"A CROSS SECTIONAL STUDY ON DIASTOLIC FUNCTION AND FACTORS INFLUENCING DIASTOLIC FUNCTION IN DIABETES MELLITUS PATIENTS WITH NORMAL SYSTOLIC FUNCTION"

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GOVT. CHENGALPATTU MEDICAL COLLEGE & HOSPITAL

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APRIL - 2016

CERTIFICATE

This is to certify that the dissertation titled **"A CROSS SECTIONAL STUDY ON DIASTOLIC FUNCTION AND FACTORS INFLUENCING DIASTOLIC FUNCTION IN DIABETES MELLITUS PATIENTS WITH NORMAL SYSTOLIC FUNCTION"** is the bonafide work of **Dr.VENKATESWARI.S** in partial fulfillment of the requirements for **M.D.BRANCH – I (GENERAL MEDICINE)** examination of **THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY** to be held in April 2016. The period of study was from June 2014 to June 2015.

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I hereby declare that this dissertation titled **"A CROSS SECTIONAL STUDY ON DIASTOLIC FUNCTION AND FACTORS INFLUENCING DIASTOLIC FUNCTION IN DIABETES MELLITUS PATIENTS WITH NORMAL SYSTOLIC FUNCTION"** is a bonafide and genuine research work carried out by me at **GOVT. CHENGALPATTU MEDICAL COLLEGE AND HOSPITAL** from June 2014 to June 2015 under the guidance and supervision of **Dr. V. R. MOHAN RAO M.D**, Professor and H.O.D , Department of General Medicine, Chengalpattu Medical College, Chengalpattu – 603 001.

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I bow my head in respect before God Almighty.

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APPROVAL OF ETHICAL COMMITTEE

To

Dr.S.Venkateswari,
MD General Medicine
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Dear Dr.

The Institutional Ethical Committee of Chengalpattu Medical College reviewed and discussed your application to conduct the clinical / dissertation work entitled

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ON 11.06.2014

The following documents reviewed

1. Trial protocol, dated _____version no
2. Patient information sheet and informed consent form in English and / or
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3. Investigators Brochure, dated _____version
4. Principal Investigators current CV
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The following members of the Ethics committee were present at the meeting held on

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

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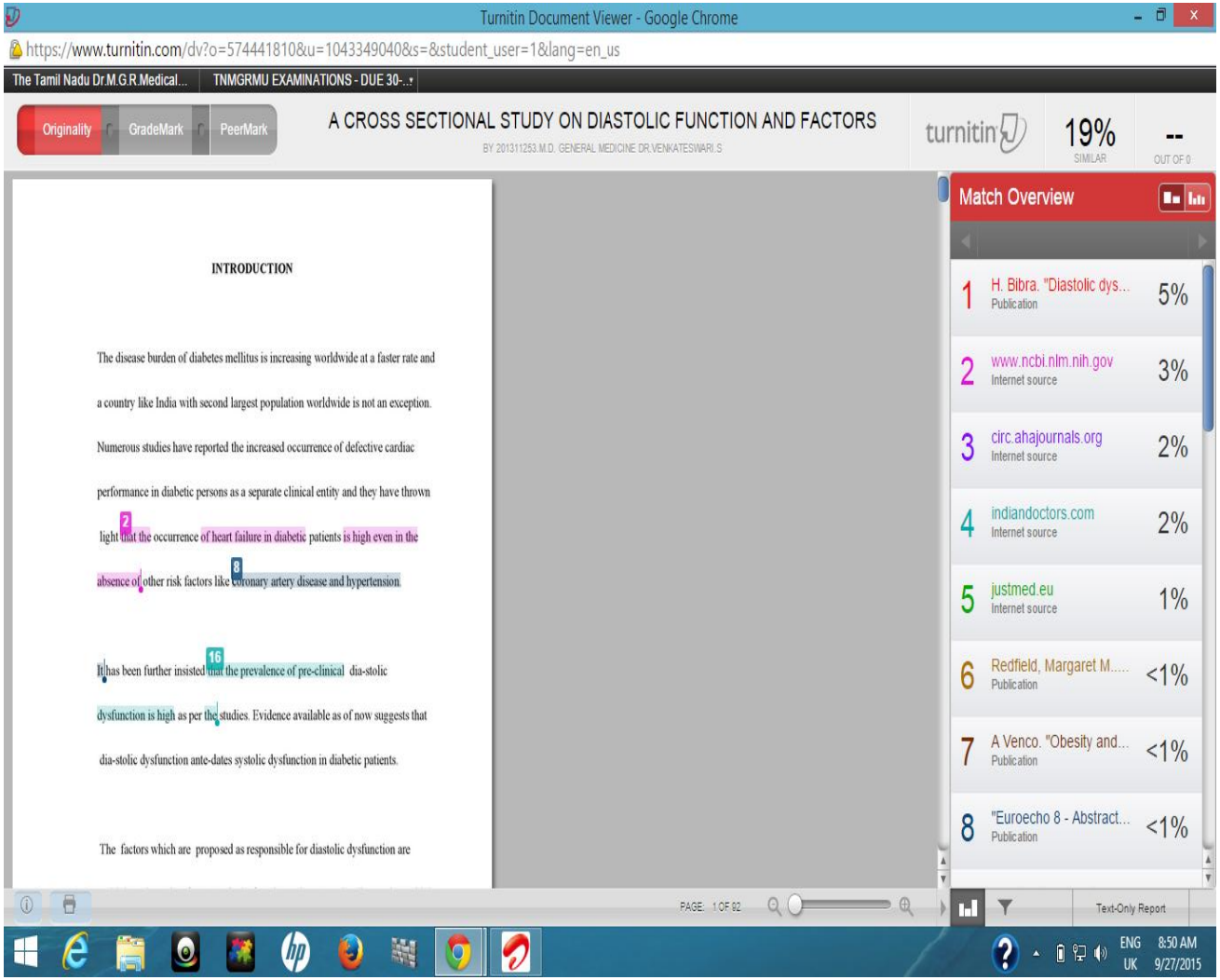
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INTRODUCTION
The disease burden of diabetes mellitus is increasing worldwide at a faster rate and a country like India with second largest population worldwide is not an exception. Numerous studies have reported the increased occurrence of defective cardiac performance in diabetic persons as a separate clinical entity and they have thrown light that the occurrence of heart failure in diabetic patients is high even in the absence of other risk factors like coronary artery disease and hypertension.
It has been further insisted that the prevalence of pre-clinical dia-stolic dysfunction is high as per the studies. Evidence available as of now suggests that dia-stolic dysfunction ante-dates systolic dysfunction in diabetic patients.
The factors which are proposed as responsible for diastolic dysfunction are
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LIST OF ABBREVIATIONS USED

CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
NYHA	New York Heart Association
EF	Ejection Fraction
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
ROS	Reactive Oxygen Species
AGE	Advanced Glycation End Products
PKC	Protein Kinase C
MAP	Mitogen Activated Protein
ADMA	Asymmetric Di Methyl Arginine
HDL	High Density Lipoprotein
VLDL	Very Low Density Lipoprotein
LDL	Low Density Lipoprotein
NEFA	Non Esterified Fatty Acids
LV	Left Ventricle
LA	Left Atrium
ACE	Angiotensin Converting Enzyme
cms	Centimeters

INTRODUCTION

The disease burden of diabetes mellitus is increasing worldwide at a tremendous rate and a country like India with second largest population worldwide is not an exception.

Numerous studies have reported the increased occurrence of diastolic dysfunction in diabetic persons as a separate clinical entity and they have thrown light that the prevalence of heart failure in diabetic patients is high even in the absence of other risk factors like coronary artery disease and hypertension.

It has been further insisted that the prevalence of preclinical diastolic dysfunction is high as per the studies. Evidence available as of now suggests that diastolic dysfunction antedates systolic dysfunction in diabetic patients.

The factors which are proposed as responsible for diastolic dysfunction are multiple and consist of autonomic dysfunction, microvascular disease, interstitial fibrosis and metabolic disorders like associated obesity and dyslipidemia. Never the less the exact etiopathogenesis of diabetic cardiomyopathy remains unclear.

Obesity is proved to be an independent risk factor for the incidence of heart failure in worldwide general population. Also available evidence suggests that over weight also carries risk of heart failure which lies intermediary between lean and obese patients.

The effects of obesity of longer duration on structure and function of left ventricle can be in the form of Left Ventricular hypertrophy of eccentric type, defective diastolic function and sometimes systolic dysfunction. Till date, the effects of obesity on the function and structure of cardiovascular system remains a subject of debate.

Smoking has negative effects almost all systems in our body, the main brunt of injury is taken by the cardiovascular and respiratory systems. In cardiovascular system, smoking affects both endothelial and cardiac structure and performance, both of which are interlinked.

Till date only few population based studies have been performed in our country to detect and evaluate the presence of diastolic dysfunction in diabetic patients and to quantify the relation between glycemic control, duration of diabetes, and coexisting and independent risk factors and their negative affection of cardiac performance.

AIMS AND OBJECTIVES

- To determine the prevalence of Left ventricular diastolic dysfunction in Type- 2 Diabetes mellitus patients with no symptoms
- To quantify the relation between Left Ventricular diastolic dysfunction and
    - Age
    - Gender
    - Duration of Diabetes
    - Control of Diabetes
    - Smoking
    - Dyslipidemia and
    - Obesity

REVIEW OF LITERATURE

The term diabetes mellitus describes a metabolic cum vascular syndrome of various etiologies which is characterized by hyperglycemia along with disturbances of metabolism of carbohydrate, protein and fat which can be due to either defective insulin secretion or defective insulin action or both resulting in changes in both small blood vessels (microangiopathy) and large caliber blood vessels (macroangiopathy).

This definition is useful in that it conveys a sense of the etiology, pathogenesis, biochemical features and implications in diabetes mellitus.

Diabetes mellitus is the most common metabolic disorder in the world. According to the data available as of now around 387 million in the world live with diabetes.

In most of the nations the number of patients with diabetes is increasing steadily. Largest number of people with diabetes are present in China (98 million) followed by India (65 million).

In India the prevalence rates of diabetes have increased tremendously since the time the initial national survey was done. The reason for this explosive increase in the case burden of diabetes in India has been the subject of interest. While a high level of genetic predisposition does plays a role, it is unlikely that the genetic makeup of the population has drastically changed in

the past thirty years as to account for the tremendous increase in the case burden of diabetes.

More likely explanation is that the increasing urbanization and prosperity have led to wholesale changes in the lifestyle of our population which cause diabetes to manifest in the individuals who have a genetic predisposition.

METABOLIC ABNORMALITIES IN DIABETES:

Type 2 diabetes represents a continuum of clinical scenarios, ranging from severe resistance to insulin along with relative insulin deficiency to severe insulin deficiency accompanied by some degrees of insulin resistance. Both insulin resistance and insulin deficiency are essential for diabetes to-develop. A person with severe insulin resistance will not develop diabetes unless his secretion of insulin drops below a critical threshold. But the converse is true and this scenario leads to type 1 diabetes mellitus.

Till now it is not very clear regarding which comes first – insulin resistance or insulin secretary defect. All persons become insulin resistant to some extent as they grow older.

However, most of the individuals have sufficient beta cell reserve to overcome this metabolic resistance and prevent3 the development of type 2 diabetes. It might be that individuals who develop type 2 diabetes have a decreased beta cell reserve, which renders them incapable of overcoming insulin resistance over a period of time.

Insulin resistance can be inherited or acquired. The most important corollary of insulin resistance is obesity, particularly abdominal type of obesity, which again can occur due to genetic or environmental factors. There are certain genetic syndromes of severe resistance to insulin, most of which are associated with diabetes. Reversible causes of resistance to insulin include chronic hyperglycaemia otherwise called as glucotoxicity and physical inactivity.

Resistance to insulin can occur at the level of the insulin receptor or in the post receptor pathways. Down regulation of the receptors as well as anti insulin and anti insulin receptor antibodies have been implicated in the etiopathogenesis of diabetes.

It is of interest that the resistance seems to develop only to the metabolic effects of insulin which are mediated by the P13K pathway but not to the mitogenic effects which are mediated by the Grb-SOS pathway.

The major contributor to the beta cell dysfunction is genetic. The genes which are responsible for this impairment in beta cell function are unknown. The beta cell defect is progressive and can be detected even in individuals those who have impaired glucose tolerance.

On an average, persons would have lost about half of their insulin reserve by the time they develop diabetes. Environmental factors that contribute to beta cell dysfunction include increased free fatty acids (lipotoxicity), chronic hyperglycemia (glucotoxicity), alterations in the incretin axis, and in utero malnutrition. Rather than a structural defect, a

functional defect seems to be responsible for the beta cell dysfunction in diabetes.

Of late, in addition to the pathophysiologic defects discussed till now, other organs have also been postulated to play a role in the pathogenesis of type 2 diabetes. The comprehensive model incorporating all these varying pathophysiologies has been termed as the ominous octet.

Though diabetes affects multiple organ systems cardiovascular disease caused and complicated by diabetes is one of the leading causes of mortality and morbidity in diabetic patients and is discussed in detail below.

DIABETIC CARDIOMYOPATHY:

Diabetic cardiomyopathy is a term used by clinicians to encompass the multi factorial etiologies of diabetes related left ventricular failure characterized by both systolic and diastolic function.[48] The Framingham Heart Study showed that men with diabetes who have congestive heart failure were twice as common as their non diabetic counterpart, and that females with diabetes had a fivefold increase, in the rate of congestive heart failure.

This spectrum ranges from asymptomatic to overt systolic failure. Diabetes complicated by hypertension represents a particularly high risk group for the development of congestive heart failure.[49] Diastolic dysfunction is exceedingly common (>50 percent prevalence in some studies) and may be linked to diabetes without the presence of concomitant hypertension.

ETIOLOGY:

The etiology of impaired left ventricular function may involve any of the following mechanisms:

1) Coronary atherosclerotic disease,
2) Hypertension,
3) Left ventricular hypertrophy,
4) Obesity,
5) Endothelial dysfunction,
6) Coronary microvasculature disease,
7) Autonomic dysfunction, and
8) Metabolic abnormalities.

Both diabetes and cardiovascular communities have embraced the concept of diabetic cardiomyopathy as a distinct entity independent of ischemic heart disease and hypertension. This was first described in the early 1970s when autopsy specimens of diabetic patients with nephropathy demonstrated a myopathic process in the absence of epicardial CHD.

It has been further insisted that there is high prevalence of preclinical diastolic dysfunction as per the studies that have been conducted so far. Evidence available as of now suggests that diastolic dysfunction precedes systolic dysfunction in diabetic patients.

As discussed above, the cardiovascular performance in a patient with diabetes mellitus is affected by various conditions like diabetic cardiomyopathy, coronary artery atherosclerosis, or autonomic neuropathy.

In a patient with diabetes mellitus poor cardiac performance may be due to predominantly any of these conditions or due to their combined effect. There is steadily growing idea which is being recognised that congestive heart failure (CHF) caused mainly by a defect in diastolic function (ie, diastolic heart failure) is quite common and might cause significant morbidity and mortality in persons having type 2 diabetes. However, the definition of diastolic dysfunction and the criteria for diagnosing diastolic heart failure have not been explained clearly.

DIASTOLIC DYSFUNCTION:

Diastolic dysfunction can be described as a condition where abnormalities in mechanical function of the cardiac musculature are present during diastole. Abnormal diastolic cardiac performance might be present along with or without a clinical syndrome of heart failure. Also, defective diastolic function of the cardiac musculature can occur in combination with normal or abnormal systolic function.

Conceptually, diastole consists of the time period during which the myocardium loses its ability to generate force and shorten and returns to an un-stressed length and force. So keeping this in mind we could say, diastolic dysfunction occurs when these processes are being slowed, incomplete or

prolonged. Whether this time period is best described by classic concepts and parameters or the newly proposed ones is under evaluation.

The measurements which might reflect changes in the normal diastolic function in general depend on factors like rate, onset, and extent of fall in ventricular pressure and filling and the relationship between strain and stress or in other words volume or pressure happening during the period of diastole. Moreover, if diastolic function is truly normal, these measurements must remain normal both at rest and during the stress, of a variable heart rate, stroke volume, blood pressure and end diastolic volume.

DIASTOLIC HEART FAILURE:

Diastolic heart failure is a clinical syndrome which comprises of symptoms and signs of heart failure along with abnormal diastolic performance and a preserved ejection fraction as assessed by appropriate parameters.

From a conceptual point of view, diastolic heart failure occurs when there is inability of ventricular chamber for acceptance of a sufficient volume of blood during diastole, at normal diastolic pressures and at volumes which are adequate to maintain an appropriate stroke volume.

These abnormalities are caused by a fall in relaxation of ventricular chamber and/or an increase in stiffness of ventricle. Diastolic heart failure can produce symptoms that occur at rest (New York Heart Association [NYHA] class IV), symptoms that occur with less than ordinary Physical activity

(NYHA class-III), or symptoms that occur with ordinary physical activity (NYHA class II).

Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.

Diastolic heart failure can occur singly or along with systolic heart failure. In persons having isolated diastolic heart failure, major abnormality in the pressure-volume relationship occurs during diastole, when increased diastolic pressures accompany normal diastolic volumes. Ultimately diastolic pressure gets elevated markedly and persons become symptomatic even at rest or with minimal physical activity (NYHA class III to IV).

Appropriate treatment may lead to fall in diastolic volume and pressure, and the individual becomes less symptomatic (NYHA class II), even then diastolic pressure-volume relationship continues to be abnormal. In patients with systolic heart failure, abnormalities occur in the pressure-volume relationship during systole and these comprise of fall in EF, stroke volume, and stroke work. Changes in the diastolic portion of the pressure-volume relationship accompany these.

All the above discussed changes lead to rise in diastolic pressures in symptomatic persons, thus indicating presence of both systolic and diastolic heart failure. Whereas the diastolic pressure-volume relationship may reflect a more compliant chamber, increased diastolic pressure and abnormal relaxation reflect the presence of abnormal diastolic function. Thus, all patients with

systolic heart failure and elevated diastolic pressures actually have combined systolic and diastolic heart failure.

Another form of heart failure as combined systolic and diastolic heart failure is also possible. Patients may have only a modest decrease in EF and a modest increase in end diastolic volume but a marked increase in end diastolic pressure and a diastolic pressure-volume relationship that reflects decreased chamber compliance. Therefore, virtually all patients with symptomatic heart failure have abnormalities in diastolic function, those with a normal EF have isolated diastolic heart failure, and those with a decreased EF have combined systolic and diastolic heart failure.

PATHOPHYSIOLOGY OF DIASTOLIC DYSFUNCTION IN DIABETES:

Diastolic phase of cardiac cycle can be discussed in four different phases and they are as follows:

1) Isovolumetric relaxation
2) Early diastolic filling, i.e. rapid filling
3) Diastasis
4) Late diastolic filling, i.e. atrial contraction.

Two aspects of diastolic function namely relaxation and stiffness is usually discussed together, but in reality they describe different properties of cardiac musculature. Relaxation is an active myocardial process which

consumes energy. This phase begins at the end of contraction and continues as long as isovolumetric relaxation and early diastolic filling occurs. Defective relaxation is one which is either delayed or partial and can be the result of regional dyssynchrony or fall in energy supply, as in myocardial ischemia or hypertrophy.

Diastolic stiffness can be estimated at the end of diastole after filling has completed and is calculated from curvilinear pressure–volume relationship. The slope of the tangent (dP/dv) of this relationship describes the stiffness of chamber at any given filling pressure. Changes in stiffness can be the result of differences in the composition and material properties of the cardiac musculature, such as interstitial fibrosis and left ventricular hypertrophy or both. In both metabolic syndrome and diabetes mellitus, diastolic dysfunction results from abnormal myocardial active relaxation and an increase in passive stiffness due to metabolic derangements and structural remodeling.

In a normal myocardium, phase of early diastolic filling which lasts roughly for hundred milliseconds extracts around 80 % of total filling volume by an energy driven active process of extension of cardiac musculature.

Diabetes causes metabolic abnormalities, including hyperglycemia, dyslipidemia, and insulin resistance, increased free fatty acid concentrations that alter normal arterial function and make arteries prone for atherosclerosis. It specifically alters the function of vascular endothelium and smooth muscle cells, as well as platelets, in ways that promote atherogenesis. Also diabetes disrupts the vasodilator function of endothelial cells and decreases the

bioavailability of nitric oxide (NO) by which it accelerates diastolic dysfunction.

Endothelial dysfunction also occurs in healthy adult offspring of type 2 diabetic parents, suggesting an inheritable abnormality as well.

Hyperglycemia decreases NO production from endothelial nitric oxide synthase (eNOS) and increases its degradation via generation of reactive oxygen species (ROS). Hyperglycemia triggers the production of ROS in vascular cells through enzymatic (protein kinase C and the reduced form of nicotinamide adenine dinucleotide phosphate [NADPH] oxidases and non enzymatic sources of oxidant stress (e.g., the formation of advanced glycation end products, AGEs). As oxidative stress increases, the eNOS cofactor tetrahydrobiopterin becomes oxidized and uncouples eNOS, which cause the enzyme to produce superoxide anion instead of NO. Superoxide anion quenches NO in a diffusion limited reaction to produce peroxynitrite.

Peroxynitrite inhibits prostacyclin synthase and endothelium-dependent hyperpolarizing factor activity. Similar to the effects of hyperglycemia, free fatty acids activate intracellular enzymatic oxidant sources, including protein kinase C, NADPH oxidases, and eNOS, yielding analogous increases in superoxide anion.

Diabetes impairs vascular smooth muscle function and augments the production of vasoconstrictor mediators, including endothelin-,1[1] which causes vascular smooth muscle growth and inflammation. Levels of other atherogenic mediators, including angiotensin II and vasoconstrictor

prostanoids, increase in diabetes as well.[1] Patients with type 2 diabetes have impaired vasodilation, possibly reflecting an abnormality in NO signal transduction.[26]

Moreover, diabetic patients have attenuated vasoconstriction to endothelin-1 and angiotensin.[54] Diabetes may alter sub cellular calcium distribution in smooth muscle cells,[55] resulting in augmented vasoconstriction in response to norepinephrine and phenylephrine. However, most diabetics have peripheral autonomic impairment at the time of diagnosis, and vascular beds regulated by these nerves have decreased arterial resistance.[1]

Similar to endothelial cells, diabetes activates atherogenic mechanisms within vascular smooth muscle cells, including protein kinase C, RAGE, NF-kB and the production of oxidative stress.[30] Diabetes heightens vascular smooth muscle cell migration in atherosclerotic lesions. Advanced atherosclerotic lesions have fewer vascular smooth muscle cells in diabetic patients than non diabetic patients, possibly resulting in decreased resiliency of the fibrous cap and thereby increasing the risk of rupture and luminal thrombosis.[56]

Other contributing agents believed to aid in the development of diabetic myocardial dysfunction is discussed in detail below. The clustering of cardiovascular risk factors in the diabetic persons induces multiple complex metabolic reactions, most prominent among which are

- ❖ Altered insulin signaling
- ❖ Glucotoxicity

- Lipotoxicity
- Elevated activity of cytokines
- Intramyocyte and interstitial triacyl glycerol deposition
- Advanced Glycation End products accumulation

All these may affect the functioning of the myocardium either directly or indirectly. In addition, all the above said risk factors trigger the endothelial dysfunction in a additive fashion.

Among the end results of progressive endothelial dysfunction are dysregulation of vascular permeability, inflammatory responses and predominantly vascular remodelling and atherosclerosis affecting coronary and systemic arteries. This response is mediated by rise in tone of vessels and associated with subsequent rise in arterial stiffness, blood pressure and pulse pressure. The resultant rise in after load in the vascular system compels heart to work in an elevated level of resting myocardial oxygen consumption.

However, this increased demand of energy leads to less favourable down regulation of perfusion of cardiac musculature, impaired intracellular bioenergetics and decreased efficiency. This situation may be considered an energy demand/supply mismatch based on abnormalities caused by metabolism inducing stress in cardiomyocytes. Subsequently, myocardial hypertrophy, autonomic dysfunction and left ventricular diastolic dysfunction may develop, characterizing the first stage of diabetic cardiomyopathy. This

stage may remain without manifesting symptoms for a quite long period and antedates the onset of systolic dysfunction.

In the advanced stages of diabetes, diastolic dysfunction may increase further due to cumulative structural abnormalities of cardiac musculature, such as steatosis cardialis, Advanced Glycation End product deposits, interstitial fibrosis and alterations in the extracellular matrix microvasculature which characterize the advanced stages of diabetic cardiomyopathy.

Early diastolic function depends on both stiffness of cardiac musculature and availability of energy for utilization. For years together, the pathophysiological mechanisms of defective filling of left ventricle were attributed to elevated myocardial stiffness due to structural changes in the myocardium. Myocardial stiffness mainly has an impact on late phase of diastolic function but may also affect relaxation properties. A recent study based on left ventricular endomyocardial biopsy samples showed that systolic heart failure in diabetic patients was due to increased myocardial stiffness caused by advanced glycation end products deposition and fibrosis.

But in reality, the major contributors to diastolic dysfunction are high resting tension and hypertrophy of cardiac myocytes. Of interest, hypertrophy of cardiac musculature in diabetes was unrelated to pressure overload instead to increased fasting levels of insulin, stating insulin resistance as a contributor to hypertrophy of cardiac myocytes. In addition to stiffness, there is also a reversible dynamic component which was based on the fact that early diastolic relaxation and filling are energy-consuming, active processes.

Two greatly accepted examples of this dynamic component are the immediate and reversible nature of diastolic dysfunction during stress testing and during coronary arterial balloon inflation, and, this may be regarded as an iatrogenic model of regional and intermittent impairment of myocardial energy supply in human beings. This model, with an exact onset and offset of perfusion blockade, has confirmed the increased susceptibility of myocardial diastolic function to energy derangements by the occurrence of diastolic dysfunction, not only before but also extending far beyond systolic dysfunction. Limitations in energy supply may arise not only, from deficiencies in circulatory transport and perfusion but also from the intracellular processes involved in biochemical energy production and substrate utilization.

Alterations in metabolism which result in decreased resource of energy are discussed as follows. Altered insulin signaling and elevated reactive oxygen species production have recently been proved in individuals with uncomplicated type 2 diabetes.

The widely proposed mechanism of action of reactive oxygen species involves the regulation of energy availability. Indirect effects may include decreased perfusion due to induction of endothelial dysfunction. Direct effects on cardiomyocytes cause resultant altered energy production in mitochondrium by disrupted supply of substrate and its utilization and mitochondrial uncoupling, the net result of which is decreased cardiac efficiency and altered insulin signaling.

The latter plays a key role in insulin resistance, decreased bio-availability of nitric oxide, altered handling of calcium and mitochondrial damage and dysfunction, finally resulting in abnormal cardiac remodeling and ventricular dysfunction. Acknowledging diastolic dysfunction as an indicator of reduced myocardial energy availability would provide a better understanding of why augmentation may be observed with short-term improvement of glycaemic control in type 2 diabetes and acute increase in perfusion of myocardium by administering C peptide in young and athletic individuals who have type 1 diabetes.

There is an increasing number of reports which show that the extent of hyperglycaemia correlates with diabetic myocardial dysfunction, and good control of blood sugar level decreases the risk of heart failure. These studies further infer that the improvement in diastolic function correlates with the extent of improved blood sugar control. The optimal glucose-lowering regimen which can aid in the protection of diabetic individuals from diastolic heart failure await to be determined in future research.

Rapid filling of the left ventricle has been shown to be a sensitive indicator of all types of myocardial damage [34], being susceptible not only to age and ischaemia but also to virtually all cardiovascular risk factors, which includes the metabolic syndrome and diabetes mellitus. In acceptance with the above said findings is the reversibility of impaired diastolic function, as demonstrated by effective treatment of any of these risk factors, including a sedentary lifestyle and obesity[23]. Notably, this reversible component of altered myocardial function associated with the metabolic syndrome and

diabetes is welcome news for diabetic individuals and their treating doctors and is in accordance with the message from the UK Prospective Diabetes follow-up study, that the most effective treatment is started early in the course of the disease.

OBESITY, DYSLIPIDEMIA AND DIASTOLIC DYSFUNCTION:

The excess adipose tissue that usually accompanies type 2 diabetes mellitus releases excess fatty acids. Reduced skeletal muscle uptake of free fatty acids further augments their plasma levels.[32] Increased concentrations of free fatty acids exert deleterious actions in several areas. In healthy humans, free fatty acid infusion impairs endothelial function and the co-infusion of an antioxidant restores it.[33] Free fatty acids also attenuate prostacyclin bioavailability by inhibiting prostacyclin synthase.[34] Moreover, free fatty acids interfere with intracellular signaling pathways to cause not only muscle and visceral insulin resistance but also vascular insulin resistance.[35]

In diabetes, hyperglycemia and increased free fatty acids increase the concentration in the cell of the metabolite diacylglycerol.[36] Diacylglycerol, in turn, activates a family of enzymes known as protein kinase C (PK-C), that perform key regulatory functions by phosphorylating proteins important in metabolic control. Recent work[30] has implicated activation of the PKC family in cardiovascular complications of diabetes. Activation of PKC can inhibit the expression of eNOS, augment cytokine-induced tissue factor gene expression and pro coagulant activity in human endothelial cells, and increase the production of pro inflammatory cytokines, proliferation of vascular wall cells, and production of extracellular matrix macromolecules that accumulate during

atherosclerotic lesion formation.[30] In vivo evidence has supported a role of PK-C activation in the pathogenesis of various aspects of vascular dysfunction in vivo. Administration of a selective inhibitor of protein kinase C-beta (PKC-b) prevents impaired endothelial function in healthy humans exposed to hyperglycemia, reduces visual loss in diabetic patients with retinopathy, and may attenuate diabetic neuropathy .[37] [38] [39]

Although typically associated with impairments in skeletal glucose muscle uptake, many tissues in the diabetic patient demonstrate insulin resistance, including adipose, liver, and endothelial cells.[27] Normal vascular function requires intact endothelial insulin signaling. For example, in genetically engineered mice that lack the endothelial cell insulin receptor, vascular endothelial nitric oxide synthase concentration decreases 60 percent.[40] Endothelial insulin resistance alters the pattern of activation of intracellular signaling pathways, favoring stimulation of mitogen-activated protein (MAP) kinases over phosphatidylinositol 3 (PI-3) kinase. Preferential activation of the MAP kinase pathway decreases nitric oxide production, increases endothelin production, stimulates the transcription of inflammatory genes, and increases the tendency to coagulation.[41] Drug-induced improvement in insulin sensitivity reduces cytokine production and inflammatory transcription factor activation and increases nitric oxide bioavailability. [42] [43]

Studies have now identified a new potential mechanism for mediating the already damaged endothelial-dependent vasodilator function. An endogenous competitive inhibitor of nitric oxide synthase, which is named as

asymmetric dimethyl arginine (ADMA), increases directly with insulin resistance in non diabetic subjects and glycemic control in diabetes[44] and improves with glycemic control.[45] The accumulation of ADMA may result from inhibition of its degradation because of reduction in activity of the enzyme dimethyl arginine dimethyl amino hydrolase. Another study has suggested that dys regulation of this enzyme raises levels of ADMA in diabetics.[46] These findings indicate another potential molecular pathway of impaired[90] vascular function in diabetes.

Adipocytes can also elaborate chemo attractant molecules, such as monocyte chemo attractant protein, which can recruit inflammatory leukocytes to enter adipose tissue.[24] Once present, these “professional” phagocytes can amplify the production of pro inflammatory mediators and perpetuate the inflammatory cycle related to insulin resistance and the vascular complications of diabetes mellitus. Some evidence has suggested that visceral adipose tissue plays a particularly pernicious role in perpetuating pro inflammatory pathways by producing proportionately more of these mediators than subcutaneous adipose tissue.[25] Waist circumference and visceral adiposity, as determined by imaging, correlate with C-reactive protein levels, indicating a relationship between inflammatory burden and central obesity. Moreover, liposuction, which evacuates subcutaneous but not visceral fat stores, does not lower C-reactive protein levels, whereas weight loss produced by restricted caloric intake or increased physical activity does diminish levels of this inflammatory marker. Thus, as with many other pro atherosclerotic risk factors, adiposity

can promote inflammation and potentiate the vascular disease associated with diabetes and its complications.[25]

Defective action of insulin in the liver leads to inappropriate release of glucose, leading to fasting hyperglycemia. Usually, the glucose production from liver is completely suppressed after a meal, mainly due to action of insulin. This suppression does not occur in diabetic persons with resistance to insulin thus resulting in postprandial hyperglycemia. Also, the production and release of very low density lipoprotein (VLDL) is stimulated, which contributes to hypertriglyceridemia. Diabetic patients with hypertriglyceridemia tend to have low levels of high density lipoprotein (HDL) in their circulation, possibly because of exchange of triglycerides and cholesterol esters between high density lipoprotein and triglyceride repletes proteins like very low density lipoprotein, rendering HDL particles more susceptible to degradation.

Also, the higher levels of very low density lipoprotein lead to increased exchange of cholesterol ester and triglyceride between very low density lipoprotein and low density lipoprotein (LDL) thus raising the triglyceride content of low density lipoprotein and rendering them more vulnerable to degradation by hepatic lipase. The resultant process is the formation of small dense LDL particles.

The lipid profile in a diabetic person is described by elevated triglyceride levels, low high density lipoprotein cholesterol levels and normal to high normal levels of low density lipoprotein cholesterol levels. There is a

relative rise in number of atherogenic small dense LDL particles. All this comprises of what is termed as “Diabetic Dyslipidemia”.

Defective insulin action in adipose tissue results in excessive break down of triglycerides and formation of non esterified fatty acids (NEFA), high levels of which can reduce insulin stimulated uptake of glucose by the tissues and can stimulate gluconeogenesis in the liver. Although lipolysis is increased, over-production of ketone bodies does not occur in type 2 diabetes because the deficiency of insulin is not absolute; smaller amounts of insulin are sufficient to prevent ketogenesis than to maintain glucose homeostasis.

SMOKING AND DIASTOLIC DYSFUNCTION:

Smoking has numerous adverse effects on various organ systems, but the most adversely affected ones are the respiratory and circulatory systems. In addition to other well documented harmful effects, smoking has been reported to have adverse effects on the diastolic function of the heart. Numerous prior studies have mainly focused on the acutely caused changes of smoking on diastolic function in different groups.

There are possible explanations for the chronic adverse effects of smoking on the diastolic function of the heart, as demonstrated in the present study. Smoking has long been known to impair the structure of connective tissue in various organ systems. Increased arterial stiffness in smokers has been linked to structural alterations in the vascular media, including calcification [16], increased collagen and reduced elastin content [17]. Regardless of the presence of atherosclerosis, arterial and myocardial stiffness

have been clinically important in smokers. In canine models exposed to nicotine, increased LV chamber stiffness was reported to be due to increased collagen deposition and collagen cross-links in the myocardium [18]. Fibrotic changes throughout the myocardium due to collagen deposition may impair diastolic function in smokers.

Impaired regulation of nitric oxide (NO) synthesis in the myocardium may be another possible mechanism explaining the impairment of relaxation in smokers. NO is synthesized via nitric oxide synthase (NOS). There are three known isoforms of NOS (NOS1, NOS2 and NOS3). Of these, NOS-2 and NOS-3[87] are known to be expressed in the human myocardium. NOS2 is an inducible isoform, and is not normally expressed, whereas NOS3 is endothelial and is physiologically expressed in the normal myocardium. The amount of NO synthesized via NO3 is generally much lower. The lower physiological amount of NO has some beneficial effects, including, an improvement in remodeling after myocardial infarction [19] and amelioration of ventricular relaxation (lusiotrophy). Smoking is a well- known factor that induces endothelial dysfunction through impairment of NO production [20, 21]. Smoking may also impair ventricular relaxation by inhibiting physiological expression of NO3 in the myocardium.

There may be clinical outcomes of asymptomatic diastolic dysfunction. The presence of diastolic dysfunction in an asymptomatic patient has been reported as a risk factor for the future development of heart failure [22]. In other terms, asymptomatic diastolic dysfunction might be an early marker of an increased risk of symptomatic heart failure and consequent mortality.

Persons with diastolic dysfunction are also considered to be susceptible to ventricular arrhythmias [23] and sudden cardiac death. An increased risk of arrhythmogenesis in diastolic dysfunction may be due to myocardial fibrosis, increased sympathetic tone, changes in ex- citation-contraction coupling [23] and also to the minimal pathological changes in coronary microcirculation that do not induce documentable ischaemic changes [24] .

AGE AND DIASTOLIC DYSFUNCTION:

Diastolic function is partly dependent on age and this property differentiates normal function from dysfunction. Tissue Doppler imaging can be used to measure myocardial velocity parameters clearly show the predominant influence of age factor on diastolic function, which confirms previous reports using various imaging modalities. There is a steep and linear decline of normal early diastolic velocity with ageing in normal people, from 16 cm/s at the age of 20 years to 6 cm/s at 80 years. This decline equals a decrease of 0.16 cm/s (i.e. 1% of the original value) every year. So, cutoff values for normality vs dysfunction must be described as a linear regression equation as a function of age [19]. Using pulsed tissue Doppler imaging, the cut-off level for normal age-related velocity is calculated as 0.15 × age (years) + 18(cm/s). This approach allows individual patients to be assigned to normality or dysfunction or risk and avoids the inconsistencies arising from normal values defined for different groups of age.

ECHOCARDIOGRAPHY:

Evaluating for diastolic dysfunction has always posed a challenge to echocardiography as the parameters assessed for the same should be easily applicable, acceptable and reproducible. Various studies have been conducted taking various echocardiographic parameters into account for finding, assessing and grading diastolic dysfunction. Though majority of the studies highlighted certain parameters like left ventricular mass, diastolic filling and mid wall systolic mechanics as potential parameters for study, they have been generalized and widely accepted after the advent of Doppler techniques which greatly complement echocardiography in identification, categorization and quantification of cardiac flow reserve and diastolic dysfunction

Although the Left Ventricular end-diastolic pressure-volume relation is believed to de- scribe the passive properties of the LV, but, in reality LV filling is not a passive or slow process3. Actually, the peak flow rate across the mitral valve is either same or higher than the peak flow rate across the aortic valve. For correct interpretation of left ventricular filling dynamics derived from a wholesome echocardiographic evaluation, one should have an understanding of the physiological basis of LV filling. During LV ejection, energy is stored as the myocytes are compressed and the elastic elements in the myocardial wall are also twisted and compressed4. Relaxation of already contracted myocardium allows the stored energy to be released as the elastic elements recoil. This process leads to rapid fall in Left ventricular pressure during isovolumetric relaxation. All the more, during the initial 30 to 40 milliseconds after opening of mitral valve, the ventricular wall tension gets

relaxed and this process is normally rapid enough to cause the LV pressure to continue to fall in spite of increase in LV volume5.

This fall in ventricular pressure produces an early diastolic pressure gradient from the LA that extends to the LV apex. This accelerates blood out of the left atrium and produces rapid early diastolic flow that quickly propagates to the apex. Because the diastolic intraventricular pressure gradient pulls blood to the apex, it can be considered a measure of LV suction. It is found that this component of suction is decreased in experimental models of various conditions like heart failure, patients with ischemia, and hypertrophic cardiomyopathy10. The pressure gradient between LA and LV apex decides the rate of early filling of ventricle. Peak filling and peak pressure gradient are interlinked. Due to this close link peak filling occurs after the peak pressure gradient. The reduction in the early diastolic LV pressure will increase the gradient for filling and this will permit the heart to fill without requiring elevated LA pressure. Also, the ability to decrease LV early diastolic pressure in response to stress allows an increase in LV stroke volume without much increase in LA pressure.7

The relaxing property of left ventricle is highly sensitive to myocardial dysfunction, and the ability to increase LV filling without an increase in LA pressure is reduced or absent in heart failure. Once the filling of left ventricle has started, the pressure gradient from LA to the LV apex falls and then reverses for short lived period. The reversed mitral valve pressure gradient decelerates and then stops the rapid flow of blood into the LV early in diastole. The time for flow deceleration is determined predominantly by the

functional LV chamber stiffness and provides a noninvasive indication of LV diastolic operating stiffness[13] During diastasis that is the midportion of diastole, there is equalization of pressure between LA and LV resulting in near cessation of mitral flow. During late phase of diastole, contraction of atrium produces a second LA- to-LV pressure gradient which aids again in the propulsion blood into the LV.

Once the systolic phase of atrium is finished, atrium relaxes causing its pressure to fall below LV pressure, which results in beginning of closure of mitral valve. The onset of ventricular systole produces a rapid increase in LV pressure that seals the mitral valve and thus the diastole is ended.

The dynamics of LV filling and their alteration with diastolic dysfunction are noninvasively assessed from Doppler measurement of mitral inflow velocity and tissue Doppler assessment of mitral annular velocity. Under normal circumstances, the peak early mitral inflow velocity (E) substantially exceeds the peak velocity during atrial contraction (A). Thus, the E/A ratio is 1.

Because the LV apex remains unchanged throughout the cardiac cycle, the mitral annular velocity provides a useful measure of rate of long-axis lengthening. Under normal conditions, peak early diastolic mitral annular velocity which has also been called Ea, E and EM) occurs coincidentally with the mitral E (16,17). This is a manifestation of the symmetrical expansion of the LV in early diastole as blood moves rapidly to the LV apex in response to a progressive pressure gradient from the left atrium to the LV apex.

Under normal circumstances, both E and e respond to changes in the LA-to-LV pressure gradient. For example, both E and e normally increase in response to volume load and exercise 17–19 In the presence of mild diastolic dysfunction with slow LV relaxation but without an increase in LA pressure, the early diastolic pressure gradient that accelerates flow is decreased as a result of a higher LV pressure .20

This results in a decrease in both the E and e and an increase in the importance of atrial contraction, producing an E/A ratio 1. The delayed relaxation results in a prolongation of E-wave deceleration time (DT) and may be associated with a mid diastolic peak of mitral flow (L wave).[21,22] With increased flow from the LA to LV with atrial contraction, the LA is relatively empty at the beginning of systole, which results in increased systolic velocities in the pulmonary veins toward the LA. This filling pattern has been called an impaired relaxation pattern or grade 1 diastolic dysfunction.[1,23]

In most patients with this pattern, the mean LA pressure is not elevated despite an increased LV end diastolic pressure that is maintained by a vigorous atrial contraction.

With progressive worsening of diastolic dysfunction associated with an increase in LA pressure, the early diastolic pressure gradient is restored despite increased diastolic LV pressures, resulting in a return of the E wave to the normal range pseudo normal mitral inflow pattern or grade 2 diastolic dysfunction.

Displacement of the Left Ventricle onto a steeper portion of the pressure-volume curve results in a shortening of the DT.13 With slower relaxation, the e is delayed, occurring after the E. This indicates that the LV is not expanding symmetrically in diastole but that propagation of filling to the apex and longitudinal expansion occur slowly after the LV is filled by movement of blood from the LA into the LV inflow tract. In the presence of slow relaxation, e does not occur during the time of the LA-to-LV pressure gradient, so e is reduced and becomes almost independent of LA pressure.16 Both the mitral annular e and the delay in e relative to E correlate with the time constant of LV isovolumetric pressure decline.16,24 Thus, the pseudo normal mitral inflow pattern is distinguished from normal by a reduced and delayed e and increase in the E/e ratio.

With even more severe diastolic dysfunction with due course of time due to the markedly slowed relaxation and elevated LA pressure, the E increases further, DT becomes very short, and e is further reduced and delayed, resulting in a marked elevation of E/e (Figures 2 and 3). With severe diastolic dysfunction, the late diastolic annular velocity (a) also may be reduced, and pulmonary venous systolic forward flow velocity is reduced and less than diastolic forward flow velocity.

Other indicators of diastolic dysfunction can be obtained from color M-mode imaging, Doppler echocardiography, and strain rate imaging.25 The presence of pseudo normalized and restricted filling patterns with elevated E/e indicates the presence of both diastolic dysfunction (impaired relaxation and elevated LV early diastolic pressures) and elevated LA pressure.17 In contrast,

the impaired relaxation pattern indicates diastolic dysfunction without a marked elevation in mean LA pressure.

The measure of systolic function which has stood the test of time is the ejection fraction. It has been stated that one can predict the clinical outcome in dilated cardiomyopathy and a variety of cardiac diseases [71, 72] using this parameter. The ejection fraction shares a curvilinear relationship with end diastolic volume and an inverse correlation with after load [72]. But the limitation is that the normalization by end diastolic volume makes it insensitive to subclinical myocardial dysfunction in a normal sized heart or a small hypertrophied ventricle [73]. The normal sized heart of patients with type 2 diabetes and correspondingly over weight body habitus frequently results in poor delineation of the endocardial borders, which are essential pre requirements for estimating the ejection fraction quantitatively.

Similarly, as discussed prior, the Doppler derived mitral valve inflow velocity pattern and its derivatives which are widely used as measures of diastolic function, have been proved difficult to comprehend because of the pseudo normal pattern, which defines grade 2 dysfunction, but may be mistaken for the normal pattern [74]), unless a differentiation procedure like Valsalva manoeuvre or pulmonary vein flow assessment is performed.

While the clinical, course of diastolic dysfunction is characterized by decreasing effectiveness of myocardial relaxation and extension associated with increasing left atrial pressure and size, the respective developments of pressure and filling cannot be mirrored by the traditional Doppler parameters. However, an even more important limitation is the non-quantitative pattern

recognition used for assessing diastolic function and the changes in the course of disease and during preventive therapy.

MANAGEMENT:

Screening:

Now that the occurrence of diastolic dysfunction in diabetic persons is found to be clearly high than the normal population, measures to treat appropriately should be made. As the diastolic dysfunction prevailing in diabetic persons is pre clinical without manifesting any symptoms regular screening for this defective cardiac performance using a echocardiogram is mandatory in decreasing morbidity and mortality in diabetic persons.

Non pharmacological Therapy:

General measures that may be used in the management consist of due monitoring of weight, attention to diet and life style, patient education, and close medical follow-up. Also aggressive control of hypertension, tachycardia, and other potential precipitants for HF decompensation should be emphasized. The role of exercise training was has also been explored.[49] Although there are no adequate clinical trials with is appropriate outcome endpoints, such as increased longevity, decreased symptoms, or improved quality of life, to prove the benefits of exercise training definitively, several clinical and experimental studies have suggested that exercise training would be beneficial for such patients. [11] [12] [27]

Pharmacologic Therapy:

Pharmacolgical therapy of diastolic dysfunction which may proceed to failure if left unattended comprises of various groups of drugs namely the ACE inhibitors , Beta blockers, Calcium chan.nel blockers, Diuretics, Digoxin and other positive inotropic agents, Endothelin agonists and Aldosterone antagonists. The drug therapy should not be generalized instead it should be tailored according to the individual needs of the persons

ACE INHIBITORS AND ARBs:

Chronic activation of the Renin-Angiotensin-Aldosterone system has been shown to increase extracellular matrix fibrillar collagen and to be associated with increased stiffness. By altering this system, ACE-inhibitors and angiotensin II receptor blockers have a direct effect on cardiac musculature in addition to the result they have on blood pressure. It is this effect which causes the decrease in LV hypertrophy, and the cardiac musculature is made more compliant and elastic.LV diastolic properties are based on myocardial stiffness which is the result of fibrosis. By judicious use of this group of drugs the changes in metabolism of type one collagen causing fibrosis is prevented.

BETA-BLOCKERS:

The reduction of hypertrophy of left ventricle by antihypertensive action of beta blockers can lead to improvement of diastolic filling. However, their use in patients with advanced diastolic dysfunction (grade III or IV) must be done cautiously.

CALCIUM CHANNEL BLOCKERS:

Although calcium channel blockers do not specifically improve diastolic function acutely, (14,15) it has shown to improve diastolic filling during exercise In persons with heart failure and normal LV systolic function and defective diastolic filling, this group of drugs may help during exercise though they may not be useful in acute stage.16) . The negative chronotropic action of these drugs helps by decreasing heart rate.

NITRIC OXIDE DONORS:

Nitric oxide (NO) is synthesized from the amino acid L- arginine by the actions of the enzyme NO synthase. In patients with dysfunctional endothelium, the loss of flow mediated and catecholamine-stimulated endotheilum derived relaxing factor (EDRF) release allows the constrictor effects of catecholamines to act unopposed. Thus, the loss of EDRF may contribute to impaired dilator responses of epicardial and resistance vessel and thereby to myocardial ischemia, which slows ventricular relaxation and increases myocardial wall stiffness. Previous studies also indicate that diastolic function of the heart appears to benefit from exogenous NO whereas its endogenous production does not play a major role in myocardial relaxation.(23,24) Similarly, NO donors have been shown to exert a relaxant effect on the myocardium which is associated with a decrease in LV end-diastolic pressure.

ALDOSTERONE ANTAGONIST:

Aldosterone antagonists are found to have negative effect on growth of cardiac myocytes and fiboblasts. In view of this unique property, this group of drugs is believed to produce desirable results in diastolic properties.

NATRIURETIC PEPTIDE:

The natriuretic peptides are used in therapy of heart failure for their properties of preload reduction, vasodilation and renin suppression. Recent in vitro (31) and in vivo (32) studies demonstrated that brain natriuretic peptide (BNP) has a positive lusinotropic effect through their second messenger, cGMP. Clarkson et al. (33) evaluated the effects of BNP on resting and exercise hemodynamics and neurohormones in 6 patients with isolated diastolic heart failure and observed that BNP infusion causes significant attenuation of the rise of pulmonary capillary wedge pressure and mean pulmonary artery pressure during exercise without effects on resting hemodynamic parameters. In response to BNP infusion during exercise, circulating BNP levels were significantly increased while circulating aldosterone was suppressed, as compared with the patients who were infused with a placebo. Beneficial hemodynamic and neurohormonal effects during exercise by BNP infusion demonstrated by this study suggest possible direct and indirect effects to improve operant diastolic function [93] and potential therapy for isolated diastolic dysfunction.

METHODOLOGY

STUDY GROUP:

The present study comprises of 100 patients of Diabetes mellitus of more than five year duration, attending both Medical and Diabetology Out Patient Departments of Chengalpattu Government Medical College.

STUDY SETTING:

Hospital based

STUDY PERIOD:

1 year

STUDY DESIGN:

Cross sectional study

STUDY POPULATION:

Rural and suburban population in and around Chengalpattu.

STUDY PLACE:

Department of General Medicine, Chengalpattu Medical College, Chengalpattu.

INCLUSION CRITERIA:

- All Type 2 Diabetes Mellitus patients of age 40 to 80 years
- Duration more than five years
- Normal left ventricular systolic function

EXCLUSION CRITERIA:

1. Subjects with evidence of coronary artery disease - CAD [excluded by history of angina, chest pain, Electrocardiogram (ECG) changes and abnormal Treadmill test (TMT) results
2. Subjects with evidence of valvular disease
3. Hypertensive
4. Subjects with poor transthoracic ECHO window

MATERIALS AND METHODS:

From all patients included in the study a detailed medical history is to be obtained using the questionnaire. The patients are then subjected to physical examination which includes general examination, system wise examination and anthropometric evaluation including weight in kilogram.

Electrocardiogram was done in all subjects. Biochemical investigations includes collection of venous blood sample after a 12 hour fast and sending it to the biochemical laboratory for estimating parameters like plasma glucose level, total serum cholesterol (TC), High density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, very low density lipoprotein cholesterol (VLDL) and serum triglyceride levels (TG).

Two dimensional directed M mode echocardiography was performed on all the study patients. They were investigated in the left lateral decubitus position with 3.5 MHz transducer. All echocardiograms were performed by experienced cardiologists.

Left ventricular systolic function is usually measured by the left ventricular ejection fraction (EF) and fractional shortening (FS).

EF was determined by measuring LV volumes in apical 2 chamber view. Left ventricular volumes were measured by Area- Length method [12], both in end diastole (LVVd) and in end systole (LVVs)

EF = LVVd – LVVs / LVVd

The mean EF in normal population is taken as 59.2 [15,16]. EF was considered decreased if it was < 50 % Diastolic function was determined by ratio of peak early diastole velocity (E) / peak atrial filling velocity (A) of LV, i.e., (E/A), measured by spectral Doppler LV inflow velocity with sample volume at the level of mitral valve.

Normal value of Doppler LV diastolic function index was taken as:

Peak velocity E (m/sec): 0.61 m/sec +/- 0.14,

Peak velocity A (m/sec): 0.48 m/sec +/- 0.14,

E/A Ratio: 1.4 +/- 0.54 [18].

LV diastolic dysfunction was considered if E/A ratio was found to be 0.8 or less.

STATISTICAL ANALYSIS:

Descriptive statistics for all data and suitable statistical tests of comparison to be done. Continuous variables to be analysed with the unpaired t-test and categorical variables to be analysed with the Chi-Square Test with Yates correction. Statistical significance is taken as $P < 0.05$.

RESULTS

The present study comprises of 100 cases of diabetes mellitus of 5 years or more duration attending medical and diabetology out patient departments during the study period of June 2014 to June 2015.

Out of 100 diabetes patients selected for the study, correlation between diastolic dysfunction and seven parameters including.

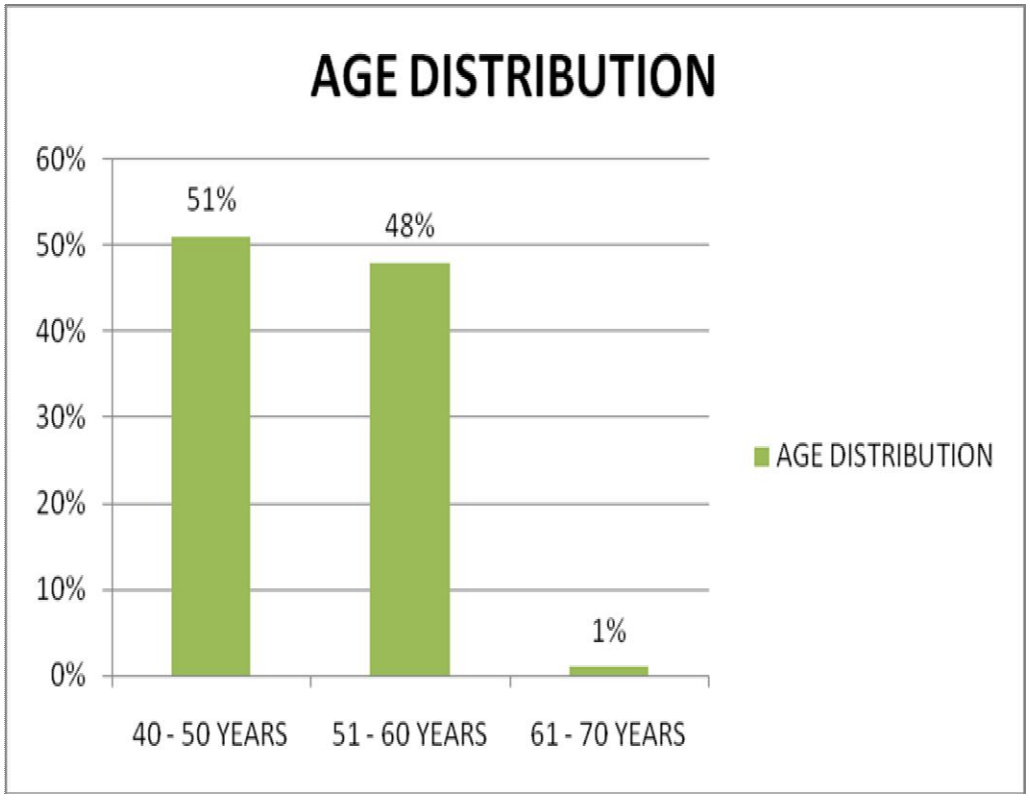
- Duration of diabetes
- Glycaemic control
- Age
- Sex
- Obesity
- Dyslipidemia
- Smoking was studied.

1. AGE DISTRIBUTION :

TABLE – 1: SHOWING AGE DISTRIBUTION OF 100 CASES

AGE (yrs)	NO. OF PATIENTS	PERCENTAGE
40 – 50	51	51 %
51 – 60	48	48 %
61 – 70	1	1%
TOTAL	**100**	**100%**

GRAPH -1: SHOWING AGE DISTRIBUTION

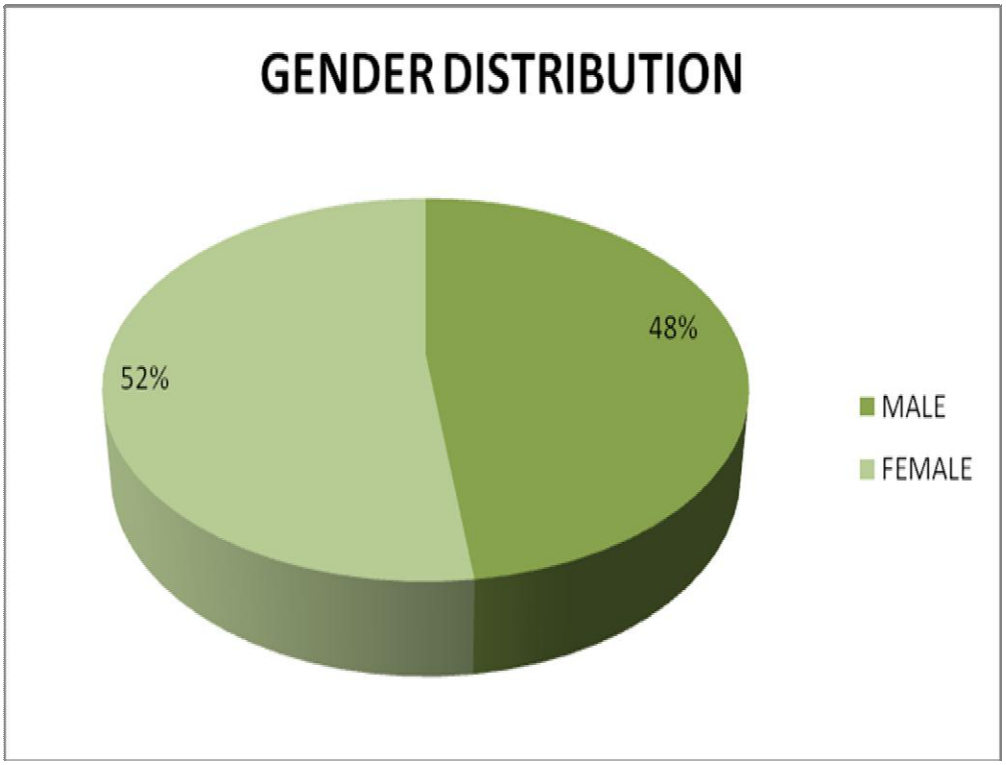


2. GENDER DISTRIBUTION:

TABLE - 2: SHOWING GENDER DISTRIBUTION OF 100 CASES

GENDER	NO. OF PATIENTS	PERCENTAGE
MALE	48	48 %
FEMALE	52	52 %
TOTAL	**100**	**100 %**

GRAPH – 2: SHOWING GENDER DISTRIBUTION



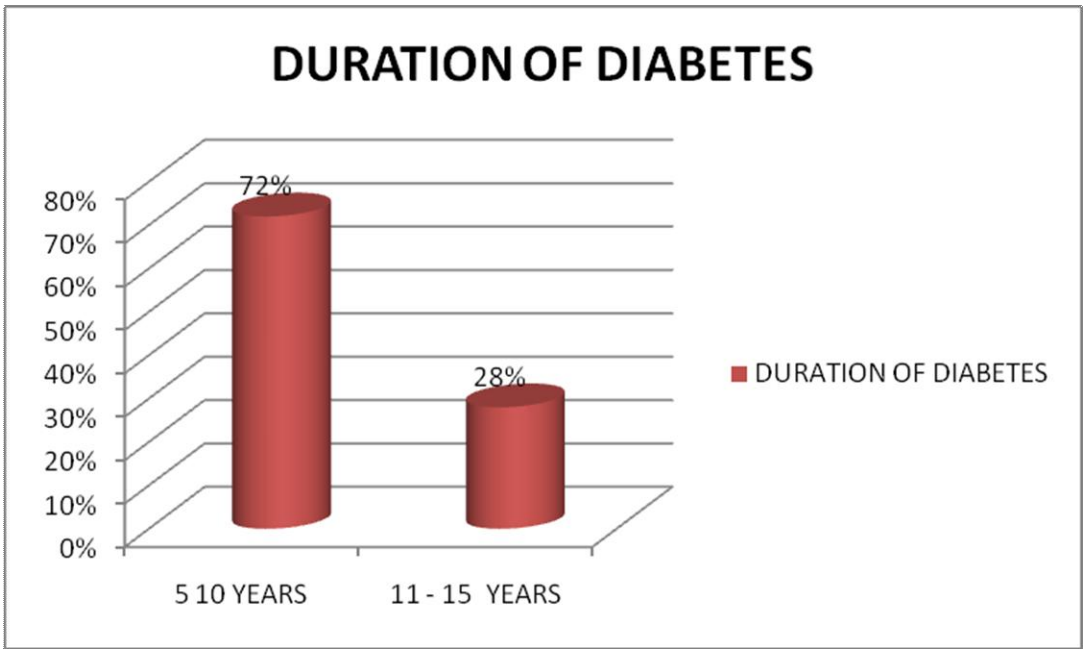
3. DISTRIBUTION OF DURATION OF DIABETES:

In the present study cases with diabetes for duration of five years or more are analysed. The duration was mainly distributed in the 5 – 10 years and 11 – 15 years group.

TABLE -3: SHOWING DISTRIBUTION OF DURATION

DURATION	NO OF PATIENTS	PERCENTAGE
5 – 10 YEARS	72	72 %
11- 15 YEARS	28	28%
TOTAL	**100**	**100%**

GRAPH – 3: SHOWING DISTRIBUTION OF DURATION



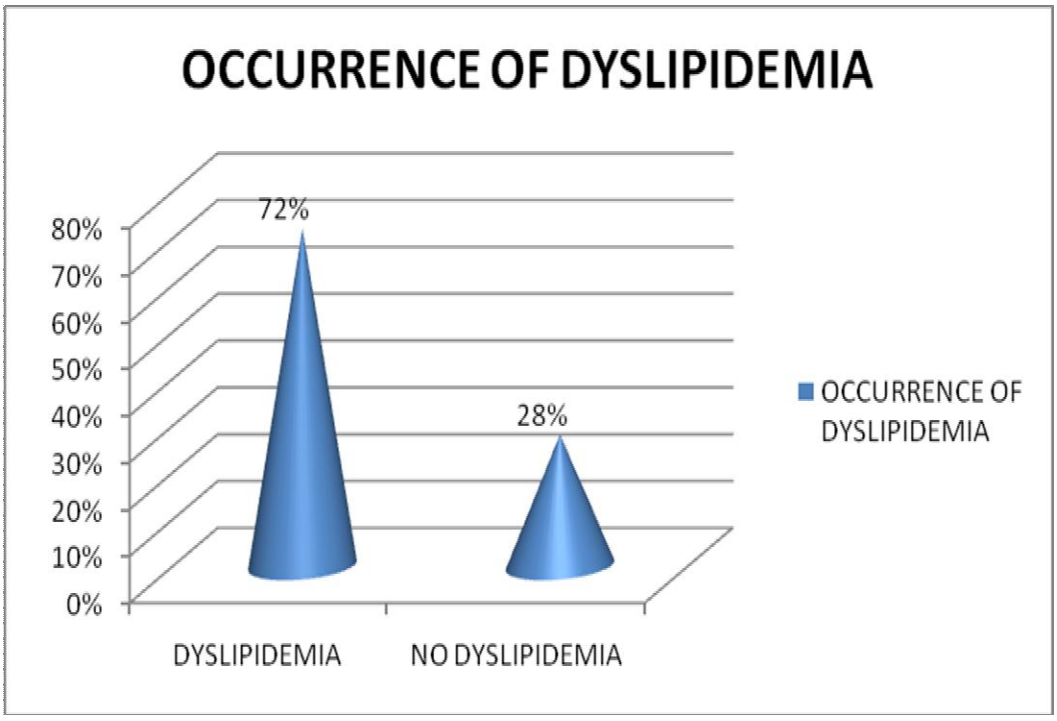
4. DYSLIPIDEMIA:

In the present study, all patients underwent fasting lipid profile examination and the occurrence of dyslipidemia was studied

TABLE – 4: SHOWING OCCURRENCE OF DYSLIPIDEMIA

LIPID PROFILE	NO. OF PATIENTS	PERCENTAGE
DYSLIPIDEMIA	72	72%
NO DYSLIPIDEMIA	28	28%
TOTAL	**100**	**100%**

GRAPH – 4: SHOWING OCCURRENCE OF DYSLIPDEMIA



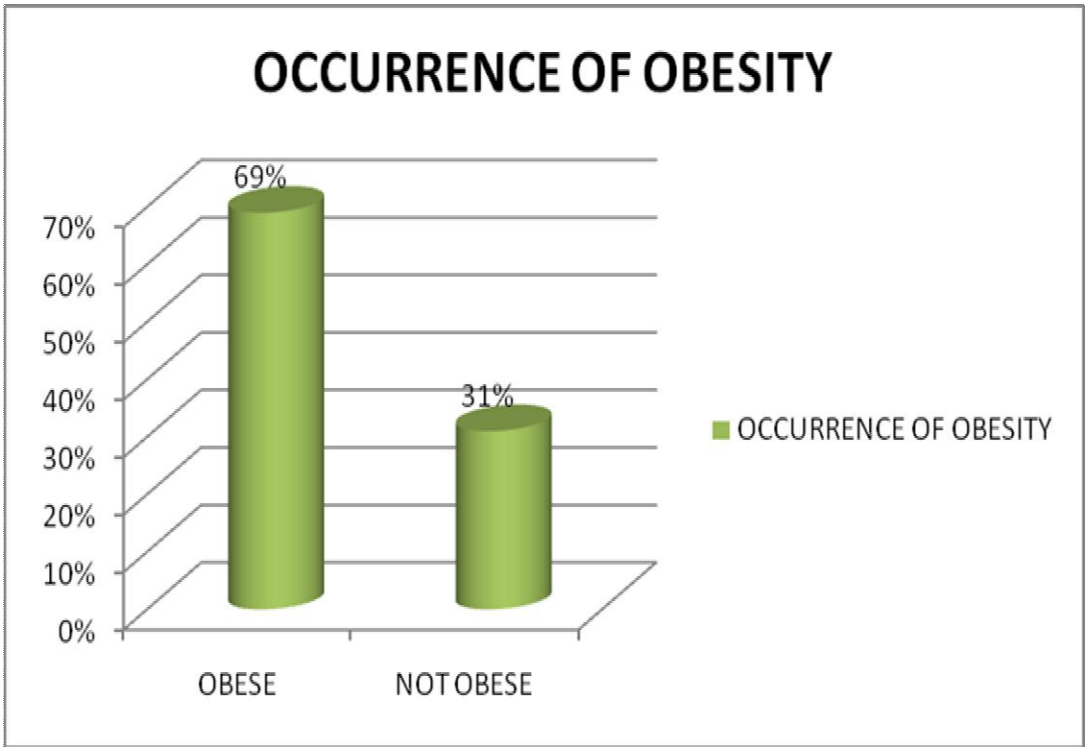
5. OBESITY:

In the current study, all cases underwent anthropometric examination and were classified based on their BMI as obese and non obese individuals

TABLE -5: SHOWING OCCURRENCE OF OBESITY

BMI	NO OF PATIENTS	PERCENTAGE
OBESE	69	69%
NOT OBESE	31	31%
TOTAL	**100**	**100%**

GRAPH – 5: SHOWING OCCURRENCE OF OBESITY



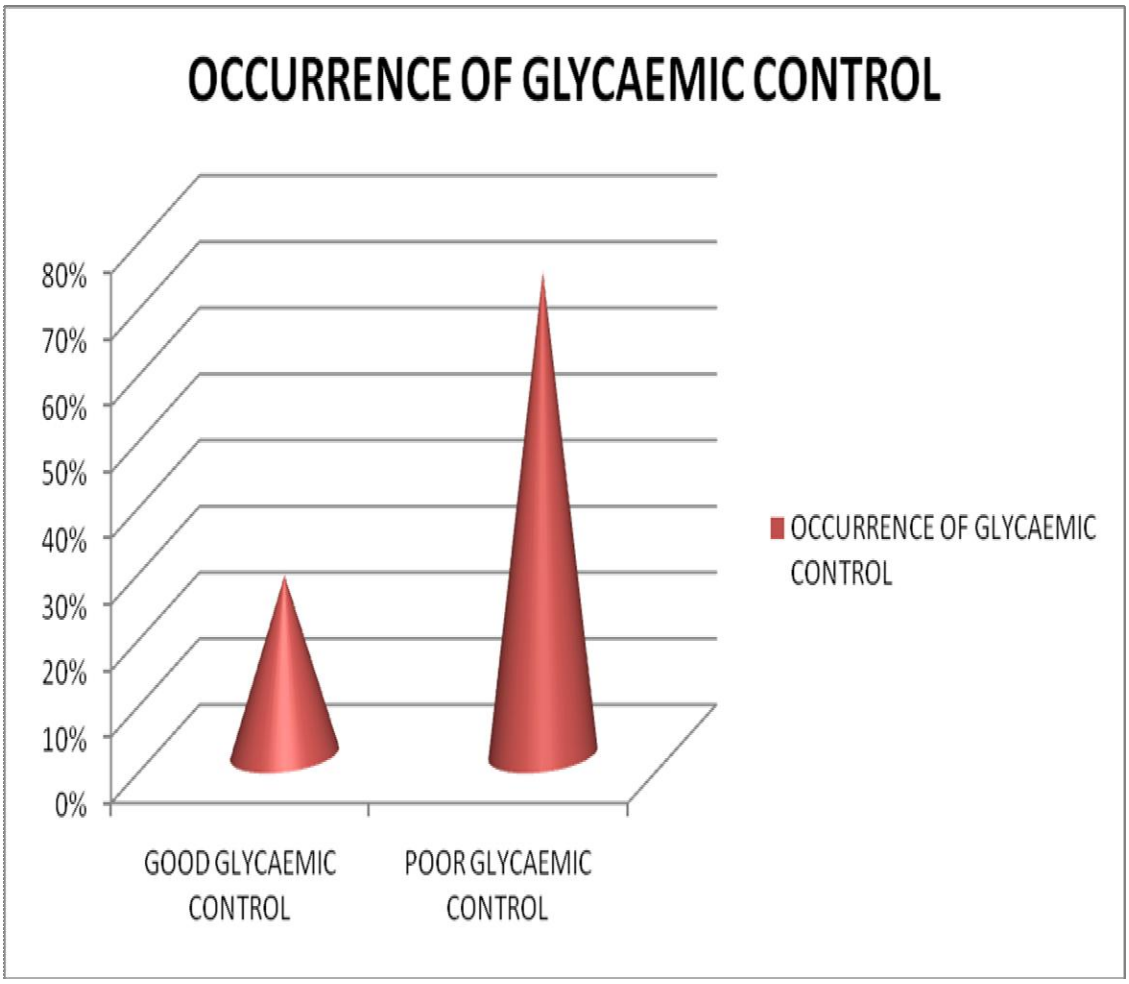
6. OCCURRENCE OF GLYCAEMIC CONTROL:

Glycaemic status of cases was assessed using HbA1C measurements.

TABLE – 6: SHOWING OCCURRENCE OF GLYCAEMIC CONTROL

GLYCAEMIC STATUS	**NO. OF PATIENTS**	**PERCENTAGE**
GOOD GLYCAEMIC CONTROL	27	27 %
POOR GLYCAEMIC CONTROL	73	73 %
TOTAL	**100**	**100 %**

GRAPH – 6: SHOWING OCCURRENCE OF GLYCAEMIC CONTROL



7 . OCCURENCE OF SMOKING:

From all cases who participated in the study, history of smoking was obtained.

TABLE – 7: SHOWING OCCURRENCE OF SMOKING

HISTORY OF SMOKING	NO OF PATIENTS	PERCENTAGE
SMOKER	26	26%
NON SMOKER	74	74 %
TOTAL	**100**	**100%**

GRAPH – 7: SHOWING OCCURRENCE OF SMOKING

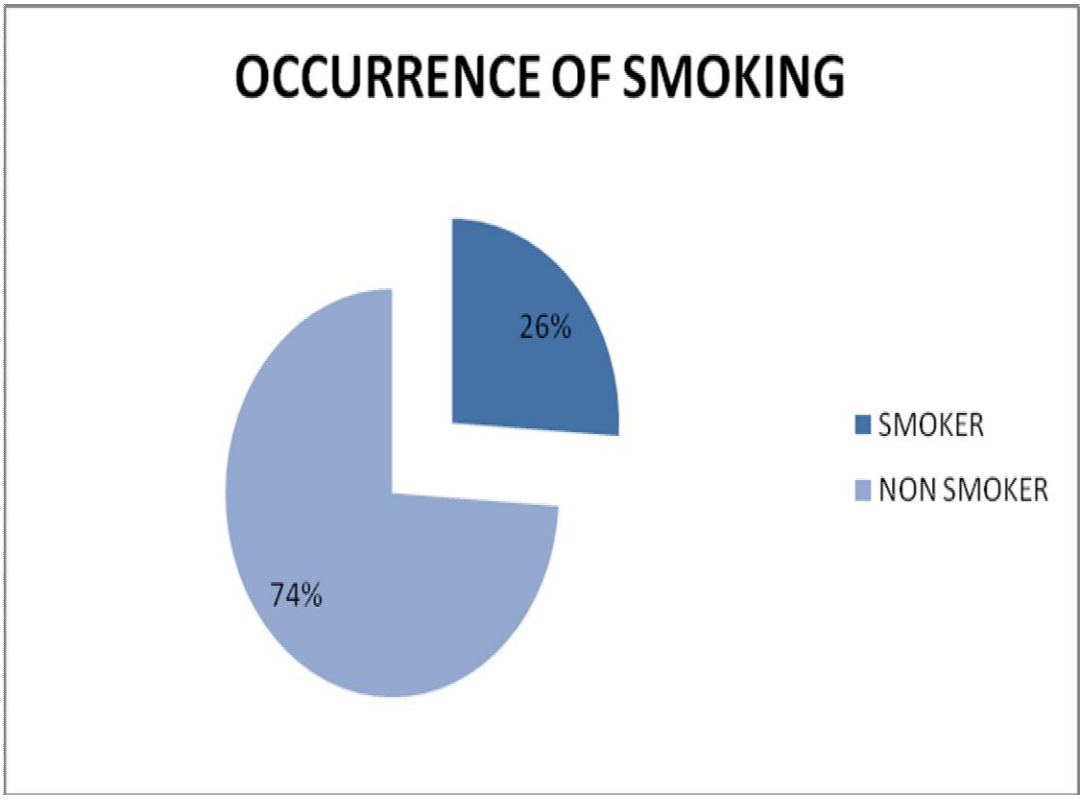


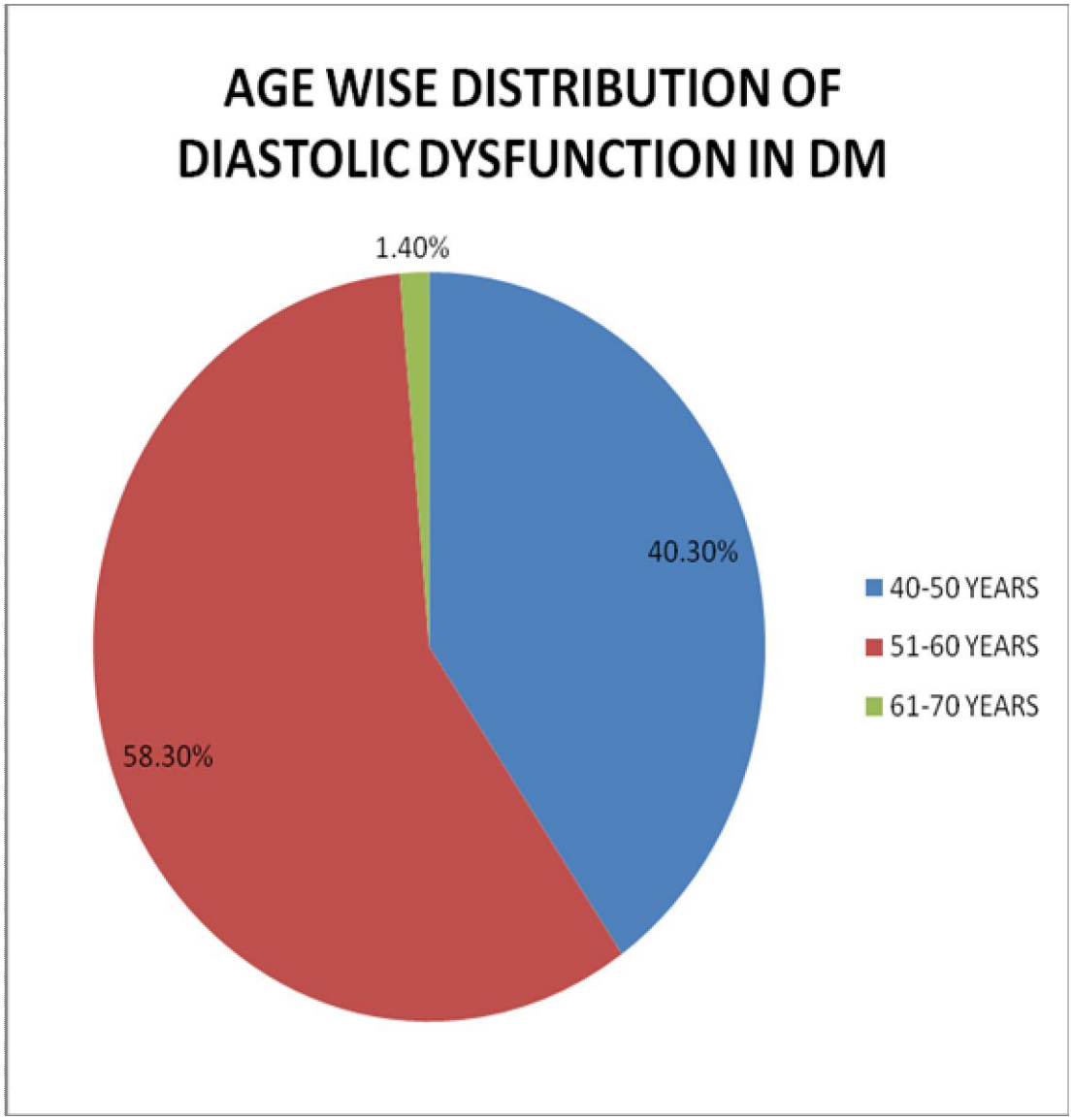
TABLE – 8: SHOWING AGE WISE DISTRIBUTION OF DIASTOLIC DYSFUNCTION IN DIABETIC PATIENTS

AGE	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN AGE	% IN DIASTOLIC DYSFUCTION
40 – 50 YEARS	29	56.9%	40.3%
51 – 60 YEARS	42	87.5%	58.3%
61 – 70 YEARS	1	100%	1.4%

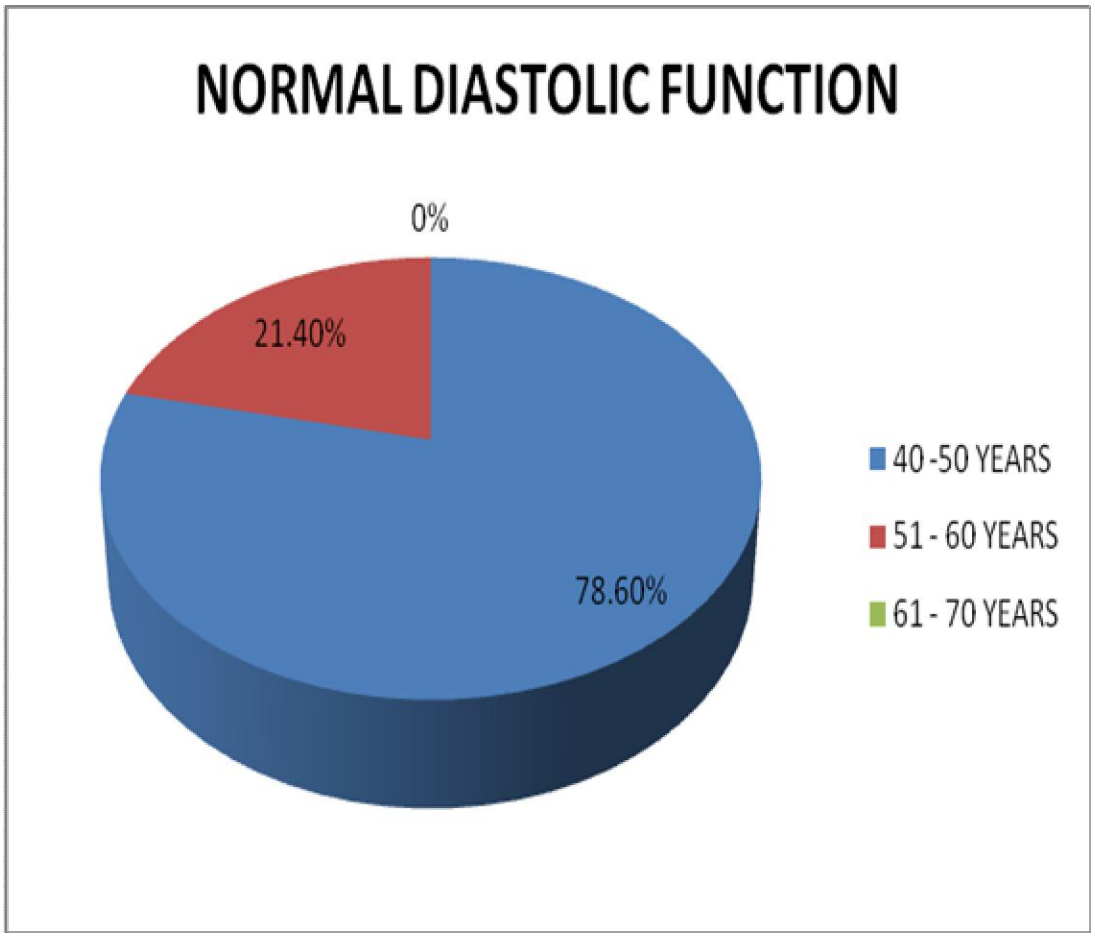
TABLE – 9: SHOWING AGE WISE DISTRIBUTION OF NORMAL DIASTOLIC FUNCTION IN DIABETIC PATIENTS

AGE	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN AGE	% IN NORMAL DIASTOLIC FUNCTION
40 – 50 YEARS	20	43.1%	78.6%
51 – 60 YEARS	6	12.5%	21.4%
61 – 70 YEARS	0	0%	0%

GRAPH – 8: AGE WISE DISTRIBUTION OF DIABETIC PATIENTS



GRAPH – 9: SHOWING DISTRIBUTION OF NORMAL DIASTOLIC FUNCTION



GRAPH – 10: SHOWING CORRELATION OF AGE AND DIASTOLIC DYSFUNCTION IN DIABETES

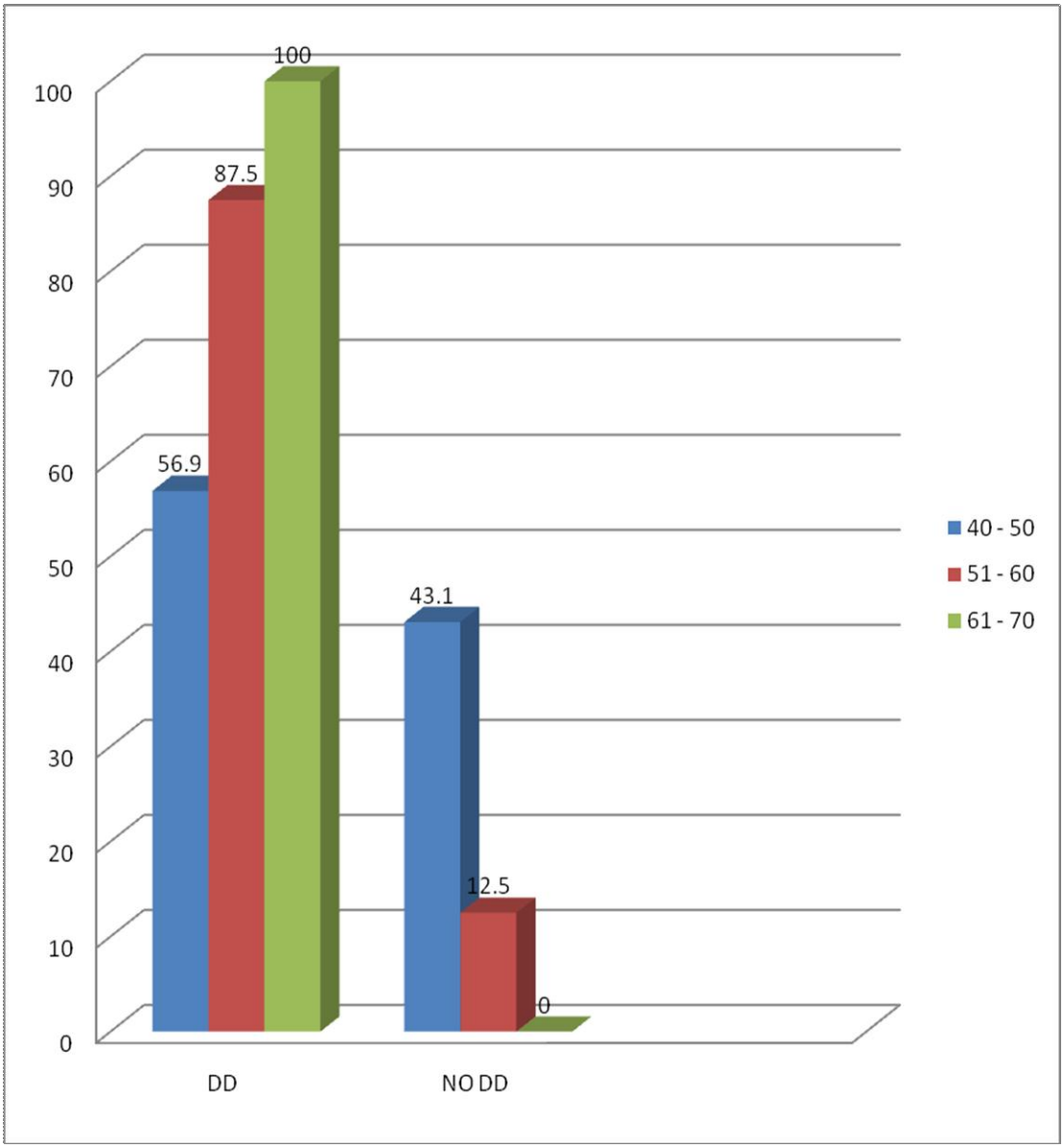


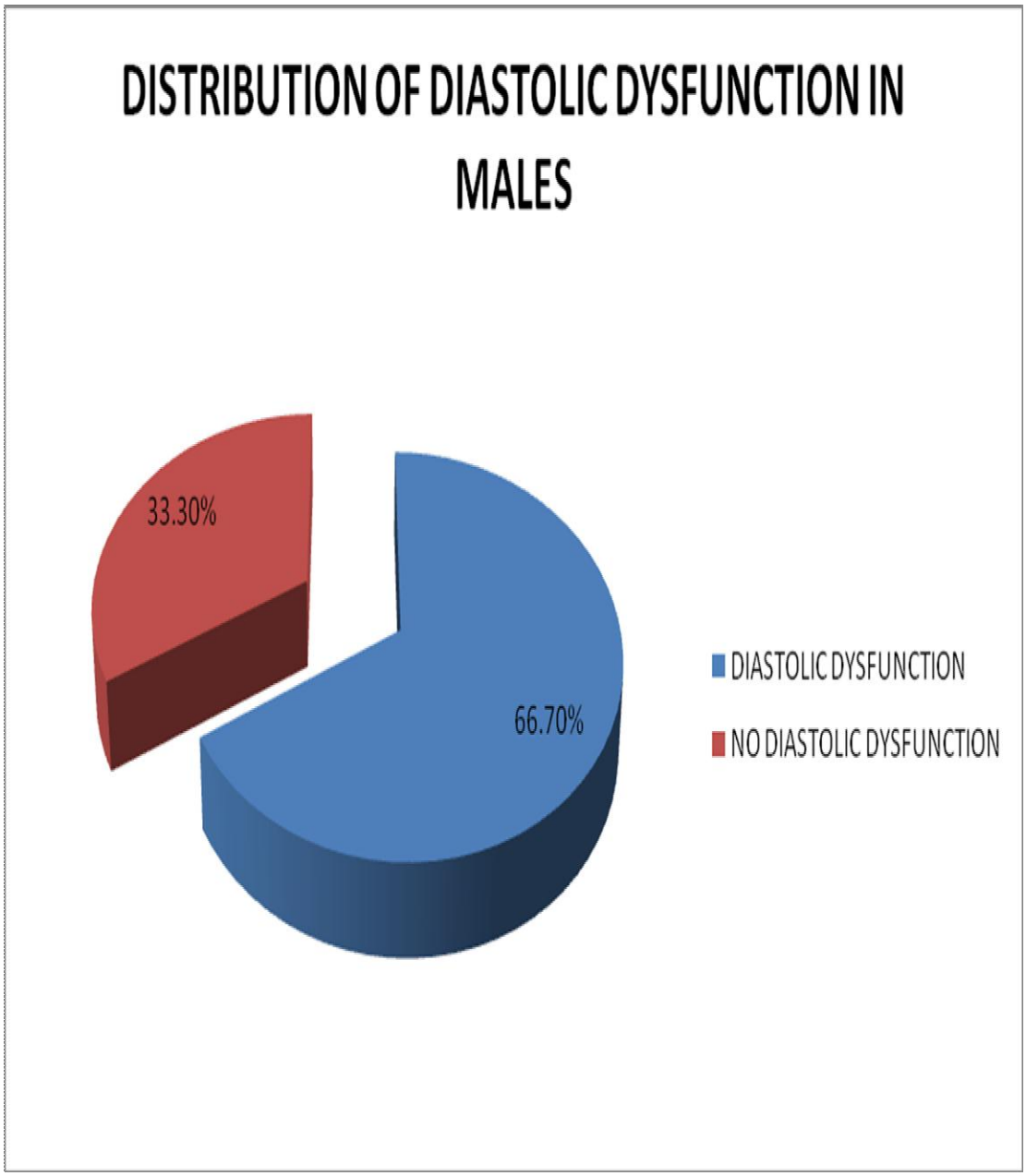
TABLE – 10: SHOWING GENDER WISE DISTRIBUTION OF DIASTOLIC DYSFUNCTION

GENDER	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN SEX	% IN DIASTOLIC DYSFUNCTION
MALE	32	66.7%	44.4%
FEMALE	40	76.9%	55.6%

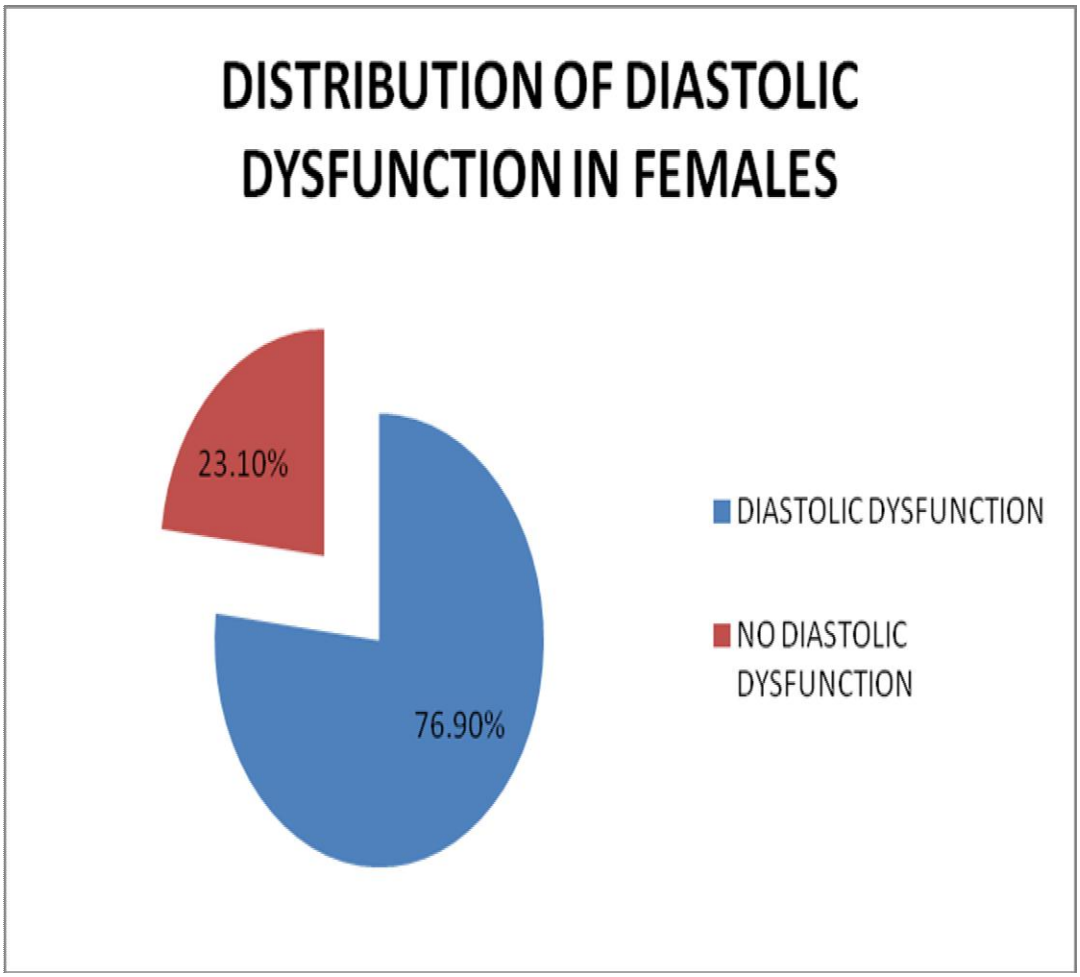
TABLE – 11: SHOWING GENDER WISE DISTRIBUTION OF NORMAL DIASTOLIC FUNCTION

GENDER	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN GENDER	% IN NORMAL DIASTOLIC FUNCTION
MALE	16	33.3%	57.1%
FEMALE	12	23.1%	42.9%

GRAPH – 11: DISTRIBUTION OF DIASTOLIC DYSFUNCTION IN MALES



GRAPH – 12: DISTRIBUTION OF DIASTOLIC DYSFUNCTION IN FEMALE



GRAPH – 13: SHOWING CORRELATION BETWEEN GENDER AND DIASTOLIC DYSFUNCTION

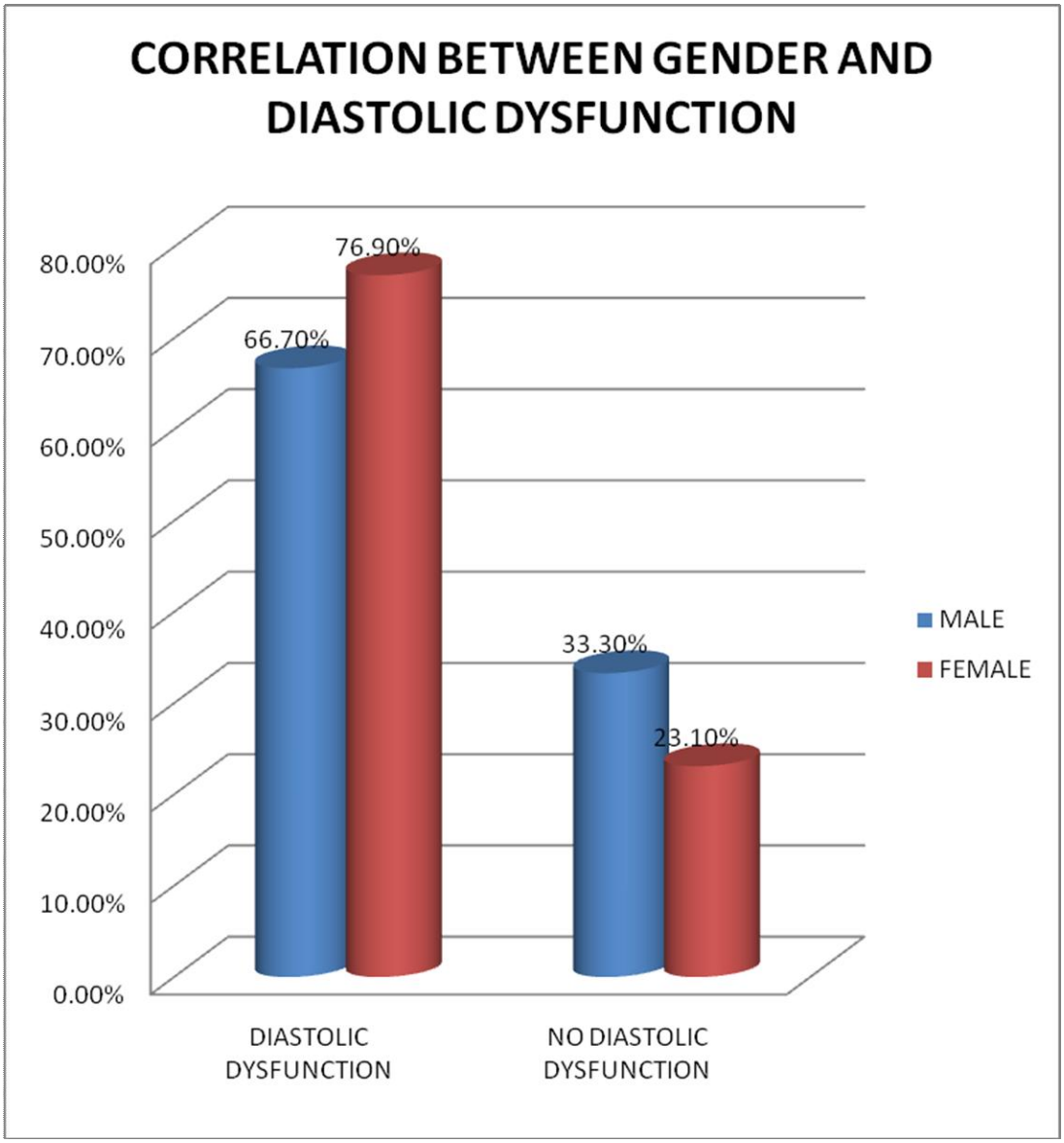


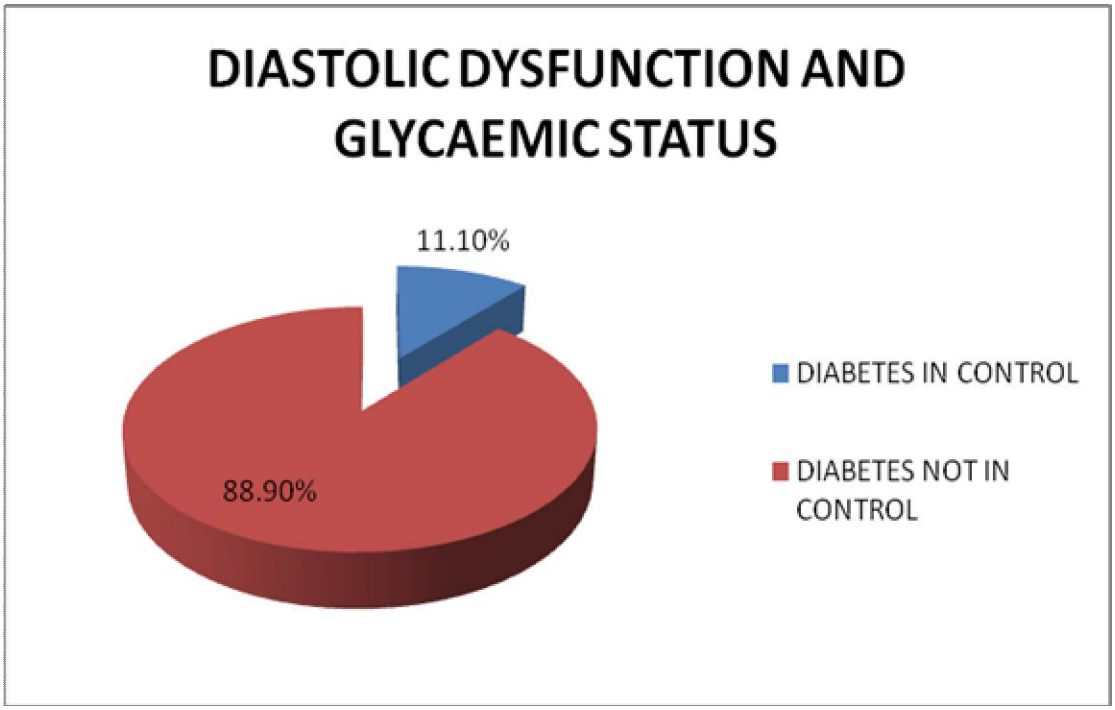
TABLE – 12: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND GLYCAEMIC CONTROL

GLYCAEMIC CON-TROL	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN CONTROL	% IN DIASTOLIC DYSFUNCTION
YES	8	29.6%	11.1%
NO	64	87.7%	88.9%

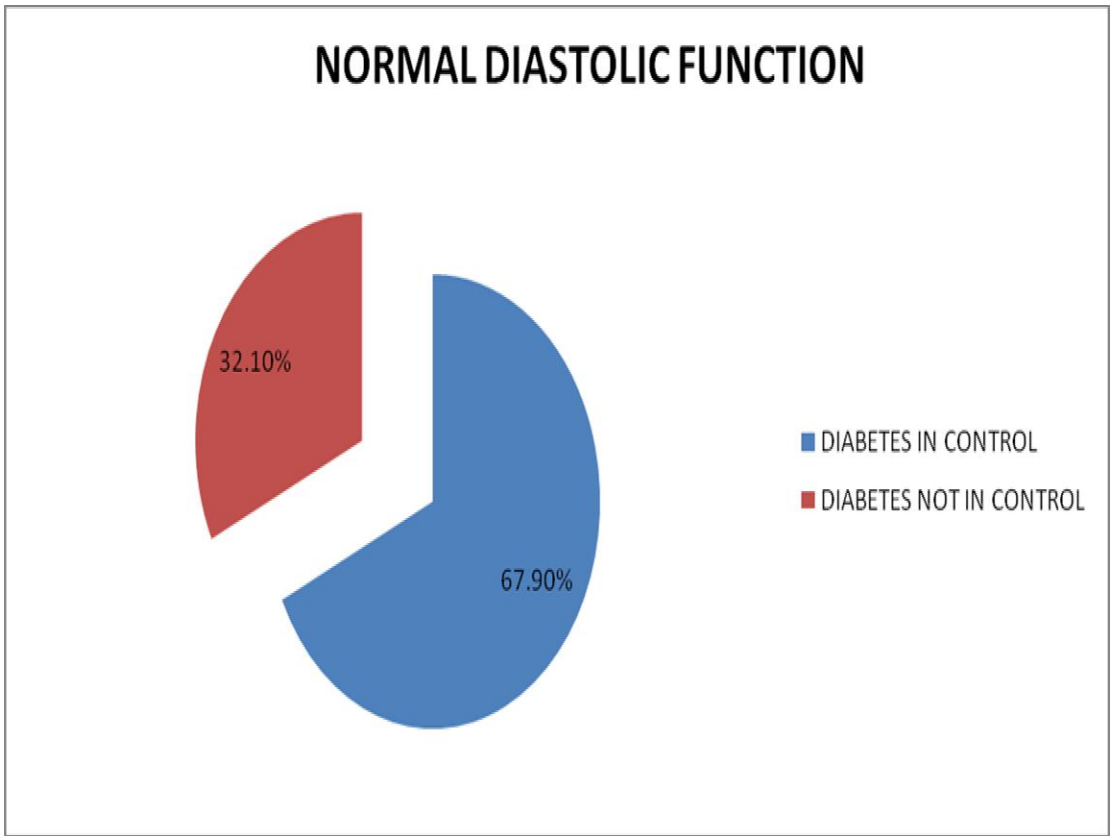
TABLE – 13: SHOWING CORRELATION BETWEEN NORMAL DIASTOLIC FUNCTION AND GLYCAEMIC CONTROL

GLYCAEMIC CONTROL	NO DIASTOLIC DYSFUNCTION		
	NUMBER	% IN CONTROL	% IN NO DIASTOLIC DYSFUNCTION
YES	19	70.4%	67.9%
NO	9	12.3%	32.1%

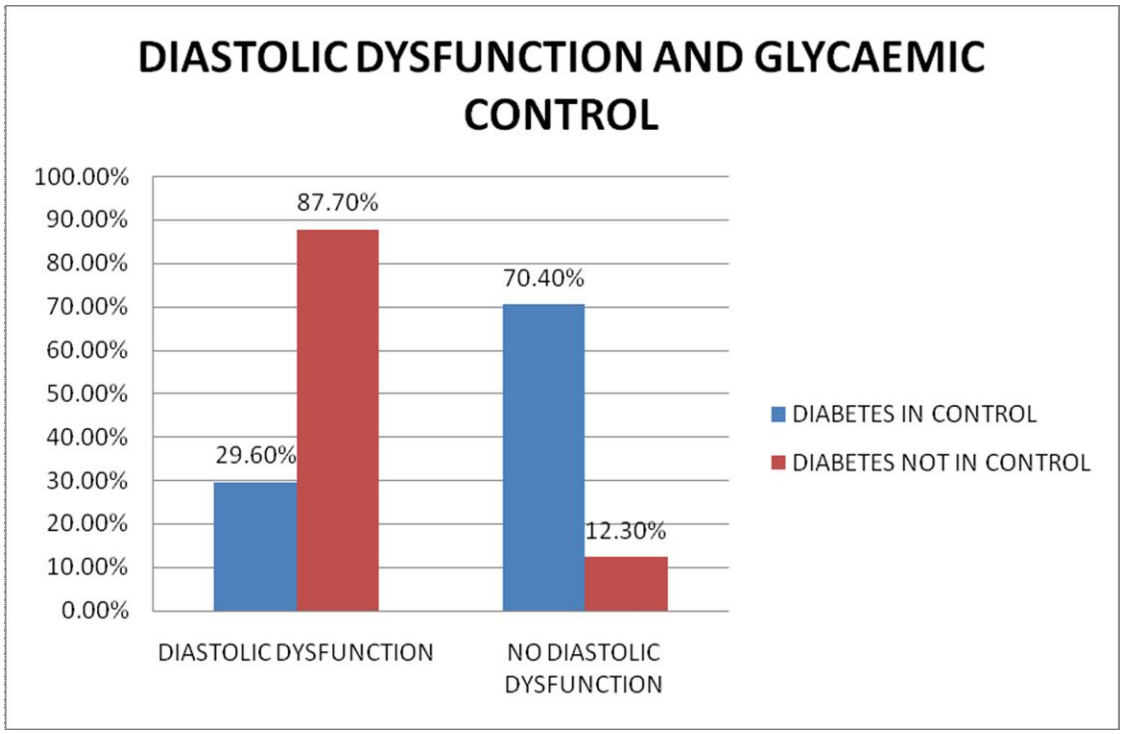
GRAPH – 14: SHOWING DIASTOLIC DYSFUNCTION AND GLYCAEMIC STATUS



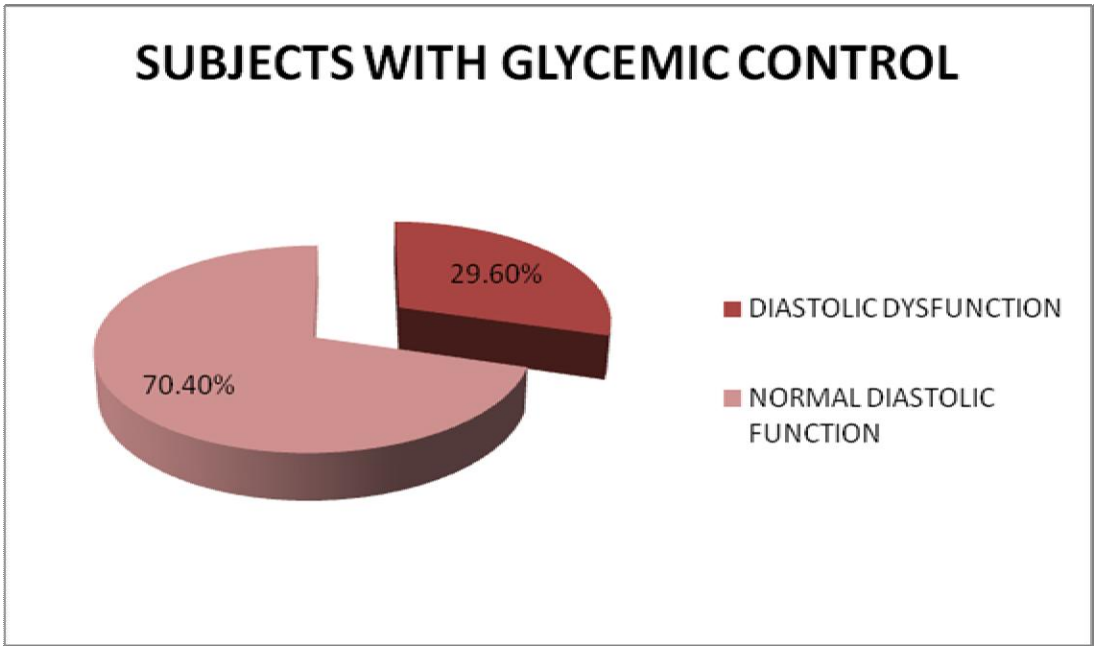
GRAPH – 15: SHOWING NORMAL DIASTOLIC FUNCTION AND GLYCAEMIC STATUS



GRAPH -16: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND GLYCAEMIC CONTROL



GRAPH – 17: SHOWING DIASTOLIC FUNCTION IN CASES WITH GOOD GLYCAEMIC CONTROL



GRAPH 18: SHOWING DIASTOLIC FUNCTION IN CASES WITH POOR GLYCAEMIC CONTROL

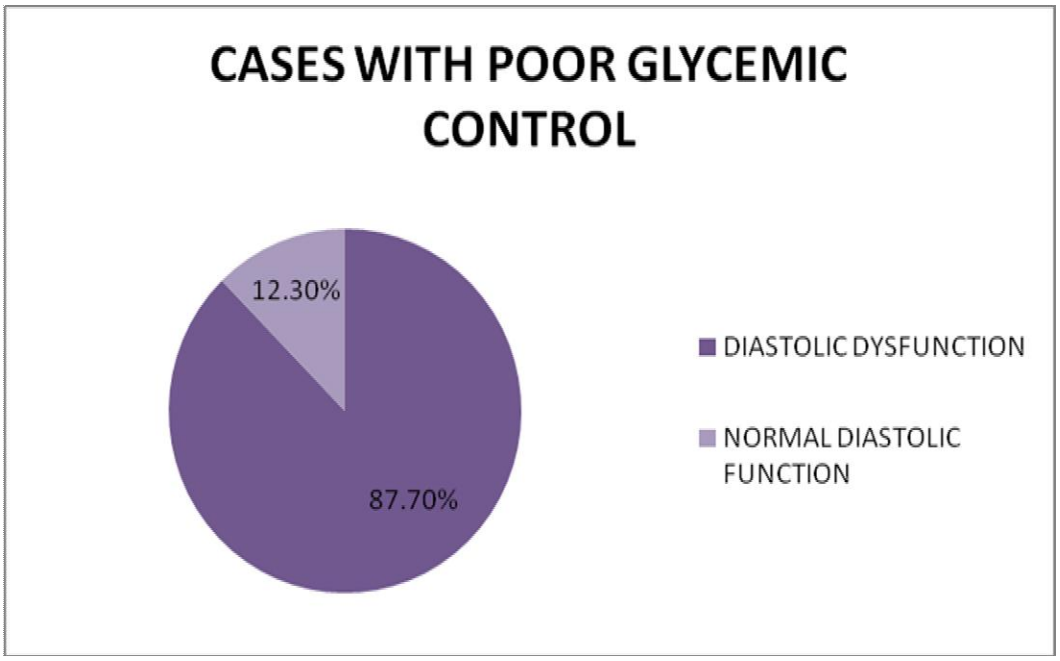


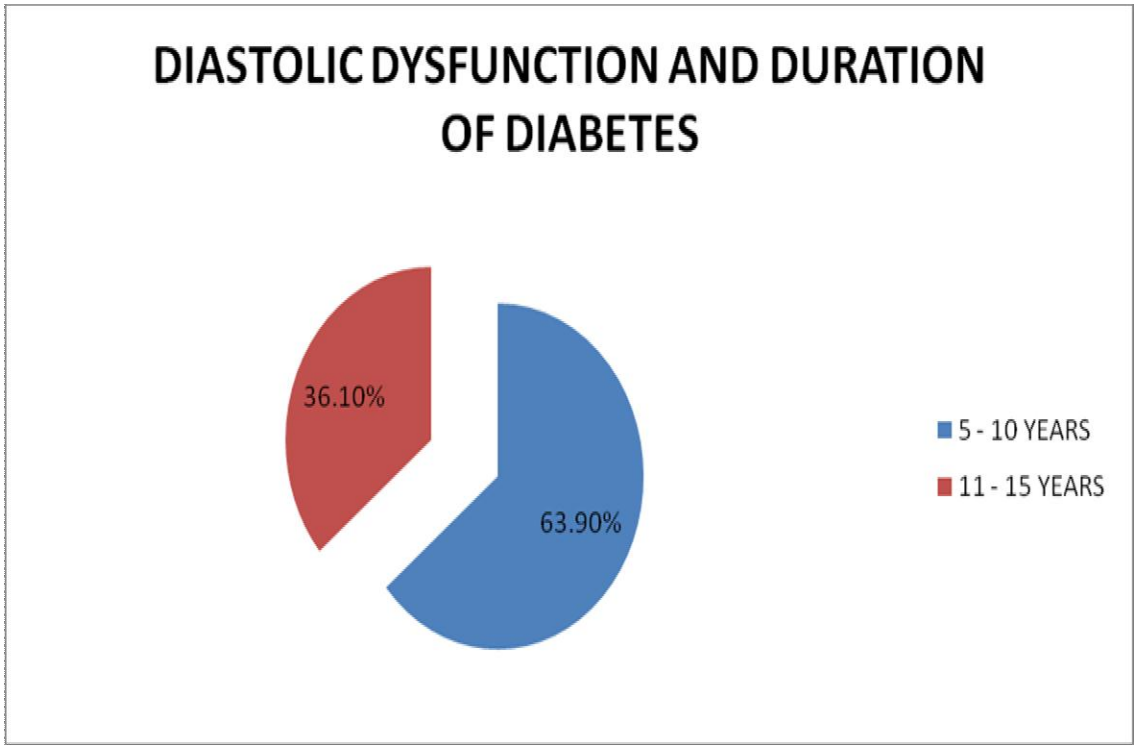
TABLE – 14: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND DURATION OF DIABETES

DURATION	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN DURATION	%IN DIASTOLIC DYSFUNCTION
5 – 10 YEARS	46	63.9%	63.9%
11- 15 YEARS	26	92.9%	36.1%

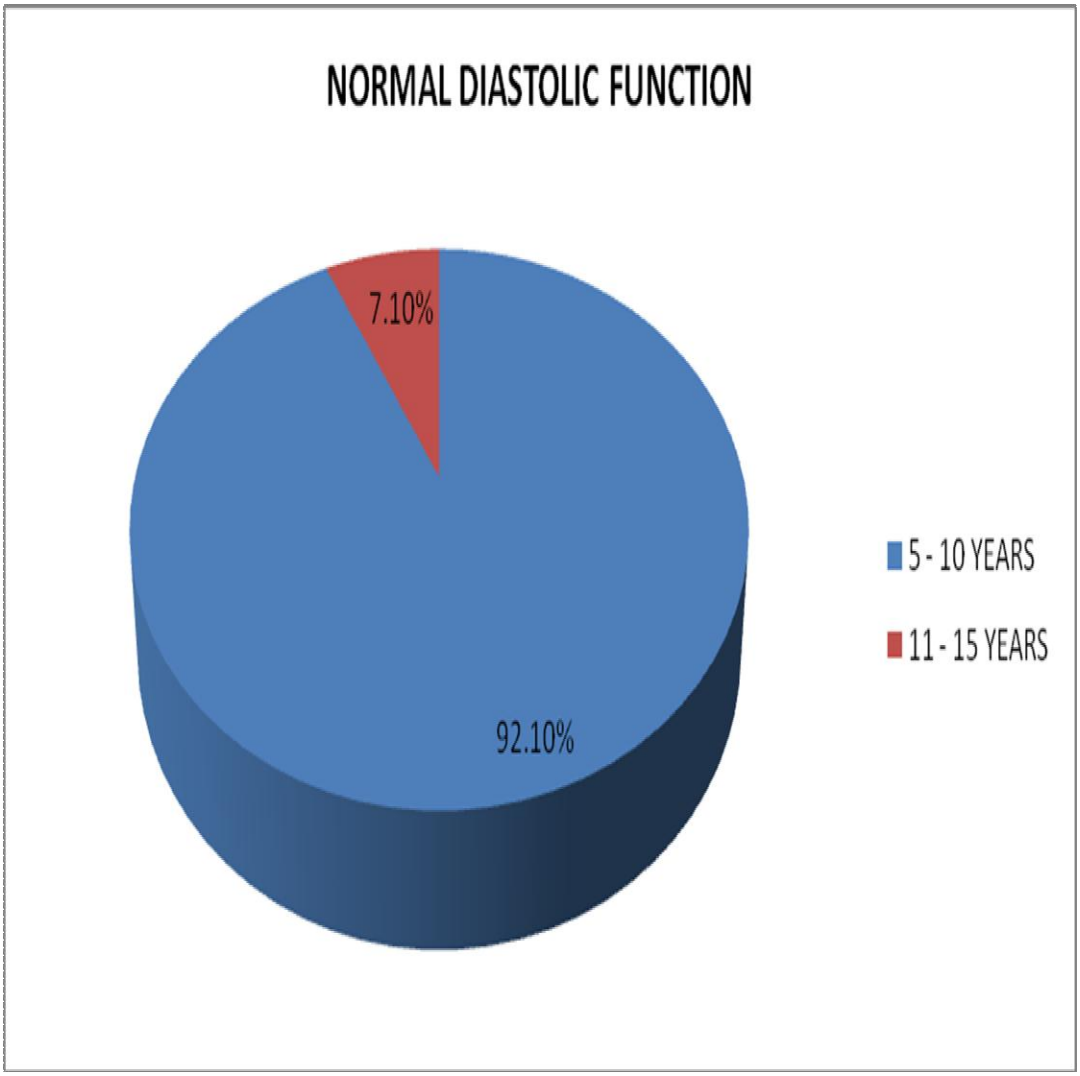
TABLE – 15: SHOWING CORRELATION BETWEEN NORMAL DIASTOLIC FUNCTION AND DURATION OF DIABETES

DURATION	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN DURATION	% IN NORMAL DIASTOLIC FUNCTION
5 – 10 YEARS	26	36.1%	92.9%
11 – 15 YEARS	2	7.1%	7.1%

GRAPH – 19: SHOWING DIASTOLIC DYSFUNCTION AND DURATION OF DIABETES



GRAPH – 20: SHOWING NORMAL DIASTOLIC FUNCTION AND DURATION OF DIABETES



GRAPH – 21: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND DURATION OF DIABETES

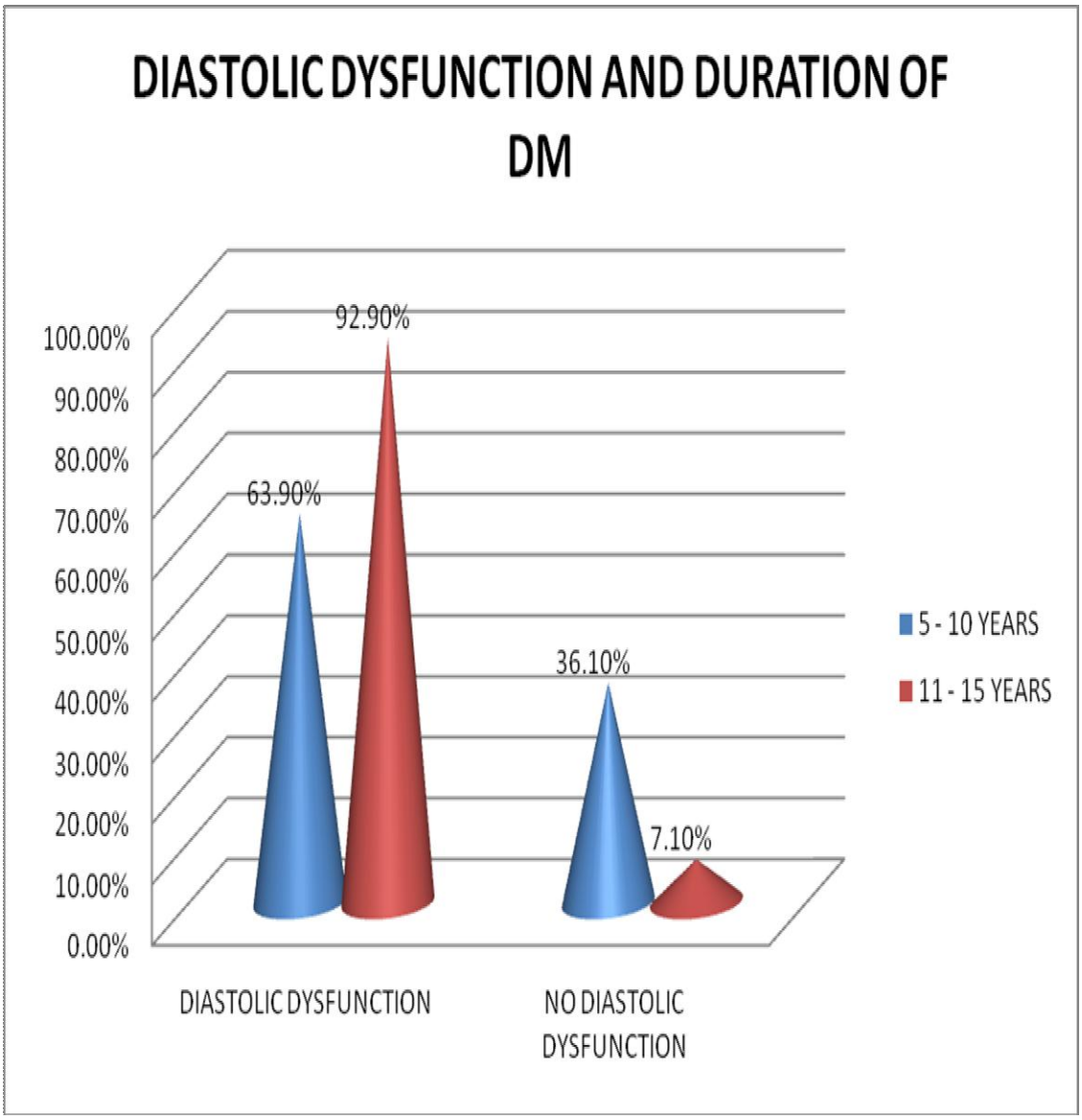


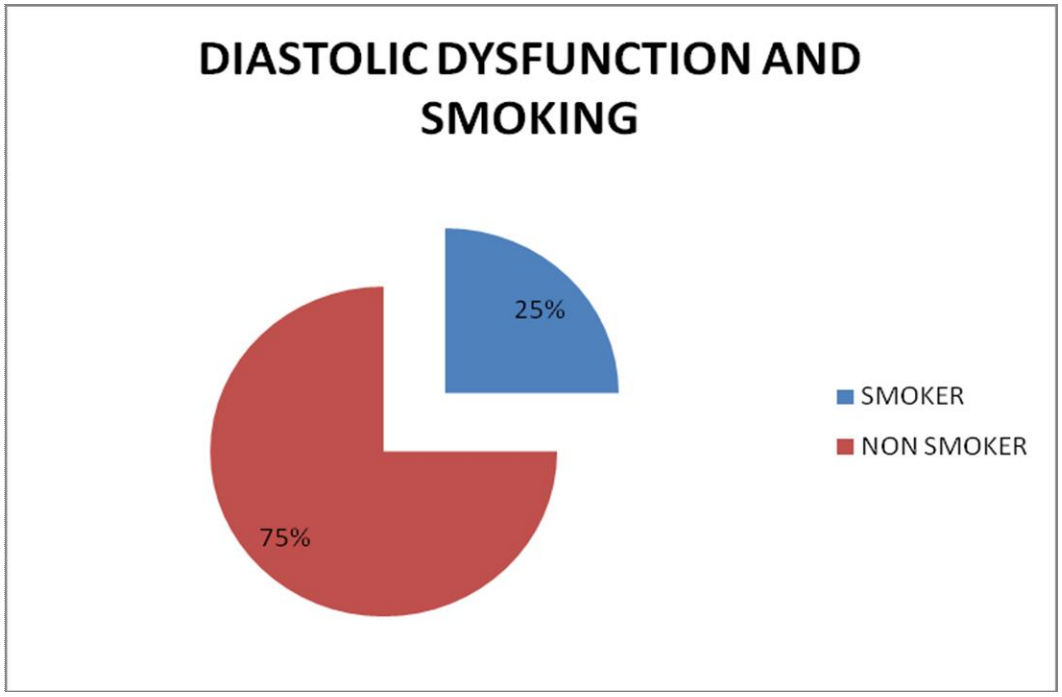
TABLE – 16: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND SMOKING

SMOKING	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN SMOKING	%IN DIASTOLIC DYSFUNCTION
SMOKER	18	69.2%	25%
NON SMOKER	54	73%	75%

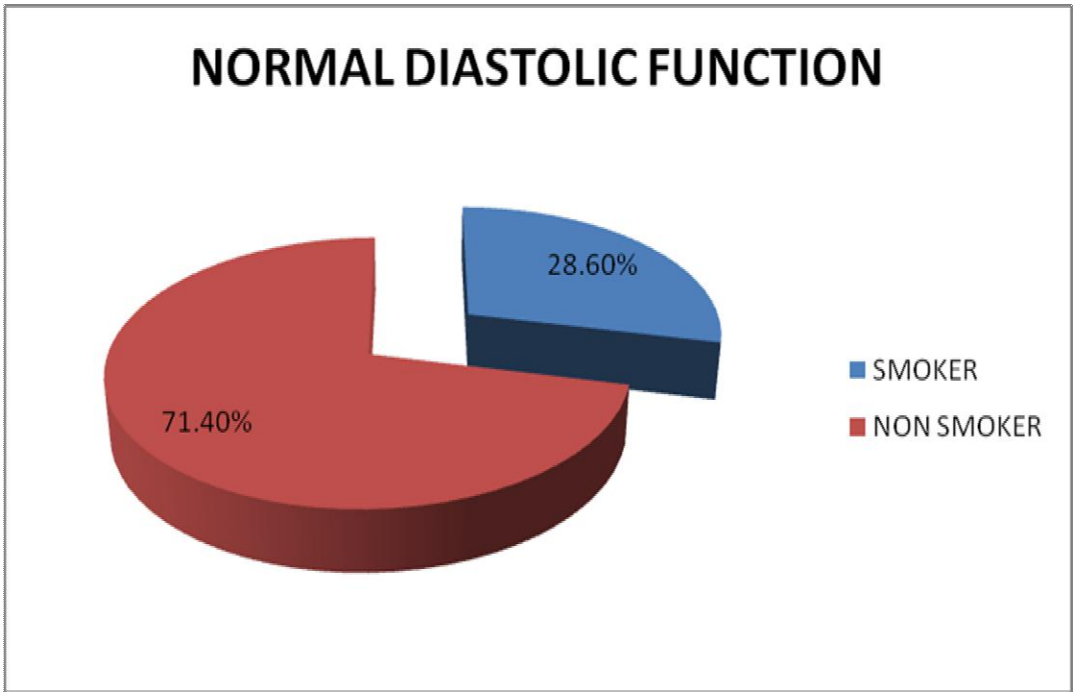
TABLE – 17: SHOWING CORRELATION BETWEEN NORMAL DIASTOLIC FUNCTION AND SMOKING

SMOKING	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN SMOKING	% IN NORMAL DIASTOLIC FUNCTION
SMOKER	8	30.8%	28.6%
NON SMOKER	20	27%	71.4%

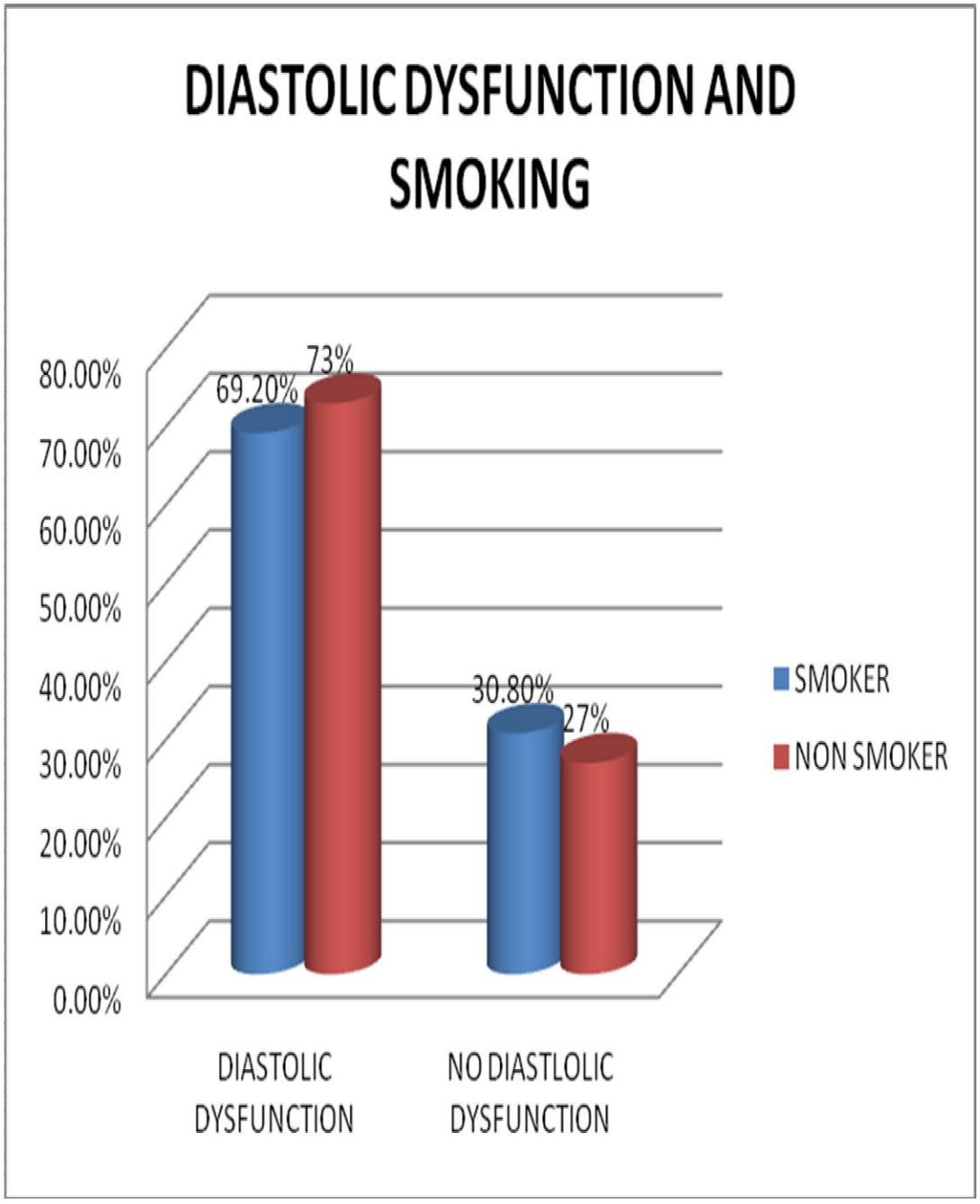
GRAPH –22: SHOWING DIASTOLIC DYSFUNCTION AND SMOKING



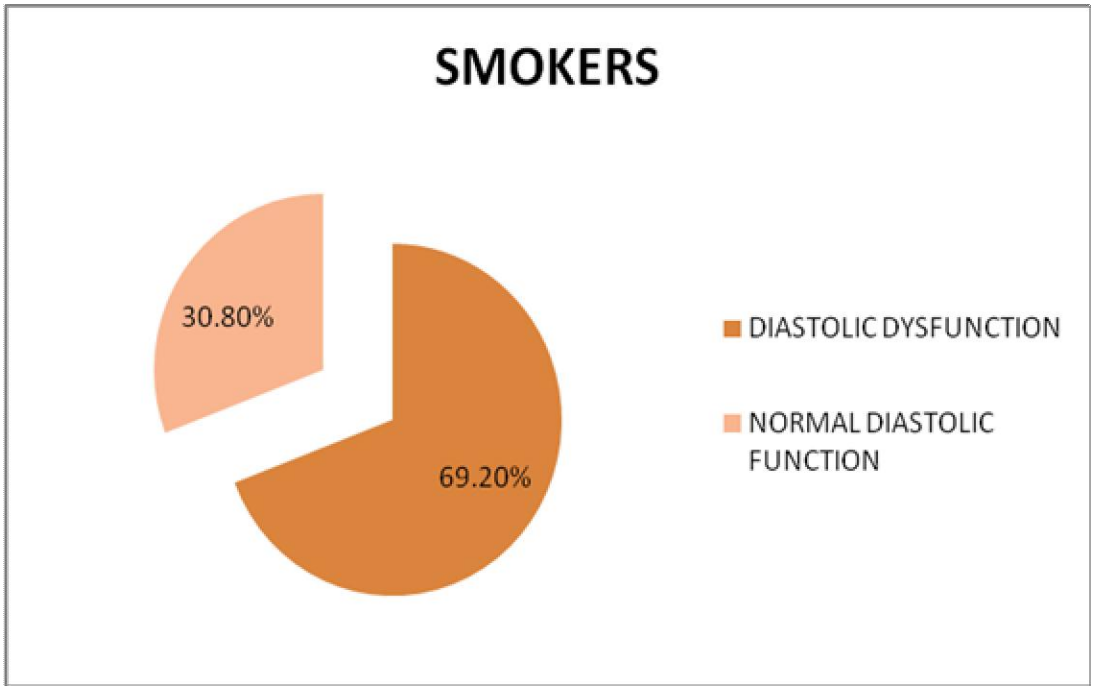
GRAPH – 23: SHOWING NORMAL DIASTOLIC FUNCTION AND SMOKING



GRAPH – 24: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND SMOKING



GRAPH – 25: SHOWING DIASTOLIC DYSFUNCTION IN SMOKERS



GRAPH – 26: SHOWING DIASTOLIC DYSFUNCTION IN NON SMOKERS

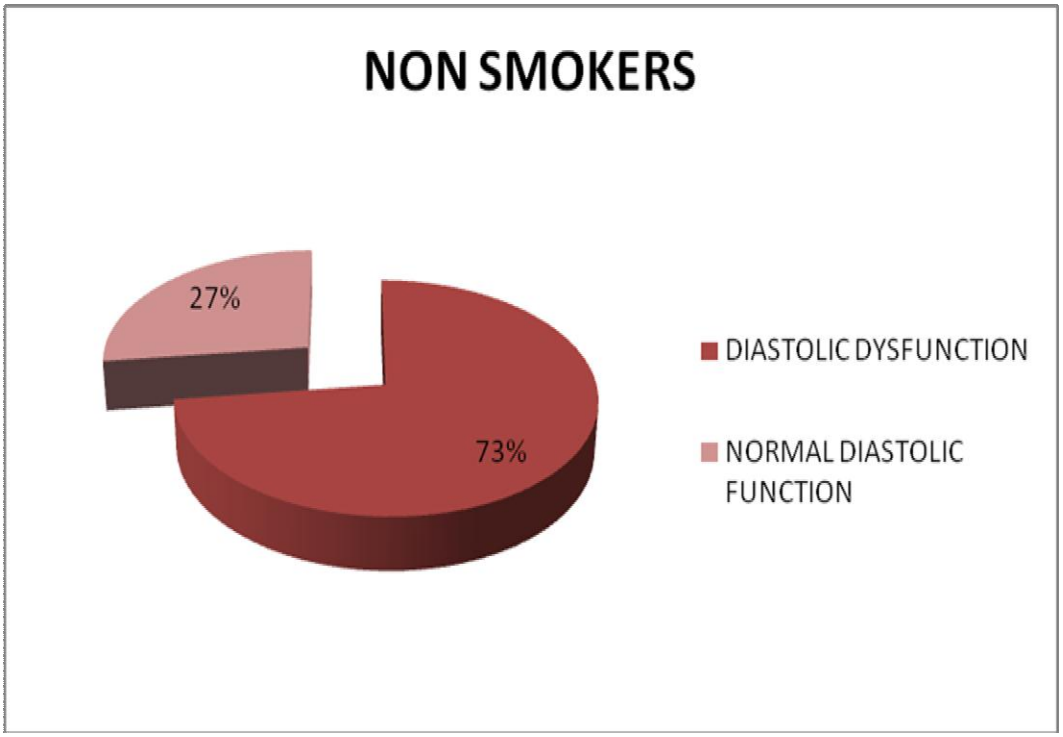


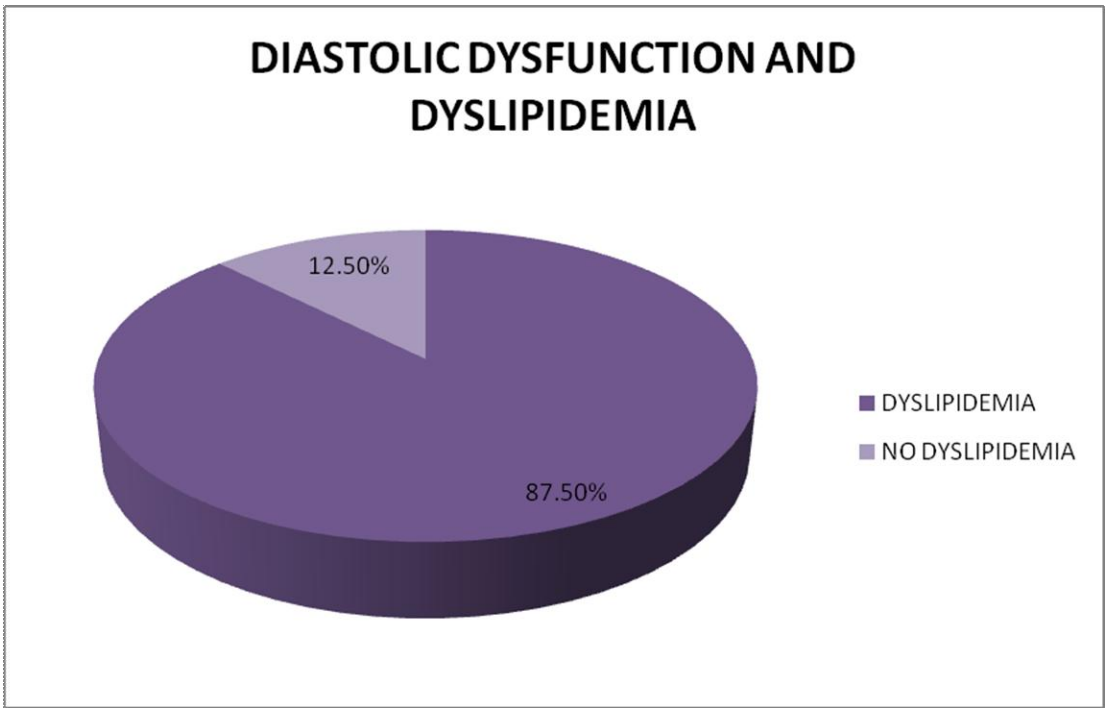
TABLE – 18: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND DYSLIPIDEMIA

LIPID PROFILE	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN LIPID PROFILE	%IN DIASTOLIC DYSFUNCTION
DYSLIPIDEMIA	63	87.5%	87.5%
NO DYSLIPIDEMIA	9	32.1%	12.5%

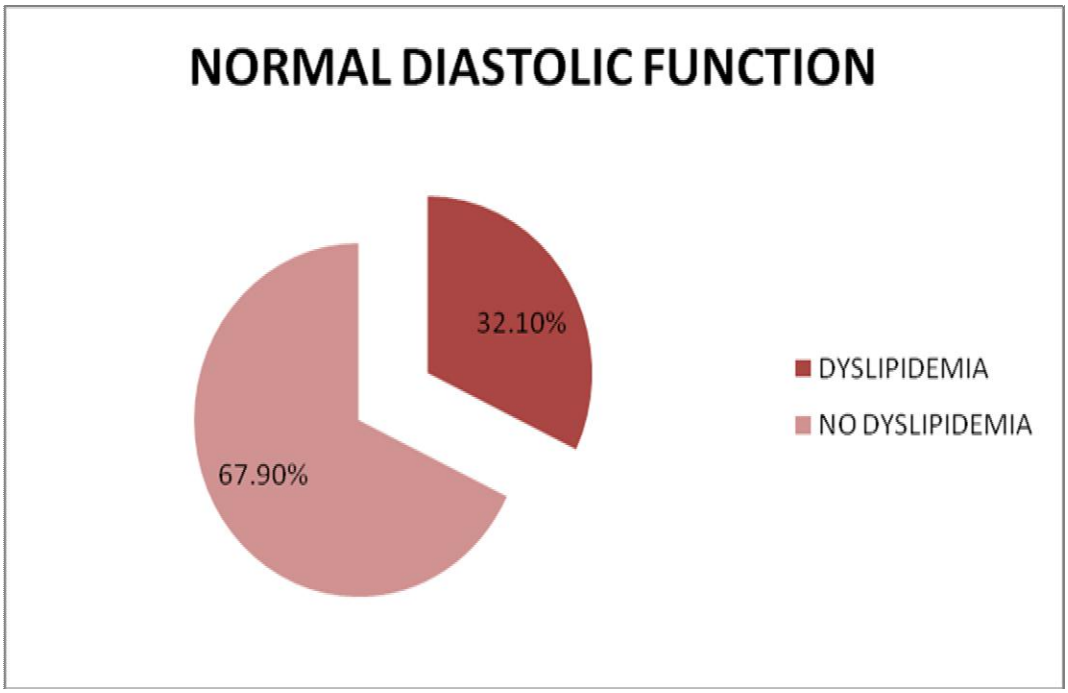
TABLE – 19: SHOWING CO-RELATION BETWEEN NORMAL DIASTOLIC FUNCTION AND DYSLIPIDEMIA

LIPID PROFILE	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN DYSLIPIDEMIA	% IN NORMAL DIASTOLIC FUNCTION
DYSLIPIDEMIA	9	12.5%	32.1%
NO DYSLIPIDEMIA	19	67.9%	67.9%

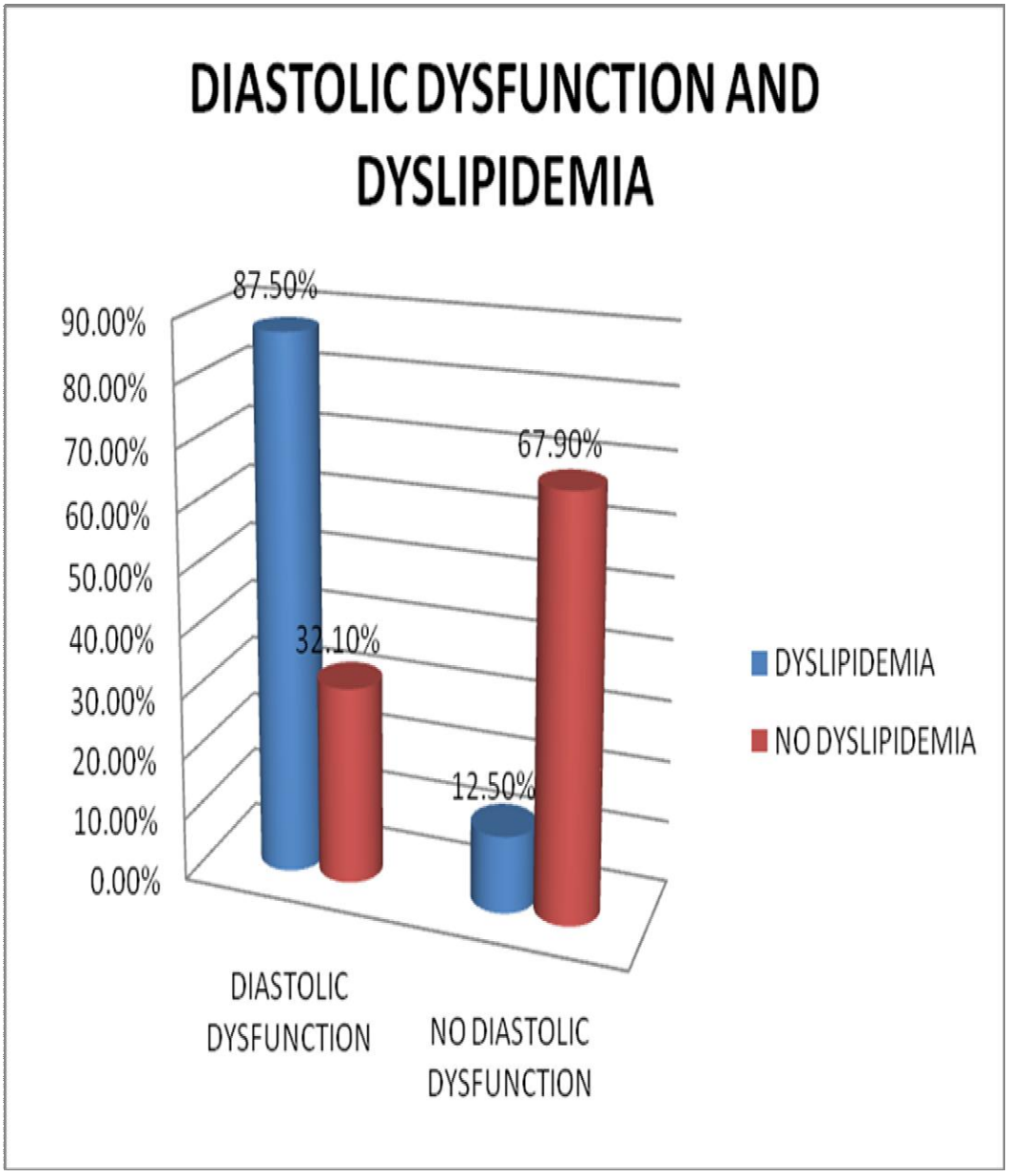
GRAPH – 27: SHOWING DIASTOLIC DYSFUNCTION AND DYSLIPIDEMIA



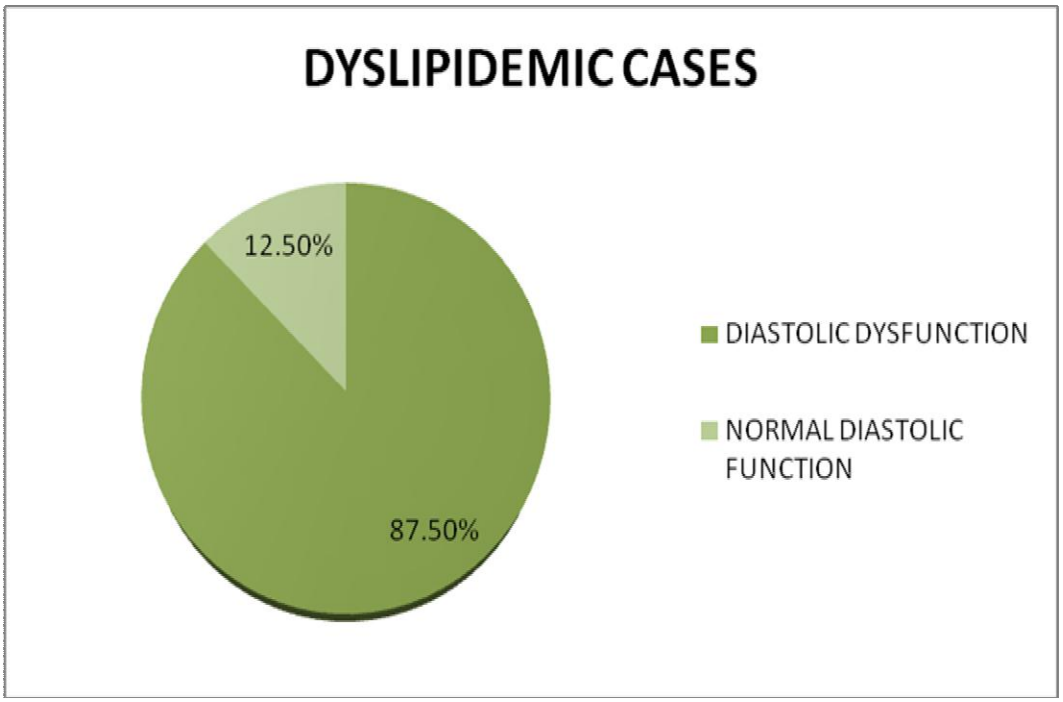
GRAPH – 28: SHOWING NORMAL DIASTOLIC FUNCTION AND DYSLIPIDEMIA



GRAPH – 29: SHOWING CORRELATION WITH DYSLIPIDEMIA



GRAPH – 30: SHOWING DIASTOLIC DYSFUNCTION IN DYSLIPIDEMIC CASES



GRAPH – 31: SHOWING DIASTOLIC DYSFUNCTION IN CASES WITH NORMAL LIPID PROFILE

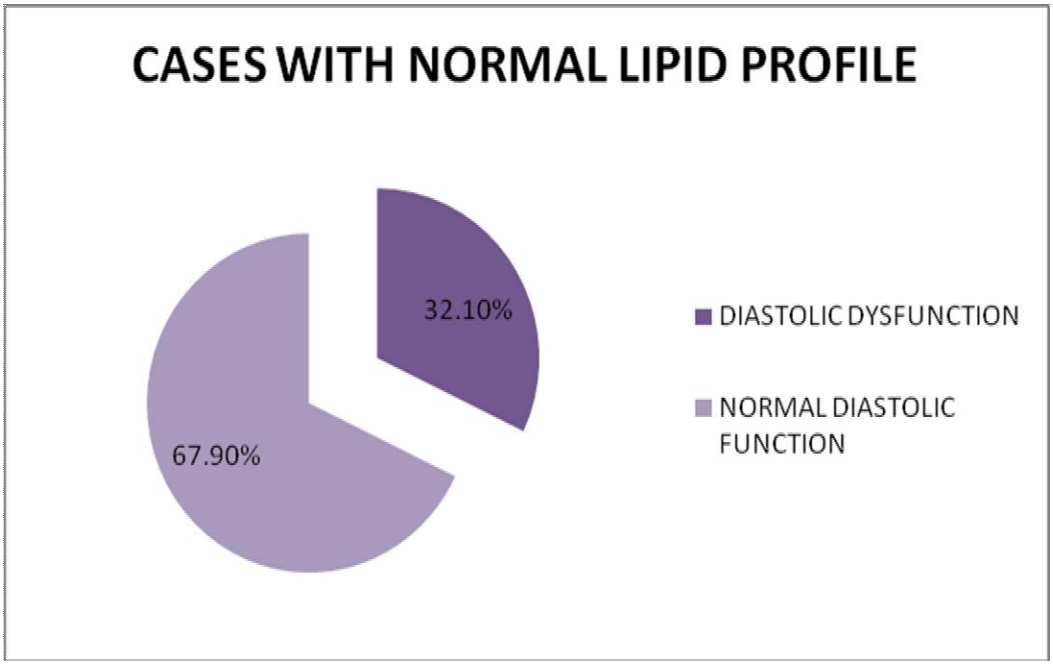


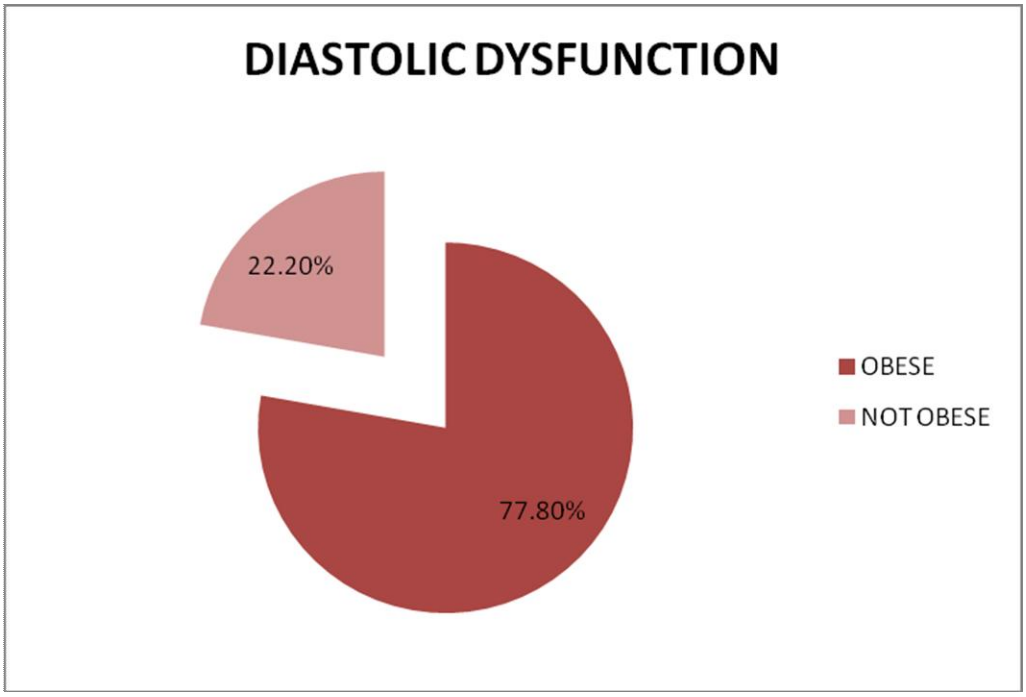
TABLE – 20: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND OBESITY

OBESITY	DIASTOLIC DYSFUNCTION		
	NUMBER	% IN OBESE	% IN DIASTOLIC DYSFUNCTION
OBESE	56	81.2%	77.8%
NOT OBESE	16	51.6%	22.2%

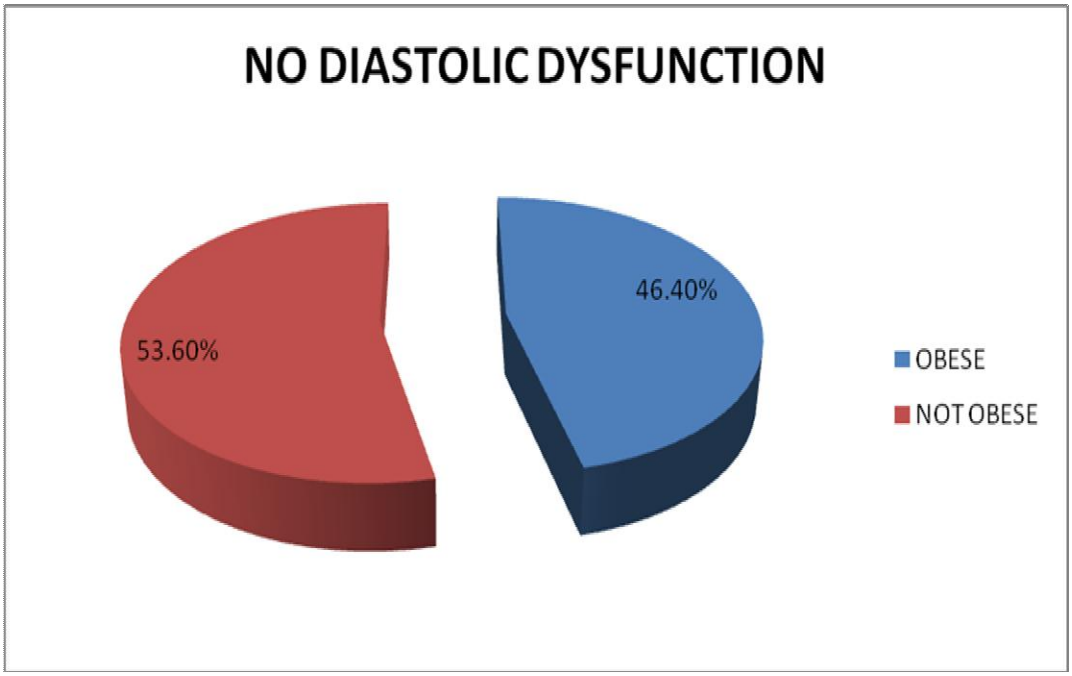
TABLE – 21: SHOWING CORRELATION BETWEEN NORMAL DIASTOLIC FUNCTION AND OBESITY

OBESITY	NORMAL DIASTOLIC FUNCTION		
	NUMBER	% IN OBESITY	% IN NORMAL DIASTOLIC FUNCTION
OBESE	13	18.8%	46.4%
NON OBESE	15	48.4%	53.6%

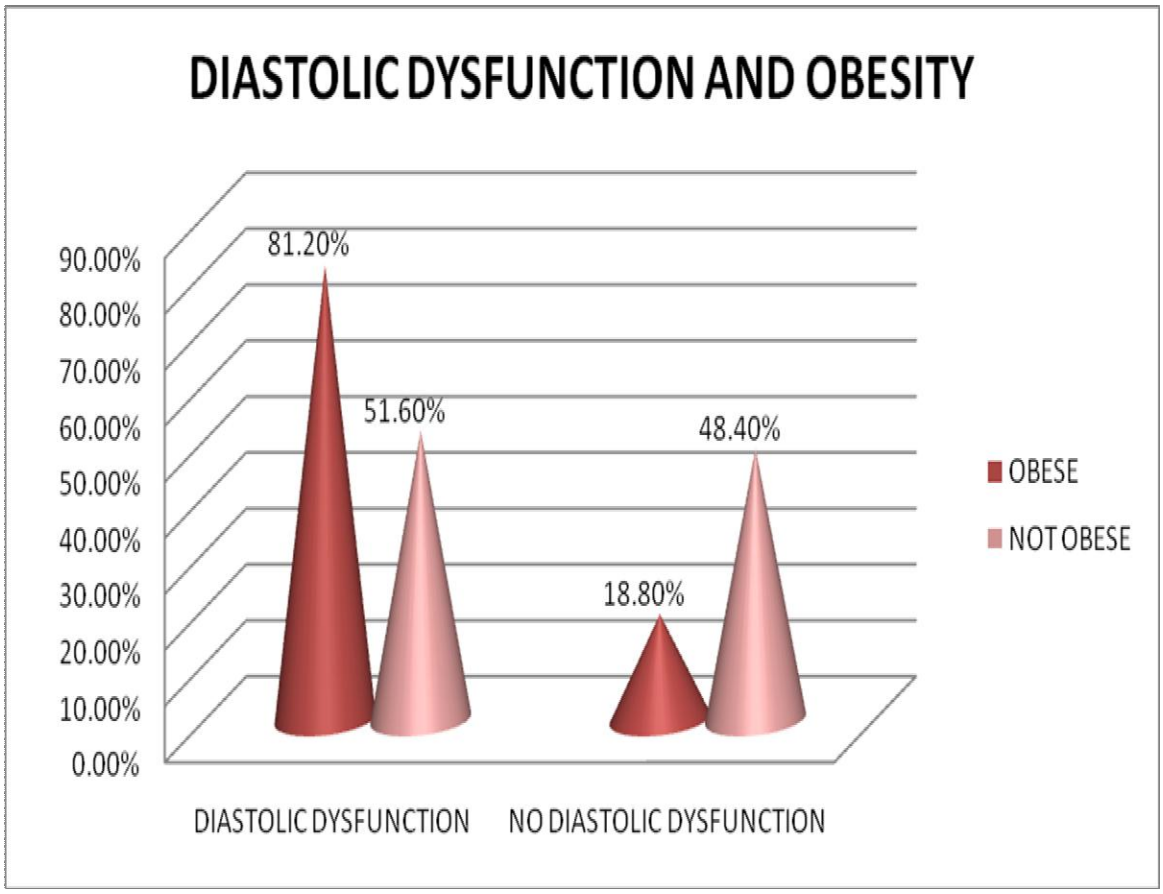
GRAPH – 32: SHOWING DIASTOLIC DYSFUNCTION AND OBESITY



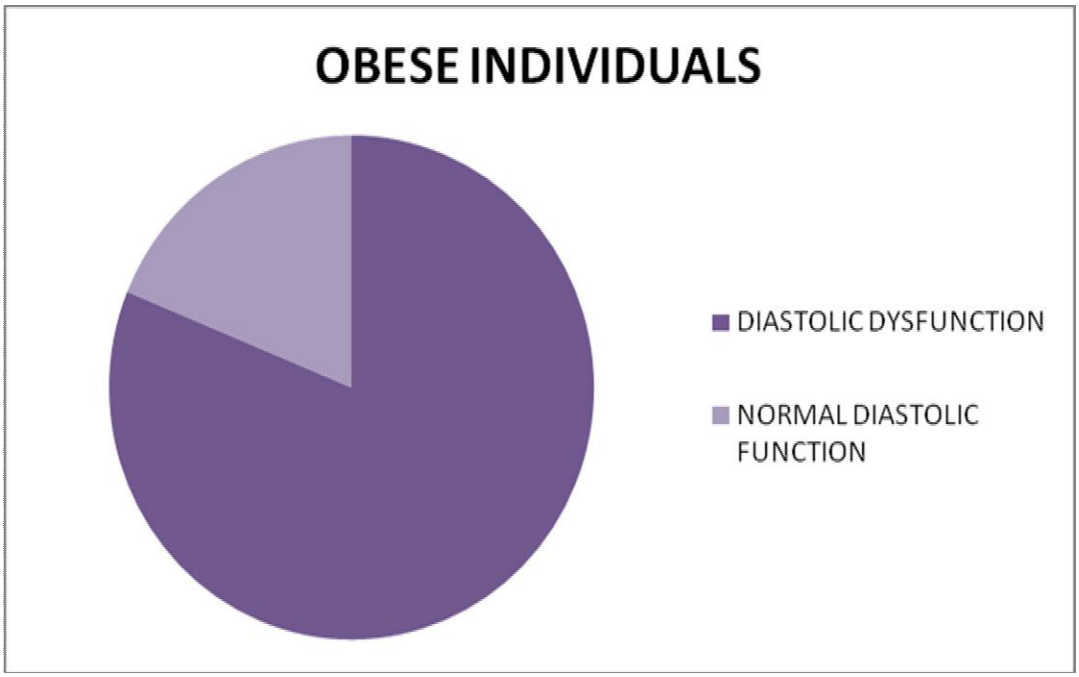
GRAPH – 33: SHOWING NORMAL DIASTOLIC FUNCTION AND OBESITY



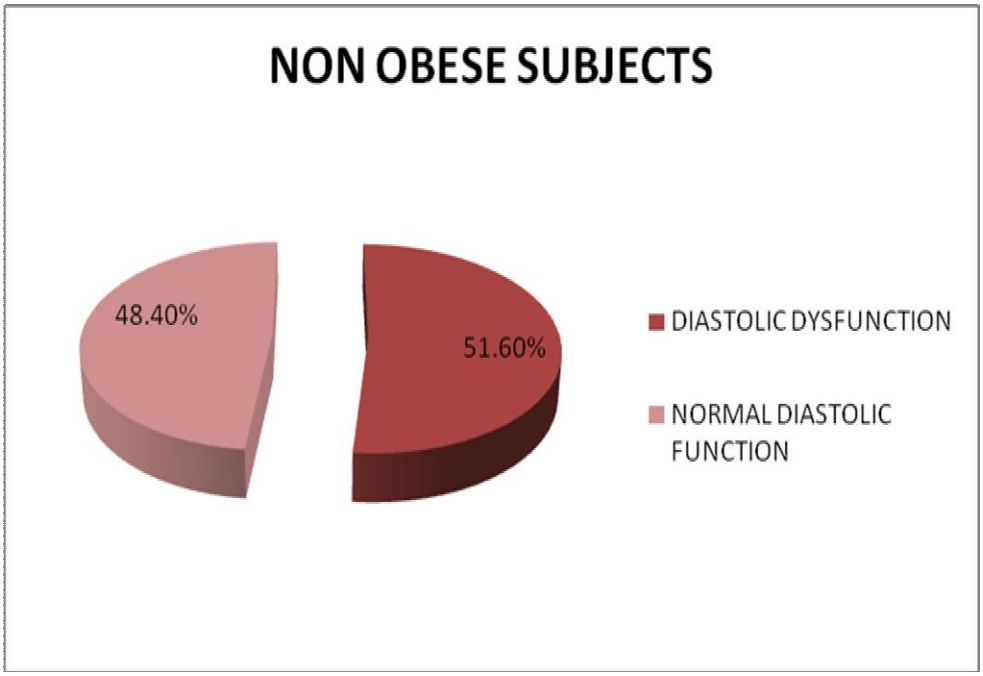
GRAPH – 34: SHOWING CORRELATION BETWEEN DIASTOLIC DYSFUNCTION AND OBESITY



GRAPH – 35: SHOWING DIASTOLIC DYSFUNCTION IN OBESE CASES



GRAPH – 36: SHOWING DIASTOLIC DYSFUNCTION IN NON OBESE CASES



DISCUSSION

Diabetes mellitus per se is a well known independent risk factor for cardio vascular disease. The most common changes in cardiovascular system associated with diabetes are left ventricular mass and structural changes, negative affection of the mid wall systolic mechanics and diastolic dysfunction.

Asymptomatic diastolic dysfunction is quite common among the population of type 2 diabetes mellitus patients. Various co- existing states like advancing age, obesity and dyslipidemia and risk factors like smoking have both independent and additive effect over occurrence of diastolic dysfunction in the diabetes patients.

The asymptomatic diastolic dysfunction in diabetes precedes systolic dysfunction and is a common echocardiographic finding in diabetes patients with normal left ventricular systolic function.

Various diagnostic modalities like echocardiography, electro cardiogram and radio nuclide scans which can be categorized as invasive and non invasive can be utilized for identifying, assessing and quantifying the diabetes associated changes in cardiovascular system among which our study focuses on evaluating diastolic dysfunction using echocardiography .

Echocardiography has emerged as an excellent non- invasive diagnostic tool to delineate the details of the structure of the cardiac cavity, dimensions of

cardiac walls and the wall movements. This is the reason why echocardiography is now widely as a tool for assessing cardiac performance and cardiac structural abnormalities.

Left ventricular diastolic dysfunction has now emerged as a leading cause of cardiac morbidity in the Diabetes patients. The rate of association of defective diastolic performance, especially even in the asymptomatic stages is calculated to be high on the basis of available data.

Numerous parameters like myocardial compliance and relaxation, atrial contraction, pre load, trans valvular pressure gradient, passive elastic properties, restraint of pericardium and the thoracic cage, respiratory variant, valve incompetence and arrhythmias influence the function of heart during diastolic phase.

The development or progression of diastolic dysfunction can be discussed in mainly three stages which are as follows: (1) reduction in the early ventricular filling phase leading to inversion of ratio of peak early to peak atrial velocity curve, (2) increased filling pressures in the atrial and ventricular chambers and reduction in ventricular relaxation causing Pseudo normalisation of E/A flow pattern, (3) restrictive pattern development due to various degrees of involvement of atrial flow.

Thus, a normal E/A flow pattern may be difficult to interpret as it may be associated with normal cardiac function or it may be associated with progressive diastolic cardiac dysfunction with raised filling pressures.

Takeda et al.[20] by a study conducted in 544 Japanese DM patients with ejection fraction ≥ 50%, found that diastolic dysfunction (impaired relaxation) plays a vital role in the induction of HF with normal systolic function in DM patients, regardless of the severity of DM and renal dysfunction.

Boyer et al.[18] stated that the prevalence of LV diastolic dysfunction persons without symptoms and hypertension but having type 2 diabetes disease is high. Diastolic dysfunction was found in 75% of the persons subjected to their study. In our study, prevalence of diastolic dysfunction was 72% in asymptomatic and normotensive patients out of the total 100 persons subjected to study.

In the current study, out of 100 patients who were subjected to the study, 73 % had poor glycaemic control and only 27% had good glycaemic control as measured using reliable parameters like HbA1C.

Among the total 72 patients who had diastolic dysfunction, 64 patients which accounts for 87.7 % in the total had poor glycaemic control. Also when assessed for correlation between glycaemic control and diastolic dysfunction the obtained value in the present study is 'P' < 0.002. This result is in concordance with study results of Soldatos et al.[8] who in their case control study of 55 individuals with type -2 DM concluded that diastolic dysfunction, present in a significant proportion of diabetic persons.

Van Heerebeek et al.[10] who conducted study in 36 type -2 DM patients concluded that, the resting tension of cardiac myocyte is more reliable

when LVEF is normal. Excessive diastolic left ventricular stiffness is an important contributor to heart failure in diabetic persons. Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products. Also, in our current study, 72 % of the diabetes patients were found to have diastolic dysfunction with normal LVEF.

Annonu et al. [12] in their case control study of 66 subjects found that there was an inverse correlation between the duration of diabetes and E/A ratio ($r = -0.4$, 'P' <.005). This result is comparable to our present study where among total 72 patients with diastolic dysfunction, 92.9 % i.e 26 of total 28 patients with duration of diabetes more than 10 years had diastolic dysfunction. Also in the total 72 patients with duration of diabetes of 5 – 10 years, 46 patients i.e 63.9 % had diastolic dysfunction. Also the correlation between duration duration of diabetes and diastolic dysfunction was calculated in present study as 'P' <0.004

Masugata et al.[11] who conducted a case control study in 77 persons with no hypertension patients found that, the cardiac diastolic dysfunction without LV systolic dysfunction in patients with type 2 DM with good glycaemic control is related neither to LV hypertrophy nor to hypertension, but rather to aging and the duration of type 2 DM. Similarly, in our current study, 72% of total subjects without hypertension and CAD had diastolic dysfunction with normal Left Ventricular systolic function.

From et al.[2] in their study of 484 subjects between 1996 to 2007 year found that a duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction (E/e' >15) with odds ratio 1.91.

Mishra et al [7] in their case control study of 71 subjects with type 2 DM found that asymptomatic diabetic patients have reduced LV systolic and diastolic function as compared with healthy subjects .

In the current study, out of 100 patients, 51 belonged to age group of 40–50 years and among them 29 persons that is 56.9 % had diastolic dysfunction. In the age group of 51 – 60 years, 48 persons were studied and among them 42 persons that is 87.5 % were evaluated to have diastolic dysfunction. As the number of patients studied above this age group were meagre, the results could not be extended.

With the available data from present study, it is seen that there is strong co-relation between age and diastolic dysfunction with a value of 'P' < 0.003. Whether this correlation could be solely attributed to age factor or due to additive effect of increase in the duration of diabetes with advancing age could not delineated by the present study as all cases studied were diabetes patients.

So far, various studies have shown various degrees of association between gender and diastolic dysfunction. In the present study, out total subjects 72% had diastolic dysfunction. Among them 55.6% were females and 44.4% were males. When calculated for correlation between gender and diastolic dysfunction the obtained value ' P' <0.254. Thus, present study does not show a strong association between gender and diastolic dysfunction.

According to present study, out of total subjects 69% were obese and 31% were not obese. Among the obese individuals who participated in the present study, 81.2% had diastolic dysfunction. Out of total 72 individuals

who had diastolic dysfunction, 77.8% that is 56 persons come under obese category whereas 22.2% that is 16 persons come under non obese category. When calculated for correlation between obesity and diastolic dysfunction, the obtained value is ‘ P’ < 0.002 showing strong correlation between obesity and diastolic dysfunction.

Peterson et al2 designed a study to determine the effects of obesity on LV structure and function in obese individuals. Fifty-one subjects were evaluated and among them 20 were obese having BMI ≥30 kg/m2 and their LV structure and diastolic function was evaluated by 2D-echo. The result showed that subjects who were obese had higher and septal and posterior wall thickness during diastolic phase.

Grandi et al11 evaluated the influence of obesity on LV diastolic function. They selected 32 non obese, 32 obese normotensives matched for age, sex and BMI. Results showed the main effect was found for obesity on LV diameter and LV mass, LV systolic function was normal in all the subjects and LV diastolic function was significantly reduced. They concluded that obesity is associated with a preclinical impairment of LV diastolic function.

Results from the above studies are in concordance of those of our present study which too shows a significant correlation between obesity and diastolic dysfunction.

From the data available from the present study, out of total 72 individuals who had diastolic dysfunction, 87.5% that is 63 persons had dyslipidemia and 12.5% that is 9 persons were found to have normal lipid

profile. When calculated for association between dyslipidemia and diastolic dysfunction, the obtained value is ‘P’ < 0.05 showing a strong co-relation between dyslipidemia and diastolic dysfunction.

Fukuta et al (12) studied the correlation between dyslipidemia and diastolic dysfunction in 45 age and sex matched cases and controls with dyslipidemia and normal lipid profile and found that there is high association between dyslipidemia and diastolic dysfunction. Result from this study is in concordance of those of our present study which also shows a significant correlation between obesity and diastolic dysfunction.

Garcia et al (8) conducted a study wherein 78 matched cases who were smokers and 78 controls who were non smokers were included. Cardiac performance of all the subjects was assessed using standardised echocardiographic parameters.

Results of the above study showed there is decline in the cardiac performance in the case group when compared to the control group as evident by increase in left ventricular mass and stiffness and poor wall compliance leading to diastolic dysfunction.

In the present study, out of 100 subjects studied only 26% were smokers and the remaining 74% were non smokers. Among the 72 individuals who were found to have diastolic dysfunction by echocardiographic parameters, 18 persons that is 25% were smokers and 54 persons that is 75% were non smokers.

When calculated for association between smoking and diastolic dysfunction the value obtained is ‘P’ >0.05 showing no significant correlation between these cause and effect. Many reasons may be attributed for this result.

Among the total study population the number of subjects with history of smoking was only 26%. Gender distribution with a female preponderance among the study population may also contribute as in a country like India the habit of smoking among the female population is low when compared to other nations. All these factors may have lead to the negative correlation between smoking and diastolic dysfunction in the present study.

CONCLUSION

The prevalence of diastolic dysfunction in asymptomatic type 2 DM patients is high and found to be 72% in the present study.

The occurrence of diastolic dysfunction seems to preceed the occurrence of systolic dysfunction in diabetes patients.

There is a significant correlation between duration of diabetes, glycaemic control, age, obesity, dyslipidemia and diastolic dysfunction among the seven parameters considered in the present study.

Persons with type 2 diabetes mellitus should be screened with echocardiography for subclinical diastolic dysfunction.

Early diagnosis and initiation of appropriate treatment for diastolic dysfunction would slow down the progression to diastolic heart failure and cause significant reduction in the morbidity and mortality in patients with diabetes.

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PROFORMA

DEMOGRAPHIC DATA OF THE PATIENT:

Name : OP No :

Age : Case Serial No :

Sex :

Address :

Occupation :

PAST HISTORY:

H/O DIABETES :

DURATION OF DIABETES :

TREATMENT FOR DIABETES :

H/O HYPERTENSION :

H/O CAD :

PERSONAL HISTORY :

H/O SMOKING :

H/O ALCOHOL CONSUMPTION :

ANTHROPOMETRY:

HEIGHT IN cms :

WEIGHT IN kgs :

BMI :

LABORATORY INVESTIGATIONS:

FASTING BLOOD GLUCOSE	
POST PRANDIAL BLOOD GLUCOSE	
Hb A1C	
TOTAL CHOLESTEROL	
HDL CHOLESTEROL	
LDL CHOLESTEROL	
VLDL CHOLESTEROL	
TRIGLYCERIDE	
ELECTROCARDIOGRAM	
ECHOCARDIOGRAM • E • A • E/A RATIO	

KEY TO MASTER CHART

Hb A1 C	Glycosylated Hemoglobin
TC	Total Cholesterol
TGL	Tiglyceride
HDL	High Density Lipoprotein
VLDL	Very Low Density Lipoprotein
LDL	Low Density Lipoprotein
BMI	Body Mass Index
E	Early Diastolic Filling
A	Atrial Contraction
EF	Ejection Fraction
BP	Blood Pressure
DD	Diastolic Dysfunction
Y	Yes
N	No

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	BP
1	Kumudha	48	F	7.3	214	173	35	38	141	27	N	7	66	0.5	0.7	0.7	Y	110/90
2	Rani	50	F	6.8	172	85	17	41	113	23	N	8	68	0.6	0.9	0.6	Y	120/90
3	Rajammal	50	F	7.1	176	136	27	32	117	21	N	6	68	0.9	0.7	1.2	N	110/80
4	Mani	60	M	6.6	193	127	25.6	53	115	27	Y	12	72	0.7	1	0.7	Y	120/90
5	Krishnammal	48	F	6.9	200	133	26	46	128	31	N	9	64	0.7	1	0.7	Y	110/80
6	Panchalai	45	F	6.5	212	173	35	51	126	29	N	6	68	0.7	0.9	0.7	Y	130/80
7	Valli	42	F	6.8	238	253	51	49	138	30	N	6	60	0.7	0.9	0.7	Y	110/80
8	Irusan	47	M	7	149	226	45	30	74	24	N	5	70	0.5	0.7	0.7	Y	120/90
9	Annapoorni	51	F	6.6	206	146	29	43	134	28	N	7	64	0.6	0.9	0.6	Y	110/90
10	Poongodai	50	F	7	176	182	36	54	86	24	N	8	58	0.5	0.6	0.8	Y	130/80
11	Ayisha	43	F	6.7	212	99	20	48	144	23	N	6	62	0.6	0.8	0.7	Y	110/80
12	Amul	49	F	7.1	239	180	36	43	160	32	Y	7	68	0.7	0.8	0.8	Y	130/80
13	Bomman	60	M	8.2	211	169	34	48	129	18.94	N	10	68	0.6	1.2	0.5	Y	120/90
14	Selvi	45	F	6.4	168	120	24	51	93	20.44	N	6	62	1.1	0.8	1.3	N	110/80
15	Aravalli	48	F	7.9	197	123	23	54	120	18.97	N	7	71	0.6	0.9	0.6	Y	110/80
16	Vijaya	49	F	7.6	194	186	37	44	113	25	N	7	66	0.7	1	0.7	Y	120/70
17	Mohan	45	M	7.4	201	200	40	40	121	23.52	Y	6	58	0.9	1.2	0.75	Y	120/90

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	BP
18	Namadev	50	M	6.5	189	122	25	68	96	25.54	N	8	64	0.6	0.4	1.5	N	110/90
19	Poongodi	48	F	7.6	190	120	24	58	108	24.79	N	7	62	0.5	0.8	0.6	Y	120/60
20	Manohar	51	M	8.1	184	206	41	45	98	20.75	N	6	62	0.7	0.5	1.4	N	110/90
21	Susila	50	F	6.4	207	220	44	60	103	31.11	N	6	66	0.7	0.6	1.1	N	120/80
22	Meenatchi	48	F	6.2	193	127	25.6	54	114	25.8	N	7	68	1.1	1.1	1	N	130/80
23	Mansur ahmed	49	M	6.3	193	186	37	54	102	25.39	Y	8	66	1	0.6	1.66	N	120/90
24	Rani	45	F	6.9	235	143	29	75	131	26.4	N	6	66	0.7	0.8	0.8	Y	110/80
25	Malliga	49	F	7.8	171	200	40	35	96	21.09	N	6	68	0.7	0.6	1.16	N	120/70
26	Ramesh	51	M	8.3	122	120	24	58	100	13.81	Y	7	64	0.6	0.5	1.2	N	100/80
27	Kumaran	48	M	7.6	198	204	41	67	90	15.66	Y	8	64	0.9	0.5	1.8	N	110/90
28	Arputhamani	45	M	7.9	196	186	37	42	117	21.84	Y	6	73	0.6	0.8	0.75	Y	120/80
29	Raja	49	M	7.1	208	120	24	46	138	22.95	Y	9	66	0.6	0.8	0.75	Y	130/90
30	Jayaraman	50	M	6.3	160	120	24	40	94	24.44	N	8	64	0.9	0.7	1.28	N	100/80
31	Alamelu	51	F	6.2	312	208	42	38	128	23.68	N	6	70	0.9	1	0.8	Y	110/90
32	Govindhammal	50	F	7.7	251	196	49	54	148	25.41	N	11	68	0.7	0.6	1.16	N	120/90
33	Lakshmi	52	F	7.4	187	200	40	54	93	23.55	N	10	74	0.9	0.7	1.28	N	110/90
34	Kumar	50	M	8.9	247	186	37.2	31.8	178	25.49	Y	9	64	0.6	0.8	0.75	Y	130/90

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	BP
35	Rajan	55	M	7.5	238	212	42.4	26.6	169	26.02	Y	11	60	0.6	0.8	0.75	Y	110/90
36	Ravi	48	M	6.4	143	172	34	49	60	27.81	Y	6	63	0.6	0.5	1.2	N	120/70
37	Kavitha	49	F	6.6	198	200	40	36	95	21.42	N	8	68	1.1	1.1	1	N	130/80
38	Gowri	60	F	7.8	209	110	22	45	142	26.81	N	7	68	0.7	0.8	0.8	Y	100/80
39	Manikandan	55	M	6.4	196	150	30	53	113	31	N	9	66	0.7	0.6	1.16	N	110/90
40	Geetha	63	F	7.9	262	196	49	49	164	29	Y	11	70	0.5	0.8	0.6	Y	110/70
41	Narayanan	65	M	7.5	241	185	37	47	157	28.84	N	14	58	0.5	0.6	0.8	Y	120/80
42	Ellappan	68	M	8.1	302	198	39	46	217	31	Y	13	53	0.5	0.8	0.62	Y	120/70
43	Perumal	59	M	7.6	189	176	35	38	116	33.34	N	11	71	0.7	0.9	0.77	Y	110/80
44	Hari	63	M	7.4	206	178	35.6	43	127.4	29.5	Y	9	62	0.9	1	0.8	Y	110/90
45	Nandhini	44	F	6.5	186	147	29.4	46	110	24.1	N	6	73	1	0.6	1.6	N	120/60
46	Devi	47	F	6.4	160	138	27.4	51	81.4	22.3	N	6	64	0.8	0.6	1.33	N	110/70
47	Vishwalingam	55	M	8	241	199	40	46	155	32.3	Y	9	73	0.5	0.6	0.8	Y	120/60
48	Venkatesan	53	M	8.2	207	177	35.4	43	128.4	31.8	Y	11	68	0.7	0.8	0.8	Y	110/70
49	Jayakumar	46	M	6.5	190	179	36	47	107	31.9	Y	6	78	0.9	1	0.8	Y	110/90
50	Muniyammal	58	F	8.8	230	165	33	41	156	33.4	N	8	61	0.5	0.6	0.8	Y	120/90
51	Ranjani	48	F	7.3	247	186	38	48	161	34.1	N	7	70	0.6	0.8	0.75	Y	110/60

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	BP
52	Vignesh	45	M	6.5	198	143	29	46	123	23.2	N	5	74	1	0.6	1.6	N	120/70
53	Rajeshwari	55	F	8	250	190	38	39	173	30.3	N	12	59	0.7	0.8	0.8	Y	110/80
54	Kavitha	50	F	7.6	210	170	34	43	133	29.8	N	9	64	0.8	0.9	0.8	Y	120/90
55	Christy	61	F	7.5	222	148	29	36	157	31.2	N	12	68	0.5	0.6	0.8	Y	110/80
56	Boopathy	48	M	6.5	208	152	30	41	137	25.1	Y	7	73	1	0.8	1.25	N	120/60
57	Mythili	51	F	7.3	312	190	38	42	232	27.2	N	8	60	0.6	0.7	0.8	Y	110/80
58	Mathi	50	M	7.1	248	173	35	38	175	28.1	Y	9	58	0.7	0.8	0.8	Y	120/70
59	Selvan	55	M	7	212	162	33	41	138	29.8	N	10	61	0.5	0.6	0.8	Y	110/80
60	Gomathy	61	F	7.7	181	149	30	50	101	35.1	N	11	60	0.7	0.8	0.8	Y	120/90
61	Prabhakar	63	M	7	311	201	40	53	218	31.2	Y	14	58	0.5	0.7	0.7	Y	110/60
62	Shankaran	58	M	7.8	297	199	39	49	209	30.9	Y	10	64	0.7	1.1	0.63	Y	120/60
63	Anandhi	43	F	7.3	198	170	34	48	116	21.8	N	8	71	0.6	0.9	0.6	Y	110/70
64	Iyyappan	47	M	6.7	186	180	36	51	99	26.1	Y	6	70	1	0.8	1.25	N	110/60
65	Sornam	54	M	8	256	179	35	39	182	27.1	Y	9	68	0.8	0.9	0.8	Y	120/90
66	Velu	62	M	8.1	289	193	38.6	46	204.4	33	Y	10	64	0.6	1.2	0.5	Y	110/80
67	Kannan	49	M	6.6	202	176	36	47	119	24	N	5	73	1	0.7	1.42	N	120/90
68	Eswari	41	F	6.5	193	180	36	52	95	20.1	N	5	70	1	0.6	1.66	N	120/70

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	BP
69	Raman	46	M	7.9	294	212	42	38	214	31.4	N	7	72	0.5	0.7	0.71	Y	110/70
70	Wasim ali	55	M	7.7	303	199	40	44	219	32.5	N	13	62	0.7	0.8	0.8	Y	110/90
71	Aruna	51	F	7.3	249	206	41.2	43	164.8	34.3	N	9	64	0.8	0.9	0.8	Y	120/80
72	Chengalvarayan	58	M	7.8	312	218	43.6	47	221.4	32.9	N	12	54	0.5	0.6	0.8	Y	120/60
73	Muthu	61	M	8.2	203	195	39	42	122	27.26	Y	12	60	0.8	0.9	0.8	Y	110/90
74	Govindan	55	M	7.1	271	208	41.6	44	185.4	28.29	N	9	64	0.9	1.1	0.8	Y	110/70
75	Nagammal	58	F	7.7	243	197	39.4	46	157.6	31.24	N	11	58	0.7	0.8	0.8	Y	120/90
76	Kamatchi	55	F	6.6	204	153	30.6	49	124.4	22.07	N	7	71	1	0.7	1.42	N	120/70
77	Jaya	47	F	7.2	201	176	35.2	39	126.8	28.91	N	9	68	0.6	0.8	0.75	Y	110/60
78	Tamil selvi	58	F	8.1	289	205	41	46	202	31.33	N	13	62	0.6	1.2	0.5	Y	124/68
79	Ganesan	60	M	8.9	303	212	42.4	43	217.6	34.1	Y	11	68	0.7	0.8	0.8	Y	112/88
80	Mahesh	49	M	7.7	241	186	37.2	49	154.8	29.27	Y	6	74	0.9	1.2	0.75	Y	126/70
81	Girija	47	F	7.8	303	199	39.8	46	217.2	34.1	N	7	70	0.7	0.8	0.8	Y	112/80
82	Vasantha	56	F	8.1	251	212	42.4	48	160.6	27.4	N	8	68	0.6	1.2	0.5	Y	110/90
83	Ramesh	49	M	6.5	242	199	39.8	47	155.2	23.6	Y	6	72	1	0.8	1.25	N	120/70
84	Raheem	57	M	7.6	287	230	46	48	193	30.6	Y	11	70	0.6	0.8	0.75	Y	110/60
85	Ayisha bee	53	F	7.1	198	178	35.6	44	118.4	30.2	N	13	68	0.9	1.2	0.75	Y	120/70

Sl.no	Name	Age	Sex	Hb A1C	TC	TGL	VLDL	HDL	LDL	BMI	Smoking	Duration of diabetes	EF	E	A	E/A ratio	DD	Bp
86	Muthamizh	42	F	8.3	220	198	39.6	42	138.4	28.96	N	7	73	0.9	1.8	0.5	Y	110/90
87	Soorya moorthy	60	M	8.1	234	186	37.2	47	149.8	33.5	N	9	64	0.6	0.8	0.75	Y	120/60
88	Premnath	47	M	6.4	199	189	37.8	45	106	22	N	6	71	1	0.7	1.4	N	110/70
89	Vimala	48	F	7.9	245	204	40.8	44	161	29.8	N	8	68	0.8	0.9	0.8	Y	110/60
90	Annadurai	59	M	7.6	250	213	42.6	43	164.4	33.2	Y	14	72	0.7	0.8	0.8	Y	120/70
91	Prakash	51	M	8	243	197	39.4	48	155.6	31.8	Y	11	64	0.9	1.1	0.8	Y	110/80
92	Muthuram	58	M	9.1	312	260	52	43	217	23	N	8	75	0.6	0.8	0.75	Y	110/90
93	Subash	51	M	8.3	270	200	40	47	183	29.6	Y	7	70	0.8	1	0.8	Y	124/68
94	Manimegalai	54	F	7.9	264	198	39.6	46	178.4	33.4	N	13	64	0.5	0.6	0.8	Y	126/70
95	Balaji	42	M	6.4	196	179	35.8	46	114.2	27	N	7	72	1	0.8	1.2	N	120/90
96	Jayalakshmi	55	F	7.2	230	203	40.6	46	143.4	21	N	8	59	0.7	0.8	0.8	Y	124/80
97	Geetharani	54	F	7.8	304	250	50	43	211	29.86	N	6	68	0.8	1	0.8	Y	120/70
98	Nithya	51	F	7.8	256	203	40.6	43	172.4	30.8	N	7	62	0.5	0.7	0.75	Y	124/90
99	Anjalai	53	F	8.1	209	199	39.8	42	127.2	22	N	12	70	0.7	0.8	0.8	Y	110/90
100	Neela veni	52	F	7.4	308	245	49	46	213	33.6	N	11	75	0.6	0.8	0.75	Y	110/70