

A Dissertation on

**STUDY TO CORRELATE HBA1C AND LEFT VENTRICULAR
DIASTOLIC DYSFUNCTION IN NEWLY DIAGNOSED TYPE II
DIABETES MELLITUS**

Submitted to

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI – 600032**

In partial fulfilment of the Regulations
for the Award of the Degree of

**M.D. BRANCH - I
GENERAL MEDICINE**



**DEPARTMENT OF GENERAL MEDICINE
STANLEY MEDICAL COLLEGE
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CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. ELANGUMANAN. P**, Post - Graduate Student (May 2013 TO April 2016) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on “**STUDY TO CORRELATE HBA1C AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NEWLY DIAGNOSED TYPE II DIABETES MELLITUS**” under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2016.

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DECLARATION

I, **Dr. ELANGUMANAN. P**, declare that I carried out this work on **“STUDY TO CORRELATE HBA1C AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NEWLY DIAGNOSED TYPE II DIABETES MELLITUS”** at the outpatient department and Medical wards of Government Stanley Hospital . I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

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STUDY TO CORRELATE HBA1c AND LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN NEWLY DIAGNOSED TYPE II DIABETES MELLITUS

INTRODUCTION

Diabetes mellitus is one of the most common diseases in the world and is acquiring epidemic proportions. Its prevalence is growing in both developed and developing countries. Globally and nationally, diabetes and its complications has become the most important contemporary and challenging health problem. Compared to other races Indians are genetically more susceptible. Diabetes is one such important metabolic disease which affects nearly every organ system in the body. The cause of morbidity and mortality in diabetic patients is due to cardiac complications. It has been estimated that by the year 2025, 11 million individuals would be affected with diabetes all over the world. In India, it is estimated that presently 19.4 million individuals are affected by this deadly disease, which is likely to go up to 57.2 million by the year 2025. India will have the largest number of diabetic subjects in the world by 2025 and one out of 5 diabetic subjects in the world will be an Indian. India is going to be the "Diabetic capital of the world" through the prevalence of both type I

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ABBREVIATIONS

DM- Diabetes Mellitus

CAD – Coronary Artery Disease

MODY – Maturity Onset Diabetes of the Young

GDM – Gestational Diabetes Mellitus

IRS – Insulin Receptor Substrate

GLUT – Glucose Transporter

IFG – Impaired Fasting Glucose

IGT – Impaired Glucose Tolerance

OGTT – Oral Glucose Tolerance Test

HDL – High Density Lipoprotein

LDL – Low Density Lipoprotein

ACE – Angiotensin Converting Enzymes

ARB – Angiotensin Receptors Blockers

CCF – Congestive Cardiac Failure

NPH – Neutral Protamine Hagedorn

DPP IV – Dipeptidyl Peptidase IV

GLP – Glucagon Like Peptide

ECG – Electrocardiogram

STEMI – ST segment Elevation Myocardial Infarction

NSTEMI – Non ST segment Elevation Myocardial Infarction

PCI – Percutaneous Coronary Intervention

CABG – Coronary Artery Bypass Graft

VEGF – vascular Endothelial Growth Factor

STI – Systolic Time Interval

ACG – Apex Cardiography

PPAR – Peroxisome Proliferator Activator Receptor

E – Early ventricular filling

A – Late ventricular filling

IVRT – Isovolumetric Relaxation Time

DT – Deceleration time

PEP - Pre Ejection Period

EF – Ejection Fraction

LVDD –Left ventricular diastolic dysfunction

1.INTRODUCTION

Diabetes mellitus is one of the most common diseases in the world and is acquiring epidemic proportions. Its prevalence is growing in both developed and developing countries. Globally and nationally, diabetes and its complications has become the most important contemporary and challenging health problem. Compared to other races Indians are genetically more susceptible .Diabetes is one such important metabolic disease which affects nearly every organ system in the body. The main cause of morbidity and mortality in diabetic patients is due to cardiac complications. It has been estimated that by the year 2025, 300 million individuals would be affected with diabetes all over the world. In India, it is estimated that presently 19.4 million individuals are affected by this deadly disease, which is likely to go up to 57.2 million by the year 2025. India will have the largest number of diabetic subjects in the world by 2025 and one out of 5 diabetic subjects in the world will be an Indian. India is going to be the “Diabetic capital of the world” Although the prevalence of both Type 1 and Type 2 DM is increasing worldwide, the prevalence of Type 2 DM is on the rise much more rapidly, which is due to increasing obesity and reduced activity levels as countries becoming more industrialised.

Diabetic individuals have been reported to develop congestive heart failure in the absence of coronary heart disease, hypertension or any structural heart disease²⁷ The term “ Diabetic Cardiomyopathy ” has been introduced for this condition. The existence of a diabetic cardiomyopathy was first

proposed by Rubler in 1972.³⁹The early and commonest hemodynamic derangement of diabetic cardiomyopathy is left ventricular diastolic dysfunction and followed by systolic dysfunction reinforcing the importance of early examination of ventricular function in individual with diabetes. Studies have shown that diastolic abnormalities are present in diabetic patients without any macro vascular complications, even newly diagnosed diabetes mellitus or even in those with disease duration of less than 1 year¹¹.

2.REVIEW OF LITERATURE

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia associated with disturbances of carbohydrates, protein and fat metabolism due to absolute or relative deficiency in insulin secretion and / or action. In due course of time diabetes more commonly damages nerves, heart, blood vessels, kidneys, eyes. Thus Diabetes is rightly described as “Metabolic cum vascular disorder”.

CLASSIFICATION

DM classified based on pathogenic process that lead to hyperglycemia.DM is broadly divided into Type 1 and Type 2 diabetes. Type 1 DM due to complete or near total insulin deficiency. Type 2 DM is a heterogeneous group of disorder comprising of insulin resistance, impaired insulin secretion, increased glucose production.

TYPE 1 DIABETES MELLITUS

Type 1 diabetes is a disease due to destruction of beta cells of pancreas. This leads to a state where insulin is required on daily basis for survival. The disease process is cited due to the presence of specific auto antibodies in the individual, like anti-GAD, anti-islet cell or anti-insulin antibody. Individuals with such auto antibodies can be into called as Type 1A and Immune- mediated Type 1 diabetics.

Some individuals without any evidence of autoantibody involved are said to belong to Type 1B or idiopathic diabetes. Type 1B patients are more prone for complications like ketoacidosis. Concomitant autoimmune disorders like Graves disease, Addison's disease, Vitiligo, pernicious anaemia, are increasingly found in Type 1 A diabetics.

TYPE 2 DIABETES MELLITUS

It is the most common form of diabetes, which is characterised by disorders in the insulin action and insulin secretion, of which either can be a predominant feature. It is associated with progressive beta cell failure with increase in duration of Diabetes. No autoimmune etiology is attributed to this type. Insulin resistance is the key factor in the pathogenesis of this type. Obesity is most often associated with this type and this in fact worsens insulin resistance.

Type 2 diabetes takes decades to progress and manifest its symptoms, but it is more devastating in nature as it leads to more of micro vascular and macro vascular complications.

OTHER TYPES OF DM

Maturity onset diabetes of the young (MODY). In this, the mode of inheritance is of autosomal dominant type. It is characterised by early onset hyperglycemia (usually <25 years) and impaired insulin secretion. Severe insulin resistance occurs due to various mutations in the insulin receptors.

Diabetes may also occur due to diseases of exocrine portion of the pancreas. Examples include fibrocalculus pancreatopathy, cystic fibrosis, pancreatitis, neoplasm of the pancreas, hemochromatosis.

Diabetes can also be caused by hormones which antagonise the insulin action. Hence, Diabetes mellitus is often seen in endocrinopathies like Cushing syndrome, Acromegaly, hyperthyroidism, pheochromocytoma, glucagonoma, and somatostatinoma.

The following drugs are linked to causation of acquired diabetes - Glucocorticoids, phenytoin, nicotinic acid, diazoxide and pentamidine. Viral infections though an extremely rare cause of DM, have been implicated in pancreatic islet cell destruction

GESTATIONAL DIABETES MELLITUS

Glucose intolerance which develops during pregnancy is defined as gestational diabetes mellitus (GDM). In pregnancy insulin requirement is high. Further insulin resistance develops due to metabolic changes of late pregnancy.

RISK FACTORS OF GDM

Older women, with a previous history of glucose intolerance, Any pregnant woman with history of babies large for gestational age.

Fetal complications of GDM include intra uterine death of the foetus and congenital abnormalities, neonatal hypoglycemia, jaundice, polycythemia, and hypocalcemia.

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS⁶

I. Type 1 diabetes (Beta cell destruction, usually leading to absolute insulin deficiency)

A. Immune-mediated

B. Idiopathic

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

III. Other specific types of diabetes

A. **Genetic defects of cell function** characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1 (MODY 3)
4. Insulin promoter factor-1 (IPF-1; MODY 4)
5. HNF-1 (MODY 5)
6. NeuroD1 (MODY 6)
7. Mitochondrial DNA

8. Subunits of ATP-sensitive potassium channel
9. Proinsulin or insulin conversion
10. other pancreatic islet regulators / proteins such as KLF 11, PAX 4, BLK ,
GAT A4, GAT A6, SLC 2A2 (GLUT – 2) RFX6, GLI S3.

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes

C. Diseases of the exocrine pancreas—Pancreatitis, Pancreatectomy, Neoplasia, Cystic Fibrosis, Hemochromatosis, Fibrocalculus Pancreatopathy, Mutations In carboxyl ester lipase

D. Endocrinopathies—Acromegaly, Glucagonoma, Pheochromocytoma, Hyperthyroidism, Somatostatinoma, Cushing`s syndrome, Aldosteronoma.

E. Drug- or chemical-induced—Vacor (rodenticide), Pentamidine, Nicotinic Acid, Glucocorticoids, Thyroid Hormone, Diazoxide, beta -Adrenergic Agonists, thiazides , calcineurin and motor inhibitors , hydantoin , asparaginase, alpha interferon, protease inhibitors, antipsychotics (atypical and others), epinephrine.

F. Infections—Congenital Rubella, Cytomegalovirus, Coxsackie virus

G. Uncommon forms of immune-mediated diabetes—

Stiff-Person -Syndrome, Anti-Insulin receptor antibodies

H. Other genetic syndromes sometimes associated with diabetes –

Down's syndrome, Klinefelter's Syndrome, Turner's syndrome, Wolfram's Syndrome, Friedreich's Ataxia, Huntington's Chorea, Laurence-Moon-Biedl Syndrome, Myotonic Dystrophy, Porphyria, Prader-Willi Syndrome

IV. Gestational diabetes mellitus (GDM)

INSULIN

Banting and Best first isolated insulin from the pancreatic tissue in the year 1921. Insulin is a major hormonal regulator of glucose metabolism and its kinetics involves biosynthesis, storage, release and its action on target tissues.

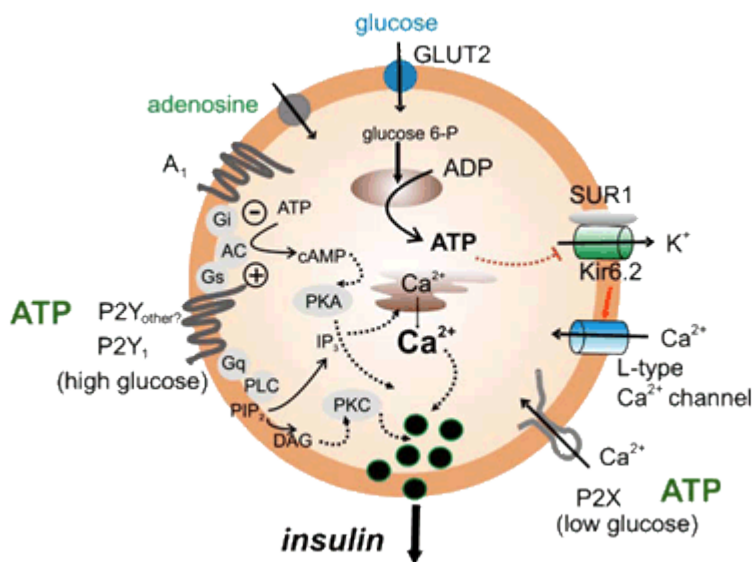
INSULIN BIOSYNTHESIS

The beta cells in the pancreatic islets are the chief producers of Insulin secretion. Insulin is initially synthesized as preproinsulin which is a single-chain 86-amino-acid precursor polypeptide. Further processing of the preproinsulin results in the removal of its amino-terminal signal peptide, giving rise to proinsulin. Structurally, proinsulin is related to insulin-like growth factors 1 and II, which binds weakly to the insulin receptor. In the C peptide, A chain (21 amino acids) and B (30 amino acids) chain are connected by disulfide bonds. They are a result of the splitting of internal 31 residue

fragment from the proinsulin. Both C peptide and insulin molecules are stored and co secreted from secretory granules in the beta cells.

INSULIN SECRETION

Glucose is the key regulator of insulin secretion while ketones, amino acids, various nutrients, neurotransmitters, and gastrointestinal peptides can also influence insulin secretion. Insulin is synthesized when the Glucose levels $>70\text{mg/dl}$.



Glucose stimulation of insulin secretion begins with its transport to the beta cell by a facilitative glucose transporter. The rate limiting step is glucose phosphorylation by glucokinase which controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP-sensitive K⁺ channel. This channel consists of two separate proteins, one is the binding site for certain oral hypoglycemics (e.g. sulfonylureas, meglitinides); the other is an inwardly

rectifying K⁺ channel protein (Kir6.2). Inhibition of this K⁺ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium) and stimulates insulin secretion. Incretins, released from neuroendocrine cells in the gastrointestinal tract following food intake, amplify the glucose-stimulated insulin secretion and simultaneously suppresses the glucagon secretion. Glucagon-like peptide 1 (GLP- 1) is the most potent incretin, is released from L cells present in the small intestine and stimulates insulin secretion when the blood glucose is above the fasting level

INSULIN ACTION

Of all the insulin secreted into the portal venous system, 50% of it is removed and degraded by the liver. It is the unextracted insulin which enters the systemic circulation and binds to the receptors in the target sites. Once insulin binds to its receptors, intrinsic tyrosine kinase activity is stimulated which leads to receptor auto phosphorylation and the recruitment of intracellular signalling molecules, such as insulin receptor substrates (IRS). These further initiate a complex cascade of phosphorylation and dephosphorylation reactions, which results in the widespread metabolic and mitogenic effects of insulin. For example, activation of the phosphatidylinositol-3'-kinase (PI-3 -kinase) pathway stimulates translocation of a facilitative glucose transporter, (GLUT4) to the cell surface, this is a very crucial event as it leads to glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signalling pathways induces protein synthesis,

glycogen synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

TYPE 2 DIABETES MELLITUS

GENETIC CONSIDERATIONS

There is a very strong genetic component which leads to the development of Type 2 diabetes mellitus. It has been found out that in identical twins the level of concordance of Type 2 DM is about seventy to ninety percent. When one of the parents has diabetes, likelihood of the child of developing diabetes is increased. And in cases where both the parents suffer from diabetes, the risk of developing diabetes is increased by forty fold in their children. The development of diabetes is polygenic. Several factors play a role in development of Type 2 diabetes other than genetic factors. The environmental factors such as nutrition, obesity and lack of physical activity, has an important role of developing diabetes in the future . Recent studies in genomics have identified several genes which increases the risk of developing Type 2 diabetes. These include PGC1a, HNF4alpha, ICCNJ11, and PPAR gamma. The way in which these genes act resulting in diabetes is not clear however it is predicted that these genes alter the function of islet and alter the development of islets and alter the secretion of insulin.

PATHOPHYSIOLOGY

Type 2 diabetes is characterised by reduction in secretion of insulin, increased resistance to the action of insulin, increased production of glucose in the liver and altered metabolism of fat. A great association has been found between central obesity and Type 2 DM. In the early stages of the disorder, the blood glucose levels remain almost normal even though resistance to insulin is present in our body. This is due to the fact that the pancreatic beta cells initially compensate by increasing the secretion of insulin. This increased secretion of insulin keeps the blood glucose levels within normal. However pancreatic beta cells cannot sustain this increased production of insulin and eventually wear out. This causes failure of beta cells resulting in decrease secretion of insulin with increased hepatic production of glucose leading ultimately to overt DM with elevated fasting glucose levels.

METABOLIC ABNORMALITIES

ABNORMAL MUSCLE AND FAT METABOLISM

The combination of obesity and genetic susceptibility reduce the action of insulin on target tissues especially fat, liver and muscle. Insulin resistance is relative , the plasma glucose level is normalised by supra normal level of circulating insulin .insulin resistance decreases peripheral utilization of glucose and increases hepatic glucose production resulting in hyperglycemia Increased fasting glucose level due to increased hepatic glucose production

and post-prandial glucose level due to decreased peripheral utilization of glucose. The exact mechanism for insulin resistance is not well defined. In skeletal muscle the levels of tyrosine kinase activity and insulin receptor are reduced but these alterations are not primary defect and this is secondarily to hyper insulinemia. The “post receptor” defects in insulin which is regulated by phosphorylation / dephosphorylation appears to play an important role in insulin resistance. It is the lipid accumulation within the skeletal muscle and impaired fatty acid oxidation which reduces mitochondrial oxidative phosphorylation and insulin stimulates mitochondrial ATP production.

Obesity is the important predisposing factor for Type 2 DM. The increase in adipocyte mass leads to increase in the production of free fatty acids in our body. It results in insulin resistance in liver and skeletal muscle. Adiponectin is an insulin sensitizing molecule which is secreted by adipose tissue. In obesity adiponectin levels are reduced resulting in hepatic insulin resistance.

IMPAIRED INSULIN SECRETION

Initially in Type 2 DM, secretion of insulin increases with response to insulin resistance to maintain a tolerance level of glucose within the body. In the initial stages of the disorder, defect in insulin secretion is mild, involves glucose-stimulated insulin secretion. But responses to secretion of insulin to other secretagogues like arginine are preserved. Over period of time the insulin secretory defect ends up in inadequate insulin secretion. The reason for this

reduced insulin secretory capacity is due to secondary genetic defect which gets superimposed upon insulin resistance ultimately leading to beta cell failure. In long standing diabetes the beta cell mass is decreased approximately 50%. The islet functions are also affected by the metabolic abnormalities of diabetes . Chronic hyperglycemia (glucose toxicity) and an elevation of free fatty acids (lipotoxicity) further worsens function of the islet cells.

INCREASED HEPATIC GLUCOSE AND LIPID PRODUCTION

In patients with diabetes the failure of increased levels of insulin to suppress gluconeogenesis is reflected by resistance to insulin. This leads to elevation of fasting blood glucose levels and decrease in the storage of the glycogen in the postprandial state. Early in the course of diabetes elevated levels of glucose production by the liver occurs. Because of resistance to insulin in the adipose tissue there is increased lipolysis and release of free fatty acids into the bloodstream leading to increased synthesis of triglycerides and very low density lipoproteins in the liver. Non-alcoholic fatty liver disease occurs in diabetes as a result of steatosis or lipid storage in the liver.

RISK FACTORS

- Physical inactivity
- Family history of diabetes
- Previously identified with IFG, IGT
- Obesity

- History of GDM or delivery of baby >4 kg
- Race/ethnicity (e.g. Africa and American, Native American, Asian American, Latino, Pacific Islander)
- Polycystic ovary syndrome or acanthosis nigricans
- History of cardiovascular disease
- Hypertension (blood pressure >140/90 mm Hg)
- HDL cholesterol level <35 mg/d and/or triglyceride level >250 mg/d L.

COMMON SYMPTOMS OF DIABETES:

- Polyuria - increased frequency of micturition
- Polydipsia - increased feeling of thirst
- Polyphagia - increased hunger
- Easy fatigability
- Blurring of vision
- Slow and poor healing of wounds
- In hands and feet there is burning tingling sensation due to diabetic neuropathy

DIAGNOSIS

American Diabetes Association, 2014 says that any of the following can be used for diagnosis of diabetes:

- HbA1c or glycosylated haemoglobin >6.5 %

- FPG -a fasting plasma glucose ≥ 126 mg/dl (7 mmol/lit)
 - 2 hour plasma glucose after oral glucose tolerance test ≥ 200 mg/ dl (11.1 mmol/lit)
 - Random blood glucose concentration ≥ 200 mg/ dl (11.1 mmol /lit)
- With symptoms of diabetes

GLYCOSYLATED HEMOGLOBIN (HBA1C)

Glycosylated Hb measurement is the cornerstone for assessing the glycemic control over a longer time. Glucose is bound to haemoglobin irreversibly by continuous slow non enzymatic process resulting in the formation of glycosylated haemoglobin. When the glucose levels in the plasma are consistently raised, there is an increase in non-enzymatic glycosylation of haemoglobin .The level of HBA1c⁷⁶ in blood is proportional to the mean blood glucose concentration. In a normal person about 3-6% of Hb is glycosylated. In diabetic the percentage of HBA1c may be twice or thrice.HBA1 is comprised of 3 distinct of fraction.HBA1a, HBA1b, HBA1c, HBA1d. HBA1c is the major component and fraction of clinical importance. The significance of HBA1a ,HBA1b and HBA1d are not known and their correlation with long term glucose control is very questionable .Glucose combines by keto-amine linkage to N-terminal valine as well as lysine residues of both alpha and beta chain of haemoglobin. This reversible adducts (pre-HBA1c) can done undergo an amadori re-arrangement to stable keto amine(HBA1c).Pre HBA1c formation

proportionally related to the amount of blood glucose. HbA1c level reflects the average blood glucose level over the previous two to three months.

There are numerous laboratory methods such as ion exchange chromatography, boronate affinity immunoassays for measuring the various forms of glycosylated haemoglobin, and these have significant inter assay variations. HbA1c levels should be measured both for diagnosis and assess the long term glycemic status. HbA1c values are misleading in conditions where life span of RBC's altered. HbA1c level increased in iron, vitamin B12 and folate deficiency, decreased erythropoiesis, alcoholism, chronic renal failure, decreased intra erythrocyte pH, hyper bilirubinemia, pregnancy, lead poisoning, opiate addiction. HbA1c level are Decreased after administration of erythropoietin, cyanocobalamin, reticulocytosis, cirrhosis and Patient taking acetyl salicylic acid, ascorbic acid, tocopherol and conditions decreases erythrocytes life span such as splenomegaly, rheumatoid arthritis, Anti-retrovirals, ribavirin and dapsone. HbA1c levels are variable in haemoglobinopathies²¹. It can be useful to distinguish stress hyperglycemia from pre existing diabetes. In situation of hyperglycemia associated with conditions like infections, myocardial infarction, stroke, surgery.

Estimated average blood glucose level in mg/dl = $28.7 \times \text{HBA1c} - 46.7$

HBA1c %	Average blood glucose mg/dl
6	126
7	154
8	183
9	212
10	240
11	269
12	298

FASTING BLOOD GLUCOSE

It is the blood glucose values which are taken in early morning with fasting for at least 8 hours from previous night.

ORAL GLUCOSE TOLERANCE TEST (OGTT)

It's a test to determine how well the body metabolises glucose. Here blood glucose values are taken in fasting. The patient is made to drink a special glucose solution and blood glucose values are taken after 2 hours.

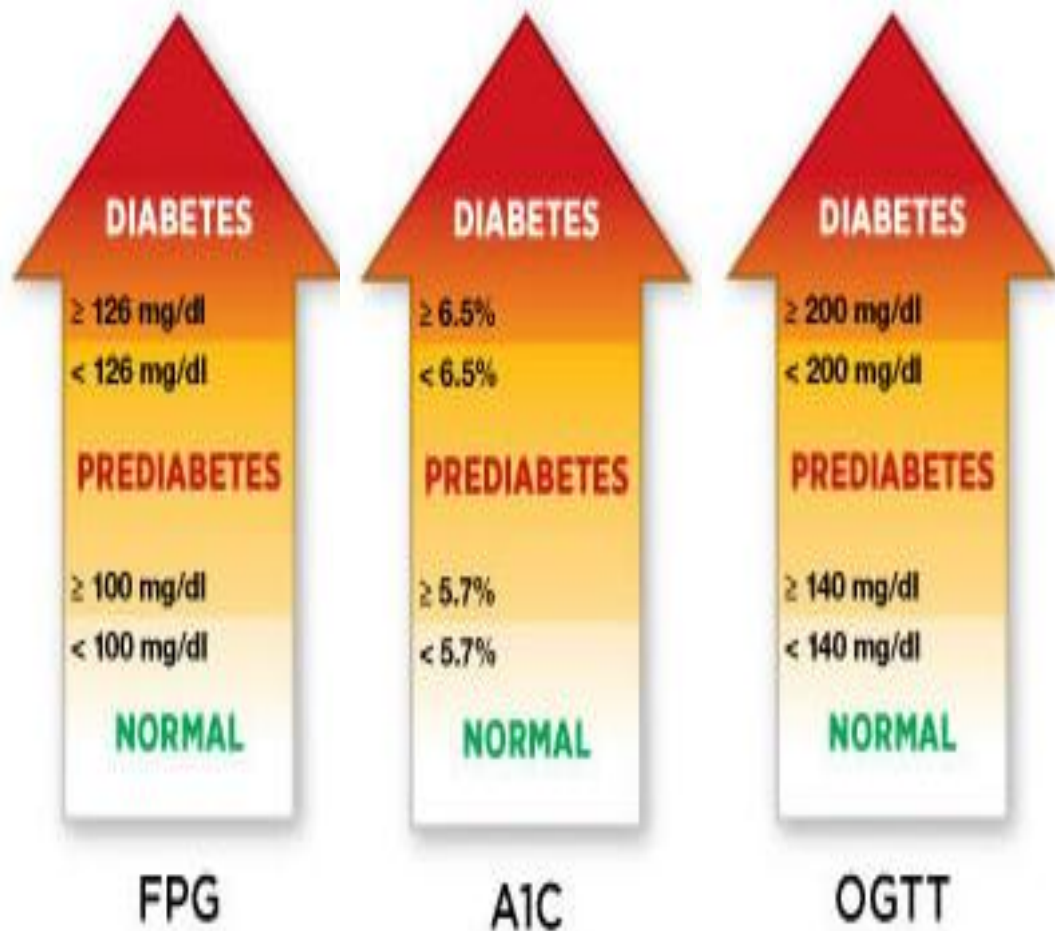
Result	Oral Glucose Tolerance Test (OGTT)
Normal	less than 140 mg/dl
Prediabetes	140 mg/dl to 199 mg/dl
Diabetes	200 mg/dl or higher ¹⁶

RANDOM PLASMA GLUCOSE TEST

This can be done at any time of the day. When the random plasma glucose values are more than 200mg/dl then it is diagnostic of diabetes

PREDIABETES

Pre diabetes is defined as blood glucose levels which are more than normal but not yet high to be diagnosed as diabetes. Both impaired fasting glucose and impaired glucose tolerance come under Pre diabetes ⁶. These people must be regularly followed up for they have a high chance of developing overt diabetes and cardiovascular complications.



MANAGEMENT

The main goal of treatment is to reduce the blood glucose values and keep the values at a level similar to that of normal people and hence to prevent both micro vascular as well as macro vascular complications of diabetes mellitus. Other goals are growth and development, normal body mass, avoiding uncontrolled hyperglycaemia or hypoglycaemia, preventing diabetic ketoacidosis and nonketotic acidosis, and immediately detecting and treating diabetic complications

Obesity is a major contributor for development of diabetes. Obesity causes insulin resistance. Hence exercise daily, diet, lifestyle modification and drugs form a corner stone in treatment of diabetes. Type 1 diabetes patients are treated with insulin for survival. Type 2 diabetes patients are treated with oral hypoglycaemic agents however these patients too might require insulin for better control.

ORAL AGENTS

An array of oral agents is now available for treatment of patients with Type 2 diabetic mellitus.

SULFONYLUREAS

The first generation sulfonylureas are no longer in use nowadays because of the increased side effects associated with these drugs. Chlorpropamide is an example of first generation sulfonylureas. Second-generation have increased potency, have minimal interactions with other drugs, and least side effects and hence have replaced the first generation. The mechanism by which sulfonylureas act is by acting on the pancreatic beta cells and causing increase in insulin secretion. This increased insulin secretion overcomes the resistance associated with Type 2 diabetes mellitus and hence more amount of glucose is transported inside the cells thereby decreasing the blood glucose value. The sulfonylureas have duration of action varying from 12

to 24 hours and depending upon that they are given as single or double dosage daily. The major adverse effect associated with sulfonylureas is hypoglycaemia. Hence the patients who take these drugs must be educated properly to take adequate amount of food after taking these tablets.

MEGLITINIDE

It stimulates pancreatic insulin secretion but are different from sulfonylureas by the pharmacodynamic properties and mechanism of action. Meglitinides undergoes rapid absorption, reaches peak plasma levels in 30 to 60 minutes, and undergoes rapid metabolism. The drug is consumed along with meals and reduces the peaks of Post prandial blood sugar which is common in Type 2 diabetes but to a greater degree than the sulfonylureas medications. These drugs are used for the treatment of post prandial hyperglycaemia due to their rapid onset and short duration of action. These drugs can also result in hypoglycaemic episodes.

BIGUANIDES

It is a preferred agent for obese patients. These drugs decrease blood glucose by decreasing the production and increasing the utilization. These drugs also inhibit the intestinal absorption of glucose. Lactic acidosis and megaloblastic anaemia due to vitamin B-12 deficiency are the major adverse

effects of these drugs. Biguanides increase the intestinal production of lactate by anaerobic glycolysis. Metformin is the only oral agent that has been demonstrated to reduce the macrovascular events in Type 2 DM.

THIAZOLIDINEDIONE

The thiazolidinedione group of drugs act as agonists of nuclear receptor PPAR gamma which regulates transcription of genes involved in glucose and lipid metabolism. These drugs are used to reverse insulin resistance in Type 2 DM. these drugs also tend to increase HDL. The adverse effect of these drugs includes weight gain, edema and plasma volume expansion. Therefore these should be avoided in CCF patients.

ALPHA GLUCOSIDASE INHIBITORS

Complex carbohydrates are converted to simple carbohydrates by alpha glucosidase. Inhibitors of this enzyme decrease carbohydrate absorption from gastro intestinal tract. Major adverse effect is flatulence due to fermentation of unabsorbed carbohydrates. These drugs help in restoring beta cell function and prevent new cases of Type 2 diabetes in pre diabetes.

DPP IV INHIBITORS

Dipeptidyl peptidase 4 is an enzyme secreted by small intestine mucosa which degrades GLP 1. The DPP IV inhibitors inhibit them there by reducing the blood glucose levels by increasing GLP 1.

MECHANISM OF ORAL HYPOGLYCEMIC AGENTS.

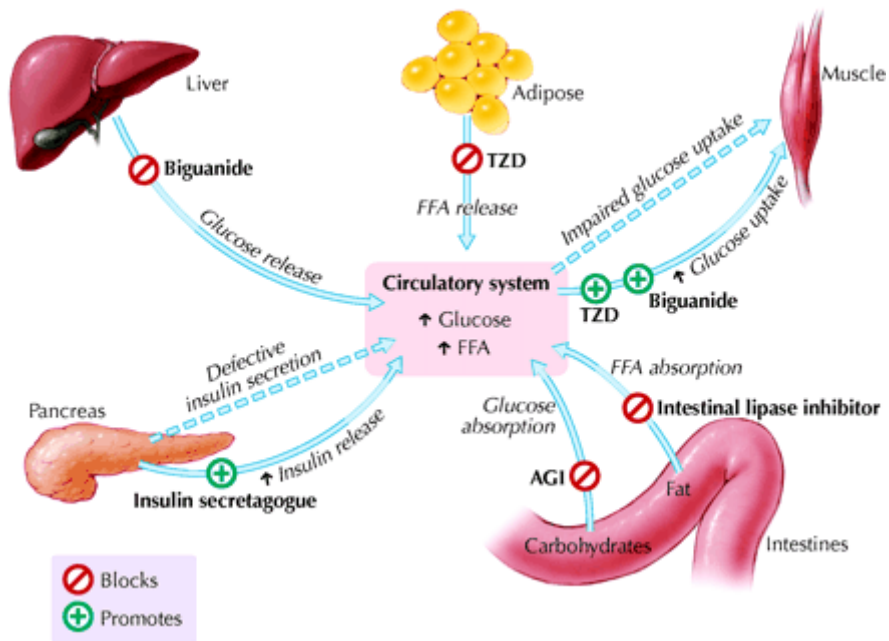


Fig: Diagram showing site of action of anti-diabetic drugs

ORAL HYPOGLYCEMIC AGENTS

CLASS	DRUGS	MECHANISM	LIMITATIONS
Sulfonylurea	1st generation Chlorpropamide, Talbutamide 2nd generation Glimeperide, Glipizide, Gliclazide, Glibenclamide	Stimulates pancreas to release more Insulin	Hypoglycemia, Hyperinsulinoma. Contraindication - Liver and renal disorders, Pregnancy, Lactation,
Meglitinide	Repaglinide, Nateglinide	Stimulates pancreas to release more Insulin	Hypoglycemia, contraindicated in liver disease, Pregnancy and Lactation
Biguanide	Metformin	Reduces glucose production by liver, improves insulin sensitivity	Lactic acidosis, GI side effects, contraindicated in Hepatic, Renal, Cardiac failure, Bronchial Asthma
Alpha glucosidase inhibitors	Acarbose, Miglitol,	Reduces glucose absorption by gut	GI side effects, Contraindicated in Inflammatory Bowel Disease

CLASS	DRUGS	MECHANISM	LIMITATIONS
Thiazolidinedione	Rosiglitazone, Pioglitazone	Stimulates nuclear PPAR gamma receptor, reduces insulin resistance	Edema, contraindicated in heart disease, Liver disease
DPP IV inhibitors	Saxagliptin, Sitagliptin, Vildagliptin	Inhibits degradation of glucagon GLP 1	GI side effects , Hypersensitive reactions.

INSULIN

The human insulin is prepared by recombinant DNA technology and has rapid absorption and shorter duration of action. Recently ultra-short acting and ultra-long acting preparations have also been developed. All insulin preparations are supplied at neutral pH of 7.2 to 7.4 except glargine which is supplied at pH of 4. Hence it is important that glargine should not be mixed with any other preparation of insulin. All insulin preparations are given by subcutaneous route only. Only regular insulin can be given by intra venous route. The factors which affect the absorption of insulin include the type and site of injection, the depth of injection and subcutaneous blood flow.

The most common complication of an insulin therapy is hypoglycaemia. This can be treated with intravenous glucose. Some people suffer from hypoglycaemic unawareness. Usually when the blood glucose levels drop less than 60mg/dl the symptoms of hypoglycaemia becomes apparent. However in patients suffering from hypoglycaemic unawareness there are no symptoms till blood glucose values drops to 40mg/dl. The patient becomes unconscious and often this condition is life threatening. Then at the site of injection it can cause lipodystrophy. Allergic reactions and sodium and water retention have found to occur.

The indications of insulin therapy include all cases of insulin dependent diabetes mellitus. Among non insulin dependent diabetes mellitus insulin is indicated when glucose levels are not controlled with oral hypoglycaemic agents, in pregnancy and in complications like diabetic ketoacidosis and hyperosmolar coma in in stressful conditions like surgery and infections.

The use of exogenous insulin provides a profile similar to the non-diabetic individual, with a continuous availability of insulin available which is enhanced by increase in availability after each meal. No single insulin preparation is available which are able to achieve this goal with one or two injections daily.

Ultralente insulin also called as "peak less" insulin is the longest acting insulin. It has a very slow action onset of action and it peaks very minimum and action is for a longer duration. Its action resembles the basal metabolic insulin

which is secreted from a normally functioning pancreas. The peak action of intermediate-acting insulin (lente and neutral protamine Hagedorn [NPH]) occurs 4 to 10 hours after injection. so if a patient takes NPH in the morning will have his or hers peak plasma levels during the lunch time . Regular insulin is shorter acting, with its onset being around about 30 minutes through 1 hour post injection and peaks at 2 -3 hours. Lispro insulin, a rapid acting insulin, due to its rapid absorption, will become active about 15 minutes post injection, and peaks at ½ to 1 1/2 hours. Rapid- and short-acting insulin are usually taken just before or during meals. Thus, regular insulin when taken before breakfast will peak at midmorning; when taken before lunch, will peak at mid-afternoon.

Insulin preparation	Onset of action	Peak	Duration of action
Lispro (Humalog)	<15 minutes	1-2 hours	3-6 hours
Aspart (Novolog)	<15 minutes	1-2 hours	3-6 hours
Glulisine (Apidra)	<15 minutes	1-2 hours	3-6 hours
Regular (Novolin R, Humulin R)	30-60 minutes	2-4 hours	6-10 hours
Humulin R Regular U-500	30-60 minutes	2-4 hours	Up to 24 hours
NPH (Novolin N, Humulin N, ReliOn)	2-4 hours	4-8 hours	10-18 hours
Glargine (Lantus)	1-2 hours	Usually no peak	Up to 24 hours
Detemir (Levemir)	1-2 hours	Usually no peak**	Up to 24 hours**

Premixed Insulins***	Onset of action	Peak	Duration of action
Novolin70/30, Humulin 70/30	30-60 minutes	2-10 hours	10-18 hours
Humalog 75/25, Novolog 70/30, Humalog 50/50	10-30 minutes	1-6 hours	10-24 hours

PREVENTION

Daily regular exercise (30 minutes /day 5 days /week), healthy food habits, weight reduction and maintain normal BMI, plays a major role in preventing diabetes and the complications. These also help in reducing the blood pressure and heart disease among Type 2 diabetic patients.

DIABETES AND HEART

Diabetes affects the heart through following mechanism.

1. Acceleration of atherosclerotic³⁰ process leads to coronary artery disease
2. Development of cardiomyopathy
- 3 Development of autonomic neuropathy

CORONARY ARTERY DISEASE

CAD is two times frequent in diabetic men and four times frequent in diabetic women compared to non- diabetes. CAD in diabetes is characterised by greater prevalence of triple vessel disease²³.

PATHOGENESIS

Diabetics have higher levels of matrix metalloproteinase and cytokines. This results in a decreased synthesis and increased collagen breakdown in the fibrous cap of the atherosclerotic plaque. Thus destabilized, the plaque becomes more prone to rupture and thrombosis³⁰. In diabetics, the platelets are larger, there is increased production of free radicals. Also hyperglycemia impairs functioning of endothelial nitric oxide synthase. This limits endothelium dependent vasodilation. There is an increased activity of inflammatory mediators in the atherosclerotic plaque. Vasoconstrictive agents like endothelin-1 and angiotensin-II are up regulated to aggregate more aggressively in response to stimulus. Diabetics also have a higher proportion of platelets circulating in an activated state. This further predisposes them to thrombotic episodes.

CLINICAL FEATURES

Diabetic patients with acute coronary syndromes may present with mild or atypical symptoms. This is thought to be the result of underlying sensory and autonomic neuropathy. Recognition of angina gets impaired with autonomic neuropathy. There is an increased incidence of atypical symptoms like nausea, vomiting, fatigue, breathlessness, dizziness, altered sensorium or disturbances of glycemic control. Silent myocardial ischemia and infarction are also common. A number of the symptoms experienced during an acute coronary syndrome, like vomiting, breathlessness, sweating and palpitations are also associated with fluctuations in plasma glucose levels.

DIAGNOSIS

ELECTROCARDIOGRAM

In patients who have unstable angina the ECG features suggesting it include inversion of T wave, transient ST segment depression or elevation. The occurrence of deviation in ST segment even if it is only 0.05 millivolt is a very important sign of adverse events in patients who have clinical features classical of unstable angina. The changes in T waves are less specific but they are sensitive for ischemia. The occurrence of deep inversion in T waves greater than 0.3 millivolt and occurrence of new T wave changes which were not present earlier are more significant.

In patients with myocardial infarction there is elevation of ST segment. The elevation in the leads occurs in correspondence to the territory of heart involved. The arterial localisation of obstruction can be made out to an extent from the electrocardiogram. The other changes include formation of q waves and loss of R waves. Most patients who have elevation in the ST segment eventually develop q waves but its magnitude depends on the reperfusion status.

SERUM BIOMARKERS

After an injury to cardiac muscle cell there is leakage of several cardiac proteins into the circulation. The levels at which these cardiac bio markers can be detected depends on molecular weight, local blood, intracellular location of enzymes and lymphatic flow. When the levels of cardiac markers rise to a level such that it exceeds the lymphatic clearance, these biomarkers become detectable in blood.

Cardiac specific troponin T and troponin I are not normally detected in blood but when an attack of injury to cardiac muscle occurs their levels get increased by twenty folds. Now cardiac troponin I and T are the most preferred biomarkers of injury to cardiac muscle. They are particularly useful when we have doubt of skeletal muscle injury and in very small MI in which the levels of creatine phosphokinase is undetectable. For about seven to ten days after myocardial infarction we can detect the levels of cardiac troponin T and troponin I. Creatine phosphokinase levels are elevated within four to eight

hours and in about forty eight to seventy two hours their levels return to normal. The most important disadvantage of using creatine phosphokinase as a cardiac biomarker is that the specificity for cardiac injury is lacking and it will be elevated in conditions causing injury to skeletal muscle including trauma, crush injury, injection, and rhabdomyolysis. This drawback can be reduced by using the isoenzyme of creatine phosphokinase which is CK MB.

ECHOCARDIOGRAPHY

Regional motion wall abnormalities are almost always present. Echo can be very useful tool for diagnosing coronary artery diseases in which ECG are inconclusive. ECHO can be used to assess the function of the left ventricle post infarction. Right ventricular infarction, aneurysm, thrombus and pericardial effusion can be assessed .Two major complications of myocardial infarction which can be diagnosed using ECHO include acute regurgitation of mitral valve and rupture of the ventricular septum.

CORONARY ANGIOGRAPHY

Patients who have unstable angina / NSTEMI depending upon the TIMI score patient who fall under category two and three must be subjected to angiography and if critical occlusion of arteries is present they must be subjected to intervention. People who had myocardial infarction and had undergone thrombolysis must be subjected to angiogram and rescue PCI.

COURSE OF ACUTE INFARCTION

In Hospital mortality of diabetic patient experiencing myocardial infarction is higher compared to non-diabetics. The high post-infarction mortality is due to severe congestive heart failure and cardiogenic shock. Recurrent infarctions, Conduction disturbances, myocardial rupture are all common in diabetic patient. Autonomic neuropathy compromises of reflex adaptation to hemodynamic stress during infarction. Predictors of poor prognosis are previous myocardial infarct, female gender, insulin therapy prior to hospitalisation.

COURSE OF NON FATAL MYOCARDIAL INFARCTION

The mortality in the immediate 6 months and later after discharge from the hospital is high in diabetics. Delayed mortality is due to persistent ischemia and on going myocardial damage following myocardial infarction.

INDICATORS OF POOR PROGNOSIS

- Symptoms of coronary ischemia one month preceding the infarction.
- Features of congestive cardiac failure during initial period of Hospitalisation.
- Premature ventricular beats greater than 10 per hour before discharge
- Reduced left ventricular ejection fraction (<40%)

PROGNOSIS

The prognosis for acute Myocardial Infarction in a diabetic is rather poor compared to a nondiabetic patient. Hyperglycemia due to poor metabolic control is strongly correlated with excess mortality. The prognosis is also influenced by very high prevalence of cardiogenic shock and congestive cardiac failure complicating in acute infarction in Diabetic subjects. Severe atherosclerosis with impaired coronary collateral circulation, frequent association of small vessel disease, microangiopathy and the proneness for ketoacidosis possibly contributing to the excess mortality in diabetic subjects.

MANAGEMENT

The management of acute Myocardial Infarction is similar in Diabetic and non-diabetic subjects excepting that the therapy with insulin is mandatory for ensuring metabolic control in diabetics.

PRIMARY PREVENTION

The steps taken to prevent the development of risk factors for coronary artery disease constitute primary prevention.

LIFESTYLE CHANGES DIET AND EXERCISE

The people must be encouraged to take a diet rich in fibres, vegetables, plant sterols and low in saturated fatty acids. The people must be encouraged to exercise. According to the American Association Of Diabetes it is

recommended that one should exercise for at least thirty minutes per day for five days in week to prevent occurrence of cardiovascular complications. Physical activity need not be exercise as such and might include day to day activities like washing, cleaning, gardening etc...

WEIGHT REDUCTION

Studies have shown that consuming a diet less in carbohydrate causes reduction in weight drastically only in the initial stages but in order to have continuous reduction in weight dietary restriction must be combined with increased physical activity .

AVOID SMOKING

Smoking causes release of toxic substances which injures the vascular endothelium and causes vasoconstriction. Hence both active and passive smoking should be avoided.

CONTROL OF HYPERGLYCEMIA

Proper monitoring of sugar levels should be done. People should be advised to avoid food having high glycemic index. When dietary and exercise modifications cannot control glucose then pharmacological intervention must be instituted and strict control of blood glucose should be maintained.

CONTROL OF DYSLIPIDEMIA

All diabetic patients who have a blood LDL level of greater than 70 mg/dl should be started on statins. Patients who have high levels of triglycerides should be started on fibrates.

CONTROL OF HYPERTENSION

JNC 8 guidelines should be followed for control of hypertension. The target level of BP control according to JNC 8 guidelines is 140/90 mm of hg and ACE inhibitors are the choice of drugs for control of hypertension in diabetics especially those who have diabetic nephropathy to reduce proteinuria.

ST ELEVATION MI

REPERFUSION THERAPY

Reperfusion therapy of myocardium can be done by using thrombolytics and primary PCI

THROMBOLYTIC THERAPY

This should be administered at the earliest as possible. it is indicated in ST elevation MI and contraindicated in unstable angina and non ST elevation myocardial infarction. Thrombolysis must be completed within first 2 hours the results of thrombolysis are same as primary percutaneous intervention but after this window period primary percutaneous intervention is better than thrombolytic therapy.

PERCUTANEOUS CORONARY INTERVENTION

PCI is more effective than thrombolytic therapy in diabetics. It is preferred for single and double vessel disease. When PCI is done along with stenting without fibrinolysis it is referred to as primary PCI. Studies have found that the short and long term prognosis with PCI have been found to be better than thrombolysis in experienced hands. And PCI can be the intervention of choice in cases where there is doubt in diagnosis, in cases of cardiogenic shock, in cases where there is risk of bleeding tendencies and in cases in which the patient presents after 2 to 3 hours when the clot has become mature and difficult for the thrombolytic agents to act.

CORONARY ARTERY BYPASS GRAFT

It's preferred for triple vessel disease and recent Q wave MI. In diabetes the chances of restenosis are high. Studies have shown that the chances of restenosis are higher after PCI when compared to CABG. Hence CABG is a preferred method of intervention for diabetic patients.

GLUCOSE INSULIN INFUSION

Insulin-glucose infusion in the acute myocardial infarction reduces the mortality. It is due to suppression of free oxidation of fatty acids. Free fatty acids potentiate ischemic injury by direct toxicity and inhibition of glucose oxidation.

ANTI THROMBOTIC AGENTS

It reduces the thrombus and maintains patency of occluded artery. Diabetic patients have increased platelet activation and accelerated turnover of platelets. All the patients of diabetic with CAD need higher doses of aspirin with additional antiplatelet drugs like clopidogrel or ticlopidine.

BETA BLOCKERS

It block the adrenergic stimulation and prevent ventricular remodelling and improve left ventricular function .it reduces the infarct size and decreases the incidence of arrhythmia and improve the survival. Beta blockers also reduce the recurrent ischemia and re infarction.

ACE INHIBITORS AND ARB

It prevents the ventricular remodelling and subsequent reduction of cardiac failure .it also reduces the recurrent infarction .It delays renal dysfunction and improves glycemic control.

STATINS

It confers long term protection from cardiovascular events in patients recovering from myocardial infarction and also reduces the complications.

UNSTABLE ANGINA AND NSTEMI

Thrombolytic therapy is contraindicated in unstable angina and NSTEMI. Low molecular weight heparin is preferred over unfractionated heparin .In high risk patients PCI is preferred over conservative treatment and this results in reduction of mortality and morbidity. Use of Anti-platelet, ACE inhibitors, beta blockers, statins is same as STEMI.

DIABETIC CARDIOMYOPATHY

First established by Rubler in 1972³⁹. In India Tripathy reported in 1973 the existence of cardiac enlargement and failure in diabetes without obvious coronary artery disease, hypertension or structural heart disease suggesting a specific of diabetic cardiomyopathy. Patients with diabetes have shown to develop heart disease through various cellular level mechanisms eventually ending up in fibrosis of myocardial tissue, hypertrophy of left ventricle and both diastolic and systolic dysfunction¹¹.

PATHOGENESIS

The proposed mechanisms responsible for development of diabetic cardiomyopathy are:

- **HYPERGLYCEMIA**

It affects contractility of heart by two main mechanisms

1. Production of advanced glycation end products⁶⁸
2. Production of free radicals

Myocardial fibrosis results from elevated collagen deposition in myocardium. This is a result of over –production of reactive oxygen species from the above mechanisms.

- FREE FATTY ACIDS

Insulin resistance is directly proportional to raised free fatty acids. It further leads to dysfunction of protein for transport of calcium and impaired glycolysis, pyruvate oxidation, lactate uptake results in apoptosis. Increased free fatty acids are associated with activation of proliferation activated receptor alpha (PPAR alpha) which promote mitochondrial uncoupling of oxidative phosphorylation and reduces myocardial high energy reserves⁶⁷. These mechanisms are responsible for cardiac dysfunction.

- PROTEIN KINASE C

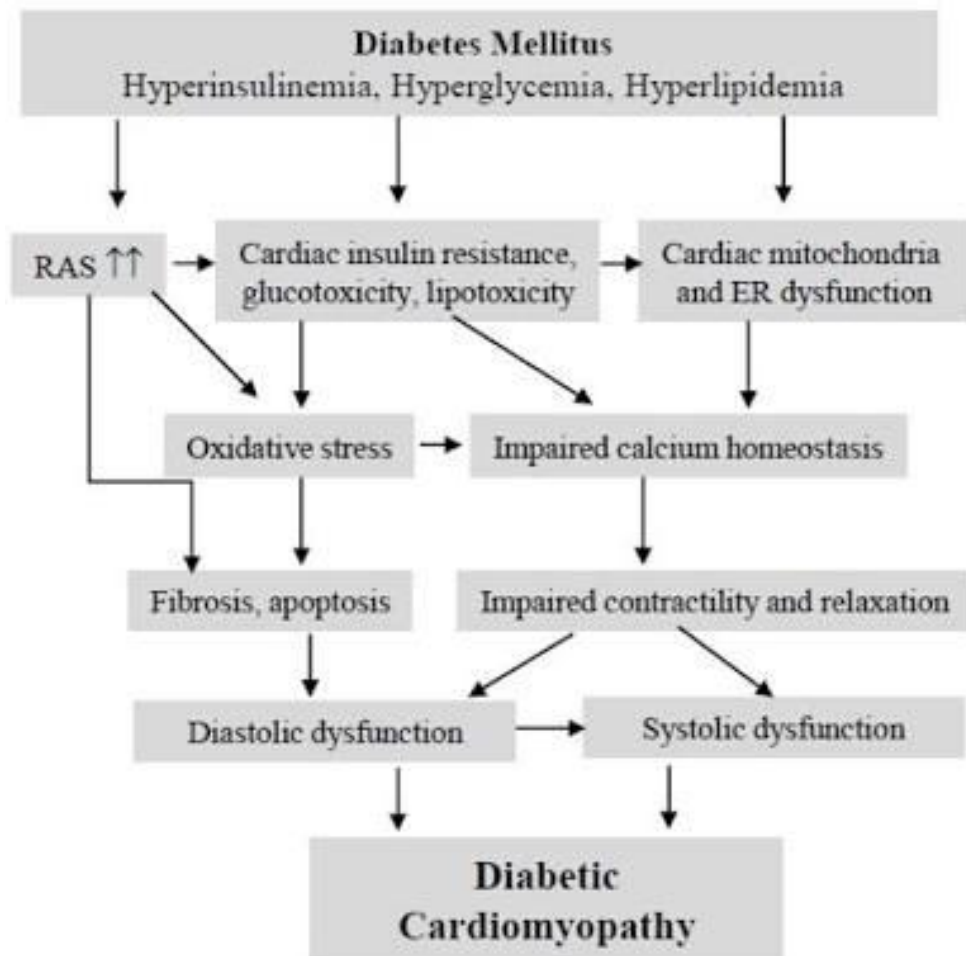
It is a signalling molecule which is present inside the cells. Protein kinase c reduces the levels of nitric oxide and increases the production of free radicals. The levels of protein kinase c are elevated in diabetic patients. These sequential changes lead to dysfunction of the endothelium⁵⁷.

- ENDOTHELIAL DYSFUNCTION

Uncontrolled diabetes mellitus results in impaired endothelium dependent vasodilation due to reduction of nitric oxide production. This results reduced myocardial flow.

- **RENIN ANGIOTENSION AND ALDOSTERONE MECHANISM**

In concomitant hyperglycemia the RAAS mechanism gets dysregulated and both aldosterone and glucose stimulate growth of myofibroblast leading to myocardial fibrosis⁷⁰.



Pathogenesis of Diabetic Cardiomyopathy

- VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

In diabetics the vascular endothelial growth factors levels are reduced, which is responsible for angiogenesis and collateral formation in cardiac ischemia.

- ARTERIAL STIFFNESS

In diabetic individual as a result of endothelial dysfunction arterial stiffness occurs. So the compliance of the large arteries is reduced and it affects the central systolic pressure and left ventricular after load. So the coronary perfusion pressure is reduced resulting in myocardial fibrosis and heart failure⁵.

- AUTONOMIC NEUROPATHY

Cardiac autonomic neuropathy is an important predisposing factor for diabetic cardiomyopathy. In cardiac autonomic neuropathy the loss of parasympathetic activity results in relative predominance over sympathetic activity in the sympathovagal balance. The sympathetic over activity stimulates renin angiotensin –aldosterone –adrenergic system which increases the heart rate, stroke volume and peripheral resistance results in left ventricle. The sympathetic over activity with myocardial sympathetic denervation leads to impairment of coronary vasodilator reserve, impaired ventricular diastolic filling and diastolic dysfunction⁶⁷.

- **DISORDERED COPPER METABOLISM**

Hyperglycemia affects the calcium transport by inhibiting the binding of calcium with ceruplasmin. It results increases the extracellular copper level which stimulates the oxidation reduction system leads to production free radicals. This free radical responsible for myocardial fibrosis.

- **MITOCHONDRIAL DYSFUNCTION**

Mitochondrion provides energy in the form of ATP by oxidative phosphorylation .In presence of insulin resistance instead of glucose fatty acid is used for ATP synthesis. Over a time this fatty acid impairs the mitochondrial respiratory function resulting in myopathy⁵⁹.

RISK FACTORS

- Chronic high blood sugar level
- Obesity
- Hypertension
- Dyslipidemia
- Smoking
- Alcoholism
- Sedentary life style.

CLINICAL FEATURES

Diabetic cardiomyopathy is a progressive state initially with myocardial diastolic dysfunction, latter on systolic dysfunction supervenes with classical features of CCF. Patient has no symptoms in early stage later progresses to fatigue ,weakness, effort intolerance, shortness of breath with cough, swelling of the feet . Cardiomegaly, atrial and ventricular gallop, pulmonary congestion is frequent.

STAGING OF DIABETIC CARDIOMYOPATHY

Stage 1

It includes Diastolic Heart failure with preserved ejection fraction with hypertrophy without hypertension.

Stage2

Diastolic and systolic heart failure with dilatation and reduced ejection fraction without hypertension.

Stage 3

Systolic and diastolic heart failure with micro vascular disease and hypertension without CAD.

Stage 4

Heart failure associated with ischemia/ infarction.

DIAGNOSIS

EVALUATION OF LEFT VENTRICULAR FUNCTION

There are two chief methods of evaluating the LV function

1. Non-invasive methods include

- a) Echocardiography and cardiac Doppler
- b) Systolic time intervals (STI)
- c) Apex cardiography (ACG)
- d) Gadolinium enhanced cardiac MRI

2. Invasive method

Cardiac catheterization.

DOPPLER ECHO CARDIOGRAPHY

It is a good non-invasive technique to demonstrate the LV function abnormalities. This is an inexpensive tool to detect the functional and structural cardiac anomaly. Earliest abnormality is LV diastolic dysfunction recorded by pulse Doppler echocardiography. LV dilatation not seen in diabetic heart with LV diastolic dysfunction but occur in LV systolic dysfunction supervene over pre existing diastolic abnormalities. the diabetic heart has a stiff and less compliant myocardium to start with (diastolic dysfunction) later becomes

dilated with poor ejection fraction (systolic failure) resulting congestive heart failure⁶⁴ .

Trans – mitral Doppler (mitral valve blood flow measured by pulse wave Doppler) is a very useful method in diagnosis of left ventricular diastolic dysfunction. The variables commonly measured are early ventricular filling (E), late ventricular filling wave (A) and E/A ratio, isovolumetric relaxation time (IVRT), deceleration time (DT), velocity at the mitral annulus level during early ventricular filling (e') Ejection fraction was calculated by modified simson criteria. LV diastolic dysfunction was considered to any one of following findings.

E/A ratio <1 or >2

DT <150 OR >220 ms

IVRT <60 OR >100ms

E/e' ratio >15 (ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'))

ECHOCARDIOGRAPHIC GRADING OF DIASTOLIC DYSFUNCTION³²

GRADE I

Abnormal relaxation pattern.

Reversal of E/A ratio

IVRT > 100ms

DT> 240 ms

E caused by accumulation of blood in the atria during previous systole.

A caused by atrial contraction.

GRADE II

Pseudonormal filling pattern.

Elevated atrial filling pressure

E/A ratio return to range of 0.8 to 1.5

IVRT <90ms

DT < 160 ms

GRADE III

Reversible restrictive pattern

Reversal of diastolic abnormalities on valsalva manoeuvre

E/A ratio >2

IVRT <80 ms

DT<160 ms

GRADE IV

fixed restrictive pattern

Most severe form of diastolic dysfunction.

No reversibility of diastolic abnormalities on valsalva manoeuvre

E/A ratio >2

SYSTOLIC TIME INTERVAL (STI)

Simultaneous recording of ECG ,phonocardiography and carotid pulse tracing at 100 mm speed is done .In diabetic patients have a shorter LV ejection time (LVET) and longer pre ejection period(PEP).The prolonged

ratio of PEP/LVET suggesting LV dysfunction in diabetics¹⁶ . It not used now a days.

APEX CARDIOGDAPHIC TRACING (ACG)

It is a mechanical displacement record with transducer kept snugly at the LV apex on the chest wall in left lateral position .This recording is done at 100 mm speed ,both systolic (systolic bulge) and diastolic abnormalities (rapid filling wave abbreviated) diagnosed .It is very rarely used .

GADOLINIUM ENHANCED MRI

It is used to assess the myocardial flow reserve and myocardial perfusion, and fibrosis. Cardiac MRI diagnosed myocardial scar without evidence of myocardial infarction. It is a non-invasive technique to assess the left ventricular function and size.

INVASIVE STUDIES

CARDIAC CATHETERISATION

Elevated left ventricular end diastolic pressure (LVEDP) > 16 mmhg

Mean pulmonary capillary wedge pressure > 12 mmhg

Normal coronary angiogram are suggestive of diabetic cardiomyopathy.

MANAGEMENT

PRIMARY PREVENTION

Prevention of risk factors and life style modification.

GLYCEMIC CONTROL

Hyperglycemia is the key factor for development of cardiomyopathy. So the Strict glycemic control reduces the incidence and progression of cardiomyopathy.

ACE INHIBITORS AND ARB

ACE inhibitor and ARB blocks the neurohormonal stimulation by which it prevents the development and progression of myocardial fibrosis, hypertrophy, myocardial dysfunction and ventricular remodelling .It also reduces the insulin resistance where by reducing the blood glucose levels⁷⁰.

BETA BLOCKERS

Blocks the sympathetic stimulation. It controls the heart rate and improves the left ventricular filling time and improves the diastolic function. It also Prevent and reverse cardiac remodelling⁶.

ALDOSTERONE ANTAGONIST

Aldosterone antagonist inhibits the production of inflammatory mediators, endothelial dysfunction and vascular stiffening which are the effects of aldosterone⁷⁰.

STATINS

It increases the collateral blood flow downstream of activated plaques and stimulates the endothelial nitric oxide synthase activity and prevents the advanced end glycation product related damage.

DIURETICS

Is indicated in advanced stage for relief of dyspnoea and edema in heart failure with fluid retention.

NOVEL THERAPIES

In the early stage of diabetic cardiomyopathy novel therapy is directed to prevent the progression of disease .In novel therapy there are advanced glycation end products inhibitors⁶⁷ (pyridoxime,aminoguanidine) advanced glycation end product cross link breakers (alanine aminotransferase),copper chelators (triamterene) , modulators of free fatty acid metabolism(trimetazidine).

3. AIM AND OBJECTIVES

To assess the correlation of HBA1C levels with left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetic patients

4. MATERIALS AND METHOD

PLACE OF STUDY

Department of General Medicine, OPD, Medical wards
Stanley Medical College and Hospital, Chennai

STUDY POPULATION

100 consecutive patients of newly diagnosed Type 2 diabetes mellitus.

STUDY DESIGN

Prospective study

ETHICAL COMMITTEE APPROVAL

Ethical committee approval was obtained for the study

DIAGNOSTIC CRITERIA (American diabetes association)

$\text{FBS} \geq 126 \text{ mg/dl}$

2 hr plasma glucose $\geq 200 \text{ mg/dl}$ during an OGTT.

$\text{RBS} \geq 200 \text{ mg/dl}$ with symptoms

(polyuria, polydipsia , polyphagia, weight loss)

$\text{HbA1C} > 6.5 \%$

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Reduction in peak velocity of early mitral flow(E) increase over peak velocity of late mitral flow(A) with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction were considered as the evidence of left ventricular diastolic dysfunction .

INCLUSION CRITERIA

All newly diagnosed Type 2 diabetes mellitus patients, who clinically had no cardiovascular symptoms and blood pressure of $< 130/80$ mmHg, with normal ECG.

EXCLUSION CRITERIA

- Known diabetic patients on insulin and OHA
- Ischemic heart disease
- Hypertensive heart disease
- Congestive heart failure,
- Valvular heart disease
- Cardiomyopathy
- Connective tissue diseases
- Renal failure
- Thyroid dysfunction were excluded from the study.

METHODOLOGY

Patients with newly diagnosed Type 2 diabetes presenting to the Medicine out-patient service and those admitted to the medical wards at Stanley medical college hospital Chennai are included in the present study. Informed consent was obtained from the subjects. Detailed medical history will be collected from each patient. Patients were subjected for clinical examination followed by relevant investigations.

The patients undergo the following investigations.

- a. FBS, PPBS.
- b. Glycosylated haemoglobin (HbA1c).
- c. Urea, creatinine.
- d. Fasting Lipid profile
- e. Urine routine
- f. ECG.
- g. Doppler Echo is done in each patient and 3-4 cardiac cycles were analysed to get best phase for better outcome of results.

In Doppler Echo study following values are being evaluated.

- 1 E-peak velocity of early mitral flow (N :50-90 cm / sec)
- 2 A- peak velocity of late mitral flow (N : 30-70 cm / sec)
- 3 E/A ratio (N :1-2)
- 4 Left atrial size (N :3 – 4 cms)
- 5 EF (N :> 60 %)

Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction (EF) were considered as the evidence of left ventricular diastolic dysfunction .

The study period is from march 2015 to September 2015

HUMAN SUBJECT PROTECTION

The full protocol along with draft questionnaire and Informed consent will be kept in Institutional ethical Committee and approval will be obtained.

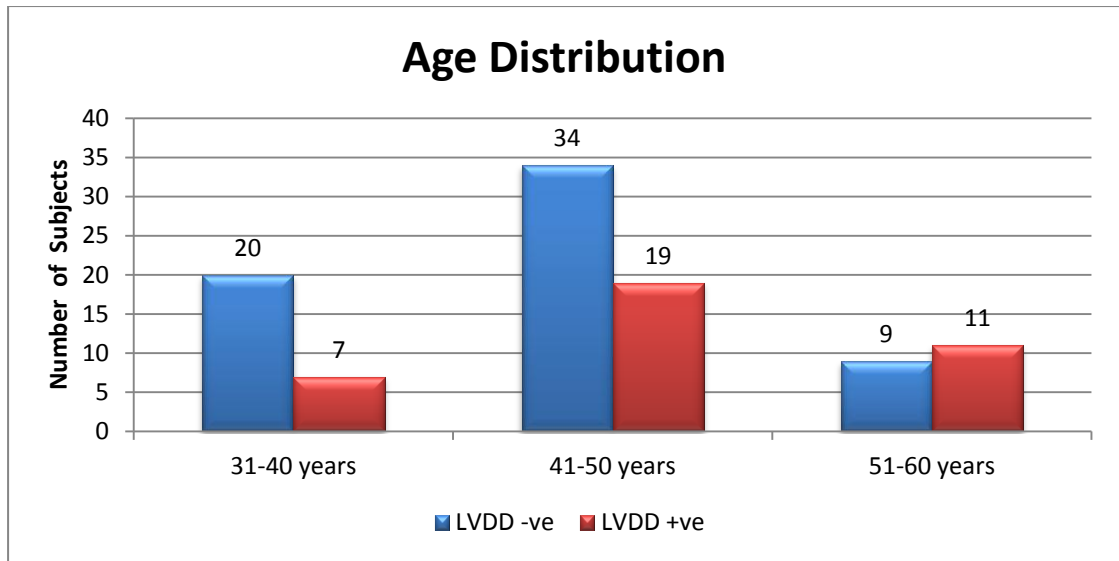
INFORMED CONSENT

Consent form will be written in both English and Tamil and consent will be obtained from the participant, confidentiality will be maintained.

5 .RESULTS

Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test.. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

AGE

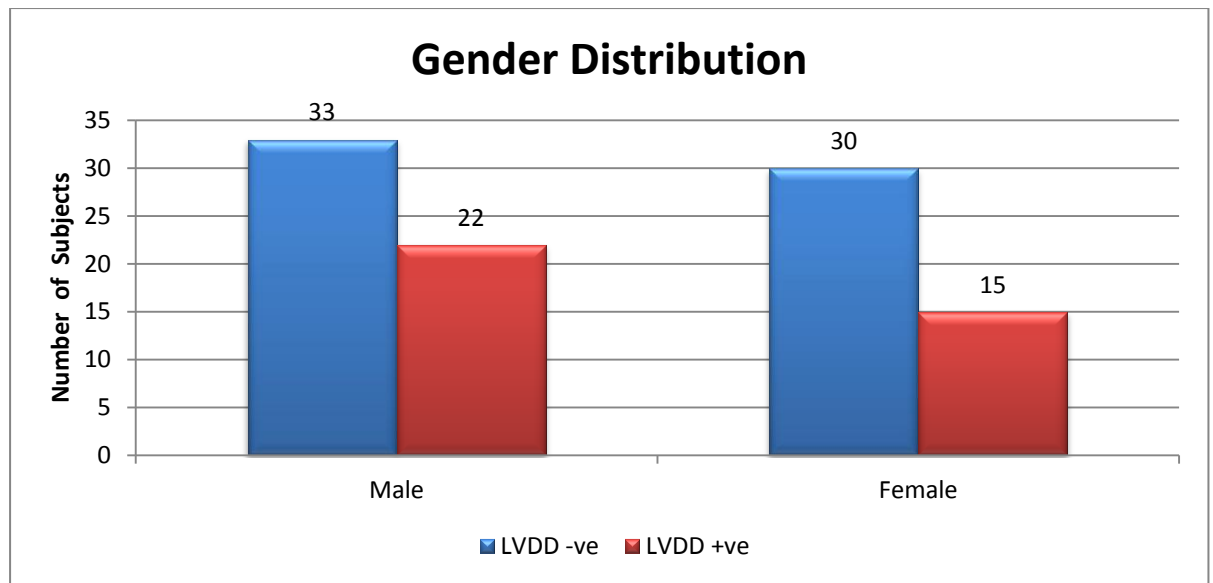


Age Distribution	LVDD -ve	%	LVDD +ve	%	All	%
31-40 years	20	31.75	7	18.92	27	27.00
41-50 years	34	53.97	19	51.35	53	53.00
51-60 years	9	14.29	11	29.73	20	20.00
Total	63	100	37	100	100	100

Age Distribution	LVDD -ve	LVDD +ve	All
N	63	37	100
Mean	45.08	45.49	45.23
SD	6.62	7.18	6.80
P value Unpaired t Test		0.7790	

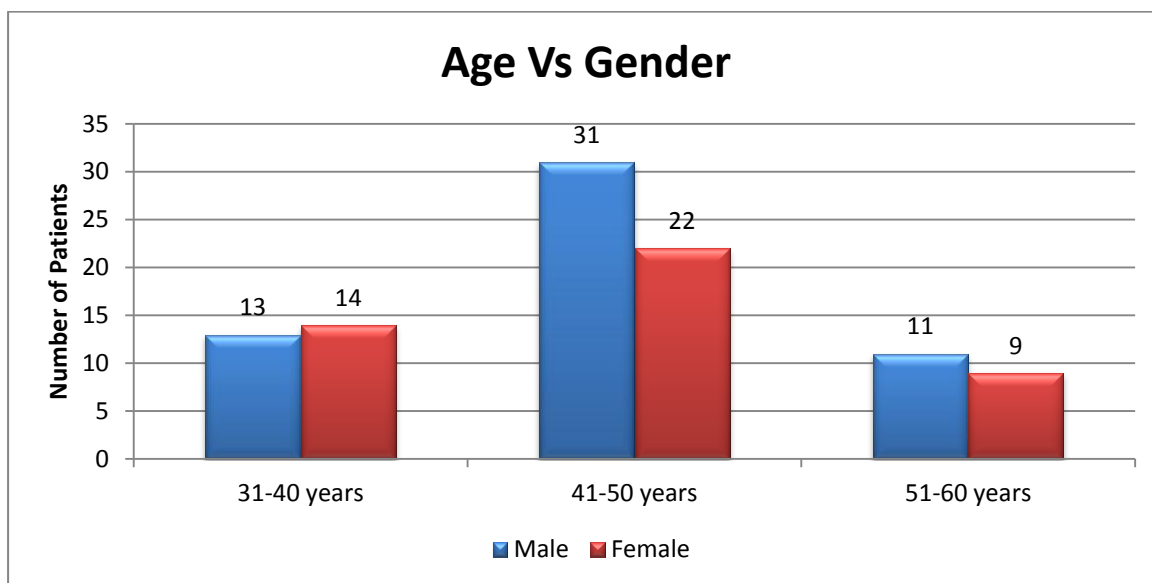
Majority of the LVDD negative group patients belonged to the 41-50 years age class interval (n=34, 53.97%) with a mean age of 45.08 years. In the LVDD positive group patients, majority belonged to the same age class interval (n=19, 51.35%) with a mean age of 45.49 years. The association between the study groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

GENDER

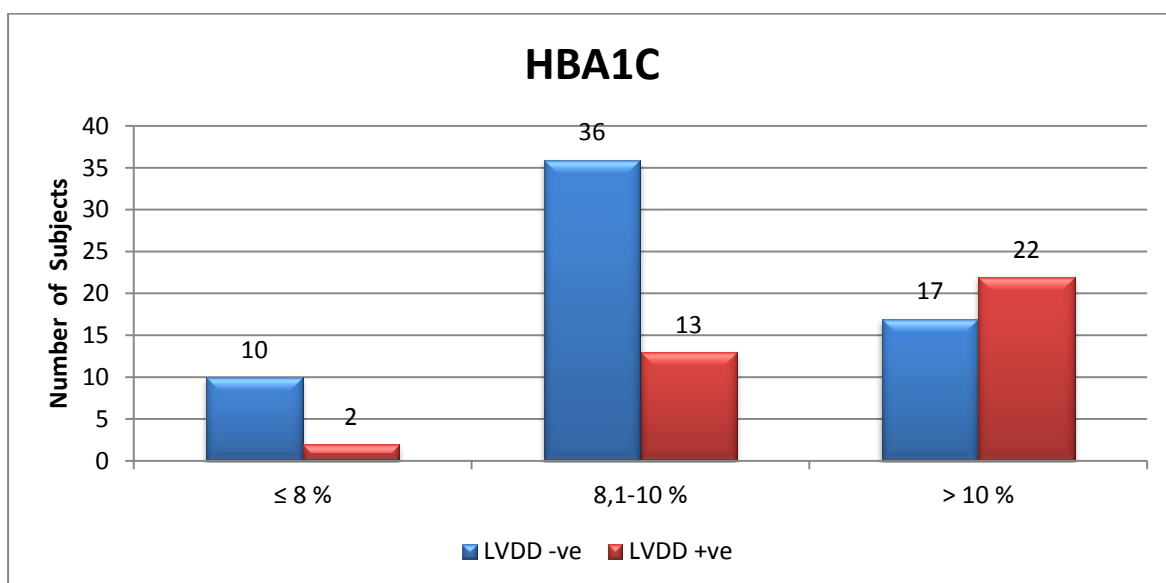


Gender Distribution	LVDD -ve	%	LVDD +ve	%	All	%
Male	33	52.38	22	59.46	55	55.00
Female	30	47.62	15	40.54	45	45.00
Total	63	100	37	100	100	100
P value Chi Squared Test				0.1489		

Majority of the LVDD negative group patients belonged to the male gender class interval (n=33, 52.38%). In the LVDD positive group patients, majority belonged to the male gender class interval (n=22, 59.46%). The association between the study groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per chi squared test.



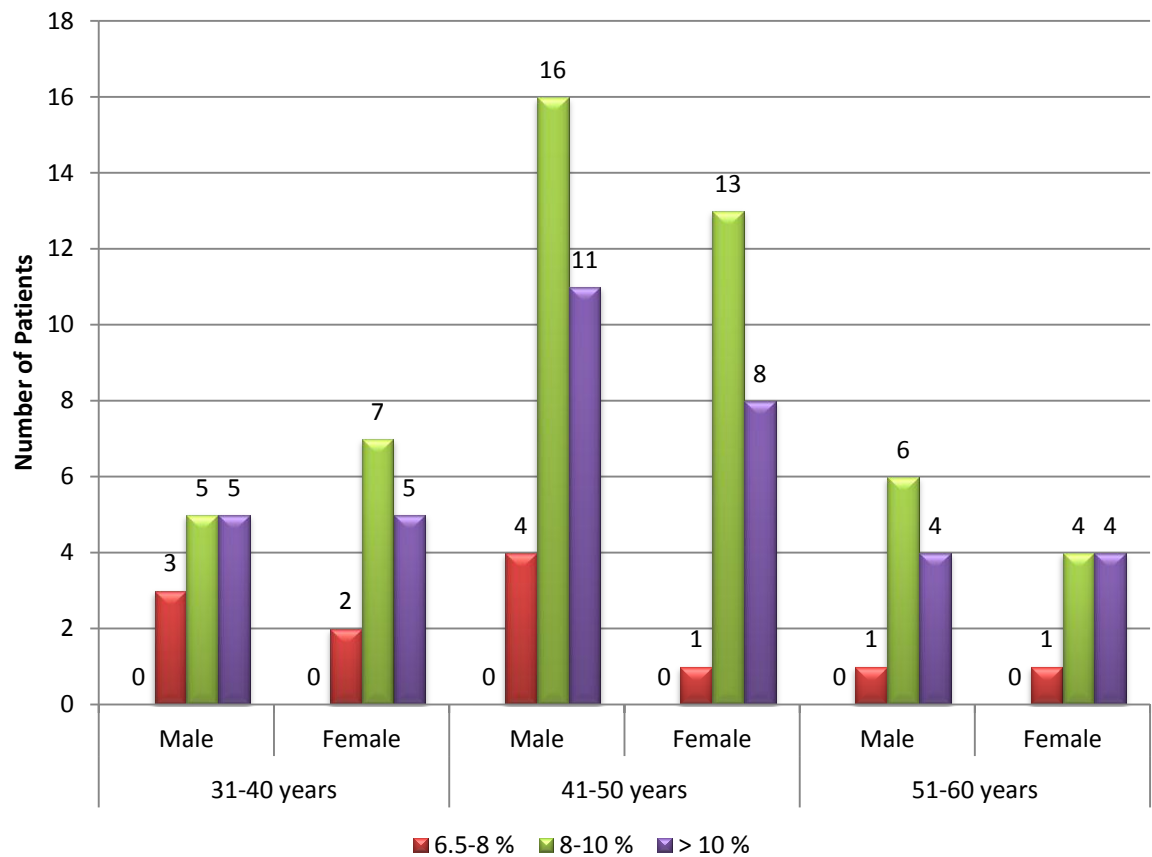
Age Vs Gender	Male	%	Female	%
31-40 years	13	23.64	14	31.11
41-50 years	31	56.36	22	48.89
51-60 years	11	20.00	9	20.00
Total	55	100	45	100



HBA1C	LVDD -ve	%	LVDD +ve	%	All	%
≤ 8 %	10	15.87	2	5.41	12	12.00
8,1-10 %	36	57.14	13	35.14	49	49.00
> 10 %	17	26.98	22	59.46	39	39.00
Total	63	100	37	100	100	100

HBA1C	LVDD -ve	LVDD +ve	All
N	63	37	100
Mean	9.13	10.46	9.62
Sd	1.25	1.58	1.51
P value Unpaired t Test		0.0000	

HBA1C levels Vs Age Vs Gender



HBA1C levels Vs Age Vs Gender		6.5-8 %	8-10 %	> 10 %	Total
31-40 years	Male	3	5	5	13
	Female	2	7	5	14
41-50 years	Male	4	16	11	31
	Female	1	13	8	22
51-60 years	Male	1	6	4	11
	Female	1	4	4	9
Total		12	51	37	100

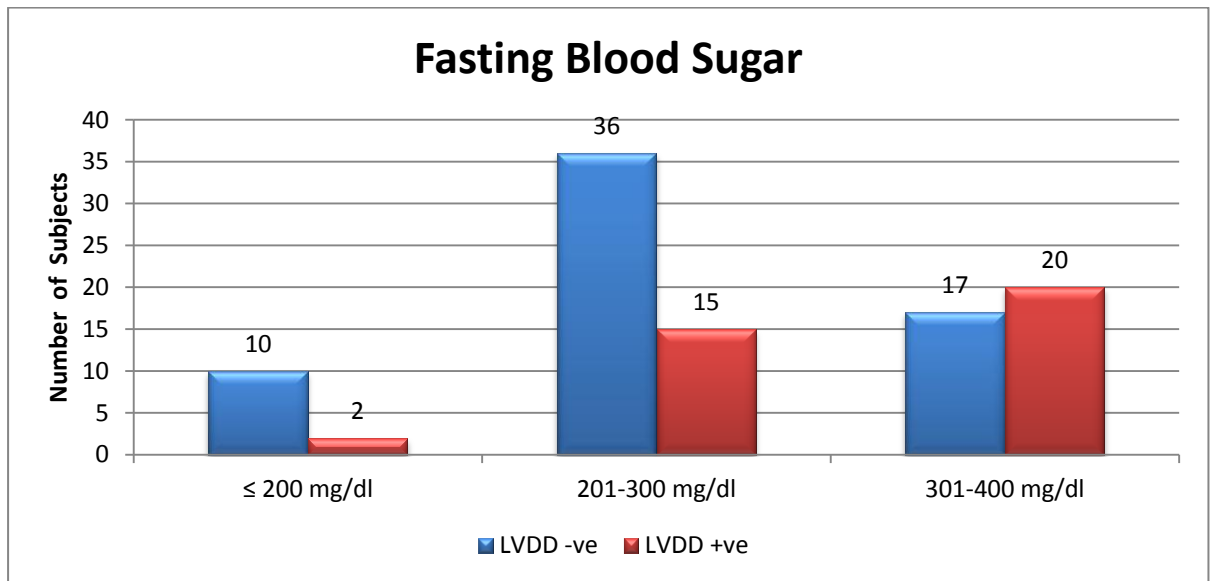
Results

In patients belonging to LVDD negative group, the mean HBA1C levels are 9.13%. In LVDD positive group, the mean HBA1C levels are 10.46%.. The decreased mean HBA1C measurements in LVDD negative group compared to the LVDD positive group is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups.

The mean HBA1C levels were meaningfully more in LVDD positive group compared to the LVDD negative group by 1.33%. This significant difference of 15% increase in mean HBA1C levels in LVDD positive group compared to the LVDD negative group is true and has not occurred by chance.

In this study we can safely conclude that mean Soluble HBA1C Levels were significantly and consistently higher in LVDD positive group compared to the LVDD negative group. Hence it can be inferred that high HBA1C levels are strongly associated with Left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetes mellitus patients.

FBS



Fasting Blood Sugar	LVDD -ve	%	LVDD +ve	%	All	%
≤ 200 mg/dl	10	15.87	2	5.41	12	12.00
201-300 mg/dl	36	57.14	15	40.54	51	51.00
301-400 mg/dl	17	26.98	20	54.05	37	37.00
Total	63	100	37	100	100	100

Fasting Blood Sugar	LVDD -ve	LVDD +ve	All
N	63	37	100
Mean	212.92	243.65	224.29
Sd	35.84	36.63	38.92
P value Unpaired t Test		0.0001	

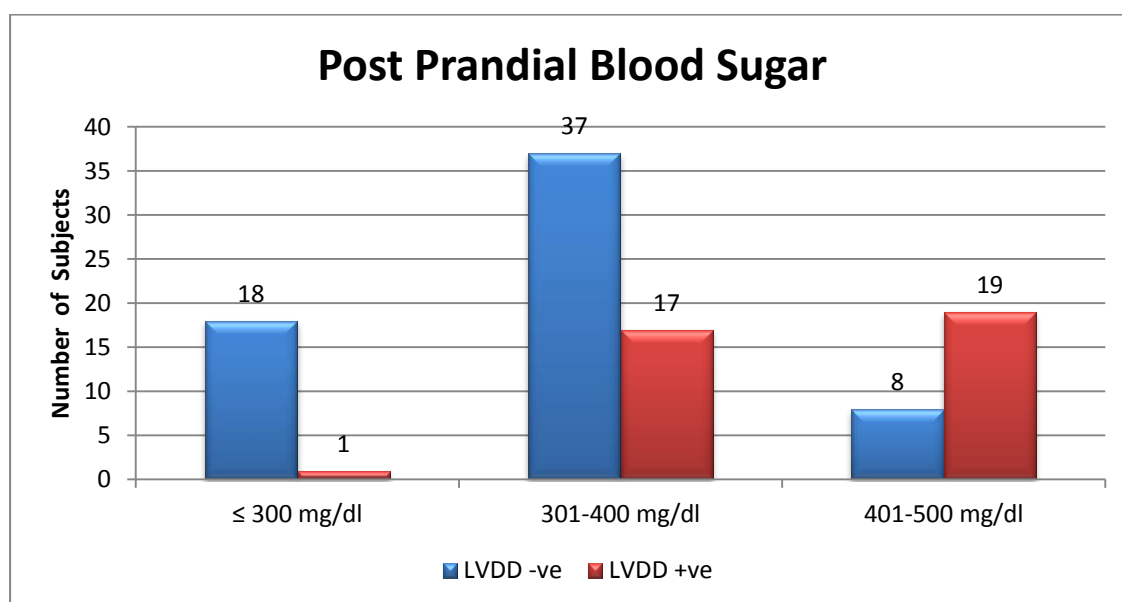
Results

In patients belonging to LVDD negative group, the mean FBS levels are 212.92 mg/dl. In LVDD positive group, the mean FBS levels are 243.65 mg/dl. The decreased mean FBS levels in LVDD negative group compared to the LVDD positive group is statistically significant as the p value is 0.0001 as per unpaired t- test indicating a true difference among study groups.

The mean FBS levels were meaningfully more in LVDD positive group compared to the LVDD negative group by 30.73 mg/dl. This significant difference of 14% increase in mean FBS levels in LVDD positive group compared to the LVDD negative group is true and has not occurred by chance.

In this study we can safely conclude that mean fasting blood sugar levels were significantly and consistently higher in LVDD positive group compared to the LVDD negative group. Hence it can be inferred that high FBS levels are strongly associated with Left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetes mellitus patients.

PPBS



Post Prandial Blood Sugar	LVDD -ve	%	LVDD +ve	%	All	%
≤ 300 mg/dl	18	28.57	1	2.70	19	19.00
301-400 mg/dl	37	58.73	17	45.95	54	54.00
401-500 mg/dl	8	12.70	19	51.35	27	27.00
Total	63	100	37	100	100	100

Post Prandial Blood Sugar	LVDD -ve	LVDD +ve	All
N	63	37	100
Mean	331.87	396.24	355.69
Sd	51.49	59.28	62.56
P value Unpaired t Test		0.0000	

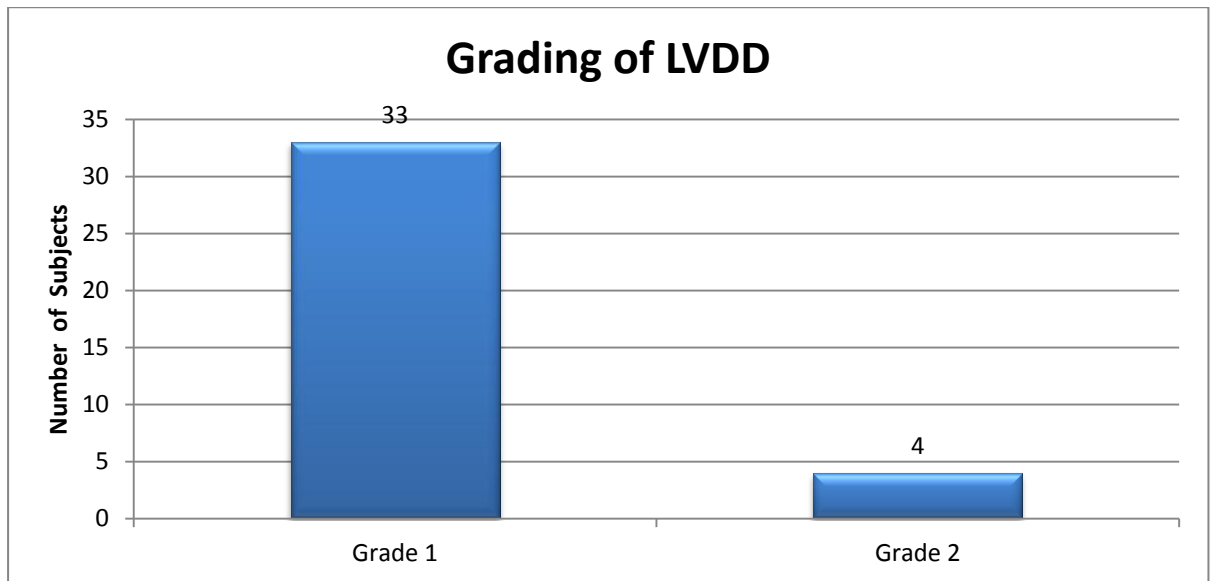
Results

In patients belonging to LVDD negative group, the mean PPBS levels are 331.87 mg/dl. In LVDD positive group, the mean PPBS levels are 396.24 mg/dl. The decreased mean PPBS levels in LVDD negative group compared to the LVDD positive group is statistically significant as the p value is 0.0000 as per unpaired t- test indicating a true difference among study groups.

The mean PPBS levels were meaningfully more in LVDD positive group compared to the LVDD negative group by 64.37 mg/dl. This significant difference of 19% increase in mean PPBS levels in LVDD positive group compared to the LVDD negative group is true and has not occurred by chance.

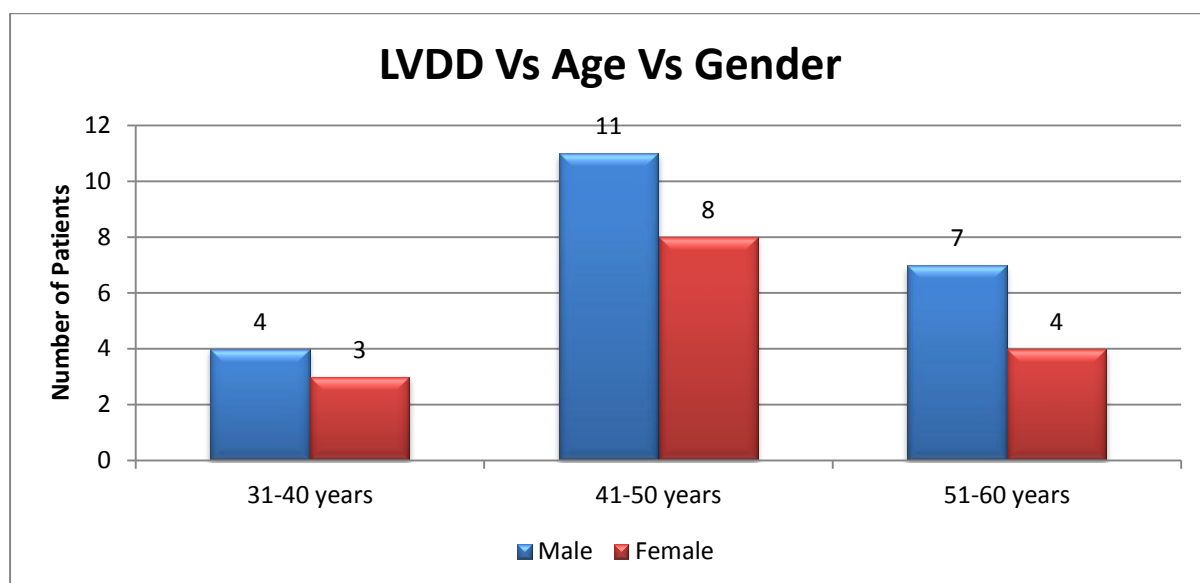
In this study we can safely conclude that mean post prandial blood sugar levels were significantly and consistently higher in LVDD positive group compared to the LVDD negative group. Hence it can be inferred that high PPBS levels are strongly associated with Left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetes mellitus patients.

GRADING OF LVDD



Grading of LVDD	LVDD +ve	%
Grade 1	33	89.19
Grade 2	4	10.81
Total	37	100

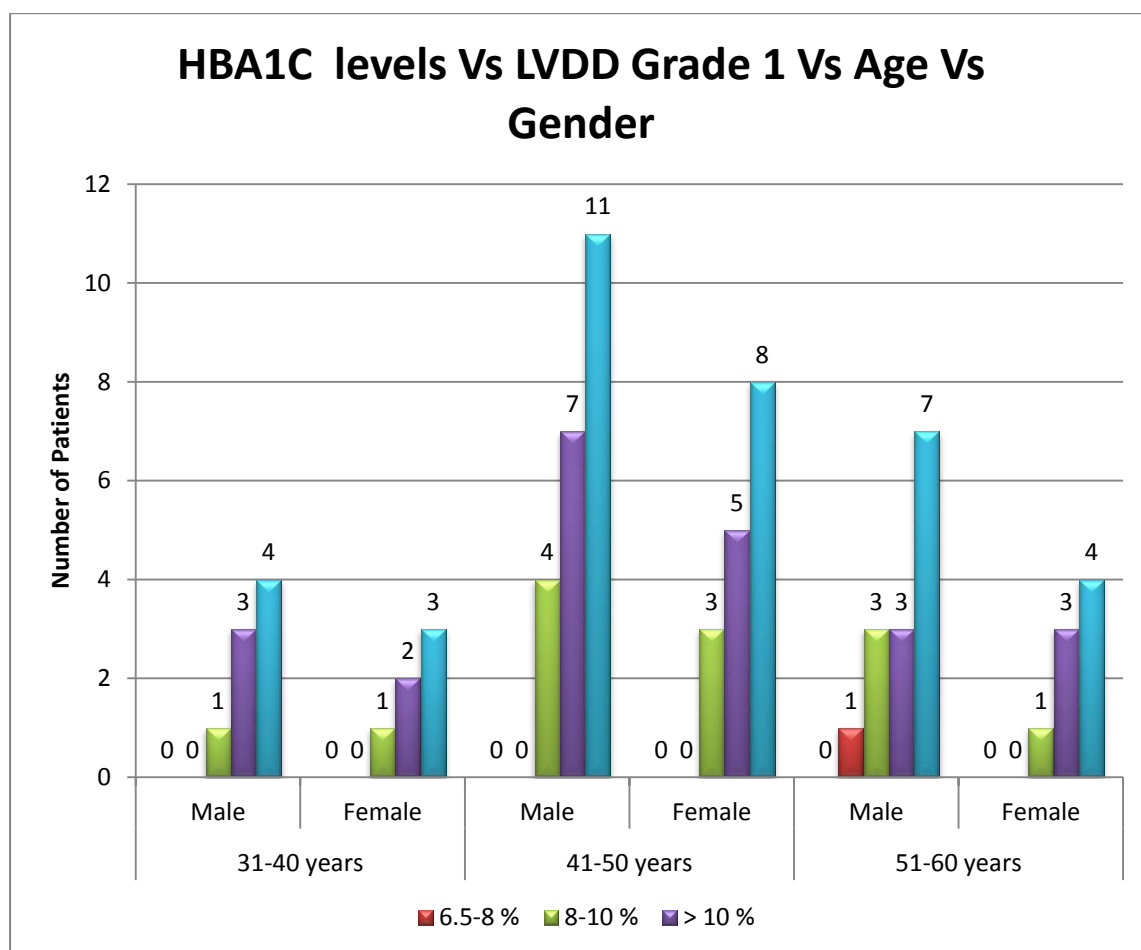
LVDD Vs AGE Vs GENDER



LVDD Vs Age Vs Gender	Male	%	Female	%
31-40 years	4	18.18	3	20.00
41-50 years	11	50.00	8	53.33
51-60 years	7	31.82	4	26.67
Total	22	100	15	100

HBA1C LEVELS Vs LVDD GRADE 1 Vs AGE Vs

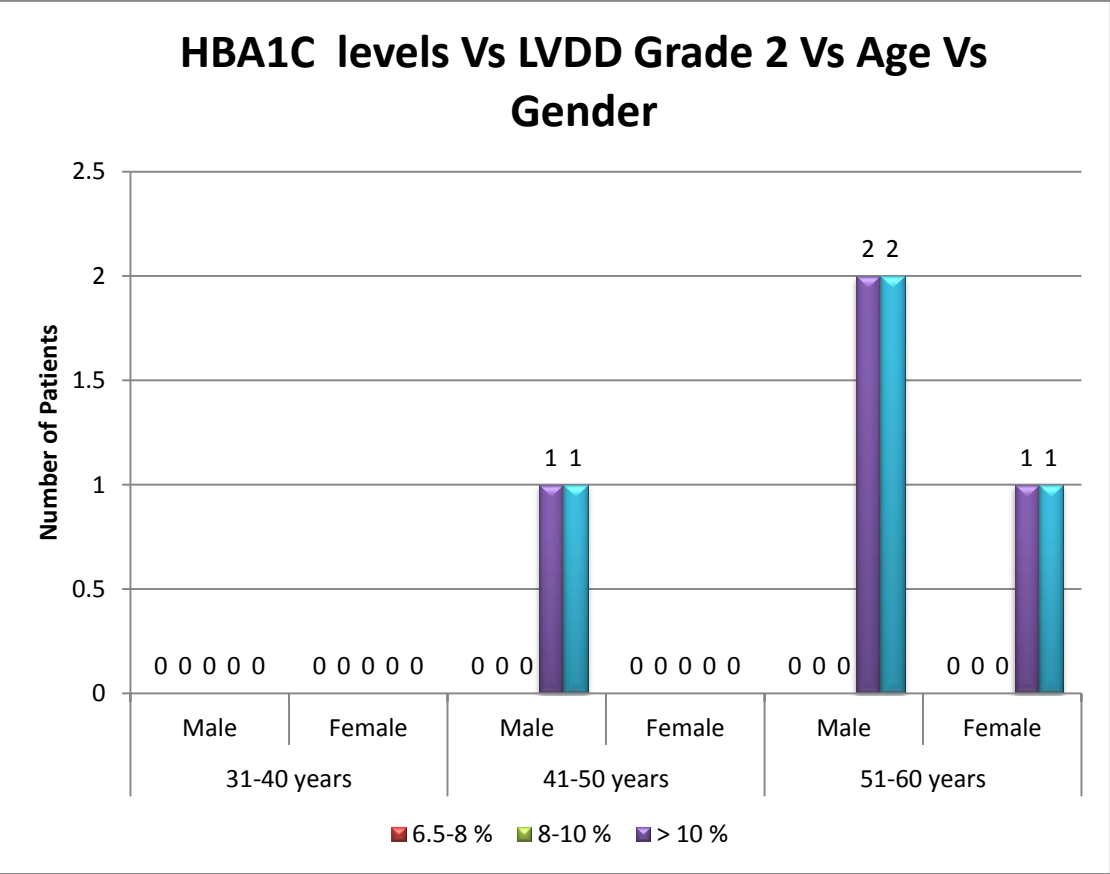
GENDER



HBA1C LEVELS Vs LVDD					
GRADE 1 Vs AGE Vs		6.5-8 %	8-10 %	> 10 %	Total
GENDER					
31-40 years	Male	0	1	3	4
	Female	0	1	2	3
41-50 years	Male	0	4	7	11
	Female	0	3	5	8
51-60 years	Male	1	3	3	7
	Female	0	1	3	4
Total		2	13	22	37

HBA1C LEVELS Vs LVDD GRADE 2 Vs AGE Vs

GENDER



HBA1C LEVELS Vs LVDD GRADE 2 Vs AGE Vs

GENDER

HBA1C levels Vs LVDD Grade 2 Vs Age Vs Gender		6.5-8 %	8-10 %	> 10 %	Total
31-40 years	Male	0	0	0	0
	Female	0	0	0	0
41-50 years	Male	0	0	1	1
	Female	0	0	0	0
51-60 years	Male	0	0	2	2
	Female	0	0	1	1
Total		0	0	4	4

6.DISCUSSION

Our study consists of 100 newly diagnosed , normotensive Type 2 diabetic patients comprising 65(65%) males and 35(35%) females. All studied patients were of age between 30- 60 years. Most of the subjects were between 41-50 years of age . Mean age of the population was 45.23 ± 6.80 years. Diastolic dysfunction was present in 37 (37%) of the cases among them 22 were males, 15 were females . Out of 37 cases of LVDD,89% cases of grade1 LVDD (19 males and 14 females) and 11% cases of grade 2 LVDD (3 males and 1 females) were found. No case of grade 3 LVDD, grade 4 LVDD or systolic dysfunction ($EF < 50\%$) was found in the study. In this study, further, the population with LVDD in 2D echo was compared with the population without LVDD using various parameters like FBS, PPBS,age, HbA1C level,. The mean HbA1C of population with LVDD was found higher ($10.46 \pm 1.58\%$) as compared to population without LVDD ($9.13 \pm 1.25\%$).Correlation was found significant using unpaired t-test ($p\text{-value}=0.0000$).This signifies that higher the HbA1C at the time of diagnosis, higher will be the incidence of LVDD.

The mean FBS of population with LVDD was found high (243.65 ± 36.63) as compared to population without LVDD (212.92 ± 35.84).Correlation was found significant using unpaired t-test ($p\text{-value}=0.0001$).The mean PPBS of population with LVDD was found high (396.24 ± 59.28) as compared to population without LVDD (331.87 ± 51.49).Correlation was found significant

using unpaired t-test (p -value=0.0000). This signifies that higher the FBS & PPBS at the time of diagnosis, higher will be the incidence of LVDD.

Majority of the LVDD negative group patients belonged to the 41-50 years age class interval ($n=34$, 53.97%) with a mean age of 45.08 years. In the LVDD positive group patients, majority belonged to the same age class interval ($n=19$, 51.35%) with a mean age of 45.49 years. The association between the study groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per unpaired t test.

Majority of the LVDD negative group patients belonged to the male gender class interval ($n=33$, 52.38%). In the LVDD positive group patients, majority belonged to the male gender class interval ($n=22$, 59.46%). The association between the study groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per chi squared test.

Abay Kumar Chaudhary et al⁵., in their study, of 100 asymptomatic subjects found the prevalence of diastolic dysfunction in asymptomatic newly diagnosed Type 2 diabetics as 41% [12]. Mean of HbA1C (%) was found higher in group with LVDD (7.67 ± 0.90) as compared to group without LVDD (7.24 ± 0.64). This concludes that HbA1C is strongly associated with presence of LVDD ($p=0.0057$). Mean FBS found higher in LVDD group (189.80 ± 30.90) as compared to LVDD negative group (179 ± 29.80). Age of the patients was very significantly associated with incidence of LVDD ($p=0.0012$), meaning that older the age at the time of diagnosis, higher the incidence of LVDD.

Sanjeev Kumar et al⁽²¹⁾, in their study, of 100 asymptomatic subjects found the prevalence of diastolic dysfunction in asymptomatic newly diagnosed Type 2 diabetics as 42%. Mean of HbA1C (%) was found higher in group with LVDD (7.69 ± 1.01) as compared to group without LVDD (7.26 ± 0.74). This concludes that HbA1C is strongly associated with presence of LVDD ($p=0.0157$). Mean FBS found higher in LVDD group (192.05 ± 29.80) as compared to LVDD negative group (173.67 ± 27.71). Age of the patients was very significantly associated with incidence of LVDD ($p=0.0012$), meaning that older the age at the time of diagnosis, higher the incidence of LVDD.

Compared to other studies, our study significantly correlated with elevated HbA1C and elevated FBS to LVDD, whereas age and gender has no statistical significance.

7.CONCLUSION

- The association between the study groups and age, gender distribution is considered to be not statistically significant.
- Elevated HBA1C levels are strongly associated with Left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetes mellitus patients.
- Elevated FBS, PPBS levels are strongly associated with Left ventricular diastolic dysfunction in newly diagnosed Type 2 diabetes mellitus patients.
- 37% of patients who have HBA1C more than 6.5gm% are associated with left ventricular diastolic dysfunction at the time of diagnosis.
- This correlation of HBA1C and LVDD seems high and significant, and our study results are similar to other Indian studies done elsewhere, where the prevalence is around 40 – 45%.
- So, our study stresses the need to periodically screen asymptomatic diabetic patients for diastolic dysfunction through Doppler echocardiogram.

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PROFORMA

NAME:

AGE:

SEX: 1.M 2.F

ADDRESS:

CONTACT NO:

COMPLAINTS :

PAST H/O DIABETES:

Duration :

HYPERTENSION: 1.Yes 2.No

VALVULAR HEART DISEASE: 1.Yes 2.No

ISCHEMIC HEART DISEASE : 1.Yes 2.No

RENAL FAILURE : 1.Yes 2.No

CONNECTIVE TISSUE DISEASE: 1.Yes 2.No

THYROID DISORDER: 1.Yes 2.No

PERSONAL H/O-

SMOKING : 1. Yes 2. No

ALCOHOL INTAKE: 1. Yes 2. No

VITALS-

BP: PR: RR:

TEMPERATURE:

SYSTEMIC EXAMINATION:

CVS:

RS:

P/A:

CNS:

INVESTIGATIONS:

FBS :

PPBS:

HBA1C:

RFT: UREA

CREATININE

FASTING LIPID PROFILE : T.CHOLESTEROL LDL

HDL TRIGLYCERIDE

URINE: ALBUMIN

SUGAR

ECG :

ECHOCARDIOGRAPHY:

1.E-peak velocity of early mitral flow

2.A- peak velocity of late mitral flow

3.E/A ratio

4.Left atrial size

5.EF

COMMENT:

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

**A STUDY TO CORRELATE HBA1C AND LEFT VENTRICULAR DIASTOLIC
DYSFUNCTION IN NEWLY DIAGNOSED TYPE II DIABETES MELLITUS AT
GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI.**

Place of study: Govt. Stanley medical college, Chennai

I have been informed about
the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the
study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and
even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any
medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:

Witness:

Name and address

Name and address

Signature/thumb impression:
impression

Signature/thumb

Date:

Date:

Investigator Signature and date

INFORMED CONSENT

புதிதாக கண்டுபிடிக்கப்பட்ட நீரிழிவு வகை 2 நோயாளிகளில் எச்.பி.ஏ 1 சி மற்றும் இடது வெண்ட்ரிகிள் விரிவடையும் தன்மை குறைபாடு ஒப்புமைபற்றியஆய்வு.

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்துக்கொண்டேன். ஆய்வில்பங்குஎடுத்தபோது, சாத்தியமான பாயங்கள் மற்றும்பயன்களைபற்றிநான் அறிந்துள்ளேன்.

நான்எந்தவொருவேளையிலும்ஆய்வில்இருந்துதிரும்பமுடியும், அதன்பின்னர், நான்வழக்கம் போல் மருத்துவ சிகிச்சைபெறமுடியும்என்றுபுரிந்துகொள்கிறேன்

நான்ஆய்வில்பங்குஎடுத்துபணம்எதையும்பெறமுடியாதுஎன்றுஅறிந்துள்ளேன். இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்படஇருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்கக்கூடாது. நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்றுதெரியும் நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்றுஉறுதியளிக்கிறேன்.

தன்னார்வளர்

சாட்சி

பெயர்மற்றும்முகவரி

பெயர்மற்றும்முகவரி

கையொப்பம் / விரல்ரேகை:

கையொப்பம் /

விரல்ரேகை:

ஆராய்ச்சியாளராக

கையொப்பம்மற்றும்தேதி

INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Study to correlate HBAIC and left ventricular diastolic dysfunction in newly diagnosed type II Diabetes mellitus.

Principal Investigator : Dr Elangumanan. P

Designation : PG M D (General Medicine)


Department : Department of General Medicine
Stanley Medical College
Chennai -01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 25.03.2015 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.


MEMBER SECRETARY,
IEC, SMC, CHENNAI
MEMBER SECRETARY,
ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE
CHENNAI-600 001.

S.NO	AGE	SEX	HBA1C	FBS	PPBS	HBA1c			LV diastolic dysfunction	GRADING OF LVDD
						6.5-8	8_10	>10	yes/ no	
1	52	F	8.1	201	302		y		no	
2	44	M	8.8	232	389		y		yes	1
3	48	M	11.7	243	401			y	yes	1
4	39	M	8.4	194	308		y		no	
5	41	F	9.6	206	326		y		yes	1
6	58	M	9.4	208	351		y		yes	1
7	38	F	7.4	185	288	y			no	
8	45	M	9.6	241	352		y		yes	1
9	46	F	8.8	198	316		y		no	
10	36	F	8.4	183	279		y		no	
11	49	M	10.2	225	401			y	no	
12	35	M	7.5	171	285	y			no	
13	54	M	10.8	221	359			y	no	
14	48	M	7.2	184	309	y			no	
15	48	F	11.5	271	485			y	yes	1
16	49	M	8.4	175	354		y		no	
17	36	M	10.2	205	311			y	no	
18	55	M	10.9	278	433			y	yes	2
19	49	F	8.9	231	396		y		no	
20	52	F	10.3	288	418			y	yes	1
21	38	M	9.2	302	498		y		YES	1
22	38	F	9.5	219	445		y		yes	1
23	47	F	7.2	189	289	y			no	
24	44	M	7.1	175	265	y			no	
25	36	F	13.1	255	403			y	yes	1
26	57	M	9.3	192	278		y		yes	1
27	43	F	10.9	195	349			y	no	
28	43	M	9.4	279	401		y		yes	1
29	47	F	9.3	183	315		y		no	
30	48	M	8.8	192	369		y		no	
31	37	M	13.2	224	448			y	yes	1

32	55	M	10.8	271	359			y	yes	2
33	35	F	8.9	208	378		y		no	
34	55	F	9.2	223	306		y		yes	1
35	49	M	8.7	258	308		y		no	
36	33	M	7.3	165	274	y			no	
37	48	F	8.7	181	319		y		yes	1
38	47	M	8.3	158	278		y		no	
39	42	M	11.7	224	317			y	yes	1
40	35	M	12.9	303	495			y	yes	1
41	58	M	8.8	201	343		y		yes	1
42	44	M	8.1	189	279		y		no	
43	39	F	9.2	178	301		y		no	
44	47	M	11.8	246	328			y	yes	2
45	43	F	8.9	232	305		y		no	
46	45	M	11.3	278	459			y	no	
47	43	M	10.9	266	389			y	no	
48	39	M	9.4	171	275		y		no	
49	47	F	12.1	275	415			y	yes	1
50	47	M	7.5	202	389	y			yes	1
51	55	F	10.9	216	342			y	yes	1
52	44	M	8.9	184	356		y		no	
53	57	M	9.3	188	371		y		yes	1
54	42	F	10.8	203	298			y	no	
55	43	M	9.2	239	342		y		no	
56	41	M	10.6	224	416			y	no	
57	43	F	9.1	249	402		y		no	
58	47	M	12.2	218	395			y	yes	1
59	34	F	11.3	285	467			y	no	
60	54	M	10.2	235	356			y	no	
61	36	M	7.6	185	274	y			no	
62	46	M	10.4	216	295			y	no	
63	47	M	10.8	242	432			y	yes	1
64	42	M	11.5	244	419			y	no	

65	55	F	7.1	208	342	y			no	
66	48	M	9.3	255	388		y		yes	1
67	39	F	7.8	204	342	y			no	
68	53	M	8.5	165	302		y		no	
69	39	M	8.9	202	298		y		no	
70	46	F	8.7	193	314		y		no	
71	47	M	9.3	186	376		y		no	
72	48	F	11.2	208	418			y	yes	1
73	59	F	10.4	236	453			y	yes	2
74	48	M	8.5	213	342		y		no	
75	46	M	8.9	198	281		y		no	
76	46	F	8.3	209	301		y		no	
77	57	F	9.1	287	342		y		no	
78	55	M	7.8	234	309	y			yes	1
79	45	F	11.1	298	482			y	yes	1
80	39	F	8.3	254	321		y		no	
81	47	M	7.3	231	287	y			no	
82	48	F	10.5	267	408			y	yes	1
83	34	M	9.6	231	365		y		no	
84	43	F	8.9	248	325		y		no	
85	36	F	8.6	178	249		y		no	
86	58	F	10.6	217	314			y	no	
87	49	M	9.2	296	414		y		yes	1
88	46	F	10.7	278	456			y	no	
89	34	F	12.5	269	427			y	no	
90	38	M	13.4	304	498			y	yes	1
91	35	F	12.3	287	463			y	yes	1
92	55	F	8.9	213	356		y		no	
93	56	M	9.1	168	301		y		no	
94	48	F	8.7	202	389		y		yes	1
95	42	F	8.5	193	259		y		no	
96	39	M	10.3	326	362			y	no	
97	44	F	8.9	252	309		y		no	

[illegible]

MASTERCHART ABBREVIATION

M-MALE

F-FEMALE

FBS-FASTING BLOOD SUGAR

PPBS-POSTPRANDIAL BLOOD SUGAR

HBA1C-GLYCOSYLATED HEMOGLOBIN

LVDD-LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Y-YES

N-NO