insulin therapy.

4. **Disordered copper metabolism**:

Serum copper levels are found to be elevated in patients with type 2 diabetes mellitus particularly in those with microvascular complications like retinopathy and co existing hypertension[35]. The copper binding properties of ceruloplasmin are lost and this leads to increased deposition of copper in extracellular matrix[36] which activates the oxidation reduction system. As a result of the activation, there is increased production of free radicals which results in oxidative stress and myocardial fibrosis[37].

CORRELATION OF THE VARIOUS CHANGES SEEN IN METABOLISM OF SUBSTRATE WITH LV DYSFUNCTION:

In an experimental study where diabetes was induced with streptozotocin the following changes were consistently noted.

- First, time to peak tension and time to half relaxation were prolonged,
- Second, peak rate of rise of tension and fall of tension was depressed,
- Third, there existed an inverse correlation between HbA1C levels and peak late filling velocity in type 2 diabetics whereas on the other hand a direct correlation existed between diastolic velocity time integral and age, duration of diabetes and serum glycated haemoglobin[38].

Therefore, it is apt to say that the cardiac dysfunction depends on the following factors:

- Duration of diabetes – longer the duration, more the cardiac dysfunction.
- Poor glycemic control
- Low serum IGF -1 levels[39]
- High glycated haemoglobin levels

Response to therapy:

In an experimental study involving mice it was noted that insulin therapy reversed some of the key morphological changes which include:

- Increase in LV systolic pressure
- Increase in LV developed pressure and overall LV chamber stiffness constant
- Decrease in the LV end diastolic pressure
- Decrease in size of LV cavity/wall volume and end diastolic volume
- Decrease in LV relaxation time constant[40]

Therefore early insulin therapy may prove very beneficial.

2. **Myocardial fibrosis**

Studies have revealed that there is increased prevalence of myocyte necrosis in diabetics particularly in those with co existing hypertension[41]. The myocyte necrosis results in a variety of changes like widening of extracellular compartments and increased collagen deposition either in a diffuse or scattered manner[42]. This results from replacement fibrosis consequent to myocyte necrosis and connective tissue proliferation[43].

Sustained hyperglycemia results in:

- Glycosylation of amino acid lysine residues results in impaired collagen degradation
- Production of reactive oxygen species resulting in oxidative stress which in turn affects the gene expression and alters signal transducing capacity leading to activation of apoptosis or programmed cell death.

An interesting fact is that there is glycosylation of p53 molecule also resulting in an increase in angiotensin II synthesis – culminating in p53 phosphorylation and increased expression of the molecule Bax leading to myocyte apoptosis.

It was also inferred from experimental data that an active endothelin system in type 2 diabetic plays a crucial role in myocardial fibrosis. This results from alterations in receptors for endothelin 1 resulting in an important effect that is focal fibrous scarring[44].

A crucial substance regulating myocardial fibrosis in diabetics is IGF 1 levels. This substance is found to reduce both angiotensin II and apoptosis. The observation was supported by the fact that treatment with insulin usually reverses the various contractile disturbances noticed in type 2 diabetics.

Role of IGF 1:

- IGF increases myocardial contractility[45] - there is accumulation of intracellular calcium and also there is increased sensitivity of the cardiac myocytes to circulating calcium
- It acts in a synergistic fashion with angiotensin II in promoting cellular development[46] – this leads to cardiac hypertrophy even when BP is in the normal range.

IGF 1 is present in cardiac cells and its expression is increased by increased peripheral vascular resistance, increased myocardial wall stress and decreased insulin concentration.

Role of TGF β:

Transforming growth factor β_1 produce chiefly by cardiac fibroblasts potentiates the effects of angiotensin II[47]. It is a well known fact that the effects of TGF β_1 are pleiotropic. TGF β_1 also increases formation of fibrous tissue and is involved in upregulation of collagen expression particularly during tissue repair. The TGF β_1 receptor II is found to be increased in the ventricle in experimental studies involving OLETF.

CORRELATION OF THE CHANGES WITH LV DYSFUNCTION:

In diabetic individuals cardiac dysfunction -both systolic and diastolic has different pathophysiologic mechanisms.

The systolic dysfunction observed may be attributed more to the degree of myocyte injury and myocyte loss. On the other hand, in contrast, the diastolic dysfunction noticed may be the consequence of both myocardial injury and accumulation of interstitial collagen. A fair relationship exists between myocardial fibrosis, metabolic disturbances and diastolic dysfunction. This can be superimposed on the stages of diastolic dysfunction as follows:

STAGES	DESCRIPTION OF DIASTOLIC DYSFUNCTION	CORRELATION WITH MYOCARDIAL CHANGES
STAGE 1 (MILD)	Impaired myocardial relaxation – both myocardial and mitral inflow E/A < 1 –impaired relaxation mitral inflow pattern	Metabolic disturbance is more pronounced than myocardial fibrosis
STAGE 2 (MODERATE)	Myocardial E/A < 1 Mitral inflow E/A>1 Pseudonormal pattern of flow	Moderate amount of myocardial fibrosis and there is increased LA pressure
STAGE 3 (SEVERE)	Myocardial E/A <1 Mitral inflow E/A > 1.5 Restricted mitral inflow pattern	Severe amount of myocardial fibrosis and theres is also markedly increased LA pressure.

Therefore it is clearly evident from the above chart that the severity of diastolic dysfunction correlates with changes noted both in substrate metabolism and myocardial fibrosis. This highlights the fact that early screening of type 2 diabetics with non invasive methods like echocardiography may reveal subtle diastolic dysfunction, a finding which can prompt initiation of therapy and retard the progression of myocardial dysfunction in type 2 diabetics.

Small vessel changes:

These can be divided into structural and functional:

A. Structural

In type 2 diabetes mellitus, there is microangiopathy invoving the arterioles, capillaries and venules. These changes include:

- Basement membrane thickening
- Arteriolar thickening
- Capillary microaneurysms
- Decreased capillary density which can be due to periarteriolar fibrosis and focal proliferation of subendothelial space and fibrosis.

These changes result in injury to myocardial cells and interstitial fibrosis[48].

B. Functional : The changes include:-

- Impaired coronary vascular reserve and this is a very crucial and change
- Abnormal endothelium dependent vasodilatation

The above structural and functional changes result in diabetic cardiomyopathy probably as a consequence of myocardial ischemia due to increases myocardial demand occurring the setting of microvascular spasm.

Apart from the above said changes, the other changes in vascular system include:

Changes in endothelium:

- Increased NK- κβ activation
- Decreased production of nitric oxide
- Decreased bioavailabilty of prostacyclin
- Increased activity of endothelin 1
- Increased activity of angiotensin II
- Increased activity of cyclooygenase 2
- Increased activity of thromboxane A_2 activity
- Increased production of reactive oxygen species
- Increased products of lipoid production
- Decreased endothelium dependent relaxation
- Increased expression of receptor for advanced gycation end products

Changes in vascular smooth musculature and matrix:

- Increased proliferation and migration into the intima
- Altered matrix composition and reduced degradation

Inflammatory changes:

- Increased levels of IL 1β, IL 6, CD36 and MCP 1
- Increased expression of ICAMs, VCAMs and selectins
- Increased advanced glycation end products and AGE /RAGE interactions
- Increased activity of protein kinase C

Changes in platelets:

- Increased metabolism of arachidonic acid
- Increased synthesis of thromboxane A_2 , a potent vasoconstrictor
- Decreased levels of vasodilators like nitric oxide and prostacyclin and antioxidants.
- Reduced fluidity of platelet membrane
- Altered homeostasis of calcium and magnesium
- Increased turnover of platelets and
- Increased formation of platelet microparticles

The aforementioned changes seen both in small and large vessels were demonstrated in experimental animals. Animal studies also revealed that angiogenic respone which should occur as a result of cardiac ischemia consuequent to small vessel changes is blunted due to markedly redu ed vascular endothelial growth factor and its receptors.

In conclusion, metabolic derangements in diabetes mellitus which occur early in the course initiate injury to the vessels by various mechanisms which over a period of time progress to cause:

a. Abnormal vascular sensitivity to various ligands
b. Decreased autonomic function
c. Increased stiffness of the arteriolar wall
d. Abnormalities of proteins controlling ion movements

These ultimately are responsible for causing 'diabetic cardiomyopathy' and this correlates well with HbA1c levels and reduces with therapy[49].

Cardiac autonomic neuropathy:

The concept of cardiac autonomic neuropathy in diabetes mellitus is also implicated in diabetic cardiomyopathy. It is detected by changes in heart rate variability in response to exercise[50] or dipyridamole stress[51] and an alteration in the balance between sympathetic and parasympathetic balance.

Sympathetic denervation is a vital feature of cardiac autonomic neuropathy in type 2 DM . A study performed using radiocontrast material - ^{123}I – MIBG showed that there was global decrease of myocardial uptake of ^{123}I – MIBG in diabetics[52] indicating cardiac sympathetic denervation. The posterior part of myocardium is predominantly involved than lateral and apical regions indicating the presence of regional heterogeneity in cardiac

sympathetic denervation[53]. Also the study revealed another spectacular fact. The maximal denervation occurred more distally[54] than proximally and this was associated with proximal ventricular islands of hyperinnervation[55]. As a result there are many unstable electrical and vascular regions in the myocardium.

The above findings were known to occur with increased severity in type 2 diabetes mellitus. Various parameters like relative tracer retention was reduced more in myocardial apical, lateral and inferior areas and also measurements of absolute tracer retention index also showed a drastic reduction in distal areas as compared with proximal areas[56] .

On myocardial infusion of adenosine, it was observed that LV myocardial blood flow and also coronary flow reserve were decreased to a significant extent in patients with neuropathy than non neuropathic diabetic individuals[57].

β adrenergic receptor density and cardiac norepinephrine content were found to be increased to a great extent particularly in short term diabetics[58]. This led to the idea that cardiac β adrenergic activity is enhanced by changes in cardiac sympathetic activity. A note should also be made of the increased bradykinin induced release of norepinephrine which is greater in diabetic individuals[59].

With regard to the parasympathetic system, heart rate variability during deep breathing can be demonstrated and with respect to sympathetic system abnormalities, alterations in both systolic and diastolic function are noted. There is decrease in the elastic properties and enhanced peripheral vascular resistance in diabetics due to augmentation of sympathetic tone[60].

Cardiac autonomic neuropathy influences LV function in three important ways:

- Disturbs the myocardial contractile response to stress ,a key feature.
- Systolic dysfunction which was found to be more evident when the patient was subjected to exercise.
- Diastolic dysfunction which was found to be more evident with patient at rest[61].

Thus, in summary, it was noted that cardiac autonomic neuropathy involves both sympathetic and parasympathetic components and in implicated in causing both systolic and diastolic dysfunction in individuals with type 2 diabetes mellitus. There is increased predisposition to sudden cardiac death in diabetics with CAN[62].

Insulin resistance:

Insulin resistance together with hyperinsulinemia are recognized risk factors in diabetic cardiomyopathy. They are also associated with thrombotic risk factors like factor VII, factor XII[63], elevated plasminogen activator inhibitor- 1[64] and fibrinogen.

It has a close relationship with C Reactive protein and hypertension and studies have revealed worse LV performance in the presence of raised CRP levels[65].

The link between insulin resistance and obesity has been in studied for many decades. Obesity is simply defined by excess if fat in the body and is quantified using BMI or body mass index. BMI is given by the formula:

$$\frac{Body\ weight\ in\ kilograms}{Height\ in\ meter\ squared}$$

In South Asian Indians, the BMI is interpreted as normal:

VALUE	INTERPRETATION
<23	NORMAL
23 – 25	OVERWEIGHT
>25	OBESE

Insulin resistance is also associated strongly with glucose intolerance. It is present in a majority of individuals with type 2 DM, their first degree relatives, and also in individuals with impaired glucose tolerance. Therefore , the effects of insulin on the diabetic myocardium are closely related to systemic abnormalities and the direct consequences of insulin on the vascular system.

Chief ingredient linked to the development of insulin resistance is TNF α[66]. – a cytokine also implicated in inflammation. This insulin resistance is linked to various other disorders other than diabetes mellitus like systemic hypertension and coronary artery disease.

It has also been linked to early diastolic abnormalities of left ventricle in diabetes as well as systemic hypertension as it has been postulated to be associated with left ventricular hypertrophy [67] or increased LV mass [68].

Thus, it is evident that various mechanisms act concurrently to cause diabetic cardiomyopathy. Since there is no specific therapy for diabetic cardiomyopathy it is necessary to know these pathogenic mechanisms well as they can act as targets for therapy.

INSULIN RESISTANCE SYNDROMES AND ITS COMPONENTS:

- Central obesity,
- Increased liver fat,
- Increased muscle fat,
- Glucose intolerance and type 2 diabetes mellitus,
- Alteration in lipids,
- High triglyceride concentrations,
- Low HDL cholesterol concentration,
- Increased coagulation,
- Increased fibrinogen,
- Microalbuminuria,
- Endothelial dysfunction,
- Hypertension,
- Increased inflammation.

Diabetes and heart failure:

To add a note on diabetes and heart failure, it is a well established fact that diabetes mellitus in itself is a recognized and independent risk factor for heart failure. In fact, a landmark study called UKPDS showed that the incidence of heart failure in patients with diabetes correlated well with HbA1c levels[69]. There is increased risk of death also in patients with diabetes and heart failure. The aims of treatment include risk reduction and providing

medical therapy in the form of ACE inhibitors, β blockers, AR blockers and aldosterone antagonists. In particular the use of ACE inhibitors should be considered in patients with diabetes and heart failure irrespective of symptom severity and in the absence of significant contraindications. This is substantiated by various trials using ACE inhibitors like – CONSENSUS, SAVE, SOLVD and TRACE. The use of diuretics is beneficial in the setting of pulmonary edema and fluid overload.

Non pharmacologic measures include considering cardiac resynchronization therapy, myocardial revascularization and ultimately cardiac transplantation[70].

Even though diabetes mellitus was a relative contraindication for cardiac transplantation studies have reported that well selected patients can benefit from transplantation.

To summarize,

1. Diabetes mellitus and heart failure frequently exist together and are inter related through various pathophysiological mechanisms which are complex.
2. To stratify risk and mange early play a pivotal role to prolong survival of the patient.

3. Even though there is no clear guidance on the treatment of heart failure and diabetes, it is reasonable and rational to say aggressive medical therapy remains mainstay.
4. Further randomized trials are necessary to conclusively lay down the guidelines for patients with diabetes and heart failure

Evaluation of diastolic dysfunction and grades of diastolic dysfunction:

Cardiac cycle has two phases called systole where there is contraction either of the atria or ventricles and diastole where there is relaxation of either atria or ventricles. Diastole is usually referred to the period in which the myocardial muscle cell generates energy, while in mechanical (as reflected by isovolumic deceleration and relaxation phase) and in electrophysiological inactivity (there is automatic depolarization)[71]. In diastolic dysfunction there is a delayed and extended diastolic phase.

Diastolic dysfunction should first be differentiated from systolic dysfunction in which the ejection fraction is reduced due to impaired myocardial contractility in contrast to diastolic dysfunction which is characterized by impaired myocardial relaxation and normal LV systolic function or normal ejection fraction.

Assessment of diastolic dysfunction in diabetes mellitus can be done by using modern non invasive methods without causing much pain such as echocardiography.

Doppler studies showing transmitral flow are done. The studies measure –

- Mitral inflow velocities
- Isovolumic relaxation time
- Deceleration time
- Assessment of flow pattern

Other measurements like size of the left atrium, LV mass etc can also be derived.

During echocardiography, assessment of transmitral flow will help us ascertain left ventricle filling patterns.

As described above, all the various pathogenic mechanisms lead to worsening of left ventricular function which initially is reflected by reduction in height of E wave and prolongation of deceleration time. As the LV functions worsens further, there is elevation of LA pressure and then LV filling pressure -increasing E wave and shortening deceleration time. This is referred to as pseudonormal and restrictive pattern.

Explanation:

Mitral inflow Doppler – this is used to assess the flow from left atrium and left ventricle across the mitral valve during early and also late phases of diastole. Transmitral flow velocity is a reflection of the pressure gradient between LA and LV.

Two waves are described. The E wave occurs and is captured during the early part of diastole when there is passive filling of the left ventricle. On the other hand, velocity of flow of blood during late phase of diastole when atrial contraction occurs plays a crucial role in LV filling is represented by A wave.

Traditionally, diastolic dysfunction is classically divided into different grades based on the height of E and A waves.

The velocity of E wave depends largely on the pressure gradient across the bicuspid mitral valve and therefore is directly related to pressure in the left atrium and inversely related to ventricular compliance. The height of A wave in addition depends on pressure in left atrium.

In general, in individuals aged less than 65 years, it is noted that the height of the E wave reflecting passive LV filling is greater than the height of A wave and the ratio between the two waves that is E/A ratio typically lies between 1.2 and 1.5.

As patients age, left ventricular compliance reduces which is compounded by the presence of co morbid illnesses like hypertension and diabetes mellitus, the height of E wave gradually declines. Initially, the left atrial contraction increases to compensate resulting in increased left atrial pressure at which time the height of E wave again rises accompanied by decline in the height of A wave resulting in pseudonormal pattern. The reason for terming it pseudonormal is that the E/A ratio may come back to normal because of the above reasons but in the presence of significant cardiac dysfunction. In late stages, worsening of diastolic function of the myocardium may result in restrictive pattern. In this the descending slope of the E wave becomes increasingly steep as a consequence of abrupt cessation of blood flow across the bicuspid mitral valve. Also, the deceleration time of the E wave becomes very rapid[72].

Therefore, diastolic dysfunction can be divided into four grades using Doppler studies as follows:

Grade 1 LVDD - characterized by the reversal of E/A ratio on mitral inflow studies. The patients are usually asymptomatic at this stage and this stage is considered to be the mildest form of diastolic heart failure and is aptly referred by the term - abnormal relaxation pattern.

Grade 2 LVDD – this phase is characterized by increasing filling pressure in the LA. The LA may also be increased in size due to increased pressure in LA. This phase is considered to be moderate stage disease. The pattern is referred to pseudonormal pattern as the E/A ratio may come back to normal.

Grade 3 LVDD - In this phase, there is restricted filling of the left ventricle; both LA and LV pressures are high. The patients are usually symptomatic requiring therapy. The pattern is referred to as reversible restrictive diastolic dysfunction as the diastolic abnormalities noted seem to reverse with Valsalva manoeuvre performed during echocardiography.

Grade 4 LVDD – In this phase also, there is restricted filling of the left ventricle but the changes are usually not reversible – hence referred to as - fixed restrictive diastolic dysfunction. Patients are usually symptomatic to a severe degree, require hospitalization and in hospital management.

There are other methods to assess diastolic dysfunction such as using pulmonary venous Doppler flow patterns.

Normally, the flow in pulmonary vein can be divided into 3 components –

- S wave – characterized by forward flow from pulmonary veins into left atrium during the period of ventricular systole.

- D wave – characterized by passive diastolic flow during the period of ventricular diastole.
- AR wave - characterized by reversal of flow into pulmonary veins during contraction of atrium.

In the presence of impairment of LV relaxation there is ‘blunting’ of S wave which is lower than D wave. The reduced compliance of left ventricle may also lead to greater flow into pulmonary veins during atrial contraction[73].

Tissue Doppler imaging:

This method uses Doppler imaging principles to assess myocardial contraction and relaxation. The technique uses filters that optimize the assessment of low velocity, high amplitude signals that arise as a consequence of myocardial motion. However, important limitations do exist like angle dependence. Tissue Doppler imaging is used to assess the diastolic phase because of its very high temporal resolution also because of its ability to adequately quantify myocardial wall motion velocity accurately – this being dependent on the rates of myocardial relaxation and contraction. The assessment of the above parameter is usually done by sampling the mitral annular motion.

The mitral annulus is noticed to move longitudinally towards the apex of the heart which usually remains fixed, in systole and stays away from apex

during the phase of diastole. Both medial and lateral annulus velocities can be sampled using Doppler imaging and the parameters which can be inferred include – systolic contraction (S'), early diatolic relaxation velocity (E') and also late diastolic relaxation velocities (A').

In this regard, E' relates to rate of relaxation of myocardium during early diastolic phase and inversely related to tau – which is the time constant of relaxation of ventricle. The E' velocity is variable according to different age groups.

The parameter E/E', where E indicates the standard mitral E wave velocity gives us a measure that has been found to clearly correlate well with filling pressure. Dividing E/E' gives a measure that reflects pressure in the left atrium and it is found that this itself depends on left ventricular end diastolic pressure.

One of the other methods used for assessing diastolic dysfunction using echocardiography includes measurement of isovolumic relaxation time or simply IVRT. This reflects the time interval between aortic valve closure and beginning of ventricular filling. Abnormal relaxation og left ventricle correlates with prolongation of isovolumic relaxation time; although a decrease in IVRT can occur in patients with a restrictive pattern of left ventricular filling.

Cardiac catheterization can be done for evaluating LV isovolumic relaxation rhythm and also LV isovolumic contraction time for more accurate measurement of diastolic myocardial function.

Mitral or E wave, deceleration time indicates the time taken from peak mitral inflow of blood to cessation of flow across mitral valve. There is, however, a drawback. In the early phase of diastolic dysfunction the decleration time can increase making the interpretation all the more difficult.

Pitfalls in the assessment of diastolic dysfunction using echocardiography:

- Grades of diastolic dysfunction does not usually correlate very well with clinical outcomes.
- Diastolic dysfunction is extremely common in patients with systemic hypertension and also elderly individuals making interpretation difficult.
- Diastolic abnormalities are not necessarily associated with clinical symptoms or overt heart failure.

On occasions it may be difficult to assess subtle diastolic abnormalities and in order to unmask abnormalities in diastolic function – diastolic function during exercise is done. This is otherwise called as “diastolic stress test.”

Other uses of echocardiography in addition to assessing diastolic dysfunction include:

- Assessment of LV Volume
- Assessment of LV systolic function
- Assessment of LA size

LV structure - size and mass:

Based on the assumption that the left ventricle approximates a prolate ellipsoid, the LV volume can be estimate using either linear or two dimensional measurements.

The Simpson method of discs (single plane or bi plane) does not rely on rigid geometric assumption and therefore has been demonstrated to be more superior and accurate in measuring left ventricular volume. This is important because the left ventricular geometry may change to a significant extent in conditions such as after myocardial infarction.

The above said method requires accurate identification of endocardial border in apical four and two chamber views with the assistance of computer to measure the diameter of equally distributed slices along the left ventricle. The ideal method would however be to use three dimensional echocardiography as it has potential to decrease some of the many limitations of two dimensional echocardiography.

LV mass can be calculated using various formulae which take into account parameters such as chamber size and wall thickness. LV mass index however involves the use of height and weight in addition to those parameters used for LV mass determination.

A major pitfall is that accuracy of LV mass measurement is greatly reduced in the setting of altered ventricular geometry such as after myocardial infarction.LV hypertrophy is defined by a wall thickness of 12 mm or more.

LV systolic function:

LV systolic function can be assessed by various methods using echocardiography. The left ventricular ejection fraction or simply LVEF reflects left ventricular systolic function. It is given by the formula:

$$\frac{end\ diastolic\ volume - end\ systolic\ volume}{end\ diastolic\ volume} \times 100$$

and this is reported as a percentage. Generally, LV function is estimated visually although it requires assessment from calculation using ventricular volumes. Even in such a situation the accuracy of measurement is affected by various factors like – definition of endocardial border, quality of image, geometry of ventricle etc.

Several other methods are available for assessment of systolic function.

The Tei index, also known as myocardial performance index is aptly defined as the sum of isovolumic contraction time and isovolumic relaxation time divide by the ejection time. This takes into account both - diastolic and systolic performance. The lower the index, better the performance.

ADVANTAGES OF TEI INDEX:

1. It is an excellent marker for myocardial performance. It is not influenced by high left atrial loading pressure which is usually present in the later stages of diastolic heart failure. Hence, it may become an important tool for early diagnosis of upcoming ischemia of myocardium.
2. In elderly, it serves as a significant prognostic marker of cardiovascular mortality and morbidity.
3. Increased TEI index is associated with increased incidence of ventricular arrythmogenecity.

DISADVANTAGES OF TEI INDEX:

It does not allow evaluation of pathological substrate of myocardial dysfunction – because it does not evaluate myocardial pressure levels during ventricular filling levels in diastole.

It is therefore important to assess systolic function because it can aid in diagnosis, monitor therapy and risk sratification of various cardiovascular diseases.

Assessment of LA size:

Several methods can be used to quantify the size of left atrium accurately. One can obtain a linear measurement of left atrium in the parasternal long axis view. LA area can be accurately assessed from apical view. The volume of left atrium can be calculated using Simpson's biplane methods to the apical four chamber and two chamber view. The volumes obtained however, should be adjusted to body size. The function of left atrium with regard to the cardiac cycle can also be calculated. There are three important phases of left atrial function:

PHASES	DESCRIPTION
Reservoir phase	Atrium fills up rapidly due to inflow from pulmonary veins during early LV systole
Conduit phase	Emptying of left atrial blood into left ventricle passively due to early LV systole
Contractile phase	Augmentation of left ventricular filling by atrial contraction in late diastolic phase

Thus, both - active and passive emptying volumes of left atrium can be assessed.

LA passive emptying – given by maximal volume of LA – LA volume during atrial contraction.

LA active emptying – LA volume before atrial contraction - minimal LA volume.

LA enlargement has been linked to various adverse cardiovascular outcomes. There are numerous causes of LA enlargement including those due to LV diastolic and systolic dysfunction and atrial fibrillation. LA size reflects LV filling pressure and hence can reflect diastolic abnormalities[74].

INTERACTION WITH HYPERTENSION:

The morphological and clinical features of heart disease in diabetics with concurrent hypertension are more severe than those with diabetes or those with hypertension alone. Experimental studies have revealed that the interstitial connective tissue deposition is greater when the two diseases are present simultaneously. Besides it was also evident that the myocardium was susceptible to myocyte necrosis when the two were present together.

Hypertension can also be secondary to diabetes because sustained hyperglycemia has been shown to increase the blood pressure in animal models and this has been linked to angiotensin II. Also, it is found that there

is premature appearance of heart failure in such patients, and even when it occurs the progression is very rapid and the prognosis is very poor.

Association between hypertension and diabetes:

- Hypertension associated with type 2 diabetes mellitus (insulin resistance, syndrome X, metabolic syndrome)
- Hypertension associated with nephropathy in type 1 DM.
- Coincidental hypertension in patients with diabetes:
  - Essential hypertension
  - Isolated systolic hypertension
  - Renal scarring (from recurrent pyelonephritis)
- Diabetogenic antihypertensive drugs – these include
  - Potassium losing diuretics (chlorthalidone, high dose thiazide diuretics.
  - B blockers (high dose)
  - Combined diuretics and β blockers
- Drugs implicated in causing obesity, hypertension and glucose intolerance:
  - Glucocorticoids
  - Combined oral contraceptive pills
  - Antipsychotics

- Endocrine disorders causing hypertension and glucose intolerance:
  - Acromegaly
  - Cushing's syndrome
  - Conn's syndrome
  - Pheochromocytoma[75]

Thus the above causes should be kept in mind while evaluating cardiac function in patients with diabetes and hypertension.

Investigation in patients with diabetes and hypertension:

Initial investigations in type 2 DM with hypertension aims to initially rule out the rare causes of secondary hypertension; to assess the degree of tissue damage caused by both disorders and to identify other risk factors for the presence of vascular disease.

In obtaining medical history the following questions should be compulsorily addressed:

- Presence of cardiovascular symptoms
- Presence of previous urinary disease
- Smoking and alcohol abuse
- Previous or current medication history
- Family history of hypertension and cardiovascular disease

On examination of the patient, the following factors should be observed very carefully:

- Careful examination of blood pressure both -erect and supine and documentation
- Any evidence of left ventricular hypertrophy
- Any evidence of heart failure
- All peripheral pulses including a search for bruit
- Ankle - brachial index
- Fundus examination to check for changes of both diabetes and hypertension.

Patient should be investigated and the following aspects need special mention:

Electrocardiographic evidence of alteration in rate or rhythm, ischemic changes and evidence of left ventricular hypertrophy.

Chest X Ray evidence of cardiac enlargement and features of acute pulmonary edema.

Echocardiographic evidence of systolic function, ischemic changes suggested by regional wall motion abnormalities, dimensions such as LV mass and LA size, grading of diastolic dysfunction, assessment of ejection fraction etc.

Other routine blood investigations like renal function tests indicating renal dysfunction, if present and urine examination to detect microalbuminuria[76] should be done.

Treatment of hypertension in diabetes:

It is absolutely necessary to treat hypertension in diabetes to delay progression to various complications. Various trials conducted such as the HOPE trial (hypertensive optimal treatment and control), ABCD trial (appropriate blood pressure control in diabetes) and FACET trial (Fosinopril versus amlodipine cardiovascular events randomized trial showed that optimal control of blood pressure in diabetes reduced the risk of cardiovascular events[77].

The recent JNC 8 guidelines also recommend that a target level of systolic blood pressure of $\leq$ 140 mmHg and a diastolic blood pressure of $\leq$ 90 mmHg is optimal to prevent adverse cardiovascular outcomes.

The following measures can be adopted to retard the progression of cardiovascular outcome in patients with diabetes and hypertension:-

- **Non pharmacologic measures**: this includes
  - Weight reduction by exercise - 30 minutes of brisk walking per day for at least 5 days in a week.

- Salt restricted diet and avoiding foodstuffs with high salt content
- Diet modification - adoption of a diet rich in vegetables and fruits, and reduced consumption of foods rich in saturated fat.
- Smoking cessation.
- Alcohol restriction - not more than 2 – 3 units per day in men and 2 units per day in women.

When followed correctly the systolic and diastolic blood pressure can be reduced as much as 11 mmHg and 8mmHg respectively equivalent to many antihypertensive drugs. Thus, it is evident that lifestyle modifications indeed make a lot of difference in not only preventing the development of disease but also delays the development of complications once it has already developed.

- **Pharmacological measures:**

There are various classes of antihypertensive drugs available in the market for the treatment of systemic hypertension. Current guidelines recommend the use of four classes of drugs for control of blood pressure. These include ACE inhibitors like captopril, enalapril etc., Angiotensin receptor blockers like losartan, valsartan etc., Thiazide diuretics like chlorthalidone, hydrochlorothiazide etc. and Calcium channel blockers like amlodipine etc.

The other classes of antihypertensives are used in special situations.

The choice of antihypertensives depends on a variety of factors like age of the patient, volume status of the patient, presence of diabetes and hypertension, presence of complications like renal failure and hence the use of antihypertensives should be individualized. By and large, thiazide diuretics are found to be very effective in the management of patients with systemic hypertension. But, ACE inhibitors or AR blockers are preferred in patients with both diabetes and hypertension as they are found to retard the progression of microalbuminuria.

DYSLIPIDEMIA IN DIABETES:

On a comparative standpoint, targeting or treating patients with dyslipidemia effectively in diabetes has shown to be more effective in preventing macrovascular complications. The increased glycation of lipoproteins deserve special mention as it has direct effects on the metabolism of lipoproteins. These glycated lipoproteins are handled ina different way by lipoprotein receptors , particularly of the scavenger group, hence promoting atherogenesis.

Increased glycation also enhances the effects of oxidative stress on lipoproteins and hence affects both type 1 and type 2 diabetics.

The term used to describe such a situation is diabetic dyslipidemia which is characterized by elevated triglycerides, small dense low density lipoproteins and low high density lipoprotein concentration.

Some of the features implicated in the development of diabetic dyslipidemia includes:

- Influence of insulin on liver apolipoprotein production
- Down regulation of lipoprotein lipase in contrast to hepatic lipase
- Enhanced cholesteryl ester transfer activity protein
- Peripheral actions of insulin on adipose tissue and muscle

It is therefore necessary to control dyslipidemia in diabetics[78].

Various trials such as the 4S trial(Scandinavian Simvastatin Survival Study) and CARE trial (Cholesterol and Recurrent Events) established the fact that a decrease in blood lipid concentration reduced cardiovascular mortality. Another trial called the MRFIT (Multiple Risk Factor Intervention Trial) showed a curvilinear relationship between coronary heart disease mortality and total cholesterol levels in diabetic men with a four fold increased risk in diabetic men.

Based on these findings, it is prudent to maintain a LDL level of $\leq$ 100 mg/dl with the use of statins, and fibrates are added if the triglyceride levels

are ≥ 200 mg/dl. Rhabdomyolysis is a major concern when the two drugs are used together.

The American Diabetes association recommends that lipid profile consisting of LDL, HDL , total cholesterol and triglyceride levels be checked on an annual basis[79].

The treatment of dyslipidemia can be divided into non pharmacological and pharmacological measures:

- **Non pharmacological measures**:

These include measures such as life style modification including smoking cessation, restricted alcohol consumption, increased physical activity and dietary modifications.

- **Pharmacological measures**:

Use of statins - Statins have pleiotropic effects. They act by inhibiting the enzyme HMG Co A reductase , a key enzyme involved in cholesterol synthesis. As a result there is increased clearance of LDL cholesterol from blood and also decreased hepatic production of VLDL and LDL.

Other pleiotropic effects include:

- Decrease in the level of CRP or C Reactive Protein
- Increase in the collagen content of atherosclerotic plaque
- Alteration in the function of endothelium
- Decrease in the inflammatory component of plaque

The statins currently in use are atorvastatin, fluvastatin, simvastatin, pravastatin etc. There are many drugs which can affect the metabolism of statins.

The major side effects of statins are chiefly related to muscle symptoms which range from diffuse myalgias to myositis, defined by the presence of diffuse muscle pain with obvious evidence of muscle inflammation in the form of raised CK levels. They also cause reversible elevation of transaminases. They are however well tolerated by the patients only rarely requiring drug discontinuation[80].

Diabetes and metabolic syndrome:

Most patients with diabetes mellitus also have metabolic syndrome or syndrome X characterized by the following features:

CRITERIA	DESCTRIPTION
Obesity	Waist circumference > 40 cm in males > 35 cm in females
Hyperglycemia	Fasting plasma glucose ≥ 100 mg/dl or is on treatment for the same
Dyslipidemia	Triglyceride level ≥ 150 mg/dl or on treatment for the same
Dyslipidemia	HDL level <40 mg/dl in malea < 50 mg/dl in females
Hypertension	>135 mmHg systolic and >85 mmHg diastolic

Any 3 of the above criteria are sufficient to make a diagnosis of metabolic syndrome.

Various other organizations have mentioned different criteria for the diagnosis of metabolic syndrome.

The presence of metabolic syndrome in a patient with diabetes mellitus should prompt intensive therapy, else cardiovascular outcomes occurs at a much faster and earlier rate and mortality is very high.

INTERACTION WITH ISCHEMIC HEART DISEASE:

There is accelerated atherosclerosis in patients with diabetes mellitus which makes them prone to ischemic heart disease. The atheromatous lesions occur much earlier, very rapidly and are present in greater density in patients with diabetes mellitus. The atheromata are extensive, diffuse and involves the distal vessels in both peripheral and coronal circulation[81]. There are various reasons for the accelerated atherogenesis some of which are:

- Abnormalities in lipid metabolism such as high levels of lipoprotein (a)
- Increased Angiotensin II
- Endothelial dysfunction

The above factors together with many more result in accelerated atherogenesis which is influenced both by duration of diabetes and diabetes control.

STAGES OF DIABETIC CARDIOMYOPATHY[82]:

A classification system has been proposed by Maisth et al for diabetic cardiomyopathy. This includes:

(A) Stage 1 diabetic cardiomyopathy:

Heart failure with preserved ejection fraction or simply HFPEF – this is the earliest form of diabetic cardiomyopathy and is detected in approximately 75% of asymptomatic diabetic patients.

Relevant CAD, valvular disease and uncontrolled hypertension are usually not present.

(B) Stage 2 diabetic cardiomyopathy

Systolic and diastolic heart failure with dilatation and reduced ejection fraction. CAD, uncontrolled hypertension and valvular heart disease are usually not present.

(C) Stage 3 diabetic cardiomyopathy

Systolic and/or diastolic heart failure in diabetes with small vessel disease. There is presence of microbial infection and/ or inflammation and/or hypertension without CAD.

Hypertension, microangioapathy and myocarditis can be contributory.

(D) Stage 4 diabetic cardiomyopathy

Heart failure attributed to infarction or ischemia and also there is significant remodelling in addition to stage 3. In this stage the term usually used is heart failure in diabetes or stage 4 diabetic cardiomyopathy.

THERAPEUTIC INTERVENTIONS FOR DIABETIC CARDIOMYOPATHY:

(A) Diabetes control:

Prompt, early and appropriate therapy of diabetes is important as it improves myocardial function. The UKPDS study(United Kingdom Prospective Diabetes Study) did not actually reveal a significant benefit of intensive control of blood glucose o the risk of developing microvascular disease. However, the trial had some pitfalls which include:

(a)methodological pitfalls in that the study was not blinded and

(b) the study continued when no difference was observed at the initial agreed time point for analysis.

In contrast, the other studies have consistently revealed that early and intensive blood glucose control resulted in delayed development of cardiovascular outcomes and also microvascular complications. The control of glucose can be done with the help of various non pharmacologic and pharmacologic measures.

a. Non pharmacologic measures:

This chiefly includes lifestyle modification like increasing physical activity, diet modification- decreased consumption of foodstuffs with high glycemic index and avoidance of sweets, increased consumption of diet rich

in fibre content which not only helps in causing satiety but also helps in reducing weight. Other measures include as those described in the treatment of hypertension and dyslipidemia.

Patients should be educated regarding self monitoring of blood glucose which can help them make alterations in treatment.

b. Pharmacological measures

Various classes of oral antidiabetic agents are used nowadays. The most commonly prescribed initial drugs are biguanides like metformin and second generation sulfonylureas like glipizide, glibenclamide and glimiperide. Metformin is an insulin sensitizer and reduces blood glucose levels chiefly by decreasing hepatic glucose output – "plug's the leaky liver" and also gluconeogenesis it also improves peripheral glucose uptake. The drug is excreted by the kidney and hence cannot be administered if CRCl < 30 ml/min.

In addition, there are other classes of oral drugs like thiazolidinediones, alpha glucosidase inhibitors and the newer ones like GLP 1 analogues, DPP 4 inhibitors. The most recent is SGLT 2 inhibitors like canagliflozin.

Insulin therapy must be initiated early in patients with type 2 diabetics because it lowers the HbA1c values more efficiently. Therapy with oral drugs

or insulin is shown to decrease the structural and functional changes in the diabetic myocardium to some extent.

The choice of drugs used depends on various factors like the type of diabetes, the age of the patient, volume status of the patient, pharmacokinetic properties, side effect profile, the presence or absence of real dysfunction, the risk of hypoglcemia and presence of co morbid illnesses.

In developing countries another chief determinant is the cost of the drug. GLP 1 analogues deserve special mention. They have an impact on glucose metabolism and therefore on diabetes. The first drug to be marketed was exenatide and data revealed a significant reduction in HbA1c levels. They have been associated with improvement in various hemodynamic variables in patients with diabetes mellitus but without symptoms of overt heart failure. It was also noted there was significant improvement in cardiac parameters post infarction and in advanced heart failure[83]. Thiazolidinediones are generally not preferred due to their influence on cardiovascular morbidity and mortality. The other classes of drugs are being tested for their accuracy.

(B) Treatment of fibrosis:

It is now well established that renin- angiotensin –aldosterone system or simply RAA system plays an important role in the pathogenesis of diabetic cardiomyopathy. The ACE inhibitors like ramipril, enalapril, etc. can prevent

myocardial fibrosis, cardiac hypertrophy and myocardial mechanical dysfunction. They have also shown to prevent another important feature – coronary artery perivascular fibrosis and interstitial collagen deposition[84].

(C) Other novel therapies targeting diabetic cardiomyopathy -these include:

(A) AGE INHIBITORS -aminoguanidine, alanine aminotranferase946 and pyridoxamine.

(B) Copper chelating agents like trientene

(C) Modulators of free fatty acid metabolism – Trimetazidine.

Other aspects in the management of diabetes mellitus:

Keeping in the mind the complex interplay of various metabolic pathways and organ systems in diabetes mellitus – it is necessary to screen patients with diabetes for complications and treat them accordingly.

- Patients should be advised not to skip meals and avoid heavy meals and adhere to medications strictly.
- Patients should be taught to identify symptoms such as breathlessness, fatigue, abdominal pain, vomiting suggestive of acute complications like diabetic ketoacidosis.

- Patients should be screened for macrovascular complications like coronary heart disease and peripheral vascular disease.
- Patients should be screened for microvascular complications like diabetic retinopathy, neuropathy and in particularly nephropathy. The development of nephropathy in patients with diabetes mellitus indicates advanced disease and the condition has to be aggressively treated. The treatment has two important advantages. The progression to end stage renal disease can be delayed and also cardiovascular morbidity and mortality can prevented.
- Patients should be advised on maintainence of proper oral hygiene.
- Patients should be instructed on care of the feet – they should be advised to examine the foot daily for any wounds which are not healing, sensations, toes and toe clefts etc. They should be instructed to meet the physician every 3 months for examination of sensation and vibration in the feet.
- Diabetics are also prone for infections. They should be educated to identify the symptoms, seek medical attention for treatment. In particular, they are prone for skin and subcutaneous infections, urinary tract infections etc.
- Patients with diabetes can also have sexual dysfunction and they should be instructed to seek medical help.

- ❖ Depression among diabetic individuals is high. They should be identified and treated accordingly.

Therefore, treatment of diabetes does not stop with control of blood sugar levels alone; it also involves identification, monitoring and treating the complications in addition to emphasizing on self management.

MATERIALS

AND

METHODS

MATERIALS AND METHODS:

The study was conducted at the Institute Of Internal Medicine, Rajiv Gandhi Goverment General Hospital, and Madras Medical College, Chennai.

ETHICAL COMMITTEE APPROVAL:

Obtained.

CONSENT:

Written informed consent obtained.

STUDY DURATION:

April 2015 to September 2015.

STUDY POPULATION:

Patients attending the outpatient department of Institute of Internal Medicine and also patients admitted under Institute of Internal Medicine who satisfy inclusion and exclusion criteria.

SAMPLE SIZE:

One hundred individuals.

TYPE OF STUDY:

Observational study.

INCLUSION CRITERIA:

- Type 2 diabetics – newly detected and of any duration with or without treatment who are less than 60 years of age.

EXCLUSION CRITERIA:

Patients with -

- Hypertension,
- Coronary artery disease,
- Pregnant women,
- Pre existing heart disease,
- Clinical evidence of macrovascular disease like stroke, MI, peripheral vascular disease,
- Clinical evidence of microvascular disease.

DATA COLLECTION AND METHODS:

Relevant history was obtained from the subjects as per the questionnaire and the patient is also subjected to detailed physical examination. Informed as well as written consent was obtained from either the patients themselves or their legal representatives. Cases were screened

according to inclusion and exclusion criteria. Blood investigations were collected from the patients. Age, duration of diabetes, medication status, past history of coronary artery disease, peripheral vascular disease or stroke were obtained from self report. Patients were also screened for microvascular complications like retinopathy, nephropathy and neuropathy. Blood pressure was recorded using standardized sphygmomanometer. Investigations collected included renal function tests include electrolyte panel, liver function tests, complete hemogram, lipid profile and urine routine. Electrocardiograph and echocardiograph were performed. HbA1c levels were also obtained. The data collected were entered into the proforma and subjected to statistical analysis.

STATISTICAL ANALYSIS:

Analysis was done using SPSS Version 20. Significance was assumed with a p value of 0.05. Association between two categorical variables was done using chi square test. All p values were two tailed and significant when values were less than 0.05.

OBSERVATION

AND

RESULTS

OBSERVATION AND RESULTS

DATA OBTAINED FROM THE STUDY:

CHART 1 : MEAN HbA1C AND GRADES OF DIASTOLIC DYSFUNCTION

GRADES OF DIASTOLIC DYSFUNCTION	N (SAMPLE)	MEAN HbA1C	STANDARD DEVIATION	
NO GRADE	15	7.450	0.5574	F VALUE – 102.036 P VALUE - <0.001
GRADE 1	48	8.946	0.8932	
GRADE 2	27	10.341	0.9271	
GRADE 3	10	13.360	1.2791	
TOTAL	100	9.519	1.8145	

CHART 2: MEAN DURATION OF DIABETES IN MONTHS AND GRADES OF DIASTOLIC DYSFUNCTION

GRADES OF DIASTOLIC DYSFUNCTION	N (SAMPLE)	MEAN DURATION IN MONTHS	STANDARD DEVIATION	
NO GRADE	15	11.250	12.1463	F VALUE – 209.379 P VALUE - <0.001
GRADE 1	48	60.250	15.9447	
GRADE 2	27	119.556	24.1109	
GRADE 3	10	182.400	29.8262	
TOTAL	100	80.436	52.7934	

CHART 3: MEAN AGE IN YEARS AND GRADES OF DIASTOLIC DYSFUNCTION

GRADES OF DIASTOLIC DYSFUNCTION	N (SAMPLE)	MEAN AGE IN YEARS	STANDARD DEVIATION	
NO GRADE	15	48.875	3.9306	F VALUE – 23.273 P VALUE - <0.001
GRADE 1	48	50.521	4.4050	
GRADE 2	27	56.481	3.1910	
GRADE 3	10	57.600	3.3400	
TOTAL	100	52.554	5.0941	

CHART 4: LV MASS AND GRADES OF DIASTOLIC DYSFUNCTION

GRADES OF DIASTOLIC DYSFUNCTION	N (SAMPLE)	MEAN LV MASS IN GRAMS	STANDARD DEVIATION	
NO GRADE	15	93.500	14.8369	F VALUE – 73.276 P VALUE - <0.001
GRADE 1	48	201.917	32.2720	
GRADE 2	27	226.889	36.5412	
GRADE 3	10	249.300	36.2861	
TOTAL	100	196.109	56.8127	

CHART 5: LA SIZE AND GRADES OF DIASTOLIC DYSFUNCTION

GRADES OF DIASTOLIC DYSFUNCTION	N (SAMPLE)	MEAN LA SIZE IN MM	STANDARD DEVIATION	
NO GRADE	15	25.419	0.6635	F VALUE – 34.966 P VALUE - <0.001
GRADE 1	48	26.715	4.1241	
GRADE 2	27	31.059	1.8923	
GRADE 3	10	35.670	1.5449	
TOTAL	100	28.557	4.3773	

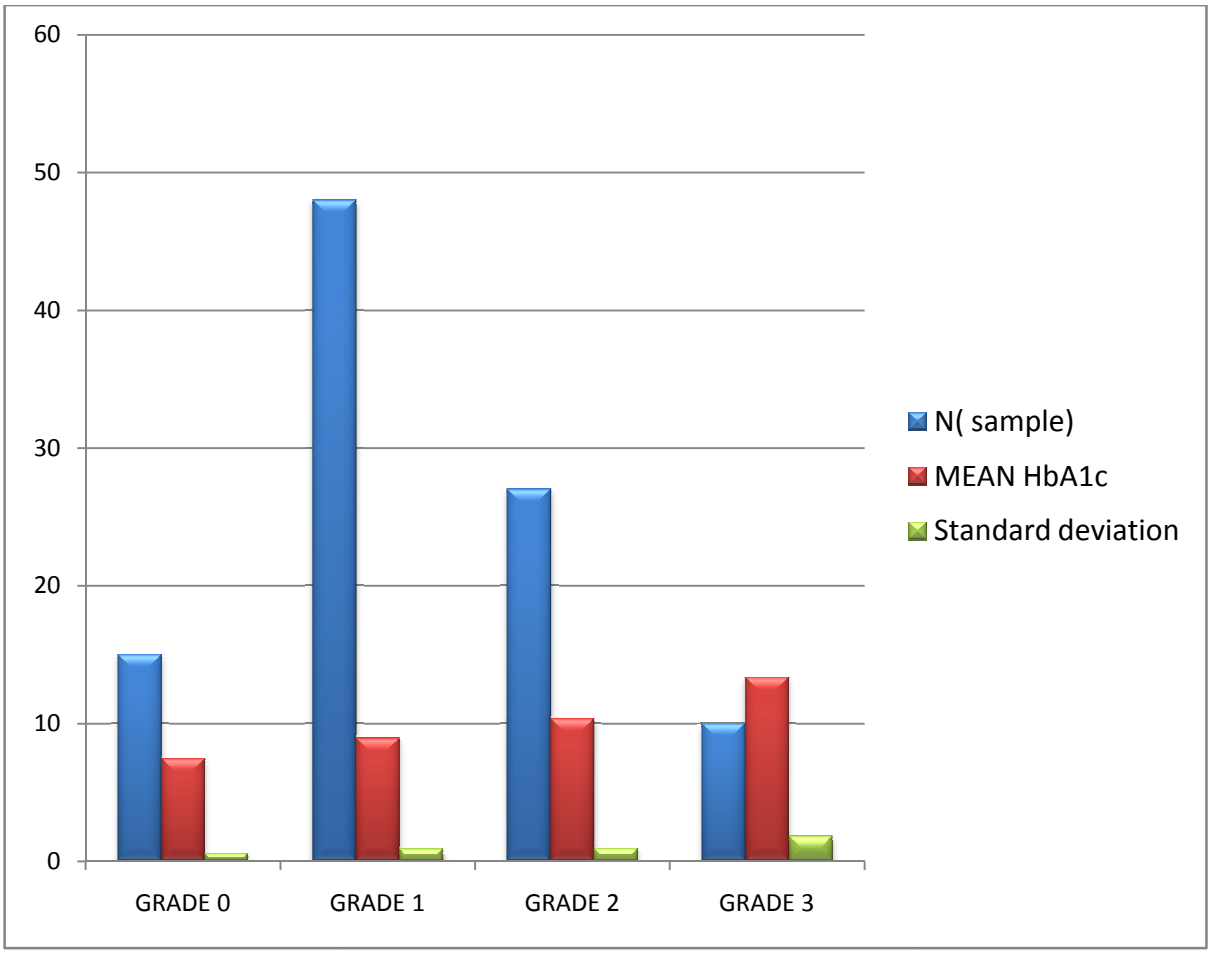
CHART 6: OHA AND INSULIN CROSS TABULATION

			GRADES OD DIASTOLIC DYSFUNCTION			TOTAL
			NO	1	2	3	
	I	COUN T	0	26	17	0	43
		% WITH INSULIN	0	60.5	39.5	0	100
		% WITH DIASTOLIC DYSFUNCTION	0	54.2	63	0	42.6
	O+1	COUN T	0	0	10	10	20
		% WITH INSULIN	0	0	50	50	100
		% WITH DIASTOLIC DYSFUNCTION	0	0	37	100	19.8
	0	COUN T	15	22	0	0	38
		% WITH INSULIN	42.1	57.9	0	0	100
		% WITH DIASTOLIC DYSFUNCTION	100	45.8	0	0	37.6
		COUN T	15	48	27	10	100
		% WITH INSULIN	15.8	47.5	26.7	9.9	100
		% WITH DIASTOLIC DYSFUNCTION	100	100	100	100	100

CHART 7: DIASTOLIC DYSFUNCTION AND SEX

			GRADES OF DIASTOLIC DYSFUNCTION				TOTAL
			NO	1	2	3	
SEX	F	COUNT	7	26	15	5	53
		% WITH DIASTOLIC DYSFUNCTION	43.8	54.2	55.6	60	53.5
	M	COUNT	9	22	12	4	47
		% WITH DIASTOLIC DYSFUNCTION	56.2	45.8	44.4	40	46.5
TOTAL		COUNT	16	48	27	9	100
		% WITH DIASTOLIC DYSFUNCTION	100	100	100	100	100

CORRELATION BETWEEN HbA1c LEVELS AND GRADES OF DIASTOLIC DYSFUNCTION

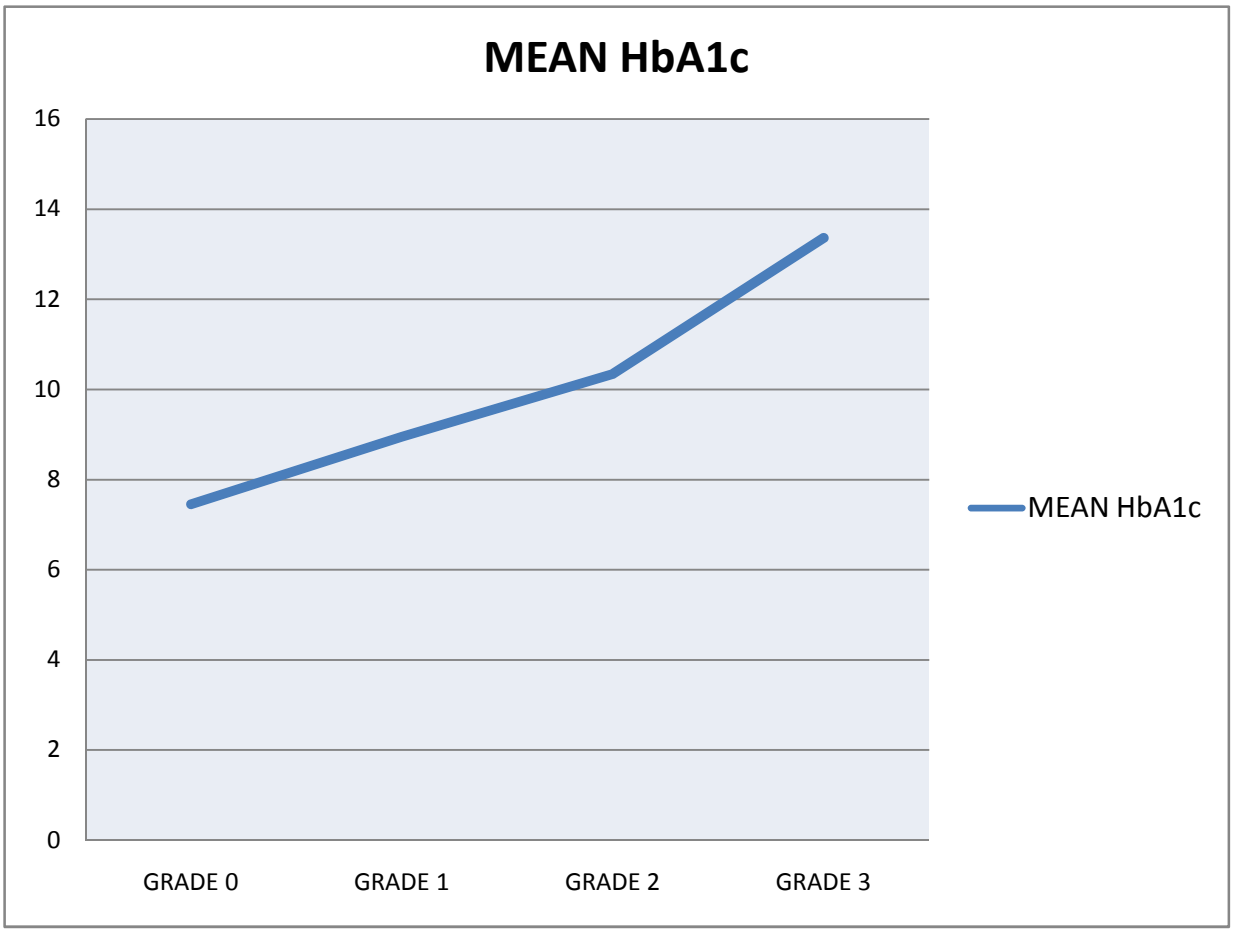


Bar diagram indicating mean HbA1c levels and grades of diastolic dysfunction.

F value – 102.036

P value - < 0.001

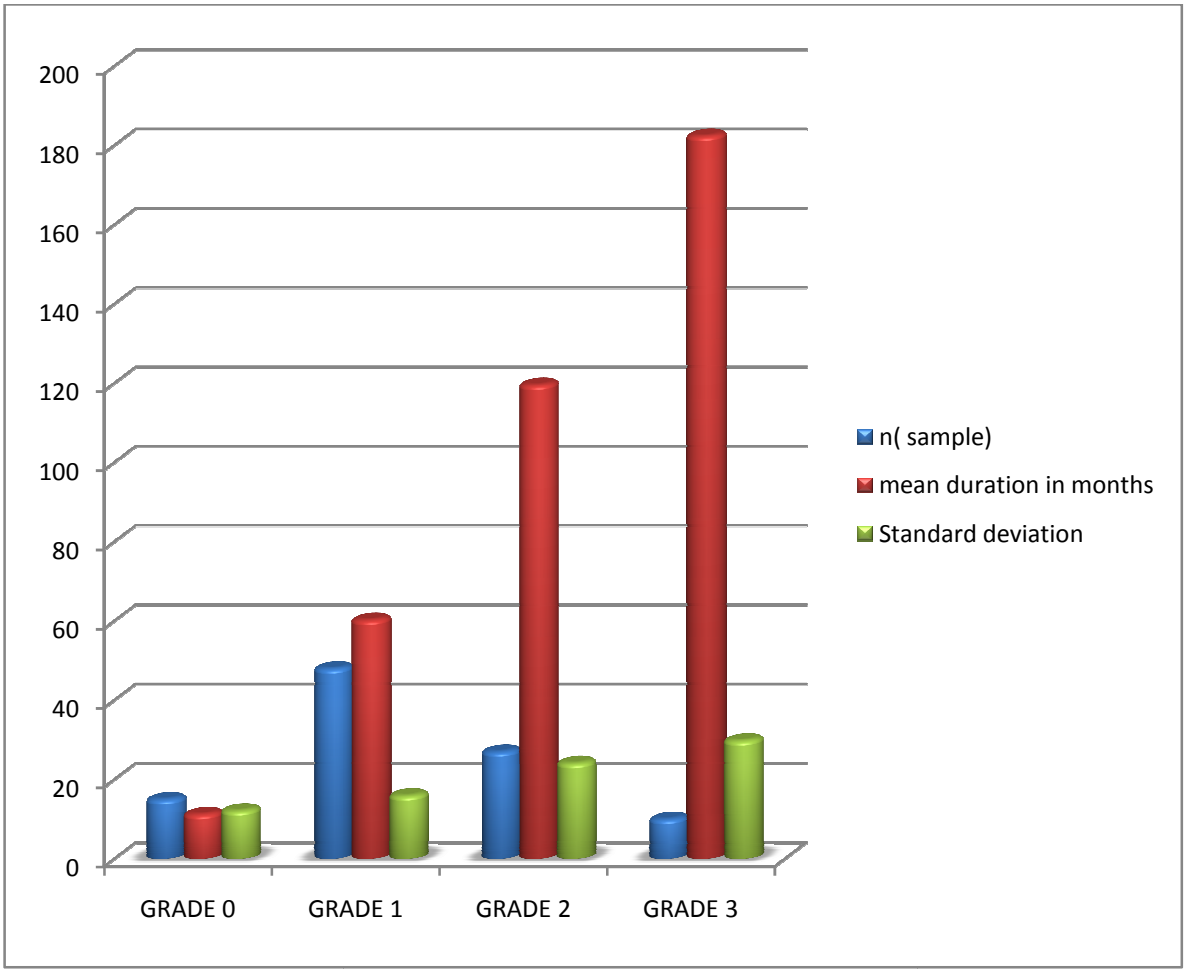
Line diagram indicating correlation between HbA1c levels with grades of diastolic dysfunction.



Bar diagram indicating mean duration of type 2 diabetes in months and grades of diastolic dysfunction.

F value – 209.379

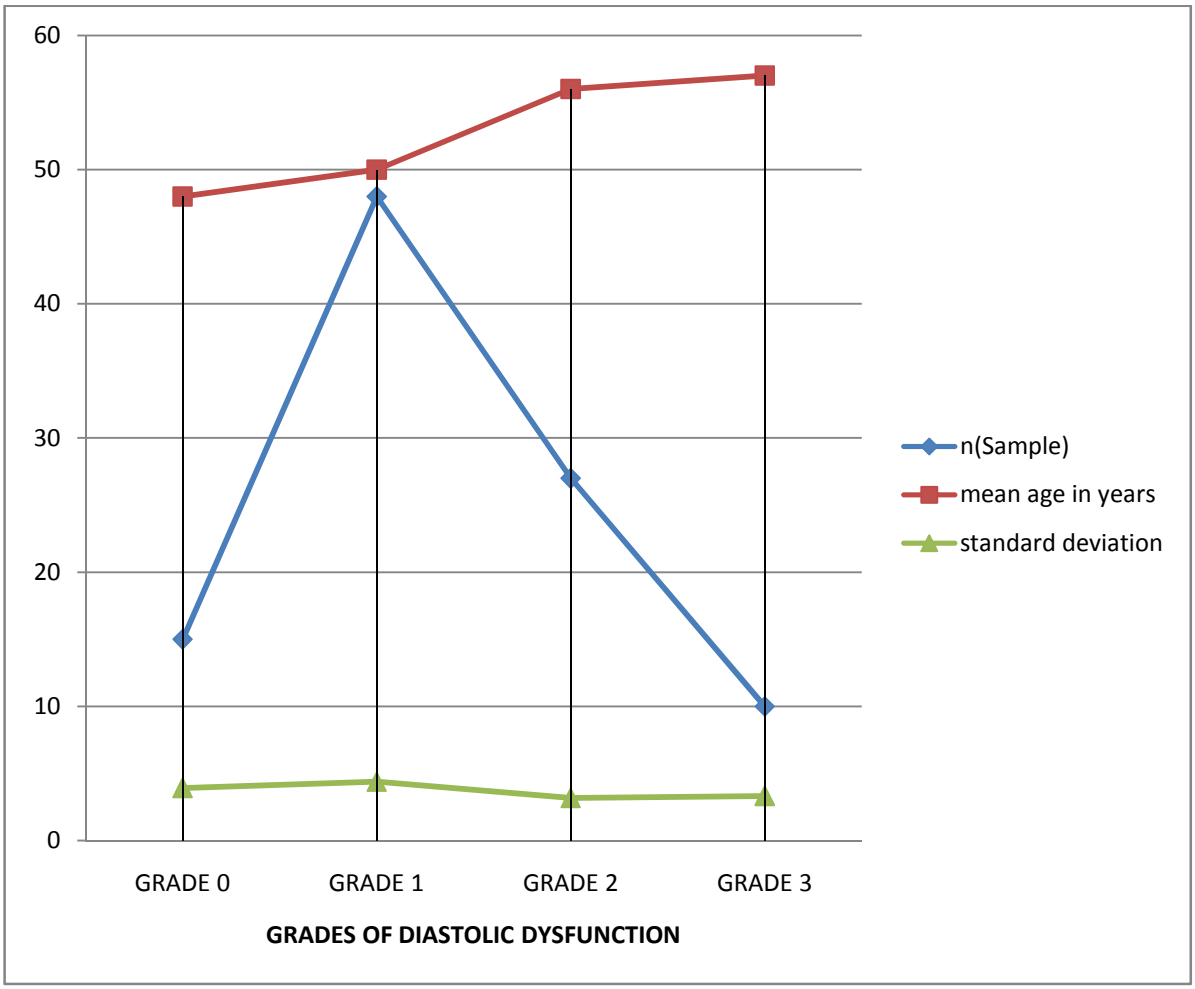
p value <0.001



Line diagram indicating correlation between mean age of patients in years and grades of diastolic dysfunction.

F value 23. 273

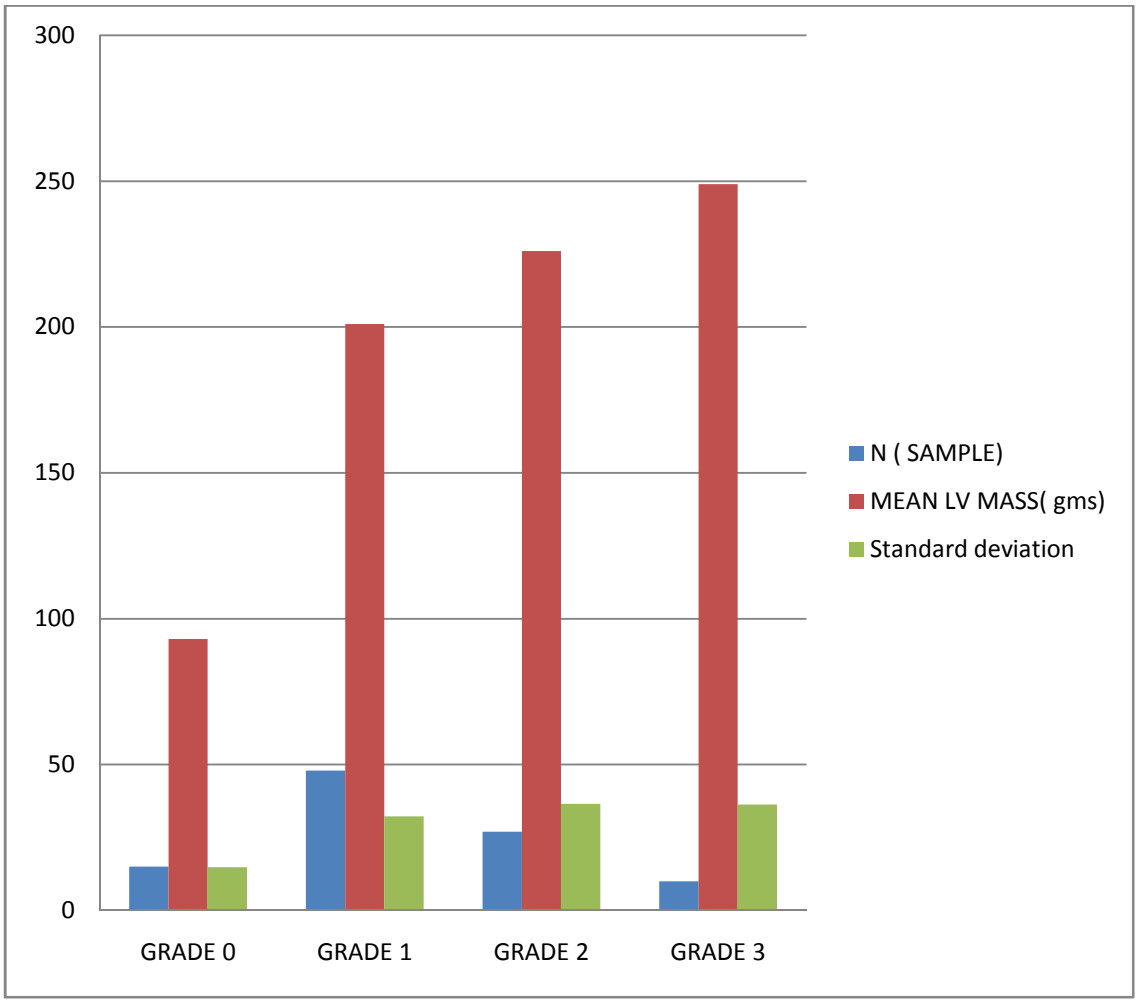
P value <0.001



LV MASS (LINEAR VIEW) AND DIASTOLIC DYSFUNCTION

F value -73.276

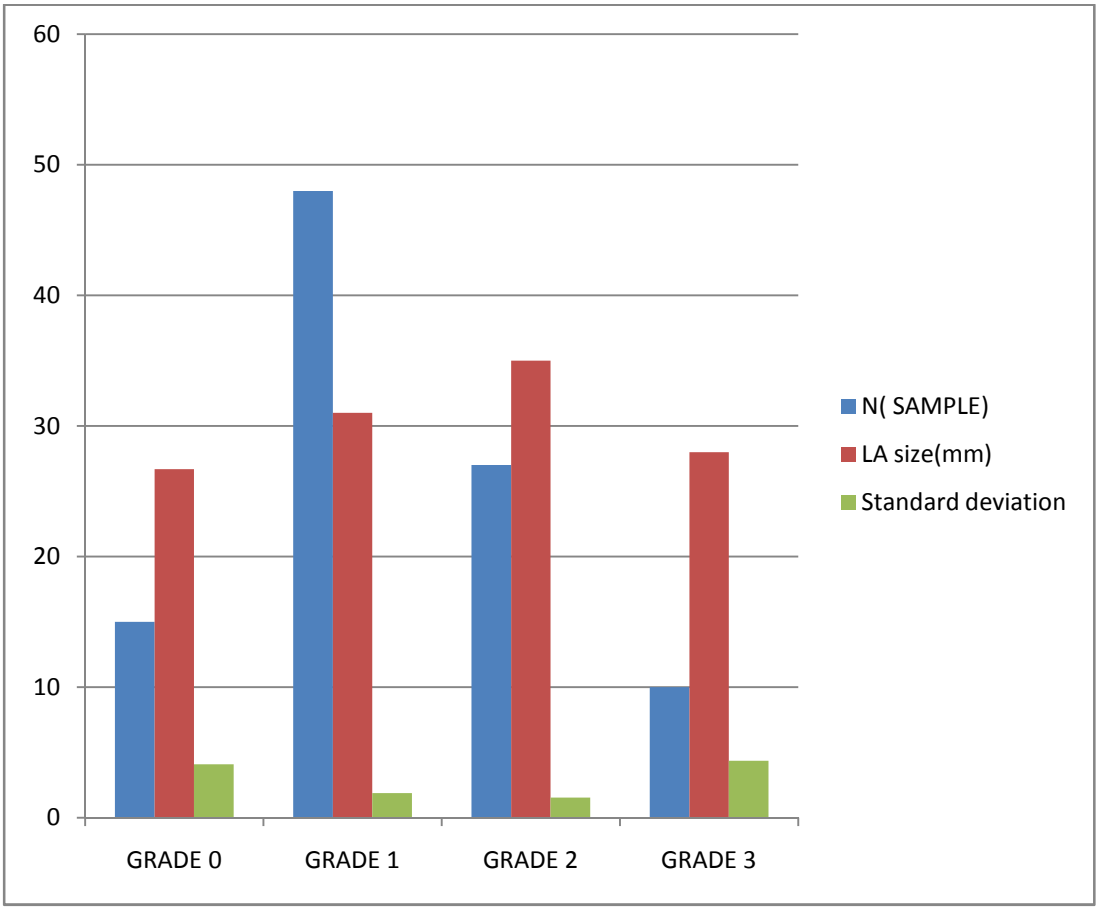
p value <0.001



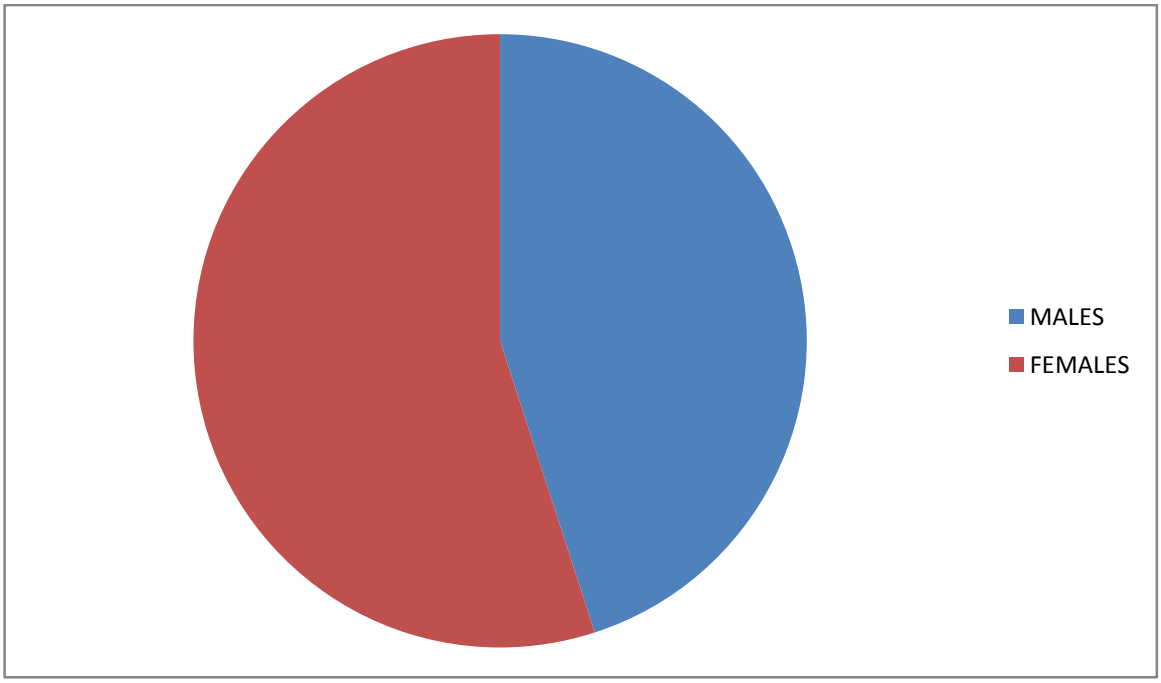
LA SIZE AND GRADES OF DIASTOLIC DYSFUNCTION

F value - 34.966

p value <0.001



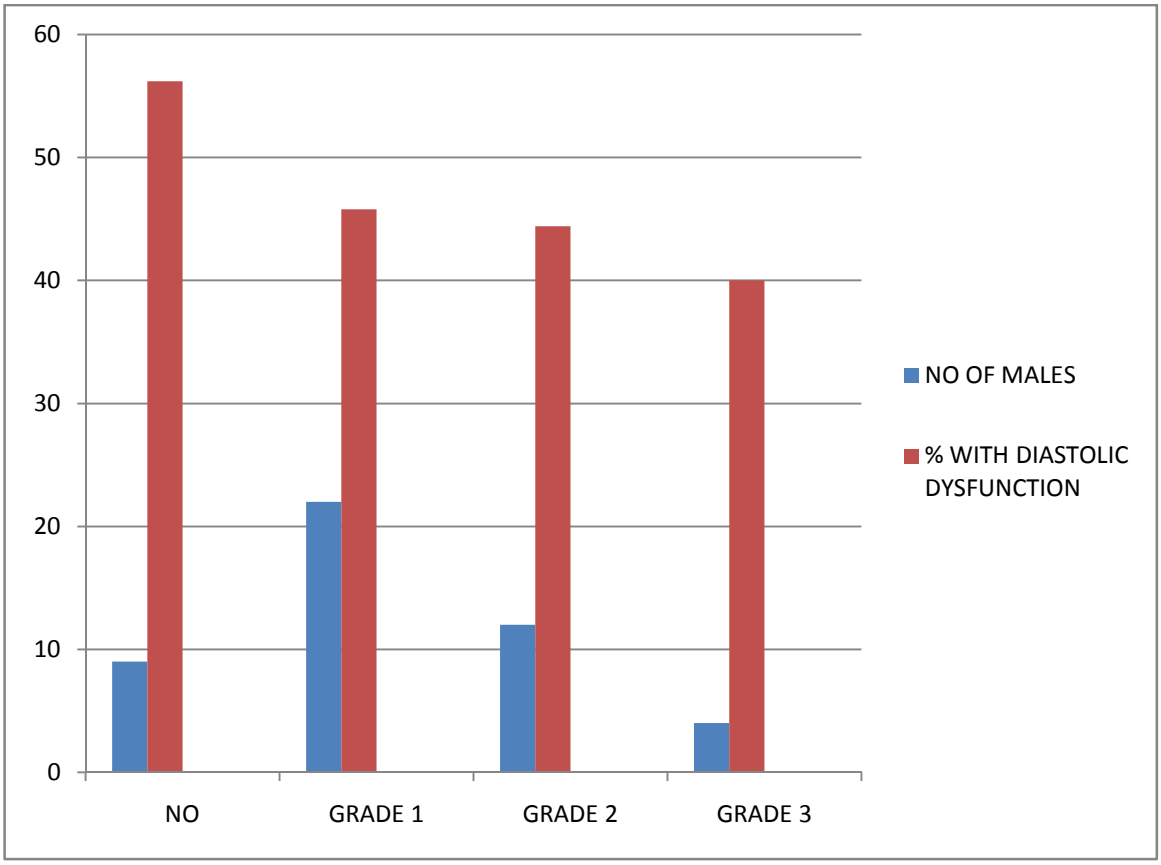
TOTAL NUMBER OF MALES AND FEMALES IN THE STUDY



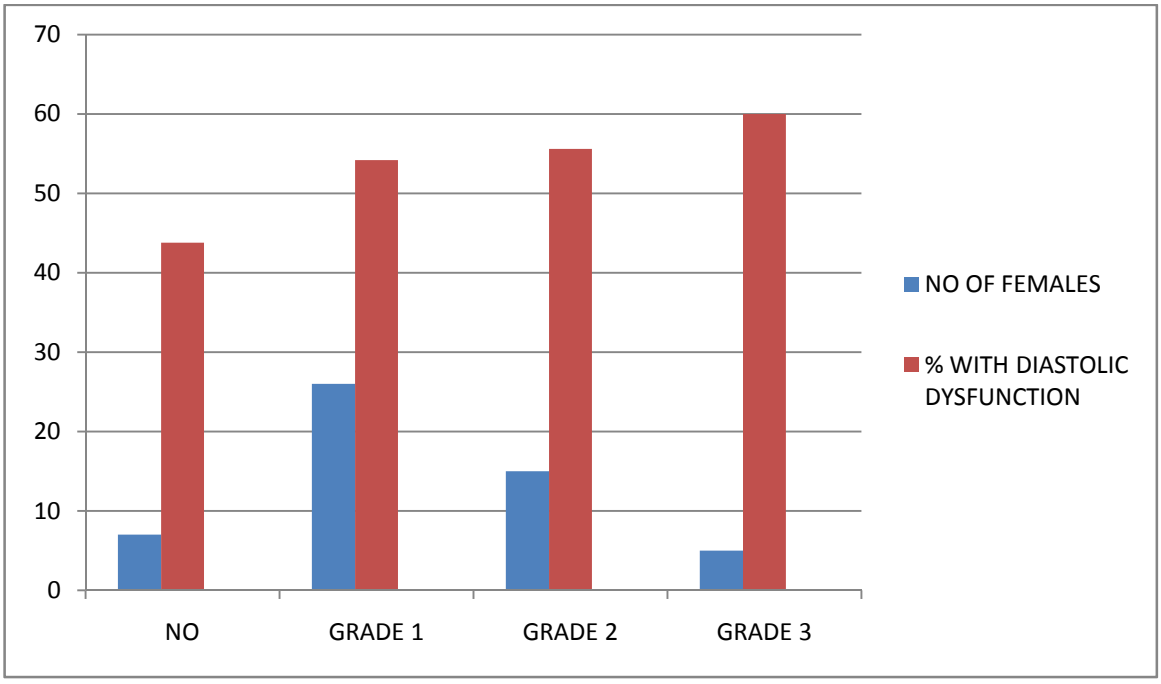
MALES : 46

FEMALES : 54

MALES AND DIASTOLIC DYSFUNCTION



FEMALES AND DIASTOLIC DYSFUNCTION



CHI SQUARE TEST -0.836 ,

df -3,

p value -0.841 (not significant)

DISCUSSION

DISCUSSION

A total of hundred patients were selected for the study which included both males and females. The study was conducted in the institute of internal medicine, Rajiv Gandhi Government General Hospital. Cases were selected from both inpatient and outpatient departments. The male population amounted to 46 and female population amounted to about 54. Routine investigations were performed. Serum glycated haemoglobin was determined by high performance liquid chromatography. ECG and echocardiography was performed for all tghe patients and the results were tabulated.

The data was documented and subjected for statistical analysis.

The following parameters or endpoints were focused upon:

1. To correlate serum HbA1c levels with grades of diastolic dysfunction.
2. To correlate mean age of the patient with diastolic dysfunction.
3. To correlate mean duration of type 2 diabetes mellitus and grades of diastolic dysfunction.
4. To correlate LA size and LV mass with grades of diastolic dysfunction.
5. To observe the number of patients on different therapeutic modalities for diabetes mellitus –either oral antidiabetic agents or oral agents plus insulin therapy or on insulin therapy alone.
6. To correlate diastolic dysfunction with sex.

Statistical analysis was performed and results were derived to find if statistically significant correlation existed or not.

1. **Correlation of serum glycated haemoglobin levels and grades of diastolic dysfunction in asymptomatic type 2 diabetics:**

The tests performed included analysis of variance. It was found that the correlation between mean serum glycated haemoglobin levels and grades of diastolic dysfunction was statistically significant with a p value of < 0.001.

It was found that around 48 patients with type 2 DM –both males and females included had a mean HbA1c levels of 8.94 and grade 1 LVDD and likewise 27 patients had mean HbA1c levels of 10.34 and grade 2 LVDD. The 10 patients who had a mean HbA1c level of 13.36 had grade 3 LVDD.15 patients were found to have no LVDD. The study was similar to other studies which demonstrated a direct correlation between HbA1c levels and grades of diastolic dysfunction[85].

2. **Correlation of mean age of patient with grades of diastolic dysfunction.**

The tests performed included analysis of variance. It was found that the correlation between mean age of patients and grades of diastolic dysfunction was statistically significant with a p value of < 0.001.

It was found that around 48 patients with type 2 DM –both males and females included had a mean age of 50 yrs and grade 1 LVDD, likewise 27 patients had mean age of 56.48 and grade 2 LVDD. The 10 patients whose mean age was 57.6 years had grade 3 LV diastolic dysfunction.

3. Correlation between mean duration of diabetes in months and grades of diastolic dysfunction:

The tests performed included analysis of variance. It was found that the correlation between mean duration of diabetes in months and grades of diastolic dysfunction was statistically significant with a p value of < 0.001.

It was found that around 48 patients with type 2 DM –both males and females included had a mean duration of diabetes for 60 months and grade 1 LVDD, likewise 27 patients had mean duration of diabetes for 119.55 months and grade 2 LVDD. 10 patients who had grade 3 LVDD had diabetes for a mean duration of 182.4 months. The study results were comparable to other studies in which higher grades of diastolic dysfunction correlated with increased duration of diabetes mellitus.

4. Correlate LA size and LV mass with grades of diastolic dysfunction.

The normal LV mass depends on the age and sex of the patients. Usually it is between 67 -162 grams in women and 88 -224 in men.

It was however noted that there existed a statistically significant correlation between LV mass and grades of diastolic dysfunction. 10 diabetics with grade 3 LVDD had a mean LV mass of 249 gms. On the other hand 27 diabetics with grade 2 LVDD had mean LV mass of 226.8 gms. Lastly, 48 diabetics with grade 1 LVDD had mean LV mass of 201.9 gms.

The results were found to be statistically significant with a p value of less than 0.001. A study performed by Voulgeri CH, Tentolouris N, Moyassakis I et al revealed similar results[86].

The normal LA size also depends on the age and sex of the individual. The usual reference range is 27 -33mm in women and 30 -40 in men.In the study, it was inferred that there exists a statistically significant relationship between LA size and grades of diastolic dysfunction.

10 diabetics with grade 3 LVDD had a mean LA size of 35.6 mm. On the other hand it was noted that 27 patients with grade 2 LVDD had a mean LA size of 31.05mm. 48 diabetics with grade 1 LVDD had mean LA size of 26.71 mm.

The results were statistically significant with a p value of less than 0.001.

5. Correlation between grades of diastolic dysfunction and sex:

The study revealed that a statistically insignificant correlation existed between grades of diastolic dysfunction and sex of the individual with a p value of 0.841.

Lastly, observations were made regarding the therapeutic modalities in type 2 diabetics and it was found that most patients with higher grades of diastolic dysfunction required dual therapy including oral antidiabetic agents and insulin therapy.

Thus it was concluded that poorly controlled hyperglycemia had a poor outcome with respect to cardiovascular function.

CONCLUSIONS

CONCLUSIONS

The study revealed the following conclusions:

Type 2 diabetics with a poorly controlled blood sugar levels had poor cardiovascular function. This is revealed in the form of:

1. Statistically significant correlation between mean HbA1c levels and grades of diastolic dysfunction.
2. Statistically significant correlation between duration of diabetes and grades of diastolic dysfunction.
3. Statistically significant correlation between age of patients and grades of diastolic dysfunction.
4. Statistically significant correlation between LV mass and grades of diastolic dysfunction.
5. Statistically significant correlation between LA size and grades of diastolic dysfunction.
6. Statistically insignificant correlation between grades of diastolic dysfunction and sex.

The study in turn highlights the fact that screening of patients with diabetes mellitus at the incipient stage and constant motivation of diabetics towards good sugar control may help preventing adverse cardiovascular outcomes.

LIMITATIONS

LIMITATIONS

There are various limitations of the study:

1. Age influences diastolic function. It is a well known fact that as a patient ages there is some degree of diastolic dysfunction.

2. Other co morbid illnesses like hypertension and obesity can also influence diastolic function. Presence of these risk factors accelerates the deterioration of cardiac function.

3. The study excluded those patients with clinical evidence of microvascular disease. This microvascular disease can already be present in a diabetic patient without the presence of overt symptoms.

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ANNEXURES

PROFORMA

CORRELATION OF HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS

Name: Age: Sex:

Patient ID: Contact number: Occupation:

- NAME:
- AGE:
- SEX:
- OP NUMBER:
- **TYPE 2 DIABETES** - DURATION:
  TREATMENT:
  OHA/INSULIN:

- **PAST HISTORY** –
  HYPERTENSION: CAD: PVD:
  STROKE: RENAL DISEASE:
  PREGNANCY - YES: NO: N/A

- **CLINICAL EXAMINATION**:
- PALLOR:
- ICTERUS:
- CYANOSIS:
- CLUBBING:
- GENERALIZED LYMPAHADENOPATHY:
- PEDAL EDEMA:

- **SYSTEMIC EXAMINATION**:

CVS: RS:

CNS: PA:

INVESTIGATIONS:

1. **FASTING PLASMA GLUCOSE:**
2. **HbA1C level**
3. **Urine routine** - **Albumin** - **Sugar –**
4. **ECG:**
5. **ECHOCARDIOGRAPHY FINDINGS:**

TRANSMITRAL INFLOW VELOCITY –

E - **A**- **DT –**

TISSUE DOPPLER LATERAL ANNULUS VELOCITY –

E’ - **A’**- **E’/A’**

LA SIZE –

LV END DIASTOLIC PRESSURE –

LV SYSTOLIC FUNCTION - EF –

LV MASS

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Sandeep Srinivas
Postgraduate M.D.(General Medicine)
Madras Medical College
Chennai 600 003

Dear Dr.Sandeep Srinivas,

The Institutional Ethics Committee has considered your request and approved your study titled **"Correlation of HbA1C levels with grades of diastolic dysfunction in asymptomatic Type 2 Diabetic individuals" No.29042015.**

The following members of Ethics Committee were present in the meeting held on 07.04.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor of Surgery, MMC	: Member
6. Prof.S.Baby Vasumathi, Director, Inst. Of O&G, MMC	: Member
7. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
10.Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

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

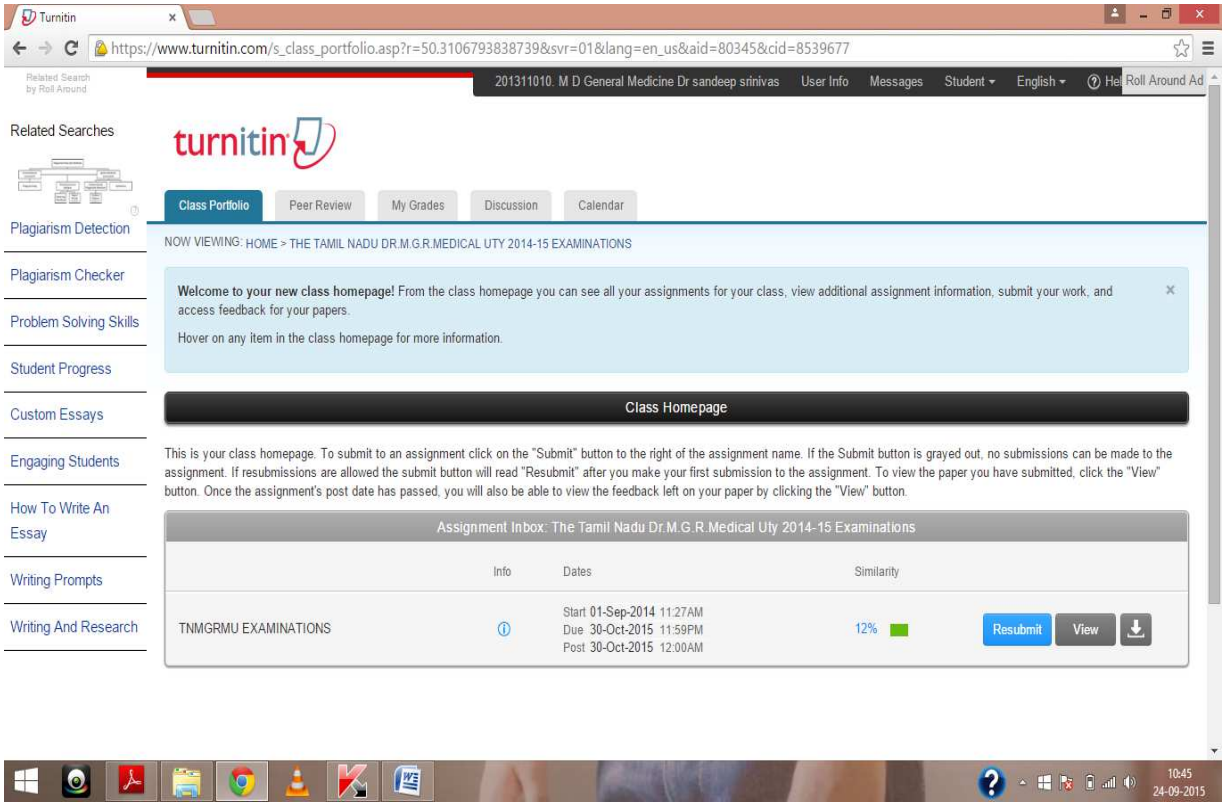
The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

13/4/15

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
Chennai-600 003

TURNITIN PLAGIARISM SCREENSHOT



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INTRODUCTION

INFORMATION SHEET

We are conducting a study on "**CORRELATION OF HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS"** among outpatients visiting Government General Hospital, Chennai and for that your sample may be valuable to us.

The purpose of this study is to correlate between HbA1C levels with grades of diastolic dysfunction in asymptomatic type 2 diabetic individuals .

We are selecting certain cases and if found eligible, we will be using your 4ml of blood sample to be collected in sodium citrate tube to perform fasting plasma glucose and HbA1C levels. A routine urine examination will also be performed. An ECG and perform a 2D echocardiography to determine the cardiac status.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

Date

ஆராய்ச்சி தகவல் தாள்

நாங்கள் ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, புறநோயாளிகளின் மத்தியில் நோய் அறிகுறி இல்லாத இரண்டாம் வகை நீரிழிவு நோய்களின் கிளைகேடட் ஹீமோகுளோபின் அளவிற்கும் இருதய விரிவுநிலை செயல்பாடு பாதிப்பு அளவிற்கும் உள்ள தொடர்பு நிலையை விளக்கும் ஆய்வு மேற்கொள்கிறோம்.

நாங்கள் உங்களிடமிருந்து பெறும் மாதிரிகள் முக்கியமானவை என்பதை தெரிவிக்கின்றோம்.

நீங்கள் இந்த ஆய்விற்கு தகுதியானவர்களாக இருக்கும் பட்சத்தில் தங்களிடமிருந்து 4 மி.லி அளவு இரத்தம் பெற்று அதில் சாப்பிடும் முன் இருக்கும் சர்க்கரை அளவும், கிளேகேடட் ஹீமோகுளோபின் அளவும் பரிசோதிக்கப்படும். சிறுநீர் பரிசோதனை, இருதய சுருள் படம் மற்றும் இருதய செயல்பாடு மின் ஒலி இருதய வரைவு (ECHO) வாயிலாக கண்காணிக்கப்படும்.

தங்களுடைய தனிப்பட்ட தகவல்களோ அல்லது தங்களின் உடல்நிலை பற்றிய குறிப்புகளோ எவ்வித வெளியீடாகவோ அல்லது அறிக்கையாகவோ வெளியடப்படமாட்டாது என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி :

CONSENT FORM

Study Title	:	**CORRELATION OF HbA1C LEVELS WITH GRADES OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETIC INDIVIDUALS**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Name	:	
Age/Sex	:	
Identification Number	:	

Patient may check (☑) these boxes

The details of the study have been provided to me in writing and explained to me in my own language ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study. ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological and biochemical tests. ❑

Signature/thumb impression of patient

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name :Dr. SANDEEP SRINIVAS

சுய ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு

நோய் அறிகுறி இல்லாத இரண்டாம் வகை நீரிழிவு நோயாளிகளின் கிளைகேடட் ஹீமோகுளோபின் அளவிற்கும் இருதய வரைவு நிலை செயல்பாடு பாதிப்பு அளவிற்கும் உள்ள தொடர்பு நிலையை விளக்கும் ஆய்வு

ஆய்வு நிலையம் : பொது நல மருத்துவத்துறை,
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 600 003.

பங்கு பெறுவரின் பெயர் :

பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

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

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

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

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

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

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

ஆய்வாளரின் பெயர் .....

MASTER CHART

S.No.	NAME	AGE	SEX	DURATION	OHA(O) / INSULIN(I)	HbA1C	LA SIZE (mm)	SYSTOLIC FUNCTION (EF)%	LV DIASTOLIC DYSFUNCTION	LV MASS (gms)
1	JAYAMMA	60	F	96	I	9.6	29	58	GRADE 2	190
2	VEERAPPAN	58	M	156	O+I	13	36	66	GRADE3	300
3	RAVANAMAL	60	F	168	O+I	14.1	37	56	GRADE 3	224
4	SUBRAMANI	55	M	12	O	7.3	25	57.3	NO	98
5	DANIEL	48	M	48	I	11.6	27	60	GRADE 1	234
6	ANBU SELVAN	50	M	24	O	7.5	26	61.7	NO	120
7	SULOCHANA	50	F	72	I	11.6	30	71	GRADE1	166
8	SABASTHIYAMMAL	50	F	180	O+I	14	37.5	64	GRADE 3	220
9	SABINA BEE	49	F	1	O	7.5	25.5	65.4	NO	75
10	EKAMBARAM	48	M	2	O	9	26.7	60	NO	106
11	MUNIYAMMAL	46	F	3	O	8	27	66	NO	110
12	ANANDHAN	50	M	60	I	9	28.2	58	GRADE 1	246
13	RAJIV	55	M	36	O	7	25.6	62	NO	98
14	ANWAR SHERIFF	60	M	240	O+I	10	37	55	GRADE 3	265
15	THANGAVEL	51	M	1	O	8	25.4	64.6	NO	108
15	MUTHU	48	M	1	O	7	25	60	NO	90
16	MUNNUSAMY	47	M	36	I	8.6	27	60	GRADE 1	244
17	ANDRUSE	57	M	180	O+I	12.7	34.5	62	GRADE 2	270
18	SRINIVASAN	51	M	120	I	11.6	33	60	GRADE 2	238
19	SHABEENA	41	F	24	O	8	31.5	66	GRADE 1	170
20	MOORTHY	50	M	60	I	9	30	64	GRADE 1	228

S.No.	NAME	AGE	SEX	DURATION	OHA(O) / INSULIN(I)	HbAIC	LA SIZE (mm)	SYSTOLIC FUNCTION (EF)%	LV DIASTOLIC DYSFUNCTION	LV MASS (gms)
21	JEEVARATHNAM	47	F	36	I	9.6	27.5	70	GRADE 1	165
22	MOHAIYAR	55	M	36	O	7.5	25	6O	NO	98
23	MANJITH BASHA	50	M	5	O	7	25.5	64.2	NO	100
24	SUBRAMANIAN	59	M	96	I	10.2	30	65	GRADE 2	265
25	KUMAR	46	M	72	I	8.2	27	60	GRADE 1	246
26	NARAYANAN	54	M	60	O	9	26.5	64.5	GRADE1	230
27	GOVINDARAJ	49	M	120	I+O	9.8	34	60.7	GRADE2	260
28	MOHAN	53	M	84	I	8.8	28	56.8	GRADE1	250
29	SELVI	47	F	8	O	7.9	24.5	67.5	NO	88
30	VANITHA	55	F	60	I	8.8	27	59	GRADE 1	170
31	KAVITHA	59	F	144	I+O	9.5	33	60	GRADE 2	190
32	SURIYA	45	F	12	O	7	25	66	NO	70
33	SANGEETHA	60	F	180	I+O	11	34	62.8	GRADE 2	201
34	CHANDRA	58	F	120	I	12.2	32	68	GRADE 2	196
35	KANDASAMY	54	M	108	I	10.5	29.5	59	GRADE 2	267
36	BALU	60	M	84	I	10.8	27	60.8	GRADE 1	235
37	MADHU	42	F	8	O	7.5	25	57.8	NO	70
38	RAJA	43	M	6	O	7	25.5	70	NO	89
39	RAVI	46	M	48	I	8.4	28	70	GRADE 1	244
40	SANTHOSH	56	F	96	I	9.4	29.7	68	GRADE 2	208

S.NO.	NAME	AGE	SEX	DURATION	OHA(O)/ INSULIN(I)	HbA1C	LA SIZE (mm)	SYSTOLIC FUNCTION (EF)%	LV DIASTOLIC DYSFUNCTION	LV MASS (gms)
41	SUMITHRA	55	F	72	I	8.2	27	56	GRADE 1	165
42	MOHAN	45	M	60	O	9	26	68	GRADE 1	226
43	VELLAMMAL	47	F	48	O	8.6	26.5	59	GRADE 1	170
44	MANI	56	M	108	I	9.4	30	57.8	GRADE 2	260
45	ARUL	60	M	144	I	10	31.5	60	GRADE 2	275
46	AMUDHA	48	F	1	O	7	25	70	NO	100
47	SURESH	58	M	60	I	8.8	26.7	62	GRADE 1	245
48	THANGAM	59	F	180	I+O	13.5	35	58.4	GRADE 3	212
49	RAMAN	49	M	48	O	9	25	63.5	GRADE 1	230
50	RAGHU	54	M	108	I	9.6	29	68	GRADE 2	266
51	DANDAPANI	60	M	84	I	10.7	28.4	55	GRADE2	270
52	SAMPATH	50	M	72	I	8.3	26	57.4	GRADE1	230
53	LAKSHMI	58	F	96	I	9	27.5	58.2	GRADE 1	180
54	VANITHA	54	F	144	O+I	14	32	64.2	GRADE 3	220
55	RAJESH	53	M	36	O	8	25.6	59	GRADE 1	226
56	SHANMUGAM	48	M	48	O	8.1	26	69	GRADE 1	230
57	MUTHUAMMAL	52	F	108	I	11	27.5	58.6	GRADE 2	198
58	SHANTHI	57	F	132	I	9.9	29	70	GRADE 2	190
59	INDIRA	51	F	48	O	8	26.5	60	GRADE 1	184
60	PONNUSAMY	60	M	180	I+O	13	35	65	GRADE 3	295

S.NO.	NAME	AGE	SEX	DURATION	OHA(O)/ INSULIN(I)	HbAIC	LA SIZE (mm)	SYSTOLIC FUNCTION (EF)%	LV DIASTOLIC DYSFUNCTION	LV MASS (gms)
61	VIJAY	54	M	48	O	8.3	26.5	60	GRADE 1	242
62	MEENAKSHI	44	F	36	O	9	26	65	GRADE 1	175
63	VELMANI	59	F	120	I	9.5	30	62	GRADE 2	194
64	SUNDARI	46	F	60	O	8.5	27	70	GRADE 1	165
65	MEENA	53	F	60	I	9.4	27.5	68.3	GRADE 1	171
66	KANNIAMMAL	60	F	120	0+I	10.8	33	56	GRADE 2	195
67	RAMANI	48	F	72	I	11	28	59	GRADE 1	182
68	RANGA	56	M	168	I+O	13.6	35.6	66.4	GRADE 3	298
69	DEVI	49	F	60	O	9.1	27	55	GRADE 1	169
70	BANUMATHI	50	F	24	O	7	25	57.5	NO	76
71	GANGA	60	F	84	I	8	27.5	60.4	GRADE 1	173
72	VANAJA	55	F	108	O+I	9	32	68	GRADE 2	180
73	RAMESH	51	M	48	O	8.9	26.7	70	GRADE 1	234
74	RANI	49	F	60	O	8.3	27	71	GRADE 1	178
75	DAYALAN	54	M	108	I	10.7	30	62.8	GRADE 2	267
76	MARY	57	F	132	I+O	11	32	59.5	GRADE 2	190
77	KAMLA	55	F	60	I	9	27	55.4	GRADE 1	171
78	BHARGAVI	47	F	60	O	9.8	28	68.1	GRADE 1	174
79	SHANTHA	53	F	156	I+O	9.9	30	57	GRADE 2	200
80	SOMU	47	M	48	O	8	26	70	GRADE 1	240

S.NO.	NAME	AGE	SEX	DURATION(months)	OHA(O)/ INSULIN(I)	HbAIC	LA SIZE (mm)	SYSTOLIC FUNCTION (EF)%	LV DIASTOLIC DYSFUNCTION	LV MASS (gms)
81	SARITHA	46	F	60	O	8.8	26	60.2	GRADE 1	170
82	MOHAN	50	M	84	I	9	27.5	59.3	GRADE 1	230
83	MOHANA	52	F	72	I	10	28	55.6	GRADE 1	175
84	KAMALI	60	F	180	O+I	13.8	35.6	57	GRADE 3	225
85	VANILLA	59	F	228	O+I	14.6	36	55	GRADE 3	234
86	PARMILA	51	F	60	I	8	26	68.4	GRADE 1	174
87	THIAGARAJ	45	M	48	O	8.2	25.6	70	GRADE 1	234
88	JEYA	53	F	72	O	8.5	28	69	GRADE 1	172
89	JAYARAMAN	56	M	108	I	9	31	64.4	GRADE 2	272
90	JANAKI	52	F	96	I	10	30.5	69.5	GRADE 2	196
91	LATHA	59	F	120	I+O	10.4	32	58	GRADE 2	208
92	DURAI	52	M	96	I	9.4	29	62	GRADE 1	235
93	DEVAGI	45	F	36	O	9	27.5	72	GRADE 1	169
94	MALA	48	F	60	O	8.2	27	67.2	GRADE 1	178
95	ANAND	60	M	120	I	11.4	30.5	59	GRADE 2	280
96	GOMATHI	55	F	72	I	9.6	27	60	GRADE 1	176
97	CHITHRA	59	F	72	I	10	28	64	GRADE 1	184
98	THANGAM	58	F	96	I+O	10.4	33.5	66.3	GRADE 2	200
99	HARISH	54	M	72	I	9	29	58	GRADE 1	232
100	VANAJA	51	F	60	O	8	28.5	68	GRADE 1	175