DISSERTATION

ON

"THE COMPARATIVE STUDY OF EFFECT OF SITAGLIPTIN AND VILDAGLIPTIN ON GLYCAEMIC CONTROL AND SERUM LIPID LEVEL IN TYPE II DIABETES MELLITUS PATIENTS IN A RURAL TERTIARY CARE HOSPITAL"

Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the regulations

For the award of the degree of

M.D PHARMACOLOGY - BRANCH-VI

CHENNAI MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE

IRUNGALUR, TRICHY- 621 105.

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032.

APRIL-2016

CERTIFICATE

This is to certify that this dissertation entitled **"THE COMPARATIVE STUDY OF EFFECT OF SITAGLIPTIN AND VILDAGLIPTIN ON GLYCAEMIC CONTROL AND SERUM LIPID LEVEL IN TYPE II DIABETES MELLITUS PATIENTS IN A RURAL TERTIARY CARE HOSPITAL"** is a bonafide research work of Dr.Bhuvaneswari. S in partial fulfilment of the requirements for M.D Branch-VI (Pharmacology) Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in APRIL -2016. The period of study was from 2013-2016.

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DECLARATION

I, Dr.S.Bhuvaneswari solemnly declare that the dissertation title **"THE COMPARATIVE STUDY OF EFFECT OF SITAGLIPTIN AND VILDAGLIPTIN ON GLYCAEMIC CONTROL AND SERUM LIPID LEVEL IN TYPE II DIABETES MELLITUS PATIENTS IN A RURAL TERTIARY CARE HOSPITAL"** was done by me at Chennai Medical College Hospital and Research Centre, Irungalur ,Trichy, under the supervision and guidance of my professor and head of the department **Dr.S.Manickavasagam .M.D.,**

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, towards the partial fulfilment of requirement for the award of M.D. Degree (Branch –VI) in Pharmacology.

Place: Irungalur

Trichy.

Date:

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The work done by Dr.S.Bhuvaneswari on titled **"THE COMPARATIVE STUDY OF EFFECT OF SITAGLIPTIN AND VILDAGLIPTIN ON GLYCAEMIC CONTROL AND SERUM LIPID LEVEL IN TYPE II DIABETES MELLITUS PATIENTS IN A RURAL TERTIARY CARE HOSPITAL"** is under my supervision and I assure that this candidate has abide by the rules of the Ethical Committee.

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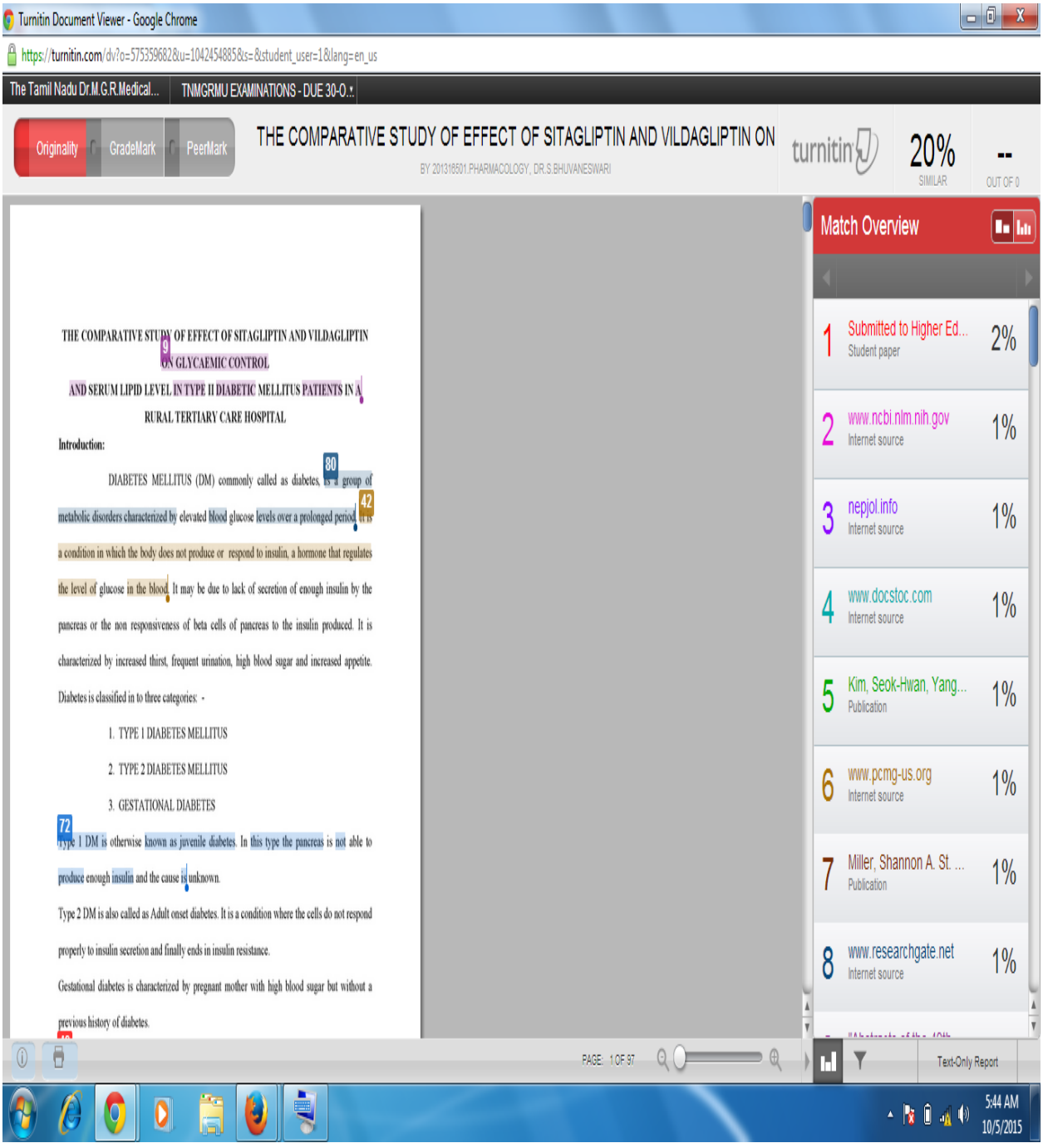
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Introduction:
DIABETES MELLITUS (DM) commonly called as diabetes, is a group of metabolic disorders characterized by elevated blood glucose levels over a prolonged period. It is a condition in which the body does not produce or respond to insulin, a hormone that regulates the level of glucose in the blood. It may be due to lack of secretion of enough insulin by the pancreas or the non responsiveness of beta cells of pancreas to the insulin produced. It is characterized by increased thirst, frequent urination, high blood sugar and increased appetite.
Diabetes is classified in to three categories: -
1. TYPE 1 DIABETES MELLITUS
2. TYPE 2 DIABETES MELLITUS
3. GESTATIONAL DIABETES
Type 1 DM is otherwise known as juvenile diabetes. In this type the pancreas is not able to produce enough insulin and the cause is unknown.
Type 2 DM is also called as Adult onset diabetes. It is a condition where the cells do not respond properly to insulin secretion and finally ends in insulin resistance.
Gestational diabetes is characterized by pregnant mother with high blood sugar but without a previous history of diabetes.
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CONTENTS

ABBREVIATIONS

1. DM-Diabetes mellitus
2. MODY-Maturity onset diabetes mellitus of the young
3. SU-Sulfonylurea
4. TZD-Thiazolidinediones
5. GLP-1- Glucagon like peptide – 1
6. GLP-1R-Glucagon like peptide – 1 receptor
7. DPP- 4i- Dipeptidyl peptidase 4 inhibitors
8. SGLT- 2-Sodium Glucose co –transport – 2
9. GIP-Glucose dependent insulinotropic polypeptide
10. HBA1c -Glycosylated haemoglobin
11. OHA-Oral hypoglycaemic agent
12. FPG-Fasting plasma glucose
13. PPG-Post prandial glucose
14. BSA- Bovine serum albumin
15. AIR -acute insulin response
16. OGTT-Oral glucose tolerance test
17. LDL-c - Low density lipoprotein cholesterol
18. HDL-c - High density lipoprotein cholesterol
19. TGL-Triglyceride
20. TC-Total cholesterol
21. AMPK-Activated protein kinase
22. OAT-Organic anion transporter
23. OATP-Organic anion transporting polypeptide
24. CrCl- Creatinine clearance
25. ESRD-End-Stage renal disease
26. FDA-Food and drug administration
27. GOD/POD-Glucose oxidase peroxidase
28. SMBG-Self Monitoring blood glucose
29. GIPRS- Glucose dependent insulinotropic peptide receptors
30. ADA- American diabetes association

INTRODUCTION

Diabetes Mellitus (DM) commonly called as diabetes, is a group of metabolic disorders characterized by elevated blood sugar levels over a prolonged period. It is a condition in which the body does not produce or respond to insulin, a hormone that regulates the level of glucose in the blood. It may be due to lack of secretion of enough insulin by the pancreas or the non-responsiveness of beta cells of pancreas to the insulin produced. It is characterized by increased thirst, frequent urination, high blood sugar and increased appetite. Diabetes is classified in to various categories, among which the most common categories are, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus and Gestational Diabetes.

Type 1 DM is otherwise known as juvenile diabetes. In this type the pancreas is not able to produce enough insulin and the cause is unknown. Type 2 DM is also called as Adult onset diabetes. It is a condition where the cells do not respond properly to insulin secretion and finally ends in insulin resistance. Gestational diabetes is characterized by pregnant mother with high blood sugar but without a previous history of diabetes.

Other specific types of DM are genetic defect of beta cell dysfunction-Maturity Onset Diabetes mellitus of the Young (MODY 1 to 6) and genetic defect in insulin action.(Type A insulin resistance) [1]

PREVALANCE:

Type 1 DM accounts for 5 to 10% and Type 2 DM accounts for 90 to 95% of diabetic population. The incidence of both the types are rising all over the world .Type 2 DM is increasing rapidly and has become a global epidemic. It depends on the lifestyle of the individual and social changes among the population. It is estimated that in the year 2000, 171 million people had diabetes and this is expected to be double by 2030. It may rise up to addition of 79.4 million in India, 42.3 million in China and in United States (US) it will be about 30.3 million. The rough estimation showed that prevalence is one quarter in rural population when compared with urban population. The national survey conducted across the metropolitan cities of India (YEAR) reported that percentage of people with diabetes is very less in north India compared to cities in south India (13.5% in Chennai, 16.6% in Hyderabad and 12.4% in Bangalore). Rising prevalence of Type 2 DM is mainly because of consumption of foods with high lipid and glucose content. In India, people got adopted to sedentary life style which leads to lack of exercise and weight gain. These factors lead to increase in the prevalence rate of diabetes in south India. [2]

Uncontrolled Type 2 DM plays an important role in the development of pathophysiological events that may lead to micro vascular and macro vascular complications. They are impaired insulin secretion, peripheral insulin resistance and excessive hepatic glucose production. It provokes a cascade of changes in endothelial, mesangial, smooth muscle and macrophage cell function in a manner which results in micro and macro vascular diseases. Microvascular changes are retinopathy,

neuropathy and nephropathy. Macro vascular manifestations are atherosclerosis leading to cardiovascular diseases and metabolic syndrome due to changes in the carbohydrate and lipid metabolism. To avoid these complications and to keep the plasma glucose under control, many newer drugs have been invented. About seven classes of oral hypoglycemic agents are currently in use in the management of Type 2 DM. They are Sulfonylureas, Meglitinide/ Phenylalanine analogues, Biguanides, Thiazolidinediones, Alpha-glucosidase inhibitors, Glucagon – like peptide – 1 receptor agonist, DPP-4 Inhibitor, SGLT2 Inhibitor and Amylin analogue.

Many oral hypoglycemic agents after repeated usage, they lose their efficacy resulting in inadequate glycemic control and adverse effects. So, there is need to invent newer drugs in the management of Type 2 DM to overcome the limitations associated with other medications. It has been found that there is reduced response produced by incretin hormones in diabetes and this defect results in the discovery of incretin based therapy in 2005. Two types of drugs are available in the clinical practice such as GLP- 1 agonist and DPP- 4 Inhibitors, Dipeptidyl peptidase 4 inhibitors (DPP-4i) have got a good therapeutic approach in the treatment of diabetes. So far, six DPP- 4i have been invented and all are available in the market for clinical practice. They are – Sitagliptin, Vildagliptin, Alogliptin, Saxagliptin, Linagliptin and Tenegliptin. The novel oral antidiabetic drugs are Dopamine D2 agonist approved by FDA in 2009 and Sodium Glucose Co Transport 2 (SGLT- 2) inhibitor. SGLT- 2 inhibitor is under trial and tolerability and safety of this drug is yet to be established.

DPP- 4 inhibitors act by enhancing the levels of active incretin hormones and thereby it reduces the plasma glucose level. Eating stimulates the secretion of multiple gastrointestinal hormones that regulates the gut motility, secretion of gastric acid, pancreatic enzymes, gall bladder contractions and nutrient absorption. One among them is incretin hormones. They are of two types such as Glucagon like peptide (GLP - 1) and Glucose dependent insulinotropic polypeptide (GIP). Both are released from the intestinal cells following meal ingestion. The GLP -1 stimulates insulin secretion from the pancreatic beta cells and GIP inhibits the glucagon secretion from the pancreatic alpha cells. These incretin hormones are inactivated by DPP - 4 enzyme as soon as they are released from the intestinal cells. DPP -4 enzyme is an aminopeptidase expressed in many tissues such as liver, lung, kidney, intestinal brush border membranes, lymphocytes and endothelial cells. Many gastrointestinal hormones, neuropeptides and cytokines are substrates of DPP -4 enzyme.

DPP – 4 inhibitors reduces serum DPP – 4 activity by more than 80 % thereby it reduces the glycosylated hemoglobin HBA1c, fasting plasma glucose and postprandial plasma glucose levels. It has got a very good safety and efficacy profile in the treatment of Type 2 DM. About six DPP – 4 inhibitors are available in the market for the treatment of Type 2 DM. Sitagliptin was the first drug discovered and approved by USA FDA in October 2006 and European Union in March 2007. Vildagliptin a selective DPP -4 inhibitor was invented and approved in February 2007, saxagliptin in 2009 and alogliptin in 2010. These are found to be associated with less hypoglycemic symptoms, weight gain, gastrointestinal distress and produces a significant reduction in HBA1c and fasting and postprandial plasma glucose levels [3].

Sitagliptin, a first DPP -4i has been found to be very effective Oral Hypoglycemic Agent (OHA) in Type 2 DM patients. It is available orally and can be used as monotherapy or as a combined therapy with other oral hypoglycemic agents. It can be used as an adjuvant therapy with insulin. It significantly reduces HBA1c, fasting and postprandial glucose levels . When sitagliptin given as an adjuvant therapy with sulfonylureas and Biguanides, it decreases the side effects produced by them [3]. With insulin, it improves the metabolic control and lipid profile by reducing low density lipoprotein cholesterol level and thereby it reduces the insulin need [3]. In cardiac patients with coronary artery disease and Type 2 DM, it improves the cardiac function, coronary artery perfusion and prevents the complications [4]. Many clinical trials showed that sitagliptin significantly reduces HBA1c, fasting plasma glucose and postprandial glucose levels when administered as monotherapy or combined therapy with other oral hypoglycemic agents .

Vildagliptin, a second selective DPP – 4i was approved by US FDA in February 2007. It is an orally active, effective, potent drug and well tolerated by patients with Type 2 DM. When administered orally, it inhibits DPP – 4 activity at different doses and has got quick onset of action. It improves the beta cell function on the basis of pharmacodynamics modelling and the sensitivity of alpha cells to glucose for both suppressive as well as stimulatory effect. It significantly reduces HBA1c, fasting plasma glucose and postprandial glucose levels. It has less hypoglycemic symptoms and weight neutralizing property when administered as monotherapy or add on therapy with other oral hypoglycemic agents. It inhibits the triglyceride absorption from the gut and thereby it reduces the low density lipoprotein cholesterol level. It

does not affect the gastric emptying and has got good gastrointestinal safety profile [5]. Compared with sitagliptin Long term trials have proved that Vildagliptin to be an effective, safe and well tolerable drug in elderly patients with Type 2 DM when given along with other oral hypoglycemic agents [5].

The advantages of DPP- 4 inhibitors in Type 2 DM patients are, insulin release is glucose dependent, suppress glucagon release, improves beta cell health and retard progression of beta cell failure, neutralizes body weight, mostly single daily dose, well tolerated with few side effects, no serious toxicity and no drug interactions expect with Saxagliptin [6].

Few studies showed that sitagliptin significantly reduces the lipid profile (Abdul Hussein et al 2011, Tremblay et al 2011, Akira Kubota et al 20l2). There is a controversial study demonstrated that there was no significant difference in the lipid profile after treatment with sitagliptin (Hidekatsu yanai et al 2012) and Vildagliptin, reduces the triglycerides absorption from the gut there by it neutralizes the weight in type 2 diabetes mellitus patients.

Recently studies are ongoing to evaluate the effect of DPP- 4 inhibitors in preventing the cardiovascular complications in type 2 DM patients. There are some limited and controversial studies available regarding the effect of sitagliptin and vildagliptin on lipid profile, so this study is structured to evaluate the comparative effect of both the drugs on glycemic control and lipid profile in type 2 DM patients.

AIMS AND OBJECTIVES:

The aim of this study is to evaluate the effect of sitagliptin and vildagliptin on glycemic control (fasting blood sugar ,postprandial blood sugar,HbA1c) in type 2 diabetes mellitus patients with hyperglycemia not controlled by other therapies and also to evaluate the effect of both the drugs on lipid profile in these patients.

REVIEW LITERATURE

Diabetes mellitus (DM) is a major health problem, which results in hyperglycemia due to failure of pancreas to secrete enough insulin or the body cells not responding to the insulin secreted. Diabetes, when not treated properly leads to many complications. Long term complications are cardiovascular disease, cerebro vascular accidents, chronic renal failure, ulcer foot and blindness. Type I DM accounts for 5% to 10% and Type II accounts for 90 to 95% of all cases of diabetes mellitus. The prevalence of type II diabetes mellitus is increasing day by day.

There are various types of diabetes mellitus based on the etiology. Etiological classification of diabetes and other specific causes are as: Type 1 DM such as, Beta cell destruction usually leading to absolute insulin deficiency, Autoimmune and Idiopathic. In Type II DM there is predominately insulin resistance. In Gestational diabetes mellitus (GDM) there is glucose intolerance developing or recognized during pregnancy. Other specific types of diabetes are, Genetic defects of beta cell dysfunction; eg Mody 1 to 6, Genetic defects in insulin action (eg) Type A insulin resistance, Disease of exocrine pancreas (eg) fibro calculus pancreatopahty, Endocrinopathies (eg) acromegaly & cushings, Drugs or chemical induced (eg) glucocorticoids, Infections (eg) congenital rubella, Uncommon forms of immune mediated diabetes, (eg) stiff man syndrome, Other genetic syndromes [1].

AETIOPATHOGENESIS OF TYPE 1 DM:

Type I diabetes is a slowly progressive T cell – mediated autoimmune disease. It has a high degree of prevalence in certain populations. It occur in subjects below 25 years though the age is exempt. Genetic autoimmunity play a determining role in the etiologic of type 1 DM. The pathophysiological picture in the pre-diabetic pancreas in type I diabetes is characterized by Insulitis Infiltration of the islets with mononuclear cells containing activated macrophages, helper cytotoxic and suppressor T lymphocytes, Natural killer cells and B lymphocytes. Other features are striking B cell specificity of the destructive process, with the glucagon and other hormone secreting cells in the islet invariably remains intact.

The Genetic factors involved in DM are twin studies, histocompatibility antigen and insulin gene. In the twin studies; about 10% of type I DM subjects have a sibling or parent with the disease. Studies of monozytic twins have established about 30 -50% concordance for type I DM among identical twins if one of them develops type 1 DM the co – twin has a 30 to 50% chance of developing the disease. Purely genetic disease will be associated with a 100% concordance in monozygotic twins, Evidences of genetic factors in the causation of type 1 DM come from vicious animals, human twin and family studies.

In the genetic factor of histocompatibility antigen, the concordance of type 1 DM in genetically identical twins is 40-60% indicating a significant genetic component. The major genetic risk is conferred by HLA Class II genes encoding HLA-DR and HLA-DQ. Insulin gene is located in the short aim of chromosome 11. The changes in the nucleotide flanking the gene have been reported in type 1 DM.

Immunological factors:

Severed evidences suggest that the hum oral and cell mediated – Auto immune response leads to destruction of beta cells. Demonstration of circulating antibodies (GG1244) to islet – cells, cell radiated abnormalities in type 1 DM patients presenting with " insulitis" - all conforms the autoimmune pathogenic mechanism.

Viruses and toxins (environmental factors):

Mumps, coxsackie B4, retroviruses, rubella, cytomegalovirus, epstien barr virus.

Dietary factory :

Dietary factors may influence the development of type I Diabetes such as consumption of cow's milk during early life may be contribution to environmental factor associated with type 1 DM. Bovine Serum albumin (BSA)n, a major constituent of cow's milk , has been implicated in triggering type 1 diabetes. The bovine serum albumin an antigen may enter in an intact from through the gut of neonates and stimulate an immune response directed against B cells. Another dietary factor linked to the causation of diabetes is the 'nitrosamines' found in smoked and cured meats

Genetic Susceptibility

⬇

Environmental Trigger

(Vines / Toxins)

⬇

Immunological activation

(Autoimmunity)

⬇

Progressive Beta cell destruction

⬇

Type 1 DM

Aetiopathogenesis of type 2 DM:

Aetiopathogenesis type 2 Diabetes is or more complex from type I DM. The role of genetic factors in the etiologic of type 2 DM has been appreciated ever since the recognition of the disease. Type 2 DM is probably homozygous in nature involving triple abnormalities in the genesis of hyperglycaemia, such as impaired pancreatic insulin secretion, peripheral resistance to insulin a chain occurring primarily in liver and muscle and excursive hepatic glucose output.

The hepatic glucose output is the principal factor for fasting hyperglycaemia and the postprandial hyperglycaemia is largely determined by the peripheral glucose utilization (Insulin Resistance)

Insulin Résistance as a Primary defect :

In type 2 DM, excretive production of glucose in the liver and under – utilisation of glucose in skeletal muscle is mainly due to the resistance to the action of insulin. Obesity is the powerful amplifier of the insulin resistance and the primary cause is unclear. Central obesity may have a particularly potent influence on insulin sensitivity in the liver and there by adversely affect hepatic gluconeogenesis and lipid metabolism. Many cross sectional studies have shown that the insulin resistance is the inherited defect that initiates the diabetic event. The hyperglycaemia to insulin resistance occurs in three places such as first phase: Plasma glucose remains normal despite demonstrable insulin resistance because the insulin levels are increased. Second Phase: Insulin resistance tends to worker so that postprandial hyperglycemias develop despite elevated insulin concentration. Third phase: Insulin resistance close not change but declining insulin secretion caused fasting hyperglycaemia.

Because of insulin resistance, the beta cells produce excess insulin. As the resistance progresses the muscle glucose uptake becomes impaired, but the insulin produced is efficient to maintain the hepatic glucose output in the normal range eventually as hyperglycaemia becomes severe the compensatory hyperinsulinemia is no longer adequate to maintain the fasting plasma glucose normal level. The development of fasting and post – prandial hyperglycaemia stimulates the beta cell further. The resultant hyperinsulinemia leads to the down regulation of the receptor number and the post receptor events. This exacerbates the insulin resistance further resulting in chronic hyperglycaemia, which is toxic to the beta-cell and is responsible for the acquired defect of impaired insulin secretion. When the insulin becomes deficient, the 'glucose transporter' system becomes severely impaired and the intracellular enzymatic steps involved in metabolism are depressed.

Impaired pancreatic insulin Secretion. (Impaired beta cell function)

The beta cell dysfunction in diabetes fall into two district types a) The pulsatile insulin delivery is lost even when the glucose is normal, b) The loss of compensatory mechanisms which include increased beta cell mass, Quantitative insulin output and maximum secretary Capacity.

Normally insulin is secreted in a pulsatile fashion and also secreted in response to meals or secretagogues. The pulsatile secretion is called ultradian oscillations. The ultradian pulses of insulin secretion occur every 90 to 120mts and are exaggerated after the ingestion of food besides the ultradian pulsation rapid oscillations of insulin

level occur every 8 to 16mts in the beta cell. These rapid oscillatory insulin pulses are effective in inhibiting hepatic glucose output.

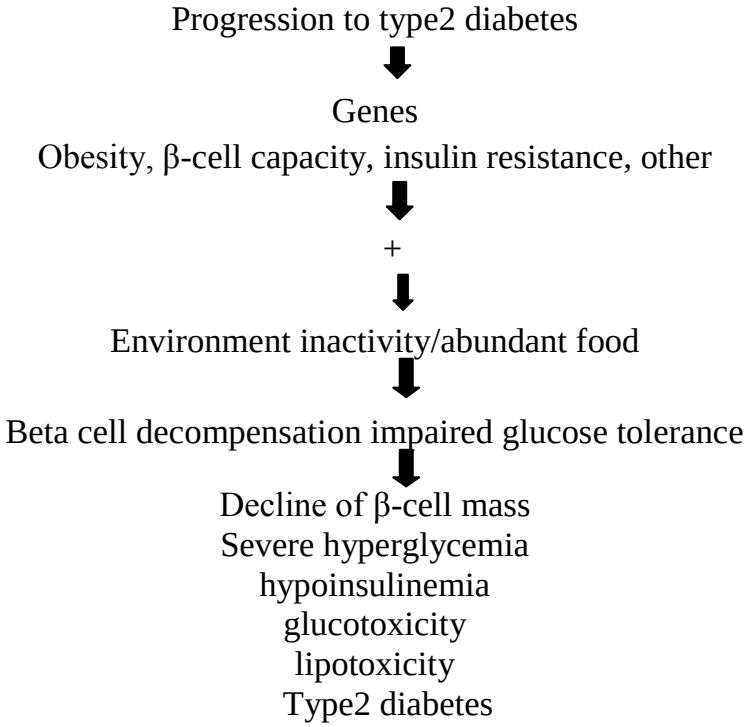
The insulin secretion following a glucose load shows a biphasic response. The first phase acute insulin response (AIR) is due to release of insulin stored in the granules, which suppresses the hepatic glucose output. This occurs within 4 to 5mts and returns to normal within 10mts. The second phase is in response to the ambers rise in the glucose level, which promotes disposal of glucose in peripheral tissue. In type 2 Dm subjects the ultiadian oscillation of insulin delivery is no longer present and the first phase of insulin release is lost.

Beta cell dysfunction

In the early stages of type 2 diabetes, there is only moderate reduction in the total mass of pancreatic islet tissue. The Beta cell mass is mildly reduced especially when obesity is taken into account. Amyloidal deposits are frequently observed in the islets. Morphologicallyislets appear normal and insulitis is never present. Amylin or the islet amyloidal polypeptide is a 37 amino acid protein normally produced by the beta cells and co-packaged with insulin in the secretary granules and co-secreted in the sinusoidal space. For reasons unknown this material tends to get accumulated extracellularly in close contact with beta cells and forms fibrils. Amylin has been reported to lower basal and insulin stimulated glycogen synthetase in the muscles and to inhibit glucose stimulated insulin secretion. These abnormalities of deficient insulin secretion and insulin action are similar to the pathogenic factors of type 2 DM.

Insulin secretary abnormalities in type 2 Diabetes mellitus:

Mainly there are decreased glucose sensing, impaired ability to respond to elevations and reductions during glucose infusion, reduced or absence first phase insulin secretion in response to intravenous glucose administration, reduced or absence early insulin secretary response to oral glucose, alterations in the rapid oscillations of insulin secretion, reduced effect of gastrointestinal hormones in potentiating glucose mediated insulin secretion and inadequate insulin secretion for the magnitude of hyperglycemia [7].



Diagnosis criteria of diabetes:-

Diagnosis of diabetes is based on the glucose level in the body. This is evaluated by doing proper blood investigations such as Random blood sugar level (more than 200gms %) or fasting plasma glucose level (more than 126mgs %). When in doubt; a standard glucose tolerance test is used to diagnose diabetes mellitus. Impaired fasting glucose and impaired glucose tolerance acts as a tool for the diagnosis of diabetes mellitus oral glucose tolerance test is the only diagnostic test for diagnosing impaired glucose tolerance.

OGTT:

This test is done in the morning following 10-16 hrs of overnight fast with unrestricted diet for at least three days. This is done to sensitize the beta cells of pancreas. During the test only, water is given to alleviate the thirst.

Procedure:

Fasting blood sample is collected before giving glucose to the patient. Then 75gms of glucose in 250ml of water is given. Again blood sample is collected 2hrs after the loading dose. Blood sample are collected in tubes containing fluoride- oxalate, to prevent the red blood cells from metabolizing glucose.

WHO guidelines of oral glucose tolerance test for diagnosing diabetes mellitus.

2hrs after the loading dose → $\geq$ 200mg/dl

Impaired glucose tolerance
(2hrs after 75gm glucose load) → 140 to 199 mg/dl

Normal Blood glucose value indicating patient is nondiabetic:

Fasting → < 100 mg/dl

2hr after 75gm load → < 140 mg/dl

Diagnostic criteria:

Glucose tolerance is normal when the fasting and the 2hr values are < 100mg and < 140mg respectively. Diabetes is diagnosed when the fasting value is ≥126 mg or 2 hr plasma glucose is ≥200mg. IGT is present when the two –hour value is in the range of 140 to 199mg/dl. IFG is present when the fasting level is ≥100 and ≤ 125mg/dl and the two hour value is ≤ 140mg/dl [1].

Glycosylated Hemoglobin:

Glucose is bound to hemoglobin irreversibly by a continuous slow non-enzymatic process resulting in the formation of glycosylated hemoglobin. The amount of adult hemoglobin that becomes glycosylated to form HbA1C is directly related to average concentration of glucose in the blood. In a normal person about 3 to 6% of Hb is glycosylated. In a diabetic the percentage of HbA1C may double or even triple. It has got the advantage of not influenced by diet, mode of therapy, physical activity. Normal value: Below 6%, Good control: 6% – 7%, Fair control: 7% - 8%, Unsatisfactory control: 8% - 10%, Poor control: above 10% [1].

Goals of therapy in diabetes:

Glycemic control HbA1C < 7.0%, Preprandial capillary plasma glucose 3.9-7.2mmol/L(70-130mg/dl), Peak postprandial capillary plasma glucose 10.0 mmol /L(<180mg/dl), Blood pressure <130/80 mmHg, Lipids: LDL <2.6 mmol /L(<100mg/dl), HDL >1.1 mmol /L (>40mg/dl), Triglycerides <1.7mmol/L(<150mg/dl). [8]

Periodic Assessment for Patients with Diabetes

Self-monitoring of blood glucose (SMBG), HbA1C testing (2-4 times/year), patient education in diabetes management (annual), medical nutrition therapy and education (annual), eye examination (annual), foot examination (1-2 times/year by physician; daily by patient), screening for diabetic nephropathy(annual), blood pressure measurement(quarterly), lipid profile and serum creatinine (estimate GFR) (annual). Other management such as Influenza/pneumococcal immunizations and antiplatelet therapy should be initiated.

Treatment of Diabetes mellitus:-

Non pharmacological Management (Life –style modification) such as education, nutrition and exercise. Diabetic Education such as Diabetic Educator (Nurse , dietician, Pharmacist) to ensure that patient know about diabetic diet, self-monitoring of blood glucose, self-administration of insulin, management of hypoglycemia and management of complications and risk factors modifying agents. Nutrition foot such as Fat 20-35% of total caloric intake, saturated fat <7% of total calories, <200mg/day of dietary cholesterol, two or more servings of fish/week provide ω-3 polyunsaturated fatty acids. Carbohydrate diet should contain 45-65% total caloric intake (low-carbohydrate diets are not recommended), amount and type of carbohydrate are important, sucrose-containing foods may be consumed with adjustments in insulin dose. Protein intake must be 10-35% of total caloric intake (high-protein diets are not recommended), fiber-containing foods may reduce postprandial glucose excursions and non-nutrient sweeteners.

Exercise has been recommended as an important adjuvant in the management of diabetes mellitus. The exercise response in a diabetic patient largely depends upon the diabetic status, blood sugar level, availability of insulin and state of hydration etc. Benefits of exercise in type 2DM are substantial. It has got beneficial effects on cardiovascular risk factors, blood pressure. Yoga has got specific role in the treatment of diabetes mellitus. This results in an increase in maximal oxygen uptake, decrement of submaximal heart rate and an augmentation of stroke volume. There are studies showing that practice of pranayama in normal healthy individuals produces a significant fall in the fasting blood sugar and postprandial sugar. Yoga in diabetic patient results in metabolic changes such as reduction in lipid profile (decreases LDL-CH and increases HDL – cholesterol).

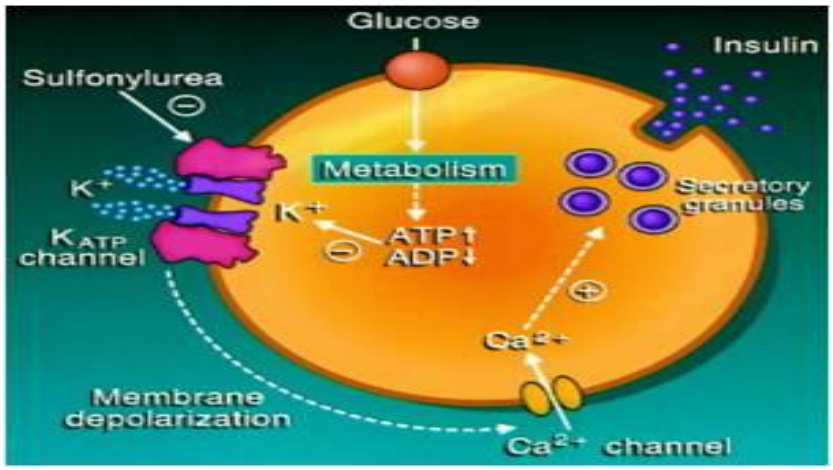
Pharmacological management of Diabetes Mellitus:

Pharmacological management includes oral hypoglycaemic agents and insulin therapy. Oral hypoglycaemic agents are predominantly indicated for the treatment of Type II DM. Oral hypoglycemic agents are defined as the drugs that are used to lower blood glucose levels and are effective orally. Hypoglycemic drugs approved by FDA and available in the market are 1. Sulfonylureas 2. Biguanides 3. Meglitinide Phenylalanine analogues (4) Glucagon like peptide -1(GLP-1) agonist (5) Thiazolidinediones (6) α-Glucosidase inhibitors. Newer drugs have been invented due to certain limitations (weight gain, hypoglycemic, increased cardiovascular motality) and loss of efficacy of already existing drugs. One among them is DPP-4 inhibitors invented in 2005 in Japan. Other novel drugs are Dopamine –D2 receptor agonist and sodium –glucose cotransport-2 (SGLT-2) inhibitor.

Drugs used in this study are Sulfonyurea, Biguanides, DPP-4 inhibitors such as Sitagliptin and Vildagliptin. Sulfonyulureas are otherwise called as insulin secretagoues. These drugs are available in the market since 1970 as First generation – Tolbutamide, Second generation - Glibenclamide, Glipizide, Gliclazide and Glimepride.

Sulfonyl ureas:

The mechanism of Sulfonyl ureas act by increasing the insulin release from the pancreas. Two other actions are reduction of serum glucagon levels and closure of potassium channels in extra pancreatic tissue. Sulfonyl ureas bind to a (140-KD receptor) specific receptor associated with a beta-cell inward rectifier ATP-sensitive potassium channel. After binding to the receptor, it inhibits the efflux of potassium ions through the channel and results in depolarization. As a result of depolarization, voltage –gated calcium channel is opened and calcium is released into the cell. Influx of calcium into the cell stimulates the insulin release from the pancreas [9].



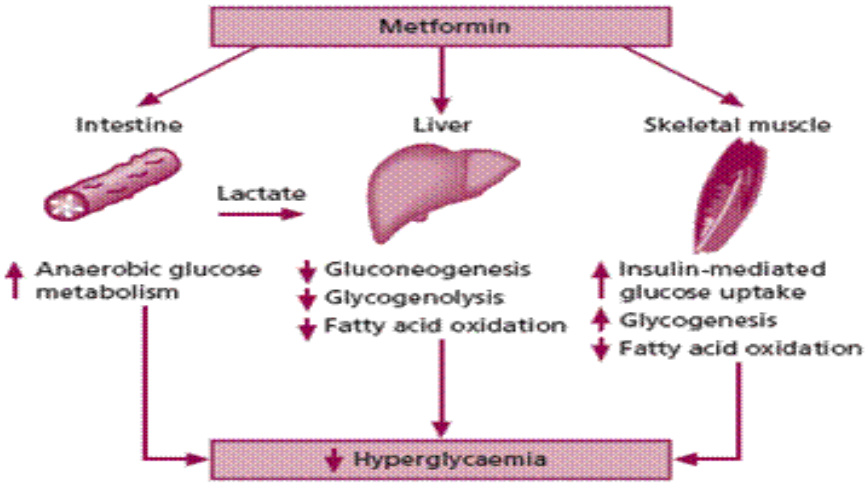
SU are well absorbed orally 90% bound to plasma proteins. The total volume of distribution is about 0.2 to 0.4 L/Kg. They are preliminary metabolized into active metabolites and excreted in urine. Adverse effects are hypoglycemia, weight gain due to insulinaemic action, nausea, vomiting, flatulence, diarrhoea or constipation, headache and parestherias are generally mild and infrequent. Hypersensitivity reactions such as rashes, photosensitivity, purpura, transient leucopenia, rarely agranulocytosis may occur. Flushing and disulfirm – like reaction after alcohol is reported in individuals consuming sulfonylurea [10]. Drugs such as salicylates, Ketoconazole, sulfonamides, Warfarin, and chloramphenicol enhance action of Sulphonylureas phenobarbitone, phenytoin, rifampicin decrease the action of Sulphonylureas [10].

Biguanides: (Phenformin, Metformin)

Phenformin has been banned in India since 2003, because of higher risk of lactic acidosis. Metformin is available since 1950s.

The metformin mechanism of action is otherwise called as insulin sensitizes. They are used to overcome the insulin resistance. They exert their action on both carbohydrates and lipid metabolism. It is highly effective in obese type 2 DM patients and is also synergistic in combination. The primary effect is to reduce the hepatic glucose production through activation of the enzymes AMP – activated protein kinase (AMPK). This action is responsible for leaving of blood glucose in diabetics. Impairment of renal gluconeogenesis, slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes,

direct stimulation of glycolysis in tissue, increased glucose removal from blood, reduction of plasma glucagon levels and reduced lipogenesis in adipose tissue and enhanced fatty acid oxidation [9].



The plasma t ½ of Metformin is 1-3 hrs. Duration of action is 6 to 8 hrs. It is used as a first line of drug in the management of type 2 diabetes mellitus. The advantages of the drug are Non hypoglycemia, weight loss promoting, has potential to prevented macro vascular as well as micro vascular complications of diabetes, no acceleration of β cell exhaustion /failure in type 2 DM , anti hyperglycemic efficacy (HbA1C reduction by 0.8 to 1.2 %), can be used as mono therapy or combined therapy with other oral hypoglycemic agents when one drug is not adequate. It is used to treat obese patients with type 2 DM, the other uses are dumping syndrome, hyperprolactinaemia, polycystic ovarian disease. It is contraindicated in hypotensive states, heart failure, severe respiratory, hepatic and renal disease.

The Adverse effect are abdominal pain, nausea, bloating, metallic taste, mild diarrhoea. In case of renal failure, it accumulates inside and results in the increased

risk of lactic acidosis. Vitamin B12 deficiency occurs due to interference with its absorption. Cimetidines, Furosemide compete with Metformin excretion and enhance its toxicity.

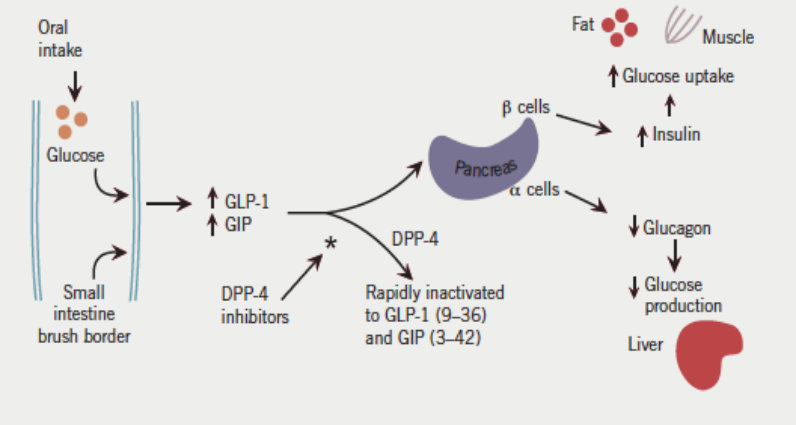
DIPEPTIDYL PEPTIDASE-4 INHIBITOR

The incretin effect of GIP in stimulating insulin secretion is almost lost in T2DM and many studies indicate the existence of a specific defect in GIP action in these patients, may be due to chronic desensitization of GIPRs (Glucose dependent insulinotropic peptide receptors) [11]. The defect in the incretin hormone response leads to the discovery of incretin based therapy. They are GLP-1 Agonist and DPP4i [12].

DPP4 inhibitors are proved to have good therapeutic effect in the treatment of type2 DM. They act by enhancing the action of incretin hormones.It inhibits the inactivation of incretin hormones by DPP4 enzyme. Incretins seems to play a major role in the regulation of glucose metabolism in healthy subjects. There are six DPP-4 inhibitors available in the market. They are sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin and teneligliptin.

Sitagliptin was the first of the DPP-4i to be approved by the US Food and Drug Administration in 2006. This was followed by the approval of vildagliptin in February 2007. Recently, saxagliptin in 2009 and alogliptin in 2010 (presently only in Japan). Compounds such as sitagliptin (β-amino acid based) and vildagliptin which are nitrile containing inhibitors [3].

PATHOGENESIS AND PATHOPHYSIOLOGY OF TYPE 2 DIABETES MELLITUS:



Gastrointestinal hormones are hormones that are secreted immediately following a meal. These hormones regulate the gut motility, gastric acid secretion, pancreatic enzymes, contraction of gall bladder and absorption of nutrients. One among them is incretin hormones. Following a meal there is an increase in the level of glucose, which stimulates the release of incretin hormones. There are two incretin hormones secreted in the body. They are glucose dependent insulinotropic polypeptide (GIP) and Glucagon like peptide – 1 (GLP-1). GIP is secreted first, and it has got potent insulinotropic action. It is a 42 – amino acid hormone produced in duodenal and jejunal endocrine K cells in the proximal small bowel. GLP – 1 was produced second following cloning of the cDNA's and genes encoding proglucagon. The GIP receptors are present on islet α and β cells and in peripheral tissues including central nervous system heart, kidney, lung and gastrointestinal tract [13].

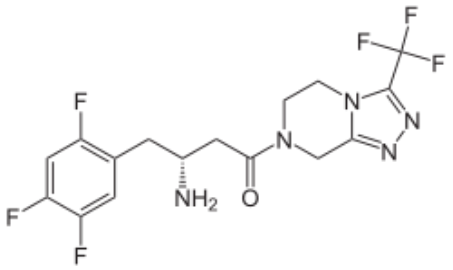
When these hormones are released, the incretin receptor present on the β cells are activated resulting in the rapid increase of insulin level by process called exocytosis. GLP – 1 acts on the pancreatic β cells and induces the secretion of insulin and reduces the secretion of glucagon from the pancreatic α – cells. GLP – 1 improves the β – cell function and delays gastric emptying. It promotes glucose disposal through neural mechanism which contribute to the control of glucoregulation. The action of GLP – 1 and GIP are affected by enzymatic inactivation due to dipeptidyl peptidase 4 enzyme.

DPP – 4 enzyme is an aminopeptidase with a membrane spanning cell – surface. It is present in many tissues such as liver, lung, kidney, intestinal blush borders membranes, lymphocytes and endothelial cells. The DPP – 4 enzyme is cleaved from its anchored – membrane at the extracellular domain and it retains its enzymatic activity while circulating in the plasma. DPP – 4 cleaves mainly peptides with proline or alanine residue present in the second position of amino terminal. Neuropeptides, cytokines, chemokines are substrates of DPP-4 enzyme. GLP – 1 and GIP are one among of them [14].

It has been discovered that there is a defective response of incretin hormones leading increase in glucose level in to type 2 Diabetes mellitus. The incretin effect of GIP hormone is lost in Type 2DM, mainly due to chronic desensitization of GIPRS [15]. Hence the results in the development of newer therapy called incretin based therapy. There are two class of drugs involved in Incretin base therapy known as GLP – 1 agonist and DPP – 4 inhibitors. DPP – 4 inhibitors inhibit the action of DPP-4 enzymes, which degrades the circulating GLP – 1. DPP – 4 inhibitors was first approved by FDA in 2005 in Japan. They reduce 80% of the DPP – 4 enzyme activity,

within 24 hr of administration. They have established a new therapeutic approach in the treatment of Type 2 diabetes mellitus. Currently available DPP – 4 inhibtors are Sitagliptin, Vildagliptin, saxagliptin, alopgliptin, linagliptin and tenegliptin. DPP- 4 inhibitory action increases the circulating levels of GLP – 1 and GIP three times higher than the normal thereby it increases the secretion of insulin from the pancreatic β cells and decreases the secretion of glucagon from the panereatic α – cells.

Sitagliptin phosphate:



Pharmacokinetics:

Sitagliptin (Sitagliptin phosphate) , β – amino acid based compound was the first DPP – 4 inhibitor invented in 2006. The absorption of Sitagliptin is rapid and oral bio availability is about 87% [16] . The inhibitory action starts immediately within 5mts following oral administration. The total volume of distribution is about 198L which is higher than the total body water. These inhibitors have very low plasma protein binding effect and it is about 38% [17]. Sitagliptin doesn't undergo proper metabolism. They are excreted as parent compound (About 80%) and the rest is metabolised via cytochrome CYP3A4 and CYP2C8. Active transport such as organic anion transporter (OAT) – 3, organic anion transporting polypeptide (OATP) – 4 CI and PGP

transporters in the proximal tubule are responsible for the excretion of 30% of the compound [18]. It has got good inhibitory effect and forms non – covalent interactions with residues in the catalytic site [19]. Sitagliptin, have no specific drug interactions. They are neither enzyme inducers or inhibitors [20].

Safety and efficacy :

Sitagliptin has got better safety and efficacy when compared with other oral hypoglycalmic agents.it significantly reduces fasting plasma fasting glucose level, postprandial plasma glucose level and glycolsylated haemoglobin (Hba1c)in type 2DMpatients .with a dose 100mgonce daily. Sitagliptin can be used with dose adjustment in type 2DM patients with renal insufficiency, based on the creatinine clearance .It can be used without adjusting the dose in mild renal insufficiency [creatinine clearance (CrCl) 50–80 ml/min] In moderate (CrCl 30–50 ml/min) or severe renal insufficiency/ end-stage renal disease (ESRD) (CrCl<30 ml/min) , the dose is adjusted to 50 and 75%, respectively [21]. There is no need for dose alteration in hepatic insufficiency patients . there is no significant alteration in the enzyme levels when treated with sitagliptin in type 2DM patient with hepatic impairment [22]. It does not cross the blood brain barrier but crosses the placenta freely so, they are not indicated during the pregnancy and lactation period [17].

Adverse Effects:

Naropharyngitis, urinary tract infections, pancreatitis, head ache, allergic reactions such as angioedema and exfoliative dermatological reactions.

Contraindications:

Acute pancreatitis, pancreatic cancer [23].

Trials with Sitagliptin:

Monotherapy:

Many trials have been done with sitagliptin as a monotherapy in type 2 DM patients.In a study done by Ascher, after 24 weeks therapy with sitagliptin 100 and 200 mg,it has reduced FPG,PPG and HBA1C levels significantly ($p<0.001$) when compared with placebo [24]. In other study organized by Raz and groups, sitagliptin 100mg and 200mg once daily with the study period of 18 weeks,it significantly showed decrease in HBA1C of in patients with 100mg and 200mg respectively. When compared with placebo with significant($p<0.001$).There was less hypoglycaemic symptoms recorded compared to placebo and weight was maintained neutrally with the patients treated with sitagliptin. In this study DPP-4 activity is inhibited by >80% with the 2-fold rise in active GLP-1 levels [25]. Type 2 DM with coronary artery disease, when treated with sitagliptin, it was found sitagliptin improves their heart function and coronary artery perfusion, which was confirmed and evaluated by doing echo-debutamin test [26]. Recently, in a study done in metabolic syndrome patients with type 2 DM, it has showed that sitagliptin minimally reduces the blood pressure (both systolic and diastolic) during the study period [27].

Combined therapy:

In a study done in 353 patients with uncontrolled hyperglycemia with pioglitazone, after 24 weeks of treatment with an add on therapy showed a very good reduction in HBA1C of 0.7% ($p<0.01$) and FPG of 17.7mg/dl ($p<0.001$) with low hypoglycaemic symptoms [28]. A study conducted by ottavio and colleagues, 31 insulin treated patients with inadequate glucose level was treated with sitagliptin for a period of 21 weeks.

After 21 weeks there was a significant reduction in fasting plasma glucose, PPG, HBA1C and it reduces the daily insulin requirement and improved the metabolic control by reducing the low density cholesterol level [29]. Cherbonnel conducted a study with 701 patient who had inadequate glycaemic control with metformin. Sitagliptin 100mg once daily was given to the patients and fasting glucose level, postprandial glucose level and HBA1C was evaluated after a period of 12 weeks. It was found that sitagliptin has reduced HBA1C, FPG and PPG level significantly and achieved the ADA glycaemic goal of HBA1C of <7% when compared with placebo treated patients [30].

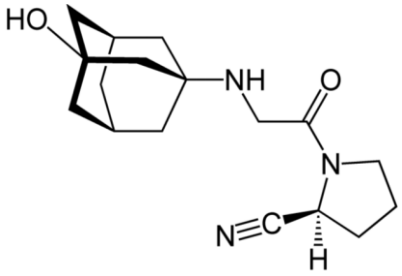
In a study organized by Nauck and colleagues, after 52 weeks therapy with sitagliptin 100mg once daily along with Glipizide 20mg once daily, it was found that sitagliptin significantly achieved HBA1C reduction of 0.67% and weight loss was found in patients with combined therapy when compared to small weight gain in patients treated with glipizide alone [31].

Goldstein demonstrated a study in type 2 DM patient to know about the effect of sitagliptin as a monotherapy and combined therapy with metformin. It was found that all treated groups showed proper reduction in FPG, PPG levels and HBA1C levels compared to placebo and add on therapy is more effective than the monotherapy [32].

VILDAGLIPTIN

Vildagliptin is the second DPP-4 inhibitor approved for human use and is indicated for the control of hyperglycemia in patients with type 2 DM. Vildagliptin produces sustained inhibition of DPP-4 when administered and produces moderate increases in

GLP-1 and GIP circulating levels. Vildagliptin is available as 50 mg and 100 mg tablets with a recommended dose of 50 mg once daily if used in combination with metformin or a TZD and 50 mg once daily if used in combination with a sulfonylurea. Vidagliptin, a second DPP-4 inhibitor was invented and approved by FDA in February 2007. Gliptins show good glycemic control and are well tolerated, particularly with regard to weight change and hypoglycemia.



Vildagliptin ((*S*)-1-[*N*-(3-hydroxy-1-adamantyl) glycyl] pyrrolidine-2-carbonitrile) chemical formula

Pharmacokinetics:

The total volume of distribution of vildagliptin is about 70L which is greater than the total body water [33]. They have very low protein binding capacity (10%). Vildagliptin are well absorbed orally and have good bioavailability of 85% [34] . Vildagliptin is metabolized in the liver via CYP450 isoenzymes into carboxylic acid metabolite (M20.7/LAY 151) and four minor metabolites. 50% of the parent compound is converted into active metabolites and 22% of the dose administered is excreted unchaged in the urine and active transportes are involved in the elimination in addition

to glomerular filtration [35]. Vildagliptin is cleared from the plasma quickly and it has very rapid onset of action [33]. The inhibitory effect is carried out as a two step process, which includes formation of reversible covalent enzyme inhibitor complex. This complex has got slow rate of inhibitor binding and inhibitor dissociation, equilibrates the active and in active forms [36]. By this action, it means that the catalytic activity will be inhibited even after the drug has been cleared from the circulation vildagliptin is a potent inhibitor of DPP-4 enzyme. The concentration required to exert inhibitory action is about 50**%** [33]. It does not have interaction with the substrates of CYP 450 isoenzymes. It has a long dissociation half –life (1hr) from DPP-4, when compared to the other competitive inhibitors [37]. They are neither inhibitors nor induce. There is no pharmacokinetic interaction has been found between viladagliptin and metformin, Piogliltazone or glibenclamide [38].

Monotherapy:

In a study organized to assess the effect of vildagliptin 100mg once daily on glycemic control plasma glucagon and insulin levels, following 4 week treatment, it showed that vildagliptin significantly reduced fasting glucose and postprandial glucose level($P<0.037$ and $P<0.001$ respectively) also HbA1C by 0.38% ($P<0.001$) Vs placebo. There were no symptoms of hypoglycemia during the study period. Glucagon levels were reduced and there was no alteration found in the insulin levels. In this study author finally concluded that vildagliptin improves the metabolic control and by reducing the glucagon levels [39].

One study done in few patients with type 2DM, who were treated with vildagliptin 50mg and 100mg once daily showed an effective decrease in HbA1C 0.43%(P=0.003) and 0.40% (P=0.004) respectively, positive decrease in PPG levels was seen in patients treated with vildagliptin 50mg once daily. Hypoglycemic events among the treated groups are very less and had a weight neutralizing effect throughout the study **[40].**

In a group of patients with T2DM, when treated with vildagliptin 50mg once daily over a period 24 weeks, who was not on prior treatment with other oral hypoglycaemic drugs, it showed an average decrease in HbA1C levels by 1.4%. A study demonstrated that after 4 weeks therapy in drug naïve type 2 DM patients with vildagliptin, it significantly improved the postprandial plasma triglyceride level and apolipo protein (B-48), containing triglyceride –rich lipoprotein particle metabolism. The main mechanism behind is the pharmacological inhibition of GLP-1 receptor (GLP-1R) signaling, reduces, intestinal secretion of triacylglycerol, cholesterol and apolipoprotein B-48 **[41].**

One study done is Japanese people around 291 type 2DM patients, proved that after 12 weeks treatment with vildagliptin 10mg, 25mg, 50mg bd presented, Significant reduction in HbA1C levels by 0.53%, 0.67% and 0.92% respectively (P<0.001 Vs Placebo) with the baseline level of 7.4% **[42].**

In an another study conducted among type 2DM patients treated with vildagliptin with different doses such as 50mg bd and 50mg od over a period of 24 weeks, showed a significant decrease in mean FPG levels in both the groups compared to placebo. Total

of 1135 patients treated with vildagliptin 50mg bd indicated a significant (P<0.05) reduction of mean fasting plasma glucose of 1.08 mmol/L from mean baseline FPG of 10.3 mmol/L after 24 weeks therapy [43].

A double blind randomized trial study was done in type 2 DM patients (N=786 with baseline HbA1C 8.7%) to compare the efficacy of vildagliptin with **rosiglitazone** 8 mg once daily.

Vildaglipting 100mg once daily was given over a 24 week period. After 24 week therapy, it has been noticed that vildagliptin significantly decreased HbA1C levels from the baseline and proved that vildagliptin is not inferior to rosiglitazone. Some patient treated with rosiglitazone showed side effects such as oedema and increase in body weight whereas such complaints were not reported by patient treated with vildagliptin [44].

Combined therapy:

In a randomized study done in 592 type 2 DM patients with uncontrolled hyperglycemia, who were treated with pioglitazone 30mg once daily (groupI), vildagliptin 100mg once daily (Group II), vildagliptin 100mg once daily plus pioglitazone 30mg once daily, (Group III), showed that group III patients treated with (vildagliptin 100mg once daily plus pioglitazone 30mg once daily) had satistically significant reduction in HbA1C levels. Compared to patients treated with pioglitazone alone (1.9% Vs 1.4% P<0.001) [45].

Another randomized trials done in 256 patients with type II DM who were on insulin therapy, addition of vildagliptin 50mg twice daily over a period 24 weeks showed a effective decrease in HbA1C by 0.5% to 0.1% in the vildagliptin group patients compared to 0.2% to 0.1% in the placebo group (P=0.022). There was only minimal hypoglycemic effect reported by patients treated with vildagliptin compared to placebo [46].

In a study organized by Galiant and colleagues, efficacy and tolerability of vildagliptin is compared with thiazolidinediones in T2DM patients with in adequate glycemic control over a study period of 3 months. After three months it was found that vildagliptin treated group has got good HbA1C reduction from the baseline compared to the TZD treated patients. It has been proved that vildagliptin is not inferior to TZD [47].

Special patient population:

In a double blind randomized active – controlled study done in 335 drug naive patients with type 2 DM aged around 65 yrs, showed that vildagliptin is an effective and well tolerable by elderly people. In this study 42% of patients has normal renal function, 57% had mild renal insufficiency and less than 2% had moderate renal insufficiency. Out of which study has resulted that vildagliptin has got good safety and efficacy in elderly people with type 2 DM without dose adjustment. Exposure to vildagliptin increase by 2-fold in elderly people and it does not have any relation with the severity of renal impairment. The lack of clear correlation between increased exposure and renal impairment contributes to both the excretion and hydrolysis metabolism of

vildagliptin. DPP-4 inhibitors can be used in patients with mild, moderate and severe or end stage renal insufficiency. With dose adjustments vildagliptin can be used for the treatment of T2DM with renal impairment base on the creatinine clearance [48].

Safety Profile:

A study done as per FDA US guidance, demonstrated that vildagliptin is safer among elderly people and have got good efficacy with dose of 50mg twice daily. Vildagliptin reduces the triglycerides absorption from the gut and there by the reduces the high plasma triglyceride concentration, increases HDL cholesterol concentration and decreases the LDL cholesterol concentration. This promotes lipid mobilization and catabolism in the post absorptive state. Vildagliptin does not cross the blood brain barrier and prevents cardio and cerebro vascular events in Type 2DM patients. It crosses the placenta freely and it is advisable for treatment in pregnant and lactating mother with diabetes [49]. A meta analysis conducted with pooled data to evaluate the efficacy of vildagliptin in hepatic impairment patients, showed that there was no elevation of the liver enzymes in vildagliptin treated patients. As a result, there is no need for dose adjustment of vildagliptin in type 2 DM with hepatic insuffiency [50].

A double blinded controlled trial done in type 2 DM patients demonstrated that treatment with vildagliptin 50mg bd does not have any pancreatic related adverse effects such as use in sr. amylase level and abdominal pain. Vildagliptin has got less hypoglycemic symptoms and many studies results (vildagliptin as monotherapy compared to metformin and rosiglitazone) have substantiated this statement. Another monotherapy study showed that patients treated with metformin had higher incidence

of gastrointestinal side effects such as nausea, abdominal pain, diarrhea, dyspepsia and flatulence compared to the patients treated with vildagliptin [51].

MATERIALS AND METHODS:

Study centre:

The study was conducted after obtaining institutional ethical clearance from institutional ethical committee (IEC), Research cell of Chennai Medical College Hospital and Research Centre (Affiliated to the Tamil Nadu Dr.MGR Medical University), Irungalur, Tiruchirappalli (enclosed A)

Study Period: 12 weeks (from June 2014 to July 2015).

Drugs used in this study are Glibenclamide 5mg od, Metformin 500mg od, Sitagliptin 100mg od, Vildagliptin 50mg bd

Inclusion Criteria

Previously diagnosed type 2 diabetes mellitus patient with the age group of 30 to 70 years on either glibenclamide and metformin for atleast 3 months with uncontrolled blood glucose levels.

Exclusion Criteria

Type 1 diabetes, Severe ketosis, Coma or reduced level of consciousness due to diabetes within the past 6 months, Pancreatitis, Severe infection, Pre and postsurgical patients , Severe traumatic patients, History of laparotomy, Chronic intestinal diseases, Pregnancy and possible pregnancy, Breast feeding, Moderate and severe renal dysfunction, Severe hepatic dysfunction, Insulin treatment, Treatment with anti-

diabetic drugs other than sulfonylurea, History of hypersensitivity Patients under medication with hypolipidemic drugs.

Methodology:

The present study is a prospective single center parallel arm open label randomized control study to evaluate the comparative effect of sitagliptin and vildagliptin on plasma glucose level HbA1C and serum lipid profile in type 2 diabetes mellitus patients, in combination with biguanides or sulphonylureas during the study period of 12 weeks. Total of 700 patients were screened out of which 180 patients fulfilled the inclusion and exclusion criteria. The study subjects were randomly divided into 6 groups, each group consisting of 30 patients. Study subjects were enrolled after obtaining informed consent. The subjects in each group were treated as follows and continued without any changes in the treatment during the entire study period.

Group	No. of subjects	Subject descriptions
I	30	Type II diabetic patients on Glibenclamide (5mg OD)
II	30	Type II diabetic patients on Glibenclamide (5mg) + Sitagliptin (100mg OD)
III	30	Type II diabetic patients on Glibenclamide (5mg) + Vildagliptin (50mg BD)
IV	30	Type II diabetic patients on Metformin (500mg OD)
V	30	Type II diabetic patients on Metformin (500mg) + Sitagliptin (100mg OD)
VI	30	Type II diabetic patients on Metformin (500mg)+ Vildagliptin (50mg BD)

[OD – Once a day; BD – twice a day]

Clinical Assessment:

All subjects were interviewed regarding family history, personal history, treatment history, past history before starting the study. Height, weight, age Gender, BMI were recorded for all the patient. Patients were advised to follow regular exercise and strict diet during the study period.

Laboratory analysis :

About 5ml of blood was collected at 0^{th} week, 4^{th} week, 8^{th} week and 12^{th} week of the study period. Blood was added with an appropriate anticoagulant before estimation.

Blood Glucose estimation:

Fasting plasma glucose was estimated after 8 hrs of overnight fast and post prandial plasma glucose was evaluated after 2 hrs following meal at 0^{th} week, 4^{th} week, 8^{th} week and 12^{th} week of the study period. Blood sample was collected and glucose estimation was analyzed by GOD/POD(Glucose oxidase peroxidase) enzymatic method.

Serum lipid profile estimation:

Blood samples were collected and estimated for serum lipid profile after overnight fast. Total cholesterol was analyzed by cholesterol oxidase peroxidase method, low density lipoprotein and high density lipoprotein was analyzed by direct enzymatic method, triglycerides was analyzed by glycerol -3-phosphate oxidase method.

Estimation of glycosylated haemoglobin

HBA1C was analyzed by high performance liquid chromatography method .

Serum amylase was analyzed by enzymatic method.

Blood urea was analyzed by urease method

Serum creatinine was analyzed by Jaffe's method

Statistical analysis:

Statistics were analyzed by SPSS statistical software package before and after therapy. The results were tabulated and values were presented as mean (+ or -) and SD. student's paired 't' test P value of <0.001 was considered to be statistically significant.

RESULTS:

Age Distribution of the Subjects:

The mean age of the study population are shown in table 1 and 2. Among the six groups, 51 to 60 years of age subjects were involved maximum in the study. The mean age of subjects in group I was 53.70 (+or-) 4.73 years. Group II was 55.53(+or-) 6.1, group III was 52.73 (+or-) 5.3, group IV was 53.03 (+or-) 5.8 years, group V was 59.20 (+or-) 6.0 years and group VI was 56.73 (+or-) 7.4 years.

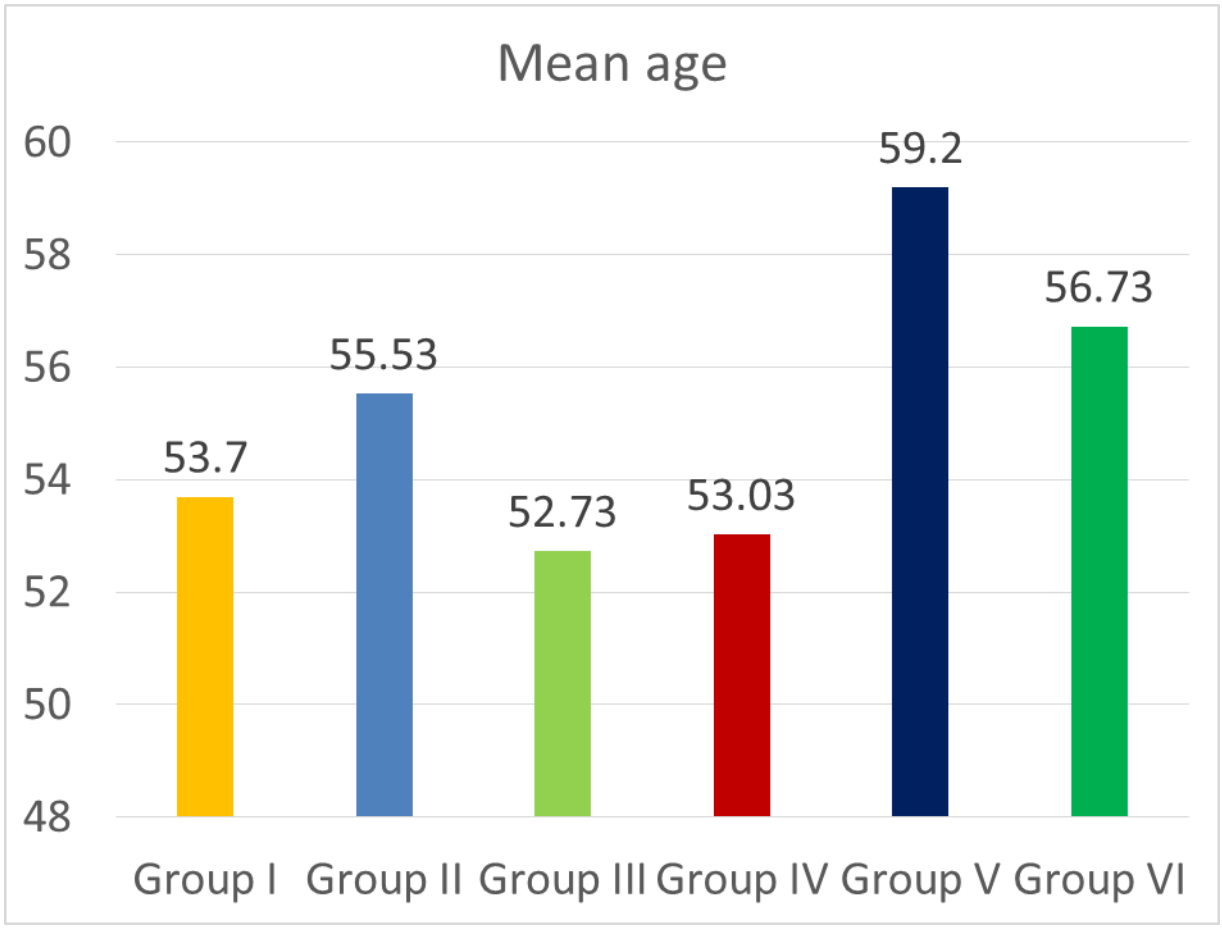
Table 1: Age distribution of the study population

Age group (in years)	No. of subjects (n=180)	Percentage (%)
36 - 40	1	0.5
41 – 45	12	6.7
46 - 50	32	17.8
51 - 55	44	24.4
56 - 60	52	28.9
61 - 65	29	16.2
66 - 70	10	5.5

Table 2: Mean age of the study population according to treatment group

Group	Treatment Group	Mean Age Std. Deviation
Group I	Gilbenclamide	53.70±4.735
Group II	Gilbenclamide + Sitagliptin	55.53±6.185
Group III	Gilbenclamide + Vildagliptin	52.73±5.336
Group IV	Metformin	53.03±5.846
Group V	Metformin + Sitagliptin	59.20±6.025
Group VI	Metformin + Vildagliptin	56.73±7.465
	Total	55.16±6.338

Figure 1: Bar chart showing distribution of mean age of all 6 groups



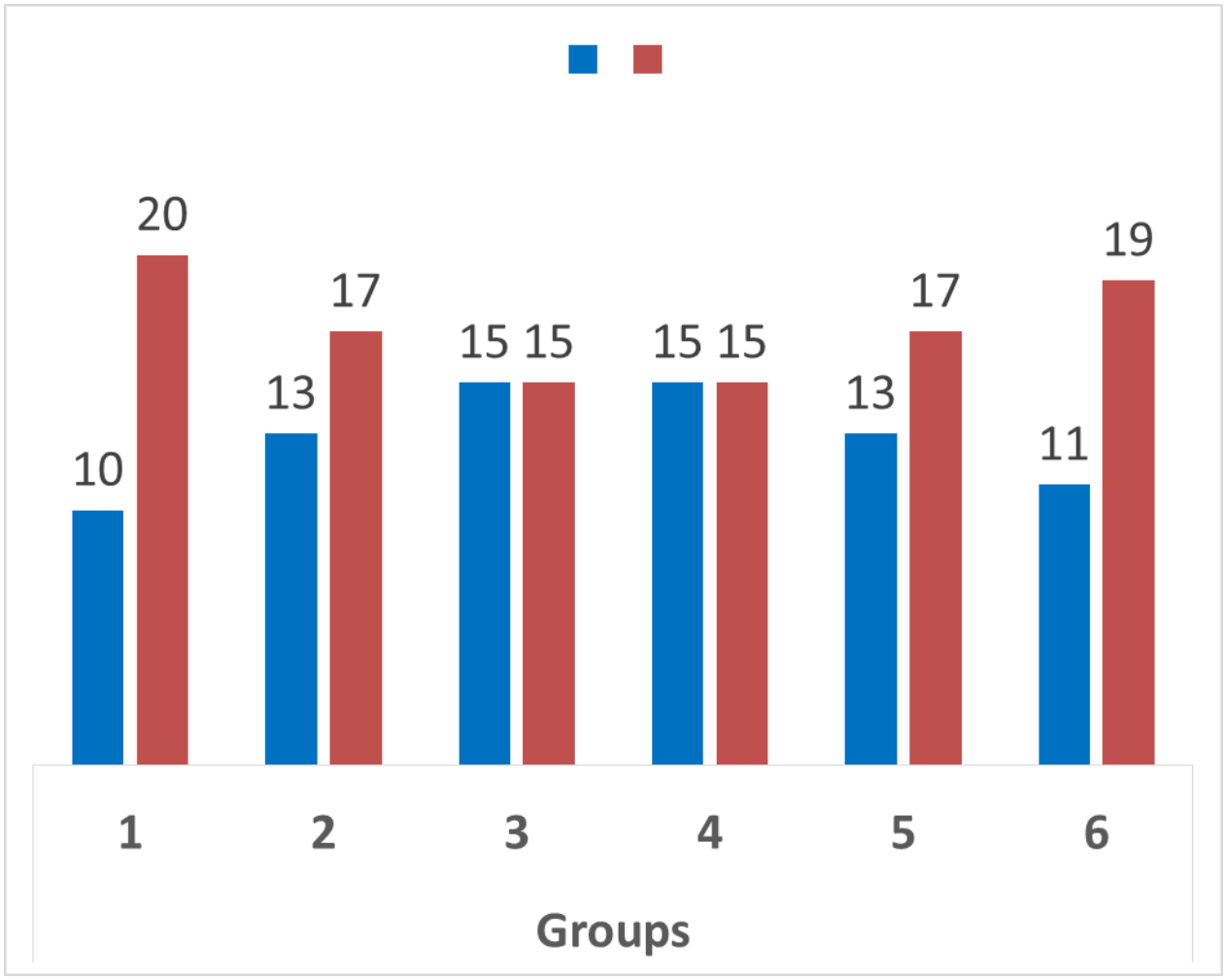
Gender Distribution of the study population:

Gender Distribution of the study population is shown in table 3. The maximum number of male patients were from group VI the followed by group II. In the female gender distribution the maximum patients were from group III and Group IV.

Table 3: Gender distribution of the study population according to treatment group

Age group	Male (%)	Female (%)	Total (%)
Group I	20 (66.7)	10 (33.3)	30 (100)
Group II	17 (56.7)	13 (43.3)	30 (100)
Group III	15 (50)	15 (50)	30 (100)
Group IV	15 (50)	15 (50)	30 (100)
Group V	17 (56.7)	13 (43.3)	30 (100)
Group VI	19 (63.3)	11 (36.7)	30 (100)

Figure 2: Bar chart showing gender distribution of all 6 groups



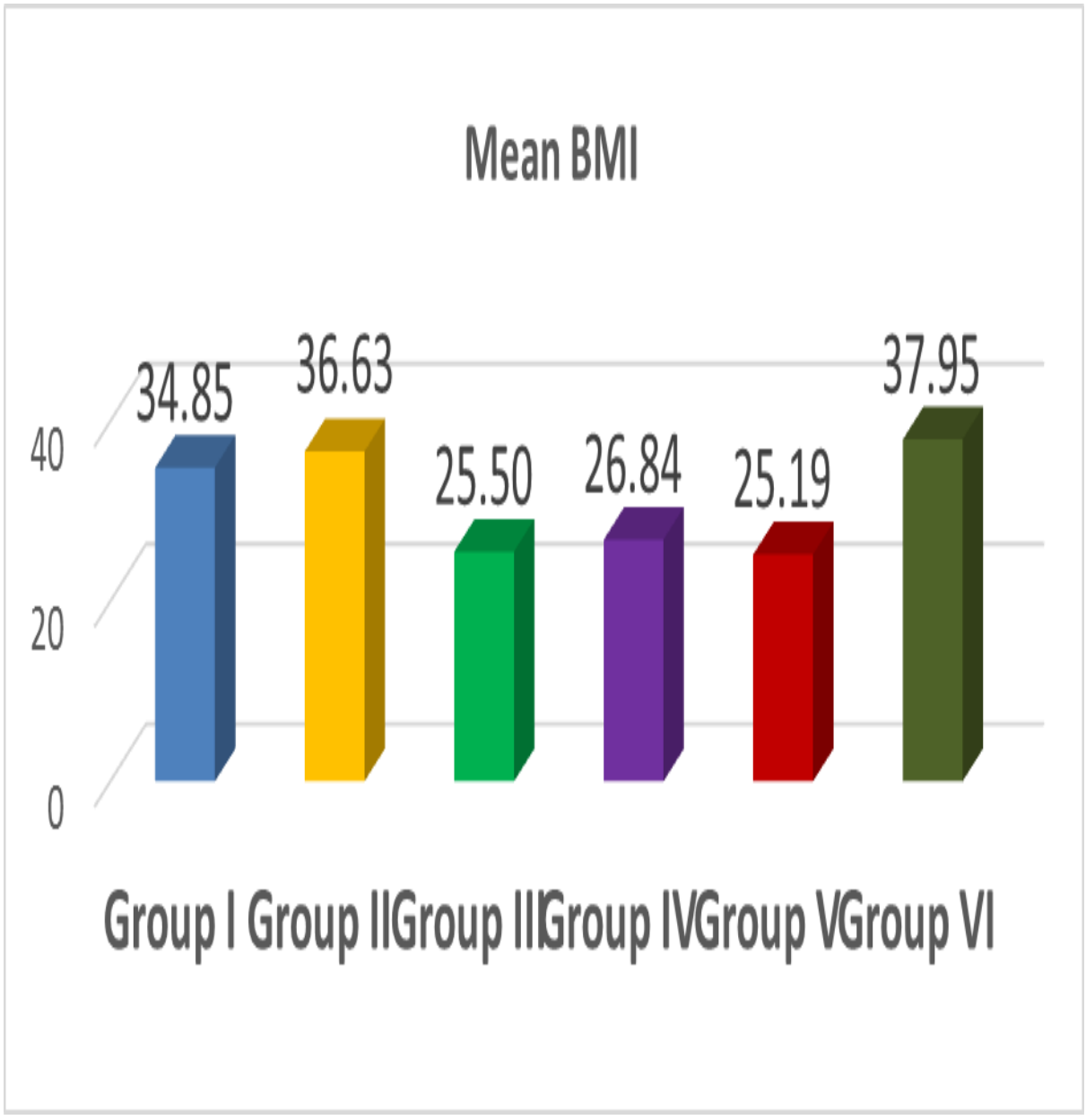
Mean BMI of the study population:

Mean body mass index of subjects recruited in the study were shown in table 4. Patients with maximum BMI were found in group VI (37.95) followed by group II and group I of value 36.62 and 34.84 respectively.

Table 4: Mean BMI of the study population according to treatment group

Group	Treatment Group	Mean ±Std. Deviation
Group I	Gilbenclamide	34.8465 ±4.28893
Group II	Gilbenclamide + Sitagliptin	36.6279±4.44404
Group III	Gilbenclamide + Vildagliptin	25.5049±3.65303
Group IV	Metformin	26.8354±3.93206
Group V	Metformin + Sitagliptin	25.1883±1.99595
Group VI	Metformin + Vildagliptin	37.9537±4.96245
	Total	31.1594±6.70646

Figure 3: Bar chart showing mean BMI of all 6 groups



Effect on fasting blood glucose level

Table 5: Mean fasting blood glucose of all groups

Groups	Fasting Blood Glucose (mg/dl)			
	0 week	**4 week**	**8 week**	**12 week**
Group I	165.90±12.834	146.30±11.173	132.60±16.126	119.13±23.780
Group II	178.67±2.444	159.60±11.560	128.27±23.779	100.80±8.462
Group III	145.70±16.011	126.90±9.083	113.03±7.122	99.53±5.643
Group IV	146.77±20.139	120.17±11.733	101.87±6.892	83.57±7.398
Group V	163.87±25.254	130.30±19.935	101.87±11.711	78.97±9.757
Group VI	168.63±24.782	139.60±17.814	106.97±12.896	79.47±8.959

Table 6: Reduction of fasting blood sugar among the groups at after 4, 8 and 12 weeks of therapy

Groups	Fasting Blood Glucose (mg/dl)		
	4 week	**8 week**	**12 week**
Group I	19.60±10.653	33.30±16.748	46.77±25.113
Group II	19.07±4.777	50.40±23.053	77.87±11.325
Group III	18.80±11.090	32.67±12.944	46.17±14.015
Group IV	26.60±18.957	44.90±19.099	63.20±19.150
Group V	33.57±12.199	62.00±19.789	84.90±22.507
Group VI	29.03±14.342	61.67±19.711	89.17±23.486

Group V subjects had significant reduction ($p<0.001$) of fasting blood glucose after 4 weeks and 8 weeks while Group VI had a mean reduction of 89 mg% after the 12 weeks therapy higher than all the other groups. Gliptins and metformin combination achieved higher glycaemic control of fasting glucose than the gliptins and sulfonylurea combination.

Table 7: Inter-group comparison of reduction of fasting blood sugar among the groups after 4 weeks of therapy

Group comparison after 4 weeks	Mean difference in reduction of fasting blood glucose
Group I vs Group II	0.533
Group I vs Group III	0.800
Group II vs Group III	0.267
Group IV vs Group V	6.967
Group IV vs Group VI	2.433
Group V vs Group VI	4.533
Group I vs Group IV	7.00
Group II vs Group V	14.50
Group III vs Group VI	10.233

The mean difference in reduction of fasting blood glucose after 4 weeks between the groups was not statistically significant except for Group II vs Group V and Group III vs Group VI. Post-hoc tests confirm that Gliptins and metformin combination achieved higher glycaemic control of fasting glucose than the gliptins and sulfonylurea combination.

Table 8: Inter-group comparison of reduction of fasting blood sugar among the groups after 8 weeks of therapy

Group comparison after 8 weeks	Mean difference in reduction of fasting blood glucose
Group I vs Group II	17.10
Group I vs Group III	0.633
Group II vs Group III	17.73
Group IV vs Group V	17.10
Group IV vs Group VI	16.76
Group V vs Group VI	0.333
Group I vs Group IV	11.60
Group II vs Group V	11.60
Group III vs Group VI	29.00

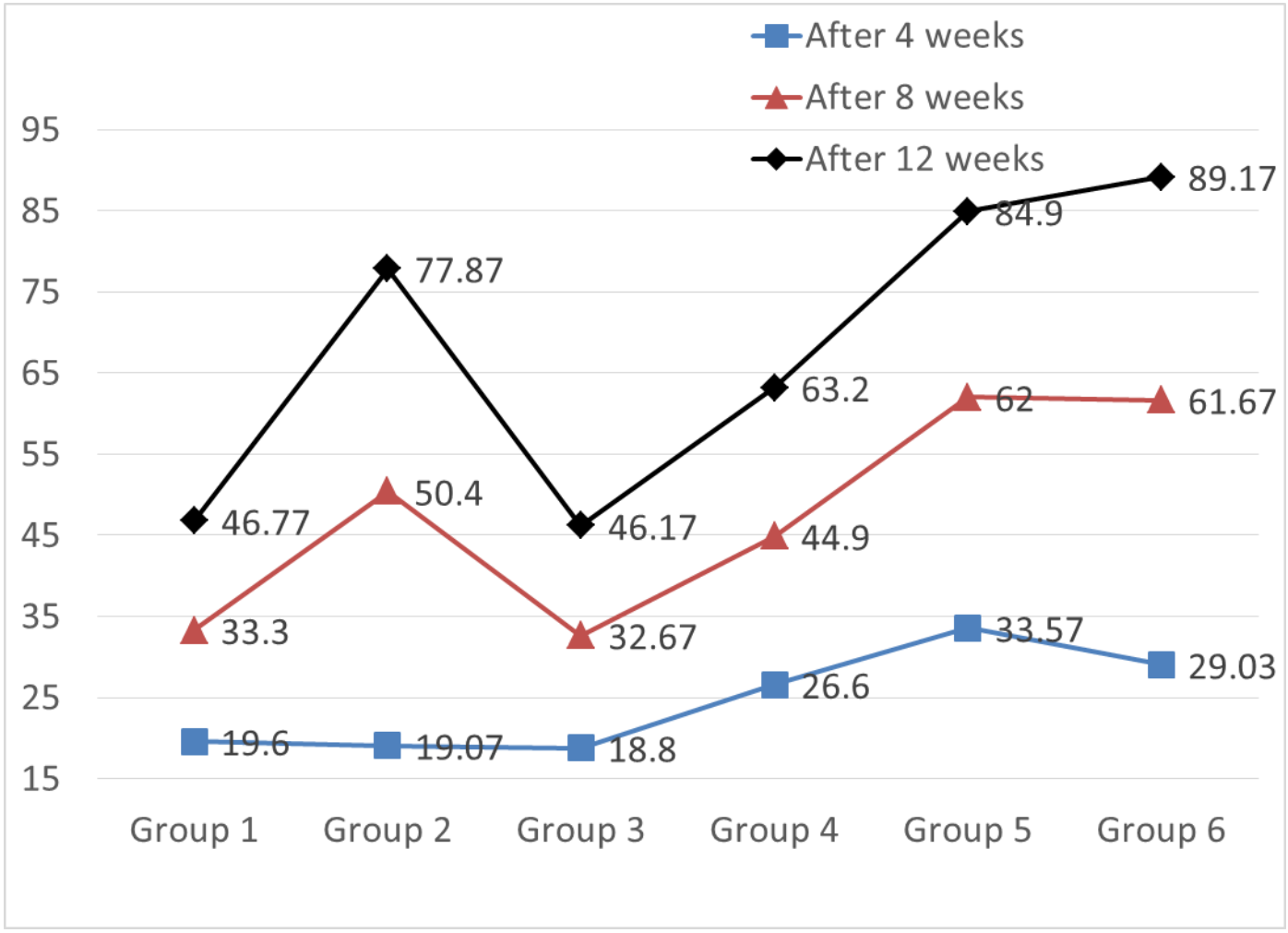
The mean difference in reduction of fasting blood glucose after 8 weeks between the groups was not statistically significant except for Group 1 vs 2, Group 2 vs Group 3, Group 4 vs 5, Group 4 vs 6, and Group 3 vs 6. Sitagliptin and sulfonylurea combination achieved higher glycaemic control of fasting glucose than the vildagliptin and sulfonylurea combination (Group 2 vs Group 3). Vildagliptin and metformin combination achieved higher glycaemic control of fasting glucose than the vildagliptin and sulfonylurea combination (Group 3 vs 6).

Table 9: Inter-group comparison of reduction of fasting blood sugar among the groups after 12 weeks of therapy

Group comparison after 12 weeks	Mean difference in reduction of fasting blood glucose
Group I vs Group II	31.10
Group I vs Group III	0.600
Group II vs Group III	31.70
Group IV vs Group V	21.70
Group IV vs Group VI	25.96
Group V vs Group VI	4.267
Group I vs Group IV	16.43
Group II vs Group V	7.03
Group III vs Group VI	43.00

The mean difference in reduction of fasting blood glucose after 12 weeks between the groups was statistically significant ($p<0.001$) except for Group I vs Group III, Group V vs Group VI and Group II vs Group V. Sitagliptin and sulfonylurea combination achieved higher glycaemic control of fasting glucose than the vildagliptin and sulfonylurea combination (Group 2 vs Group 3). Vildagliptin and metformin combination achieved higher glycaemic control of fasting glucose than the vildagliptin and sulfonylurea combination (Group 3 vs 6). Dual drug therapy with gliptins was better than monotherapy with metformin or sulfonylurea. In monotherapy, metformin achieved higher fasting glucose reduction than sulfonylurea.

Figure 4: Reduction of fasting blood glucose of all 6 groups at various time intervals



Effect on postprandial blood glucose level

Table 10: Mean postprandial blood glucose of all groups

Groups	postprandial Blood Glucose (mg/dl)			
	0 week	**4 week**	**8 week**	**12 week**
Group I	188.43±14.383	162.20±12.277	146.73±14.157	136.30±15.614
Group II	195.40±15.644	172.83±10.593	151.17±6.550	133.20±5.549
Group III	248.90±50.498	197.60±45.477	158.20±28.974	121.70±13.742
Group IV	201.60±23.440	164.97±8.524	141.63±13.161	128.17±10.596
Group V	249.80±31.072	202.73±22.019	157.70±13.550	126.80±9.890
Group VI	258.77±49.535	214.10±23.271	163.20±13.242	125.83±9.581

Table 11: Reduction of post-prandial blood sugar among the groups after 4, 8 and 12 weeks of therapy

Groups	Postprandial Blood Glucose (mg/dl)		
	4 week	**8 week**	**12 week**
Group I	26.23±8.541	41.70±15.018	52.13±16.968
Group II	22.57±7.366	44.23±1.264	62.20±14.048
Group III	51.30±22.908	90.70±33.715	127.20±42.087
Group IV	36.63±16.130	59.97±19.352	73.43±20.358
Group V	47.07±18.939	92.10±25.356	123.00±27.885
Group VI	44.67±55.972	95.57±50.018	132.93±49.218

Group V subjects had maximum reduction of post prandial glucose after 4 weeks while Group VI had a mean reduction of 95 at the end of 8 wk and 132 mg% after the 12 weeks therapy higher than all the other groups. Gliptins and metformin combination achieved higher glycaemic control of PPG than the gliptins and sulfonylurea combination.

Table 12: Inter-group comparison of reduction of post-prandial blood sugar among the groups after 4 weeks of therapy

Group comparison after 4 weeks	Mean difference in reduction of post-prandial glucose
Group I vs Group II	3.667
Group I vs Group III	25.067
Group II vs Group III	28.73
Group IV vs Group V	10.43
Group IV vs Group VI	8.03
Group V vs Group VI	2.40
Group I vs Group IV	10.40
Group II vs Group V	24.50
Group III vs Group VI	6.633

The mean difference in reduction of post-prandial blood glucose after 4 weeks between the groups was not statistically significant except for Group I vs Group III, Group II vs Group III and Group II vs Group V. Vildagliptin and sulfonylurea combination achieved higher glycaemic control of post-prandial glucose than the sitagliptin and sulfonylurea combination at 4 weeks (Group 2 vs Group 3).Sitagliptin and metformin combination achieved higher glycaemic control of post-prandial glucose than the Sitagliptin and sulfonylurea combination (Group 2 vs 5).

Table 13: Inter-group comparison of reduction of post-prandial blood sugar among the groups after 8 weeks of therapy

Group comparison after 8 weeks	Mean difference in reduction of post-prandial glucose
Group I vs Group II	2.53
Group I vs Group III	49.00
Group II vs Group III	46.46
Group IV vs Group V	32.13
Group IV vs Group VI	35.60
Group V vs Group VI	3.467
Group I vs Group IV	18.26
Group II vs Group V	47.86
Group III vs Group VI	4.867

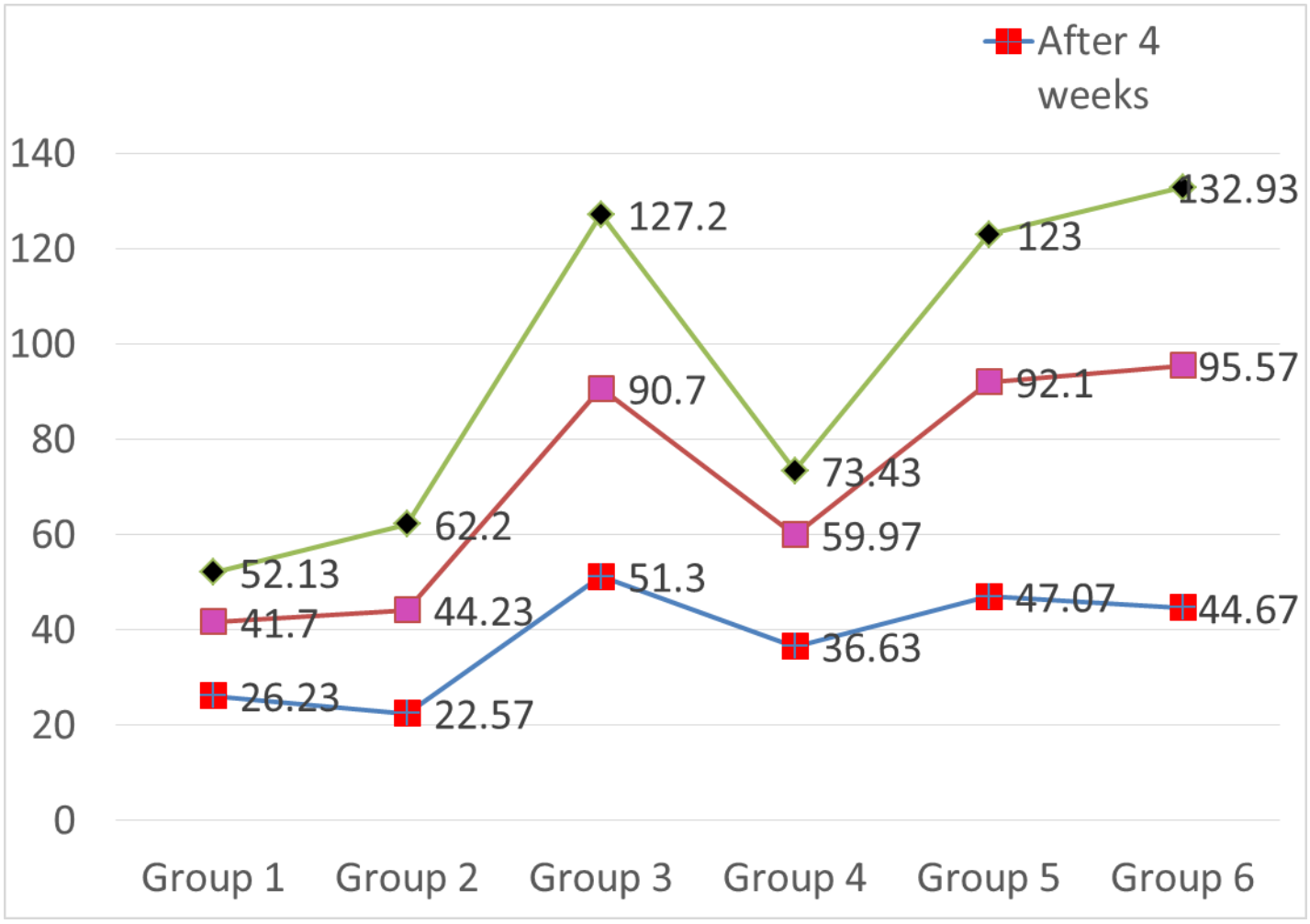
The mean difference in reduction of post-prandial blood glucose after 8 weeks between the groups was not statistically significant except for Group I vs Group III, Group II vs Group III, Group IV vs Group V, Group IV vs Group VI and Group II vs Group V. Vildagliptin and sulfonylurea combination achieved higher glycaemic control (90 vs 44) of post-prandial glucose than the sitagliptin and sulfonylurea combination at 8 weeks (Group 2 vs Group 3).Sitagliptin and metformin combination achieved higher glycaemic control of post-prandial glucose than the Sitagliptin and sulfonylurea combination (Group 2 vs 5).Dual drug therapy with gliptins achieved higher post-prandial glycaemic control than monotherapy with metformin or sulfonylurea.

Table 14: Inter-group comparison of reduction of post-prandial blood sugar among the groups after 12 weeks of therapy

Group comparison after 12 weeks	Mean difference in reduction of post-prandial glucose
Group I vs Group II	10.06
Group I vs Group III	75.06
Group II vs Group III	65.00
Group IV vs Group V	49.56
Group IV vs Group VI	59.50
Group V vs Group VI	9.93
Group I vs Group IV	21.30
Group II vs Group V	60.80
Group III vs Group VI	5.73

The mean difference in reduction of post-prandial blood glucose after 12 weeks between the groups was statistically significant ($p<0.001$) except for Group I vs Group III, Group II vs Group III, Group IV vs Group V, Group IV vs Group VI and Group II vs Group V. Vildagliptin and sulfonylurea combination achieved higher glycaemic control (62 vs 127) of post-prandial glucose than the sitagliptin and sulfonylurea combination at 12 weeks (Group 2 vs Group. Sitagliptin and metformin combination achieved higher glycaemic control of post-prandial glucose than the Sitagliptin and sulfonylurea combination (Group 2 vs 5). Dual drug therapy with gliptins achieved higher post-prandial glycaemic control than monotherapy with metformin or sulfonylurea.

Figure 5: Reduction of post-prandial blood glucose of all 6 groups at various time intervals



Effect on HbA1C

Table 15: Mean HbA1C of all groups

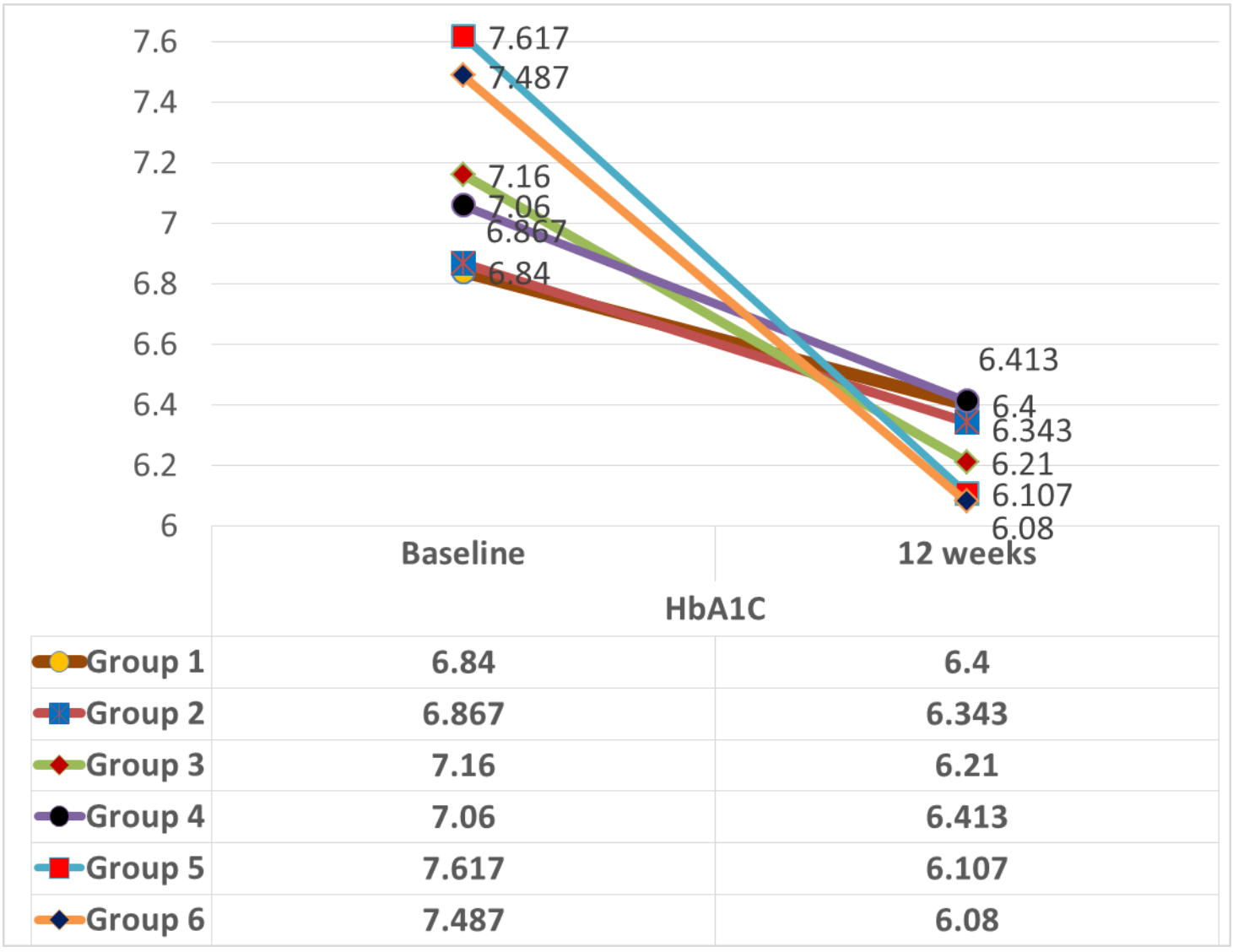
Groups	HbA1C Blood Glucose (%)	
	0 week	**12 week**
Group I	6.84±0.145	6.40±0.233
Group II	6.86±0.229	6.34±0.192
Group III	7.160±0.3635	6.210±0.2468
Group IV	7.060±0.2554	6.413±0.3246
Group V	7.617±0.3742	6.107±0.3542
Group VI	7.487±0.3471	6.080±0.3718

Table 16: Reduction of HbA_1C among the groups after 12 weeks of therapy

Reduction of HbA_1C	Group	Mean Std. Deviation
After 12 weeks	Group I	0.440±0.2111
	Group II	0.523±0.2161
	Group III	0.950±0.2502
	Group IV	0.647±0.2569
	Group V	1.510±0.4147
	Group VI	1.407±0.2970

All the groups lowered the mean HbA_1C levels after 12 weeks and this reduction of HbA_1C levels after 12 weeks among the groups was statistically significant ($p<0.001$) and was maximum in Group V (1.5%)(metformin and sitagliptin combination) and group 6 (1.4%) (metformin and vildagliptin combination).

Figure 6: Line diagram showing HbA1C of all 6 groups at various time intervals



	HbA1C	
Group 1	6.84	6.4
Group 2	6.867	6.343
Group 3	7.16	6.21
Group 4	7.06	6.413
Group 5	7.617	6.107
Group 6	7.487	6.08

Effect on serum lipid profile

Table 17: Comparison of Total cholesterol values of the groups before therapy and after 12 weeks

Group	Treatment Duration	Mean Std. Deviation	Mean difference
Group 1	Baseline	179.23±14.395	2.267
	12 weeks	176.97±13.675	
Group 2	Baseline	186.80±5.910	7.767
	12 weeks	179.03±5.720	
Group 3	Baseline	175.27±10.302	2.567
	12 weeks	172.70±9.289	
Group 4	Baseline	171.53±9.104	2.133
	12 weeks	169.40±9.004	
Group 5	Baseline	178.33±14.274	4.033
	12 weeks	174.30±12.731	
Group 6	Baseline	180.3±9.585	5.30
	12 weeks	175.0±8.894	

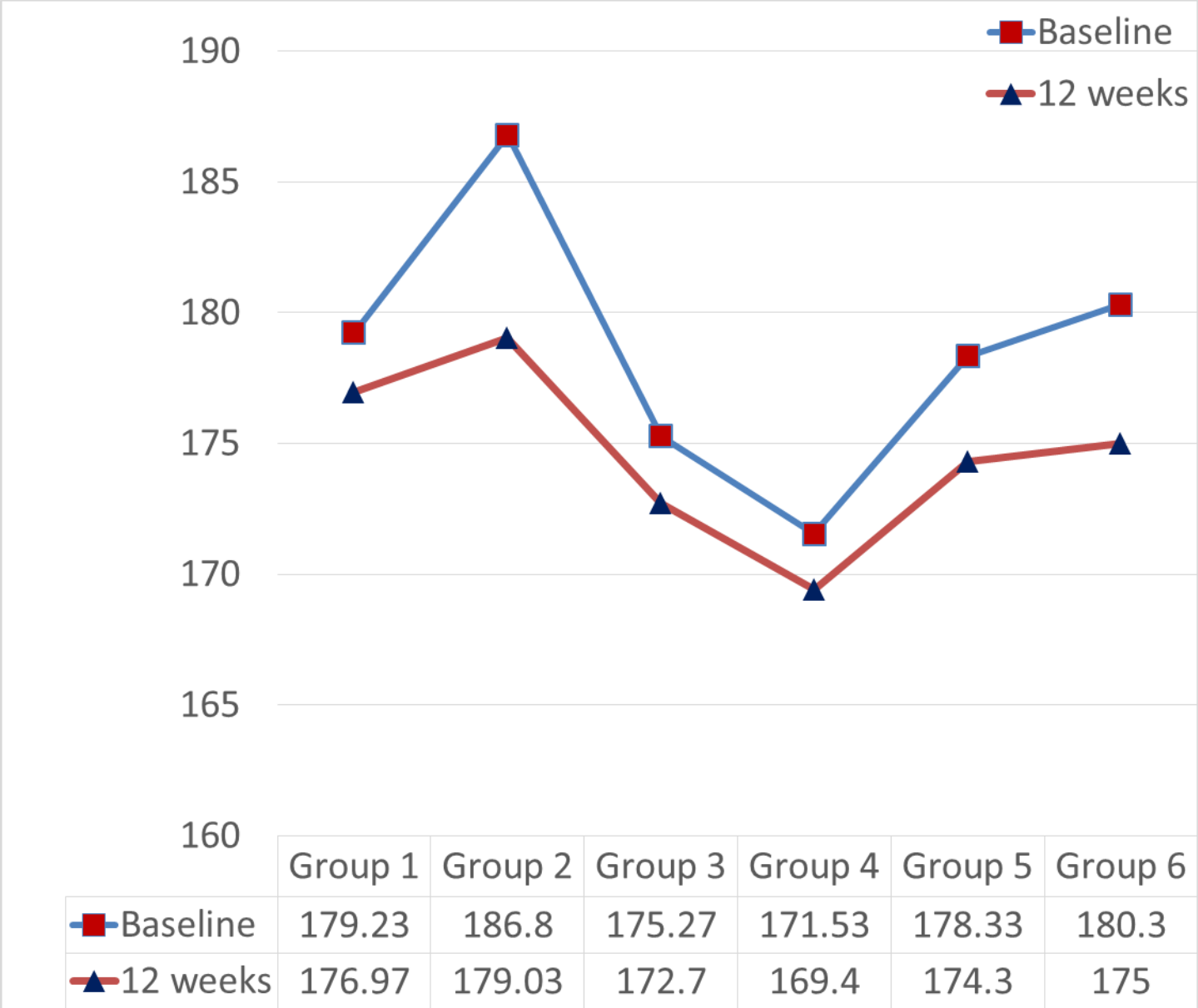
The mean total cholesterol levels were lowered by all the drug combinations and this reduction of total cholesterol levels after 12 weeks was statistically significant ($p<0.001$). Maximum reduction of total cholesterol levels after 12 weeks was observed in group 2 (Gilbenclamide and Sitagliptin combination)

Table 18: Reduction of total cholesterol among the groups after 12 weeks of therapy

Reduction of total cholesterol	Group	Mean ± Std. Deviation
After 12 weeks	Group I	2.27±3.331
	Group II	7.77±2.128
	Group III	2.57±2.837
	Group IV	2.13±0.973
	Group V	4.03±6.145
	Group VI	5.30±2.938

All the groups lowered the mean total cholesterol levels after 12 weeks and this reduction of total cholesterol levels after 12 weeks among the groups was statistically significant ($p<0.001$) and was maximum in Group II (7.7mg%) (Gilbenclamide and sitagliptin combination) and group 6 (5.3 mg%) (metformin and vildagliptin combination).

Figure 7: Line diagram showing total cholesterol of all 6 groups at before and after therapy



	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Baseline	179.23	186.8	175.27	171.53	178.33	180.3
12 weeks	176.97	179.03	172.7	169.4	174.3	175

Table 19: Comparison of triglyceride values of the groups before therapy and after 12 weeks

Group	Treatment Duration	Mean triglyceride Std. Deviation	Mean difference
Group 1	Baseline	134.10±7.522	2.267
	12 weeks	131.83±7.557	
Group 2	Baseline	140.40±5.210	8.467
	12 weeks	131.93±4.941	
Group 3	Baseline	132.37±10.35	2.40
	12 weeks	129.97±10.45	
Group 4	Baseline	131.80±5.215	2.033
	12 weeks	129.77±4.987	
Group 5	Baseline	145.93±12.05	11.36
	12 weeks	134.57±10.89	
Group 6	Baseline	141.83±13.39	8.367
	12 weeks	133.47±12.48	

The mean triglyceride levels were lowered by all the drug combinations and this reduction of triglyceride levels after 12 weeks was statistically significant ($p<0.001$).Maximum reduction of triglyceride levels after 12 weeks was observed in group 5 (metformin and Sitagliptin combination)

Table 20: Reduction of triglycerides among the groups after 12 weeks of therapy

Reduction of triglycerides	Group	Mean Std. Deviation
After 12 weeks	Group I	2.27±1.929
	Group II	8.47±2.389
	Group III	2.40±2.848
	Group IV	2.03±.809
	Group V	11.37±7.025
	Group VI	8.37±5.611

All the groups lowered the mean triglycerides levels after 12 weeks and this reduction of mean triglycerides levels after 12 weeks among the groups was statistically significant ($p<0.001$) and was maximum in Group V (11.3 mg%) (metformin and sitagliptin combination) and group II (8.47 mg%) (Gilbenclamide and sitagliptin combination).

Figure 8: Line diagram showing triglyceride levels of all 6 groups at before and after therapy

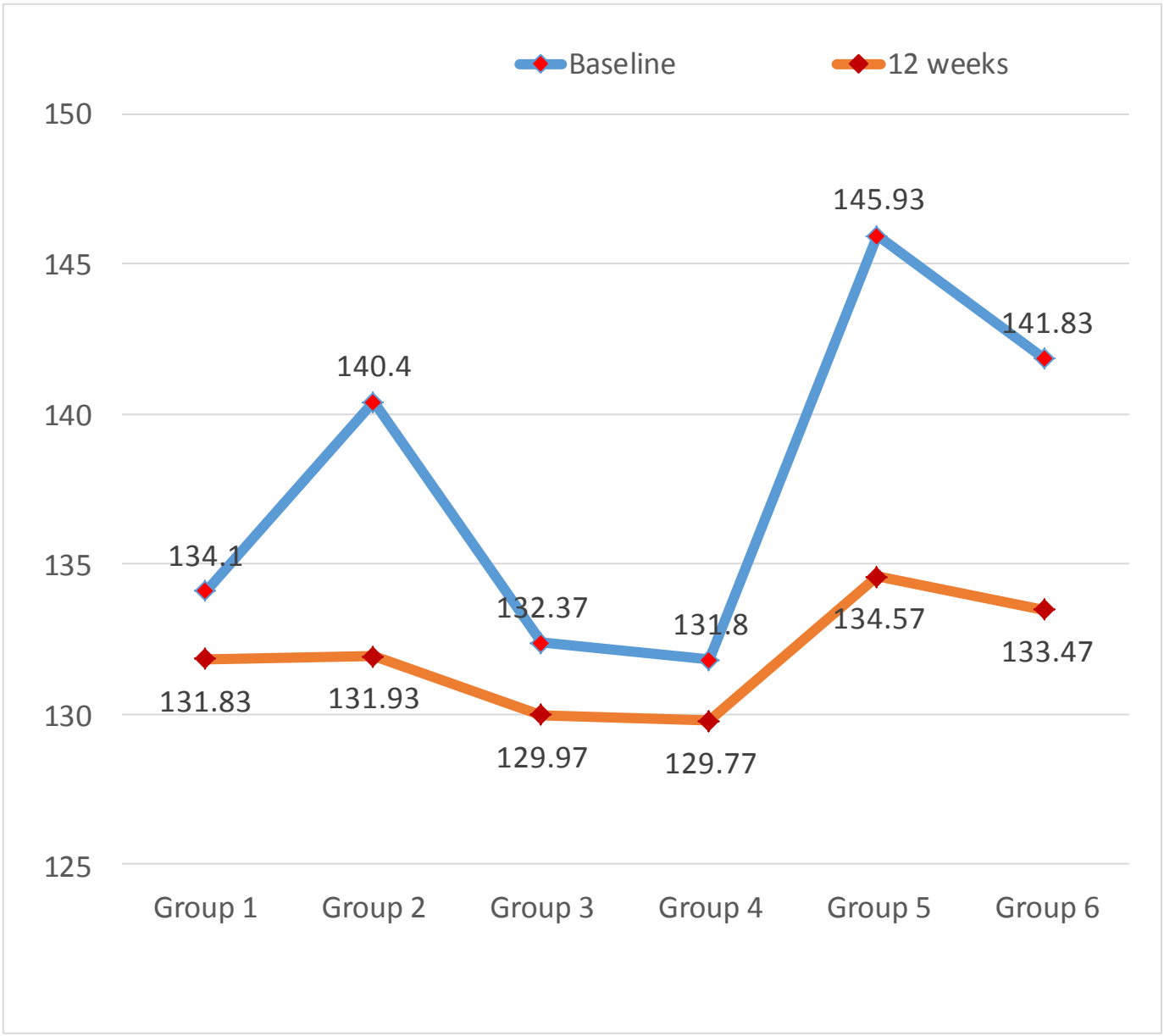


Table 21: Comparison of LDL values of the groups before therapy and after 12 weeks

Group	Treatment Duration	Mean LDL Std. Deviation	Mean difference
Group 1	Baseline	74.93±5.252	2.50
	12 weeks	72.43±5.969	
Group 2	Baseline	85.73±4.127	10.43
	12 weeks	75.30±4.793	
Group 3	Baseline	77.10±13.304	10.13
	12 weeks	66.97±12.050	
Group 4	Baseline	79.40±4.53	1.90
	12 weeks	77.50±4.54	
Group 5	Baseline	95.50±12.102	17.267
	12 weeks	78.23±6.168	
Group 6	Baseline	78.03±12.18	10.63
	12 weeks	67.40±9.205	

The mean LDL cholesterol levels were lowered by all the drug combinations and this reduction of LDL cholesterol levels after 12 weeks was statistically significant ($p<0.001$).Maximum reduction of triglyceride levels after 12 weeks was observed in group 5 (metformin and Sitagliptin combination)

Figure 9: Line diagram showing LDL cholesterol levels of all 6 groups at before and after therapy

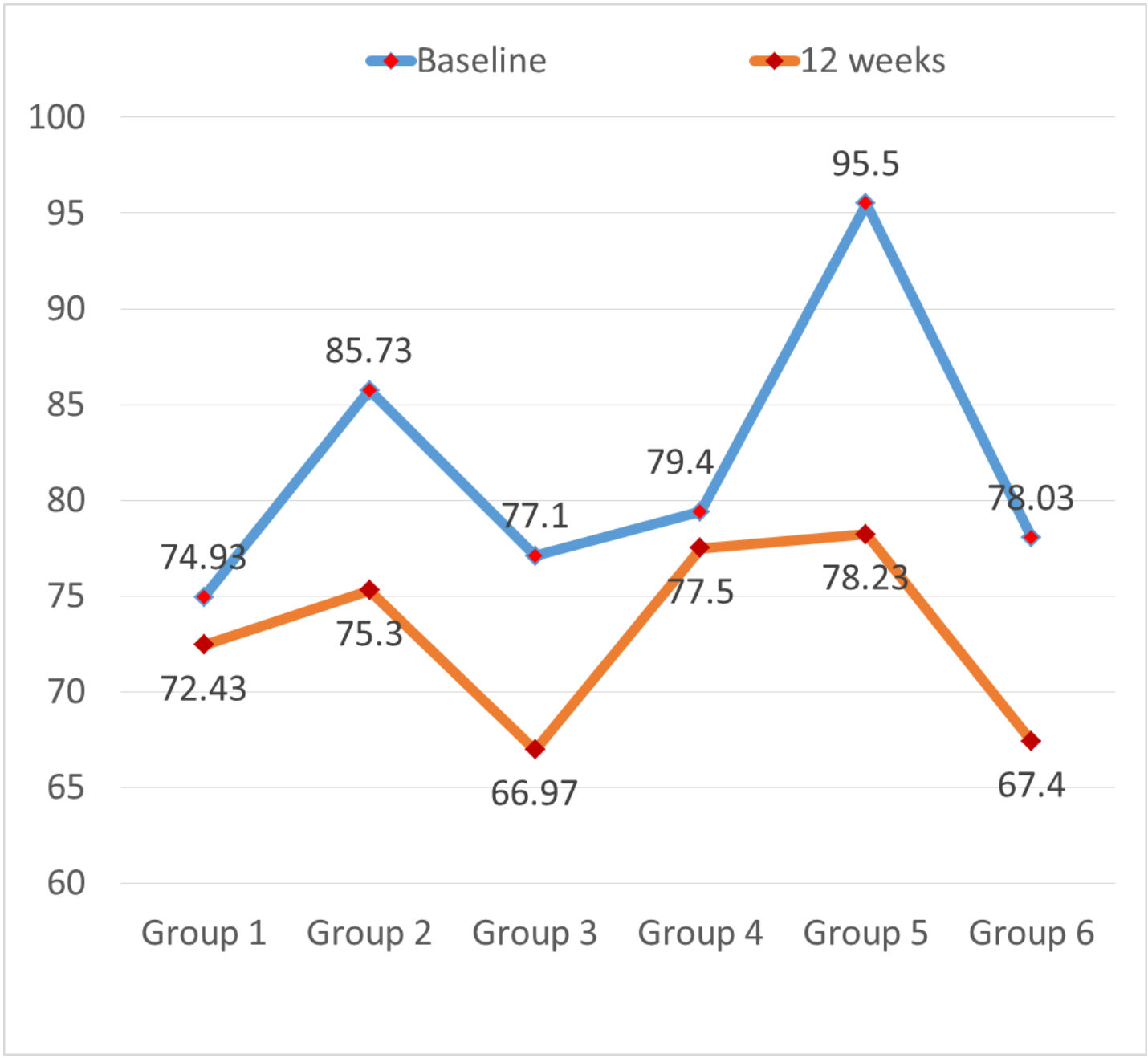


Table 22: Reduction of LDL cholesterol among the groups after 12 weeks of therapy

Reduction of LDL cholesterol	Group	Mean Std. Deviation
After 12 weeks	Group I	2.50±1.717
	Group II	10.43±3.617
	Group III	10.13±4.191
	Group IV	1.90±0.845
	Group V	17.27±8.658
	Group VI	10.63±4.881

All the groups lowered the mean LDL cholesterol levels after 12 weeks and this reduction of mean LDL cholesterol levels after 12 weeks among the groups was statistically significant ($p<0.001$) and was maximum in Group V (17.2 mg%) (metformin and sitagliptin combination) and group 6 (10.63 mg%) (metformin and vildagliptin combination).

Table 23: Comparison of HDL values of the groups before therapy and after 12 weeks

Group	Treatment Duration	Mean HDL Std. Deviation	Mean difference
Group 1	Baseline	65.20±8.719	-1.033
	12 weeks	66.23±8.784	
Group 2	Baseline	41.73±6.716	-17.50
	12 weeks	59.23±4.289	
Group 3	Baseline	42.20±6065	-1.20
	12 weeks	43.40±5.87	
Group 4	Baseline	47.37±4.382	-0.633
	12 weeks	48.00±4.480	
Group 5	Baseline	54.63±7.753	-7.83
	12 weeks	62.47±5.698	
Group 6	Baseline	41.27±5.445	-1.93
	12 weeks	43.20±4.582	

The mean HDL cholesterol levels were increased by all the drug combinations and this improvement in HDLs cholesterol levels after 12 weeks was statistically significant ($p<0.001$).Maximum increase of HDL levels after 12 weeks was observed in group 2 (Gilbenclamide and Sitagliptin combination)

Table 24: Improvement of HDL cholesterol among the groups after 12 weeks of therapy

Improvement of HDL cholesterol	Group	Mean Std. Deviation
After 12 weeks	Group I	1.03±1.732
	Group II	17.50±5.865
	Group III	1.20±1.424
	Group IV	0.63±0.765
	Group V	7.83±6.623
	Group VI	1.93±1.552

All the groups improved HDL cholesterol after 12 weeks and this rise in mean HDL cholesterol levels after 12 weeks among the groups was statistically significant ($p<0.001$) and was maximum in Group II (17.5 mg%) (Gilbenclamide and sitagliptin combination) and group V (7.83 mg%) (metformin and sitagliptin combination).

Figure 10: Line diagram showing HDL cholesterol levels of all 6 groups at before and after therapy

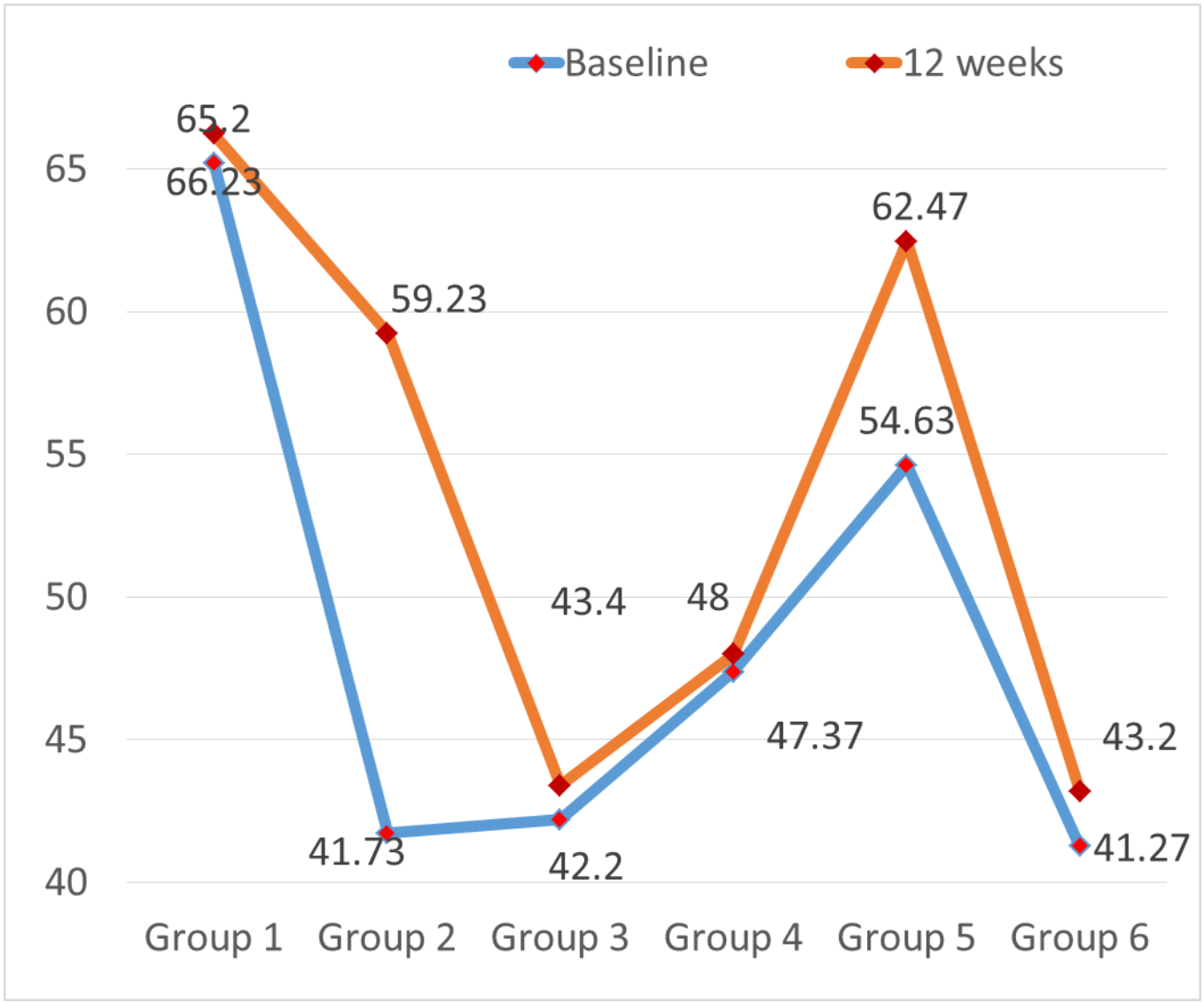


Table 25: Comparison of serum amylase of the groups before therapy and after 12 weeks

Group	Treatment Duration	Mean serum amylase Std. Deviation	Mean difference
Group 1	Baseline	50.93±6.269	0.200
	12 weeks	50.73±7.153	
Group 2	Baseline	48.90±8.442	0.467
	12 weeks	48.43±8.341	
Group 3	Baseline	37.00±4.371	0.840
	12 weeks	37.84±4.587	
Group 4	Baseline	45.63±6.261	0.632
	12 weeks	45.00±5.970	
Group 5	Baseline	41.72±6.617	0.276
	12 weeks	41.45±6.658	
Group 6	Baseline	58.27±13.663	0.700
	12 weeks	57.57±13.325	

The mean serum amylase levels were unaltered by all the drug combinations and the minor changes observed was not statistically significant.

DISCUSSION:

Diabetes mellitus is a condition in which the body does not produce or respond to insulin, a hormone that regulates the level of sugar in the blood. There are three types of Diabetes mellitus Type I and Type II diabetes mellitus and gestational diabetes mellitus based on the etiology. There are also specific types of diabetes mellitus depending on the cause of disease. By 2030, India will be called as capital world of diabetes. So far six oral hypoglycaemic agents are available in the market due to loss of efficacy and certain limitations, there is necessary for the discovery of newer agents. One such agent is DPP-4 inhibitor. It has been found that the incretion effect is lost in T2DM and this result in the invention of DPP-4 inhibitors in 2005.DPP-4 inhibitors acts by inhibiting the DPP-4 enzyme action thereby it increases the circulating GLP-1 and GIP levels. GLP-1 acts on the pancreatic Beta cells and increases the insulin secretion and GIP acts on the pancreatic alpha cells and reduces the glycogen secretion.

Sitagliptin, first DPP-4 inhibitor invented in 2006.They have good inhibitory effect and well tolerated by elderly people with T2DM.It has not good safety and efficacy. It reduces the LDL level and thereby prevents the cardiovascular risk disease in elderly people. It has very less hypoglycaemic symptoms and compensates the weight gain produced by the other OHA .It reduces FPG, PPG, HBA1C, significantly in T2DM patients. Vildagliptin selective potent second DPP-4 inhibitor reduces FPG, PPG, HBA1C significantly. There are controversial studies regarding the effect of DPP-4 inhibitors on lipid profile. This study is framed to know about the effect of these inhibitors on lipid profile.

In this study, mean age of study subjects included was 55 (+ or -) 6 years with maximum age group of 60 to 70 years and minimum age group of 30 to 40 years respectively.

The age difference between group IV and group V was found statistically significant (P<0.05) compared with other groups. Regarding both male and female were equally distributed in all six group. BMI comparison between the certain groups showed statistically significant (P<0.05), while group I vs group II and group IV vs group V where satisfactorily significant. In our study there is reduction in FPG at 4^{th},8^{th}, 12^{th} week of therapy in all 6 groups. Group V treated subjects showed significant reductions (P<0.001) with mean value of 33.57(+or-)12 at the 4^{th} week and 62(+or-)19 at the 8^{th} week. Group VI also showed significant reduction in FPG by mean of 89% with P value (P<0.001). Intergroup comparison of FPG at 4^{th} week showed that group II vs group V had significant P value(P <0.01). As a result, Combined therapy of metformin and Gliptins has achieved good glycemic controlled compared to gliptin with sulfonylurea group.when we compared group III and group VI treated subjects, it was found that metformin c vildagliptin is very effective in controlling FPG when compared to sulfonylurea c Vildagliptin with mean difference of 29% and P<0.0001 at the group showed statistically significant reduction (P<0001). Vildagliptin add on therapy with metformin and sulfonylurea with sitagliptin combination has achieved good glycemic control when compared to the controlled group. Add on therapy was better than the monotherapy with metformin or sulfonylurea. When we compared monotherapy groups, it was found that monotherapy with metformin has given better reduction in FPG level than sulfonylurea.

By comparing the reduction reduction in post prandial glucose levels among the groups at the end of 4th8th and 12th week, it was found that group V subjects showed maximum reduction at 4th week and group VI showed significant reduction (P<0.001) with mean of 95% and 132 mg at 8th & 12th week respectively. At the end 4th week add on therapy metformin with sitagliptin and sulphonylurea with vildagliptin has showed (P<0.001) with mean of 28.73% (group II vs group III) and metformin with sitagliptin group II achieved proper glycemic control of post prandial glucose than group V with mean of 24.50% and (P<0.009). 8th week results shows that group II vs group V, metformin with sitagliptin has achieved good glycemic control with mean of 47.86% and (p<0.001). When compared with monotherapy groups (group I and group IV), combined therapy are very effective than monotherapy with significant (p<0.01) and mean of 49% (group I vs group III).

At the end of 12th week the mean difference in postprandial glucose level between the groups were except(group I vs group II, group V vs group VI, group I vs group IV). Combined therapy of vildagliptin with sulfonylurea has achieved higher glycemic control compared (62 vs 127) to sitagliptin with sulfonylurea. Metformin with sitagliptin group has shown higher reduction in PPG level with p<0.01 and mean of 60.8% compared with sulfonylurea with sitagliptin groups. Add on therapy has showed better reduction in PPG level compared to monotherapy group (group I and group V). At the end of 12th week, compared with other groups, group V and VI showed significant reduction in HbA1c level with p<0.001.

The mean triglyceride level of 133.47(+or_) 12.48 was achieved in all the combined group at the end of the 12th week with significant P<0.0001. The Metformin

with sitagliptin group has proved significant reduction in triglyceride level compared to the other combined groups. Similarly, combined therapy with sitagliptin has significantly reduced the LDL-CH level at the end of the 12th week with mean of 78.23(+ or-) 6.1 with p<0.001.This similar effect was seen in ottavio et al, which showed that after 21 weeks with sitagliptin 100 mg has reduced the low density lipoprotein levels and there by prevents cardiovascular events, insulin requirements. Increase in HDL level was significantly seen in group II therapy (sitagliptin with sulfonylurea) and group V at the end of 12th week with P<0.001.The mean total cholesterols levels showed that significant reduction is seen in group II(7.7mg %) and group VI(5.3mg%) when compared to other groups.

At the of 12th week, maximum reduction of tryglyceride is seen in group V and group II with mean of 11.3 mgms % and 8.47 mgms%. Similarly maximum reduction of low density lipoprotein level is seen in group V and group VI with mean of (17.2 mgms%) and (10.63 mgms%) respectively. Among all the groups, the serum amylase levels were found un altered throughout the study in all the treated groups.

In Braz et al, sitagliptin combined with metformin demonstrated that there is significant reduction in FPG by 20.3mg/dl with p<0.05. Similar results was reported in this study that metformin and sitagliptin showed significant reduction in FPG,PPG after 12 weeks therapy. In a randomized control trial done in 444 patients who were treated with combined therapy of sulfonylurea and Sitagliptin over a period of 24 weeks. Author observed that there is a significant reduction in HbA1c by 0.74%, FPG by 20.1mg/dl(p<0.001). In our study the same combined therapy has showed significant reduction in FPG,PPG, and HbA1c levels at the end of 12th week [52].

Bosi et al proved that T2DM patients with inadequate glycemic control when treated with (metformin and vildagliptin) combined therapy over a period of 24 weeks, resulted in significant decrease of FPG,PPG and HbA1c level by 0.7(+or-)% and 36(+or-)5 mg/dl respectively. In this study metformin with vildagliptin combination therapy has resulted in effective reduction of FPG,PPG and HbA1c levels at the end of 12^{th} week [53].

In comparative study organized by Ahren and colleagues, T2DM subjects with uncontrolled glycemic control following monotherapy with metformin and glimipride was treated with vildagliptin 50mg bd over period of 12 weeks. After 12 weeks treatment author conducted that vildagliptin combined therapy is very effective compared to the monotherapy with glimipride and metformin [39].

The present study reported that combined therapy of metformin with vildagliptin ,metformin with sitagliptin, sulfonylurea with sitagliptin groups had showed an significant reduction in FPG,PPG and HbA1c levels with significant P value of $P<0.001$. As a result, it has been proved that combined therapy is very effective when compared to the monotherapy with metformin and sulfonylurea.

CONCLUSION:

Diabetes mellitus is a major health that accounts for morbidity and mortality. There are three categories based on the etiology. Diabetes when not treated properly leads to many complication leading to death in severe cases. Many drugs have been invented and about six groups are approved and available in the clinical practice. Day by day after repeated usage, they lose their property and becomes uneffective with adverse effects also. As a result of which newer drugs are invented and the few drugs are also under trial for therapy. One among them is Dipeptidyl peptidase -4 inhibitor, invented and approved by FDA in 2005 for management of type 2 DM.

The incretion defect in type II DM patients was corrupted by DPP-4 inhibitors and GLP-1 against drugs. DPP-4 inhibitors act by increasing the incretin hormone level by blocking the DPP-4 enzyme action there by increasing the insulin secretion by the pancreatic beta cell. There are six DPP-4 inhibitors available in the market. Sitagliptin was first DPP-4 inhibitor invented in 2006. They have a new therapeutic approach in the therapy of T2DM patients. They are effective both as monotherapy and combined therapy with other oral hypoglycemic agents. Sitagliptin significantly reduces FPG,PPG, HbA1C levels in type 2 DM patients. They reduce the low density liproprotien level their by prevents the risk of cardiovascular events in elderly people. It has good safety and efficacy compared to other OHA's. It compensates the side effects produced by other OHA's such as metformin and sulfonylurea. It has got less hypoglycemic symptom and weight neutralising effect vildagliptin, a second selective and potent DPP-4 inhibitor was discovered in February and approved by FDA. Both sitagliptin has got good oral bio availability. vildagliptin is well tolerated by elderly

people. It is also more effective as monotherapy and combined therapy with other oral anti diabetic agents. Vildagliptin significantly reduces the FPG,PPG,HbA1c levels in T2DM patients. Patients improve the beta cell function by pharmacodynamic remodeling and there by increases the insulin secretion. It has good safety and efficacy profile. Many trials proved that vildagliptin 50mg twice daily and sitagliptin 100mg once daily is effective and safe for the management of uncontrolled hyperglycemia in T2DM patients. The present study showed that sitagliptin and vildagliptin as combined therapy with metformin has significantly ($p<0.001$) reduced FPG, PPG and HBA1C in T2DM patients. They also had significant effect on serum lipid profile by reducing triglycerides and low density lipoprotein cholesterol after 12 weeks of therapy. Combination of metformin with vildagliptin was found to be significantly effective in the management of T2DM patients.

Limitations of Study:

- Short duration
- Minimal Sample size
- Requires further study to demonstrate the effect of gliptins on cardiovascular diseases and their safety and efficacy.

GROUP I- SULFONYL URE

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C
1	51	M	161	167	0	168	200	6.9
					4	124	172	
					8	103	148	
					12	88	136	6.4
2	53	M	164	80	0	174	210	6.9
					4	153	172	
					8	122	151	
					12	90	138	6.5
3	54	M	158	75	0	172	196	7
					4	118	170	
					8	101	149	
					12	88	134	6.6
4	47	M	154	87	0	186	210	7.1
					4	128	170	
					8	112	142	
					12	94	136	6.8
5	46	M	157	92	0	156	170	6.7
					4	148	160	
					8	142	158	
					12	140	156	6.4
6	53	F	154	80	0	170	200	6.9
					4	128	176	
					8	104	142	
					12	90	136	6.2
7	61	F	149	74	0	156	188	6.8
					4	129	152	
					8	116	142	
					12	78	130	6.1
8	55	M	161	86	0	150	180	6.7
					4	132	162	
					8	112	148	
					12	86	136	6.4
9	48	M	159	98	0	174	198	6.9
					4	134	171	
					8	106	150	
					12	90	134	6.3
10	56	M	164	94	0	180	200	6.9
					4	156	164	
					8	121	152	
					12	90	140	6.2
					0	166	188	6.8

11	55	F	156	70	4	128	154	
					8	103	141	
					12	88	130	6.2
12	62	M	159	87	0	182	200	6.9
					4	140	162	
					8	121	142	
					12	90	128	6.5
13	54	F	146	75	0	174	190	7
					4	128	158	
					8	100	142	
					12	86	136	6.8
14	62	F	149	69	0	162	180	6.7
					4	136	149	
					8	120	140	
					12	92	132	6.4
15	52	M	153	98	0	148	170	6.6
					4	122	146	
					8	108	132	
					12	70	129	6.3
16	55	M	161	99	0	154	178	6.7
					4	122	152	
					8	106	128	
					12	82	126	6.2
17	58	M	152	108	0	166	183	6.8
					4	132	154	
					8	102	141	
					12	86	122	6.1
18	47	F	145	75	0	146	170	6.7
					4	116	152	
					8	100	136	
					12	72	130	5.8
19	52	F	143	78	0	168	190	6.9
					4	132	164	
					8	109	152	
					12	78	138	6.1
20	57	M	153	89	0	188	220	7.2
					4	126	190	
					8	106	152	
					12	84	140	6.4
21	53	M	159	85	0	180	200	7
					4	146	174	
					8	122	162	
					12	78	140	6.8
22	52	F	149	74	0	166	190	6.9
					4	113	171	
					8	102	154	

					12	86	136	6.5
23	43	F	151	78	0	148	170	6.6
					4	119	162	
					8	98	141	
					12	72	124	6.4
24	56	M	162	92	0	158	176	6.7
					4	122	158	
					8	108	137	
					12	86	122	6.5
25	55	M	158	98	0	154	172	6.8
					4	124	154	
					8	108	138	
					12	84	128	6.4
26	60	M	161	72	0	176	188	6.8
					4	132	152	
					8	102	140	
					12	86	126	6.4
27	56	M	158	78	0	159	174	6.7
					4	130	143	
					8	116	131	
					12	98	124	6.5
28	48	F	154	84	0	144	166	6.7
					4	130	150	
					8	98	132	
					12	72	130	6.4
29	52	M	156	92	0	188	210	7
					4	149	196	
					8	122	189	
					12	90	200	6.8
30	58	M	165	98	0	164	186	6.9
					4	151	156	
					8	114	190	
					12	80	172	6.6

A(GLIBENCLAMIDE 5mg)

BLOOD UREA	SR.CREATININE	LIPID PROFILE				SERUM AMYLASE
		TC	TG	LDL	HDL	
26	0.6	190	138	76	58	45
		188	132	74	58	47
24	0.6	186	120	68	56	51
		184	119	66	57	48
26	0.8	198	136	78	64	41
		194	132	76	67	40
30	0.9	200	140	75	70	52
		198	137	73	72	51
21	0.7	170	130	66	62	46
		168	127	64	63	44
24	0.3	166	126	76	56	54
		161	124	74	57	52
28	0.6	189	140	84	62	61
		187	138	83	62	60
21	0.2	159	140	80	72	56
		156	137	76	75	54
36	0.8	176	138	66	82	43
		175	134	62	84	42
24	0.3	188	148	76	66	47
		185	146	74	68	47
26	0.4	186	134	72	54	42

		184	132	70	56	44
28	0.7	168	130	80	66	64
		166	128	78	66	68
21	0.6	194	129	69	62	53
		192	126	65	64	59
31	0.7	184	146	74	82	47
		183	141	71	86	45
41	0.8	158	128	82	78	52
		156	124	81	75	50
24	0.2	176	138	74	52	53
		177	136	72	52	50
32	0.6	158	144	82	68	56
		156	141	80	69	57
21	0.1	194	126	74	74	42
		191	124	72	76	41
24	0.4	172	132	68	66	47
		170	131	66	65	49
32	0.8	189	142	72	64	58
		186	140	70	61	56
28	0.7	200	120	74	64	47
		188	118	72	68	45
24	0.8	174	126	82	58	49

		176	129	76	59	50
21	0.7	156	142	68	54	51
		159	144	61	56	48
24	0.9	182	134	76	78	54
		184	130	70	76	50
28	0.6	166	128	80	72	61
		169	126	78	72	65
28	0.7	158	142	80	54	43
		154	144	78	56	42
24	0.8	196	124	72	64	47
		198	121	71	64	49
27	0.6	178	130	82	56	51
		174	128	84	58	56
31	0.6	166	138	70	78	54
		161	136	66	79	50
34	0.9	200	134	72	64	61
		189	130	70	66	63

GROUP II- SULFONYL URE

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C
1	58	F	162	85	0	180	220	6.8
					4	162	180	
					8	146	162	
					12	94	130	6.2
2	61	M	168	96	0	174	200	6.6
					4	164	176	
					8	132	148	
					12	90	126	6.2
3	64	M	164	110	0	170	208	7
					4	152	183	
					8	124	152	
					12	98	134	6.6
4	65	F	156	78	0	180	190	6.8
					4	162	168	
					8	134	150	
					12	90	136	6.2
5	58	F	151	68	0	176	184	6.6
					4	156	164	
					8	124	148	
					12	100	134	6.1
6	58	F	146	85	0	170	180	6.6
					4	158	168	
					8	124	146	
					12	88	130	6.2
7	47	F	149	78	0	162	176	6.8
					4	144	156	
					8	120	142	
					12	100	132	6.4
8	64	M	161	89	0	158	200	6.8
					4	132	183	
					8	120	152	
					12	102	126	6.1
9	50	M	162	96	0	164	184	6.8
					4	146	164	
					8	120	148	
					12	96	134	6.2
10	59	M	156	108	0	180	170	7
					4	156	158	
					8	132	140	
					12	106	130	6.6
11	54	M	162	108	0	170	210	7
					4	160	186	
					8	142	152	
					12	108	140	6.6

12	61	F	143	88	0	168	190	6.8
					4	146	174	
					8	122	156	
					12	110	138	6.2
13	55	M	156	96	0	180	170	6.8
					4	168	156	
					8	138	140	
					12	106	130	6.6
14	56	M	158	98	0	200	220	6.9
					4	180	184	
					8	148	154	
					12	110	142	6.5
15	47	F	146	74	0	206	210	7.1
					4	182	188	
					8	146	154	
					12	98	138	6.3
16	62	F	148	89	0	170	200	7.1
					4	158	182	
					8	124	162	
					12	88	136	6.4
17	53	M	155	104	0	178	198	6.8
					4	158	180	
					8	130	160	
					12	110	130	6.4
18	54	M	158	112	0	182	184	6.6
					4	164	162	
					8	14	142	
					12	106	132	6.1
19	46	F	149	78	0	176	180	6.6
					4	154	168	
					8	128	146	
					12	90	130	6.1
20	54	M	154	94	0	194	210	7
					4	176	180	
					8	148	158	
					12	110	142	6.6
21	62	M	165	92	0	194	210	7.4
					4	172	188	
					8	140	156	
					12	110	130	6.7
22	53	F	163	84	0	180	186	7
					4	162	163	
					8	136	143	
					12	100	128	6.2
23	58	F	163	86	0	170	182	7.2
					4	152	160	
					8	122	146	
					12	96	130	6.2
					0	200	220	6.9

24	52	M	160	80	4	174	188	
					8	150	158	
					12	114	146	6.4
25	43	F	159	79	0	168	180	6.8
					4	142	160	
					8	120	152	
					12	86	132	6.2
26	45	M	164	87	0	170	190	6.2
					4	156	168	
					8	120	150	
					12	90	138	6.3
27	66	M	160	98	0	190	210	7
					4	168	180	
					8	140	162	
					12	110	142	6.6
28	52	F	156	83	0	182	200	7
					4	162	176	
					8	134	148	
					12	100	126	6.2
29	53	M	151	92	0	168	180	7.1
					4	150	162	
					8	126	150	
					12	108	124	6.3
30	56	M	146	70	0	200	220	6.9
					4	172	180	
					8	144	158	
					12	110	130	6.6

:A+SITAGLIPTIN

BLOOD UREA	SR.CREATININE	LIPID PROFILE			
		TC	TG	LDL	HDL
40	0.9	182	146	80	52
		170	138	72	60
28	0.6	180	146	82	50
		172	136	74	58
30	0.9	200	140	82	40
		188	136	76	50
36	1	186	138	80	38
		180	130	70	52
24	0.9	184	142	78	50
		178	136	70	60
28	1	190	146	90	35
		182	136	83	65
30	0.9	184	140	88	35
		178	134	78	55
30	0.9	190	140	88	40
		184	138	76	60
26	1	186	144	90	42
		178	136	78	56
24	0.6	180	146	86	42
		170	132	74	60
36	0.8	194	148	86	38
		182	138	80	55

28	1	186	148	86	30
		180	136	76	50
20	0.8	190	138	90	38
		184	130	88	58
24	1	180	140	90	50
		174	132	80	60
30	0.9	196	140	86	52
		188	132	76	60
30	1	180	146	90	34
		172	138	80	58
28	1	184	140	90	36
		176	130	76	58
26	0.9	190	136	88	50
		180	128	80	60
26	0.6	186	140	80	48
		182	132	72	64
20	1	194	138	86	40
		186	130	72	58
26	0.8	182	150	92	40
		176	140	80	60
28	1	180	140	90	40
		172	128	80	62
18	1.2	180	136	86	32
		170	128	74	58
20	0.9	200	136	80	34

		192	130	70	58
24	1	190	130	84	36
		182	120	72	60
24	0.9	180	130	86	40
		174	122	76	60
20	1	190	130	90	52
		183	124	70	68
18	0.6	186	140	80	50
		178	130	70	64
30	0.8	184	138	88	40
		180	128	68	62
20	0.8	190	140	80	48
		180	130	68	68

SERUM AMYLASE
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GROUP III- SULFONYL UR

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C
1	46	F	160	72	0	123	298	8
					4	111	202	
					8	108	173	
					12	96	132	6.9
2	50	F	148	56	0	140	306	7.4
					4	120	237	
					8	109	169	
					12	102	128	6
3	44	M	170	74	0	136	222	7.6
					4	116	108	
					8	108	143	
					12	97	109	6.2
4	57	F	156	59	0	162	320	7.4
					4	139	276	
					8	118	204	
					12	102	140	6.4
5	60	M	163	54	0	149	272	7.8
					4	126	218	
					8	118	156	
					12	100	126	6.4
6	55	M	170	68	0	184	320	7.2
					4	136	240	
					8	117	187	
					12	102	138	6.2
7	49	M	163	49	0	139	200	7
					4	128	163	
					8	106	129	
					12	94	107	6.2
8	53	F	150	64	0	186	340	7.4
					4	136	290	
					8	120	209	
					12	108	136	6.1
9	48	M	159	56	0	176	273	6.9
					4	129	209	
					8	120	187	
					12	100	147	6
10	60	M	164	52	0	119	170	7.1
					4	108	120	
					8	100	102	
					12	92	94	6.3
11	59	F	149	68	0	146	228	7
					4	128	186	
					8	110	140	
					12	92	109	6.1

12	57	F	156	72	0	154	242	7.2
					4	138	206	
					8	119	148	
					12	103	116	6.6
13	59	M	179	98	0	160	302	7.5
					4	139	273	
					8	120	218	
					12	104	110	6.3
14	49	M	172	86	0	152	290	6.9
					4	136	200	
					8	108	169	
					12	93	126	6.2
15	50	M	176	77	0	142	209	7.1
					4	128	173	
					8	120	156	
					12	104	120	6.3
16	54	F	152	64	0	146	296	7.2
					4	128	222	
					8	120	128	
					12	104	120	6
17	49	F	156	51	0	140	270	6.9
					4	124	236	
					8	118	175	
					12	99	129	5.9
18	57	M	164	59	0	136	256	6.3
					4	128	208	
					8	119	146	
					12	107	120	5.5
19	59	F	173	65	0	145	290	7.2
					4	130	220	
					8	126	168	
					12	104	130	6.4
20	43	M	175	85	0	160	302	7.9
					4	140	256	
					8	121	184	
					12	109	140	6.4
21	60	F	148	54	0	129	188	7.2
					4	108	174	
					8	100	160	
					12	94	120	6.3
22	49	M	168	70	0	132	200	7
					4	118	164	
					8	112	148	
					12	103	130	6.2
23	54	F	152	63	0	126	176	6.7
					4	120	144	
					8	104	126	
					12	89	105	5.9
					0	149	230	6.6

24	48	F	143	68	4	136	201	
					8	118	174	
					12	110	140	6
25	50	F	159	71	0	136	260	7.1
					4	126	204	
					8	104	189	
					12	93	135	6.2
26	54	F	138	46	0	140	220	7
					4	120	186	
					8	106	162	
					12	98	120	6.2
27	56	M	168	75	0	140	232	7.2
					4	136	170	
					8	118	120	
					12	102	106	6.4
28	45	M	170	72	0	142	200	7
					4	126	156	
					8	106	130	
					12	94	110	6.3
29	48	F	163	58	0	143	176	7.1
					4	129	156	
					8	109	130	
					12	98	100	6.3
30	60	M	168	82	0	139	179	6.9
					4	120	130	
					8	109	116	
					12	93	108	6.1

EA+VILDAGLIPTIN

BLOOD UREA	SR.CREATININE	LIPID PROFILE				SERUM AMYLASE
		TC	TG	LDL	HDL	
22	0.9	180	109	86	39	32
		180	108	77	39	32
28	0.8	172	128	73	45	40
		170	128	66	46	38
34	0.9	176	130	59	46	34
		174	128	48	46	33
32	1	165	140	86	52	42
		162	128	64	53	43
29	0.8	180	130	110	36	38
		175	126	98	39	45
28	0.8	192	140	86	45	36
		190	136	73	46	38
31	0.9	173	128	59	53	32
		172	120	46	55	34
32	0.9	186	129	63	39	41
		180	129	55	40	40
34	0.9	176	130	69	42	29
		176	130	53	43	30
29	0.8	180	120	58	39	42
		180	120	52	43	43
28	0.8	172	123	69	42	40
		170	120	60	42	43

32	1	164	131	75	36	36
		164	130	65	38	39
29	0.9	180	130	73	41	41
		180	128	69	42	44
30	1	190	140	86	39	37
		184	136	73	40	34
26	0.9	158	113	63	50	39
		158	112	59	50	40
28	0.9	180	126	79	39	32
		179	126	64	40	34
32	1	173	148	82	46	38
		172	146	73	46	40
32	1.1	154	118	59	52	42
		153	118	56	53	44
26	0.8	186	151	88	33	46
		179	150	78	39	44
24	0.9	188	150	108	35	38
		180	150	90	35	40
26	0.8	180	146	80	51	29
		174	144	73	52	30
24	0.9	179	128	76	43	37
		168	120	62	43	39
32	1	170	132	86	39	35
		170	126	80	43	37
20	0.8	192	129	60	33	37

		190	126	51	33	39
31	1.1	178	142	73	50	41
		175	140	64	50	43
28	0.8	160	136	84	36	32
		160	134	75	36	34
32	0.8	158	130	80	40	38
		156	129	71	41	40
26	1	173	138	86	39	29
		172	138	75	40	30
30	0.8	180	146	88	36	36
		176	145	77	37	35
24	0.9	163	130	69	50	41
		162	128	62	52	40

GROUP IV- METFORMIN

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C
1	43	M	170	86	0	124	180	6.9
					4	118	160	
					8	104	148	
					12	86	126	6
2	49	M	173	77	0	130	198	7.1
					4	126	172	
					8	116	156	
					12	96	134	6.6
3	54	F	151	50	0	104	210	7
					4	139	172	
					8	104	139	
					12	98	160	6.2
4	48	M	168	74	0	150	208	6.8
					4	126	169	
					8	108	141	
					12	92	132	6.4
5	44	F	156	70	0	121	184	7.2
					4	118	170	
					8	100	142	
					12	76	124	6.1
6	49	M	168	69	0	139	210	7.1
					4	116	196	
					8	98	154	
					12	76	138	6.6
7	56	F	149	54	0	149	189	6.9
					4	128	162	
					8	94	141	
					12	78	126	6.5
8	57	F	152	49	0	136	229	7.2
					4	112	201	
					8	104	178	
					12	84	133	6.8
9	60	F	154	72	0	154	196	7
					4	126	176	
					8	101	154	
					12	88	127	6.4
10	55	F	156	68	0	162	218	6.8
					4	138	194	
					8	112	156	
					12	84	136	6.2
11	49	M	175	64	0	141	182	7.1
					4	108	160	
					8	99	149	
					12	79	134	6.2

12	57	M	170	76	0	126	178	7.3
					4	120	159	
					8	100	128	
					12	81	109	6.7
13	53	F	163	70	0	149	166	6.9
					4	112	136	
					8	104	120	
					12	86	116	6
14	47	F	148	58	0	134	186	7.2
					4	112	139	
					8	100	128	
					12	78	124	6.8
15	48	M	159	84	0	192	220	7.3
					4	128	170	
					8	108	152	
					12	94	138	6.6
16	56	F	163	73	0	168	220	7.4
					4	132	184	
					8	109	146	
					12	96	132	7
17	47	F	159	64	0	154	191	6.8
					4	126	152	
					8	112	139	
					12	81	123	6.2
18	60	M	175	80	0	164	196	6.9
					4	109	150	
					8	98	138	
					12	92	118	6.4
19	53	F	136	70	0	110	162	6.6
					4	98	136	
					8	94	112	
					12	75	109	6.1
20	58	M	167	76	0	138	186	6.9
					4	101	160	
					8	90	142	
					12	79	137	6.2
21	62	M	176	88	0	164	220	7.5
					4	129	169	
					8	99	142	
					12	84	131	7
22	61	M	179	75	0	134	166	7.1
					4	112	128	
					8	94	114	
					12	72	109	6.9
23	52	F	158	75	0	168	242	7.8
					4	114	194	
					8	102	138	
					12	87	128	6.7
					0	144	261	7

24	51	F	168	84	4	108	171	
					8	86	152	
					12	76	134	5.9
25	64	M	170	54	0	168	229	7.3
					4	120	164	
					8	109	132	
					12	82	114	6.1
26	42	M	159	56	0	174	218	7.1
					4	129	172	
					8	102	146	
					12	82	136	6.8
27	51	M	168	72	0	167	194	6.9
					4	148	143	
					8	112	138	
					12	91	128	6.1
28	61	F	148	68	0	150	195	6.8
					4	124	156	
					8	101	140	
					12	75	131	6.2
29	52	M	173	89	0	128	188	6.7
					4	102	152	
					8	96	141	
					12	72	124	6.1
30	52	F	149	63	0	161	226	7.2
					4	126	182	
					8	100	143	
					12	87	134	6.6

BLOOD UREA	SR.CREATININE	LIPID PROFILE				SERUM AMYLASE
		TC	TG	LDL	HDL	
24	0.6	176	134	86	43	41
		170	130	82	43	41
26	0.2	152	124	81	52	45
		150	123	80	54	45
32	0.8	164	132	76	47	39
		161	130	74	47	38
21	0.9	175	137	82	54	48
		172	135	80	55	47
18	0.7	168	141	79	49	52
		165	140	77	49	51
24	0.4	178	132	75	42	41
		175	130	71	42	39
28	0.8	162	128	80	49	38
		160	126	79	49	36
34	0.9	158	121	74	47	54
		157	120	72	48	52
40	0.9	173	134	84	46	44
		170	133	83	47	44
22	0.6	178	126	88	42	53
		176	125	87	43	50
28	0.2	172	136	78	45	41
		172	135	77	46	40

18	0.1	161	124	82	52	38
		160	122	80	53	38
24	0.6	159	132	76	58	45
		157	130	75	58	44
30	0.4	164	138	79	49	47
		162	135	77	49	44
32	0.2	179	131	80	45	51
		177	130	79	46	50
28	0.6	182	136	78	42	48
		180	134	77	40	47
32	0.8	178	128	84	44	51
		176	125	81	45	49
21	0.2	174	136	82	41	38
		172	134	80	42	38
18	0.4	156	124	72	48	58
		154	122	70	49	57
22	0.6	174	138	78	44	46
		172	135	76	45	44
24	0.2	174	129	78	49	44
		172	127	75	49	42
21	0.4	166	134	76	51	37
		164	132	74	52	37
18	0.8	182	139	68	52	41
		180	135	66	52	41
26	0.7	173	128	77	46	34

		172	126	76	46	33
32	0.9	162	134	84	52	51
		160	132	81	53	50
28	7.1	176	132	76	48	42
		174	130	74	49	40
30	0.8	182	138	84	46	54
		180	135	82	47	53
22	0.2	178	128	76	41	48
		176	126	75	43	46
18	0.4	186	134	87	54	56
		184	132	85	55	54
24	0.6	184	126	82	43	44
		182	124	80	44	44

GROUP V- METFORMIN + S

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C
1	58	F	152	54	0	170	260	7.6
					4	148	211	
					8	112	167	
					12	105	129	6.4
2	62	M	164	68	0	196	222	7.2
					4	162	171	
					8	108	132	
					12	80	110	6.4
3	50	F	150	58	0	164	276	7.3
					4	116	218	
					8	94	156	
					12	72	137	6.1
4	65	M	168	70	0	141	219	7.9
					4	109	182	
					8	92	134	
					12	78	117	6.6
5	68	M	162	76	0	189	288	8
					4	148	211	
					8	104	156	
					12	87	131	5.9
6	56	F	154	60	0	158	291	7.4
					4	103	214	
					8	86	162	
					12	72	136	6.2
7	58	F	152	58	0	179	263	7.1
					4	124	208	
					8	86	156	
					12	94	142	5.6
8	66	M	162	74	0	131	241	7.5
					4	98	198	
					8	82	145	
					12	74	129	6.8
9	62	M	170	72	0	126	246	7.8
					4	107	204	
					8	82	173	
					12	77	134	6
10	48	F	164	64	0	146	227	7
					4	106	198	
					8	84	152	
					12	66	124	5.3
11	68	M	168	74	0	147	267	77
					4	123	194	
					8	108	142	
					12	74	129	6.1

12	54	F	152	54	0	162	253	7.4
					4	134	214	
					8	106	142	
					12	87	116	6.6
13	60	M	164	68	0	159	182	7.9
					4	123	168	
					8	97	136	
					12	74	116	5.8
14	63	M	162	76	0	212	314	8.2
					4	163	235	
					8	127	181	
					12	104	147	6.4
15	52	F	156	58	0	186	228	7.9
					4	147	184	
					8	110	158	
					12	88	127	5.5
16	54	F	156	60	0	162	234	7.3
					4	126	196	
					8	104	154	
					12	81	136	5.8
17	48	F	158	58	0	138	187	7.6
					4	112	152	
					8	94	138	
					12	71	114	6.1
18	60	M	168	72	0	164	228	7.8
					4	138	186	
					8	107	158	
					12	74	114	6.4
19	66	M	164	76	0	158	284	8
					4	126	246	
					8	101	178	
					12	83	127	6.3
20	58	M	172	70	0	176	218	7.3
					4	142	192	
					8	108	164	
					12	71	124	5.8
21	64	M	170	68	0	174	236	7.4
					4	121	197	
					8	96	152	
					12	67	123	6
22	66	M	166	72	0	186	227	7.9
					4	145	184	
					8	116	158	
					12	78	134	6.4
23	52	F	156	52	0	154	242	7.3
					4	126	216	
					8	102	164	
					12	78	126	5.8
					0	147	279	8.1

24	65	M	164	78	4	122	225	
					8	94	158	
					12	72	118	6.6
25	58	F	152	52	0	136	284	7.8
					4	119	216	
					8	99	171	
					12	74	136	5.8
26	60	M	168	74	0	182	229	7.5
					4	158	192	
					8	124	167	
					12	78	136	6.1
27	58	F	154	54	0	167	246	7.1
					4	142	208	
					8	116	164	
					12	64	128	5.8
28	50	F	156	58	0	146	265	7.8
					4	124	237	
					8	104	173	
					12	82	121	6.2
29	65	M	170	76	0	124	276	8.1
					4	116	241	
					8	99	182	
					12	78	137	6.3
30	62	M	168	72	0	236	282	8.3
					4	181	184	
					8	114	158	
					12	86	106	6.1

SITAGLIPTIN

BLOOD UREA	SR.CREATININE	LIPID PROFILE				SERUM AMYLASE
		TC	TG	LDL	HDL	
22	0.7	179	161	96	62	41
		188	132	74	58	47
18	0.5	142	146	110	45	36
		148	138	82	52	36
16	0.4	174	181	118	42	44
		182	149	86	54	43
26	0.8	168	144	98	78	47
		161	138	76	71	47
19	0.3	172	136	85	67	51
		174	128	71	69	50
21	191	143	110	58	47	
	182	138	91	69	46	
30	1	164	162	118	57	32
		162	156	84	59	32
17	0.5	186	147	92	61	36
		188	138	81	64	36
19	0.4	156	154	112	57	48
		159	138	91	62	47
24	0.6	184	162	96	58	42
		186	148	81	61	42
26	0.9	178	148	98	58	32
		174	136	81	61	30

27	0.7	186	141	88	59	44
		182	124	74	64	44
16	0.3	168	138	91	54	35
		162	123	78	58	34
19	0.8	186	156	118	54	42
		178	141	86	65	42
23	0.5	192	136	92	59	37
		184	128	84	68	36
19	0.2	188	136	98	58	41
		184	134	82	65	40
29	0.7	193	144	88	54	34
		186	136	72	68	34
14	1	182	148	88	42	33
		178	132	72	55	33
32	0.3	176	146	96	57	46
		172	138	82	62	45
23	0.5	168	148	86	51	42
		161	132	71	68	42
14	0.4	186	142	88	57	45
		188	138	71	62	44
22	0.8	198	139	92	43	47
		182	132	74	61	46
26	0.2	184	141	92	51	42
		182	136	78	64	42
30	0.9	178	146	87	45	38

		172	131	64	68	38
18	0.5	169	148	92	56	36
		162	134	78	67	35
22	0.2	188	156	110	55	38
		176	148	84	62	38
33	0.8	196	141	96	44	42
		182	138	81	58	41
21	0.6	196	136	92	56	47
		188	132	78	67	47
18	2.1	176	147	92	58	51
		168	136	86	66	51
11	6.4	194	138	98	54	61
		182	132	76	69	60

GROUP VI- METFORMIN+VILDAGLIPTIN

S.NO	AGE	SEX	HEIGHT	WEIGHT	WEEKS	FBS	PPBS	HBA1C	BLOOD UREA	SR.CREATININE	LIPID PROFILE				SERUM AMYLASE
											TC	TG	LDL	HDL	
1	55	M	160	98	0	126	243	7.2	24	0.7	176	133	68	41	46
					4	118	214								
					8	92	148								
					12	74	108	5.8			174	126	61	42	45
2	60	M	151	110	0	194	268	7.2	28	0.9	186	144	83	34	52
					4	163	243								
					8	118	189								
					12	82	114	6.4			181	133	74	37	52
3	58	F	156	82	0	131	29	7.8	32	0.6	180	139	84	48	64
					4	116	265								
					8	87	178								
					12	74	136	6.1			176	126	70	49	63
4	65	F	146	74	0	123	246	6.9	21	0.4	183	141	69	48	43
					4	110	204								
					8	91	168								
					12	71	122	5.5			180	133	65	48	40
5	63	M	164	87	0	232	296	7.8	26	0.1	194	152	79	38	78
					4	184	211								
					8	126	158								
					12	85	138	6.4			190	146	70	40	74
6	61	F	145	84	0	149	237	7.6	34	0.3	160	146	51	52	62
					4	116	182								
					8	82	148								
					12	68	126	6.5			158	124	57	52	60
7	58	M	156	99	0	182	251	7.3	26	0.9	170	142	64	40	55
					4	128	196								
					8	94	143								
					12	84	116	5.8			164	129	56	41	51
8	54	M	158	114	0	164	249	7.4	24	0.5	173	144	65	39	42
					4	118	170								
					8	86	142								
					12	71	134	6.2			165	136	57	42	43
9	68	M	166	94	0	197	283	7.8	32	0.8	204	187	98	35	38
					4	124	206								
					8	92	173								
					12	85	137	6.1			196	174	79	40	39

10	58	F	148	76	0	146	231	7	23	0.4	168	138	64	42	47
					4	128	185								
					8	93	149								
					12	68	128	5.4			164	126	55	45	43
11	62	M	154	89	0	173	293	7.6	28	0.4	180	109	86	39	58
					4	134	226								
					8	106	168								
					12	78	127	6.2			180	108	77	40	55
12	54	M	162	96	0	164	236	7.4	26	0.9	183	112	84	42	72
					4	138	184								
					8	106	149								
					12	81	112	6.1			174	110	76	42	70
13	60	F	148	86	0	156	294	6.8	34	1	185	140	86	53	61
					4	133	204								
					8	106	173								
					12	74	137	6			180	129	69	53	58
14	58	F	156	78	0	141	276	7.1	18	0.1	168	138	75	36	83
					4	136	203								
					8	109	164								
					12	93	128	5.4			164	131	64	38	81
15	67	M	167	114	0	158	238	7.3	16	0.4	192	144	85	39	74
					4	133	194								
					8	114	146								
					12	76	106	6.1			181	136	70	41	73
16	57	M	163	118	0	148	256	7.4	34	0.6	172	136	86	36	43
					4	128	202								
					8	99	164								
					12	62	128	6			170	133	76	37	41
17	63	M	158	98	0	186	293	8	26	0.4	184	146	88	39	56
					4	150	220								
					8	122	169								
					12	94	128	6.2			181	140	74	42	54
18	56	F	149	73	0	162	310	8	14	0.2	198	154	86	39	68
					4	136	256								
					8	113	174								
					12	101	139	6.9			192	139	69	40	65

19	64	M	152	96	0	154	261	7.5	16	0.6	172	148	84	43	77
					4	138	216								
					8	102	159								
					12	82	117	6.1			169	136	71	45	75
20	58	F	165	83	0	167	245	7.4	26	0.2	179	128	76	43	49
					4	141	198								
					8	120	136								
					12	97	109	6.2			168	120	63	47	47
21	63	M	154	107	0	141	242	7.2	34	0.9	179	133	76	45	58
					4	124	204								
					8	103	169								
					12	81	126	6			171	126	64	47	56
22	44	M	158	94	0	167	274	7.4	13	0.6	183	149	60	38	61
					4	143	241								
					8	114	187								
					12	74	128	5.6			179	126	50	39	62
23	48	F	147	83	0	188	296	8	18	0.3	187	151	88	33	47
					4	164	248								
					8	123	163								
					12	89	122	6.6			178	146	73	39	49
24	38	M	166	98	0	194	313	8.1	22	0.1	186	150	108	35	74
					4	153	241								
					8	116	172								
					12	84	138	6.4			182	150	90	39	73
25	45	M	162	103	0	188	275	7.8	28	0.8	174	138	59	53	88
					4	166	249								
					8	128	174								
					12	74	124	6.3			170	134	47	53	86
26	60	M	166	87	0	184	248	7.4	14	0.6	176	138	70	40	52
					4	158	216								
					8	123	164								
					12	79	122	6.3			173	129	65	43	51

27	41	F	149	86	0	193	269	7.6	19	0.2	179	146	80	38	47
					4	148	218								
					8	109	174								
					12	78	131	5.4			176	148	70	40	46
28	49	F	159	78	0	183	293	7.9	28	0.8	183	148	83	46	54
					4	151	215								
					8	109	172								
					12	74	136	6.4			176	141	74	46	55
29	56	M	156	118	0	174	272	7.1	34	0.6	187	149	85	45	62
					4	146	208								
					8	118	164								
					12	73	134	5.7			176	142	73	47	61
30	59	M	164	96	0	194	246	7.6	20	0.2	168	132	71	39	37
					4	163	204								
					8	108	159								
					12	78	124	6.3			162	127	63	42	35

CASE SHEET

Registration no: **Date:**

Name: **Age:** **Sex:**

Address:

Occupation: **Marital Status:** **Weight (Kg):**

Height (Cm): **BMI:**

Chief Complaints:

H/o Present illness:

Past History:

Personal History:

Family History:

Obstetric History:

Treatment History:

General Examination:

BP:

PR:

Temp:

RR:

Systemic examination:

Investigation:

Plasma glycosylated haemoglobin (HbA1C)

Fasting blood sugar

Postprandial blood sugar

Lipid profile- Total cholesterol, Triglycerides, High density Lipoprotein, Low density Lipoprotein

Urea

Serum Creatinine

Serum Amylase

Treatment:

Signature of the Investigator

CONSENT FORM

(To be obtained from subject)

Introduction:

You are requested to participate in a study conducted in **department of Pharmacology**, Chennai Medical College Hospital & Research Centre, Irungalur, Tiruchirapalli, Tamil Nadu entitled.

"The comparative study of effect of sitagliptin and vildagliptin on glycaemic control And serum lipid level in type II diabetic mellitus patients in a rural tertiary care hospital"

Your participation in this study is Voluntary. You at liberty to participate/ withdraw from the study. Please read this consent form carefully and ask the Consultant, any questions you may have about the study before signing.

Explanation of Procedure:

If you agree to participate in this study, we will ask some question to you and collect relevant information/ Blood sample. You may be examined by the investigator, data from the study will be used for research purposes only. The results of the study will not to be given to you directly. There will be no cost to you participating in this study.

Potential benefits:

Your participation will help us to know the risk factor of this problem and results of this study will be beneficial for future generations.

Assurance of Confidentiality:

The information concerning your participation in the study will be kept confidential to the full extent permitted by law and used only for scientific purposes. No one except members of the research team will have access the results. Your name will not be disclosed in any report or released in any way.

Patient Consent:

I have read the explanation about this study and have been given an opportunity to discuss it and to ask questions. I have not received any money for participating in this study.

Signature of Subject Signature of Witness Date

Signature of Researcher

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