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A comparative Study in the Efficacy and Toxicity of Sitagliptin and Metformin in Type 2 Diabetes Mellitus

(Prospective Study)

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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صدق الله العظيم

DEDICATION

THIS WORK IS DEDICATED TO ALL MEMBERS OF MY FAMILY, & TO ALL PEOPLES WORK IN DIABETES FIELD

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In the beginning, I would like to present my thankfulness & greatest glory to Allah who gave me power to complete my thesis, & who always behind all successful achievement I got in my life.

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Certificate

I hereby certify that the work embodied in this thesis is the result of my own investigations except where a reference has been made to published literature.

Signed…….……supervisor of study.

Signed……joint supervisor of the study.

Declaration

I here declare that, this work has not already been accepted for any degree and is not been concurrently submitted in candidature for any degree.

Signed……candidate.

Abbreviations

ADA	American diabetic association
ALT	Alanine amino transferase
AST	Aspartate amino transferase
BDC	Benghazi diabetic center
BMI	Body mass index
CHF	Congestive heart failure
CKD	Chronic kidney disease
CVD	Cardio vascular disease
DASH	Dietary approach to stop hypertension
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DPP-4	Di peptidyl peptidase—4
EASD	European Association for the Study of Diabetes
FBS	Fasting Blood Sugar
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GDM	Gestational diabetes mellitus
GFR	Glomerular filtration rate
GIP	Glucose dependent insulin tropic peptide
GIT	Ggastro intestinal tract
GLP-1	Glucagon-like peptide-1
GOT	Glutamic oxaloacetate transaminase
GPT	Glutamic pyruvate transaminase
HbA_{1C}	Glycosylated haemoglobin

HDL	High density lipoprotein
HNS	Hyper osmolar non ketotic state
IADPSG	International Association of Diabetes and Pregnancy Study Groups.
IAF	International American federation
IDF	International diabetic federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
LADA	Latent autoimmune diabetes in adults
LDL	Low density lipoprotein
LFT	Liver function test
MNT	Medical nutrition therapy
NGSP	National Glyco hemoglobin Standardization Program
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
PCOS	Poly cystic ovarian syndrome
PPBS	Post Prandial Blood sugar
RDA	Recommended education and self-management
RFT	Renal function Test
RPG	Random plasma glucose
TC	Total cholesterol
TG	Triglyceride
TZD	Thiazolidinedione
VLDL	Very low density lipoprotein
WHO	World health organization

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INTRODUCTION

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Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia; this high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger (polyuria, polydipsia, and polyphagia).

Resulting from defects in insulin secretion, insulin action, or both that result in carbohydrate, protein and fat metabolism disturbance. The chronic hyperglycemia of diabetes is associated with acute complications include diabetic ketoacidosis and non-ketotic hyperosmolar coma and long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is associated with reduced life expectancy (WHO, Retrieved 4 April 2014).

I.2. Classification of DM:

There are mainly four broad categories of diabetes;

I.2-1 **Type 1 diabetes:** is immune-mediated and requires daily administration of insulin

I.2-2 Type 2 diabetes: is the most common form and comprises of 90% of people with diabetes around the world, it characterized by insulin resistance or relative insulin deficiency (Rippe 2010).

I.2-3 Gestational diabetes: has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Although most cases resolve with delivery, the definition applied whether or not the condition persisted after pregnancy and did not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy (Metzger et al. 2008).

In women of childbearing age, the number of pregnant women with undiagnosed type 2 diabetes has increased. Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually.

I.2.4 Other specific types of diabetes:

I.2.4.1 Genetic defects of beta-cell function

- Chromosome 20, HNF4alpha (MODY1)
- Chromosome 7, glucokinase (MODY2)
- Chromosome 12, HNF1alpha (MODY3)
- Chromosome 13, IPF-1 (MODY4)
- Mitochondrial DNA 3243 mutation
- Others

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I.3. Abnormality in blood sugar level:

I.3.1 Hyperglycemia: is a condition in which an excessive amount of glucose circulates in the blood plasma. Hyperglycemia occurs when blood glucose level exceeded 11.1 mmol/l (200mg/dl) (Kitabchi et al. 2009).

I.3.2 Hypoglycemia: a condition in which low blood glucose concentration below 4mmol/l. it is a medical emergency, (Kenny C et al. 2014).

I-4 Epidemiology of diabetes mellitus:

Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide (American Diabetes Association, 2005). Type 1 diabetes is usually diagnosed during childhood or early adolescence and it affects about 1 in every 600 children (Shi and Hu 2014).

The world prevalence of type 2 diabetes in Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000. In 2010, making up about 90% of the cases.In 2014, according to International Diabetes Federation, (IDF) an estimated 381 million people had diabetes (IDF, 2014). Its incidence is increasing rapidly, and by 2030, this number estimated to almost double.Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries (IDF, 2014).

Between 2010 and 2030, there is an expected 70% increase in numbers of adults with diabetes in developing countries and a 20% increase indeveloped countries(Shaw et al. 2010). The greatest increase in prevalence is however, expected to occur in Asia and Africa, where most patients will probably be found by 2030. The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s).

In 2011 diabetes resulted in 1.4 million deaths worldwide, making it the 8th leading cause of death (IDF, 2014).This number expected to increase by more than 50 percent over next decade, (Mathers 2006). Estimated global healthcare expenditures to treat and prevent diabetes and its complications is at least 376 billion US Dollar (USD) in 2010.

I-5. Pathophysiology of diabetes:

Insulin is the hormone that regulates the uptake of glucose from the blood into most cells of the body, especially brain, liver, muscle, and adipose tissue.so, deficiency of insulin or the resistance to its receptor plays a central role in all forms of diabetes mellitus (ADA, Retrieved 24 April 2014).

Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can transport glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen (Shoback, et al. 2011). Insulin released into the blood by (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, especially after eating. Insulin used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process mainly controlled by the hormone glucagon, which acts in the opposite direction to insulin (Kim et al. 2012). If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), then glucose will not be absorbed properly by the body cells that require it and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis.

When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will excreted in the urine (glycosuria) (Robert et al. 2012). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will replaced somatically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).

I.5.1-Type 1 (beta-cell destruction, usually leading to absolute insulin deficiency)

Although type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood (Rother 2007).

- **I .5.1.1 Autoimmune Diabetes Mellitus**

This form of diabetes, previously encompassed by the terms insulin-dependent diabetes, Type 1 diabetes, or juvenile-onset diabetes, results from autoimmune mediated destruction of the beta cells of the pancreas. Some patients, particularly children and adolescents, may present with ketoacidosis as the first manifestation of the disease

(Ozougwu 2010). Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Still others, particularly adults, may retain residual beta-cell function, sufficient to prevent ketoacidosis, for many years, individuals with this form of Type 1 diabetes often become dependent on insulin for survival eventually and are at risk for ketoacidosis (Ozougwu 2010).At this stage of the disease, there is little or no insulin secretion as manifested by low or undetectable levels of plasma C-peptide (Lambert and Bingley 2002)

The peak incidence of this form of Type 1 diabetes occurs in childhood and adolescence, but the onset may occur at any age, ranging from childhood to the ninth decade of life (IDF, 2009).

There is a genetic predisposition to autoimmune destruction of beta cells; it also related to environmental factors that still poorly defined. Although patients are usually not obese when they present with this type of diabetes, the presence of obesity is compatible with the diagnosis. These patients may also have other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease (Fontaine et al. 2009).

- **I.5.1.2 Idiopathic**

There are some forms of Type 1 diabetes, which have no known etiology. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity (Lambert 2002). This form of diabetes is more common among individuals of African and Asian origin. In another form found in Africans an absolute requirement for insulin replacement therapy in affected patients may come and go, and patients periodically develop ketoacidosis (Fontaine et al. 2009).

I.5.2 Type 2 (predominantly insulin resistance with relative insulin deficiency or predominantly an insulin secretory defect with/without insulin resistance)

Diabetes mellitus of this type previously encompassed non-insulin-dependent diabetes, or adult-onset diabetes. It is a term used for individuals who have relative (rather than absolute) insulin deficiency. People with this type of diabetes frequently are resistant to the action of insulin (Ozouguw et al. 2013). At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. This form of diabetes is frequently undiagnosed for many years because the hyper glycaemia is often not severe enough to provoke noticeable symptoms of diabetes (Ozouguw et al. 2013). Nevertheless, such patients are at increased risk of developing macro vascular and microvascular complications (Ozouguw et al. 2013).

The majority of patients with this form of diabetes are obese, and obesity itself causes or aggravates insulin resistance. Many of those who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region (Shoback et al. 2011). Ketoacidosis is infrequent in this type of diabetes; when seen it usually arises in association with the stress of another illness such as infection. Whereas patients with this form of diabetes may have insulin levels that appear normal or elevated, the high blood glucose levels in these diabetic patients would be expected to result in even higher insulin values had their beta-cell function been normal. Thus, insulin secretion is defective and insufficient to compensate for the insulin resistance (shoback et al. 2011).next table demonstrate some causes of insulin resistance.

Table 1. Some causes of insulin Resistance

S/No.	Causes
1	Obesity/overweight (especially excess visceral adiposity)
2	Excess glucorticoids (Cushing's syndrome or steroid therapy)
3	Excess growth hormone (acromegaly)
4	Pregnancy, gestational diabetes
5	Polycystic ovary disease
6	Lipodystrophy (acquired or genetic, associated with lipid accumulation in liver)
7	Autoantibodies to the insulin receptor
8	Mutations of insulin receptor
9	Mutations of the peroxisome proliferators' activator receptor γ (PPAR γ)
10	Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
11	Hemochromatosis (a hereditary disease that causes tissue iron accumulation).

(Raju et al. 2010).

On the other hand, some individuals have essentially normal insulin action, but markedly impaired insulin secretion. Insulin sensitivity may be increased by weight reduction, increased physical activity, and/or pharmacological treatment of hyper glycaemia but is not restored to normal (Washington et al. 2010).

Table 2. Clinical characteristics of patients with Type 1 and Type 2 diabetes mellitus.

Features	Type 1	Type 2
Age of onset	Usually less than 20 years	Usually greater than 30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	insulin	Thiazolidinediones, metformin, sulfonylureas, insulin

Rotell et al. (2013).

I.6. pre diabetes:

Before people develop type 2 diabetes, they usually have pre diabetes. In people who have pre diabetes, blood sugar levels are higher than normal but not high enough to say they have diabetes (Barr et al. 2007). Normal blood sugar is between 70 and 99 mg per dL. Blood sugar between 100 and 125 mg per dL suggests pre diabetes (WHO 2006). Blood sugar higher than 126 mg per dL is considered diabetes. People who have pre diabetes have a high risk of eventually developing diabetes in less than three years (Barr et al. 2007).

Table 3 Diagnosis of pre diabetes and Diabetes: Diagnostic Tests and Glucose Values:

Dignostic Test	Normal	Pre-diabetes	diabetes
Hemoglobin A_{1c}***a***	< 5.7%	5.7 - 6.4%	≥ 6.5%
Fasting plasma glucose ***a***	< 100 mg/dL	100-125 mg/dL	≥ 126 mg/dL
Random plasma glucose ***b***	< 130 mg/dL	130-199 mg/dL	≥ 200 mg/dL
Oral glucose tolerance test (OGTT) 2hrs after a 75 gm oral glucose load	< 140 mg/dL	140-199 mg/dL	≥ 200 mg/dL

(ADA 2010)

aFor HbA_{1c} and fasting glucose, the diagnosis must be confirmed by a second test
bA random glucose ≥ 200 mg/dL must be confirmed with a fasting glucose ≥ 126 mg/dL or the OGTT.

I.6.1 Pre diabetes Treatment Overview:

The treatment for pre diabetes will focus on losing weight, eating right, and getting active. Even if they have risk factors for pre diabetes, they can still take steps to prevent the disease. There is evidence that combined diet and exercise, as well as drug therapy (metformin, acarbose), may be effective at preventing progression to diabetes in pre diabetic and IGT (Impaired Glucose Tolerance) subjects (Mayo Clinic Diabetes 2009) .

I.7 Diagnostic Testing for Diabetes:

Patients presenting with symptoms of diabetes should be tested, the classic symptoms of diabetes include polyuria, polydipsia and unexplained weight loss, excessive hunger, fatigue or wounds that are slow to heal or frequent skin infections.

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed (American Diabetes Association 2010) Possible tests to assess for diabetes include fasting plasma glucose, an oral glucose tolerance test or an HBA_{1c} measurement, as seen in table 4 below:

Table 4. Diabetic diagnostic criteria.

Condition	2 hour glucose mmol/l(mg/dl)	Fasting glucose mmol/l(mg/dl)	HbA_{1c} %
Normal	< 7.8 (<140)	< 6.1 (<110)	< 6.0
Impaired fasting glycaemia	< 7.8 (<140)	≥ 6.1(≥110) & < 7.0(<126)	6.0 – 6.4
Impaired glucose tolerance	≥ 7.8 (≥140)	< 7.0 (<126)	6.0 – 6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥ 6.5

(WHO/IDF consultation, 2011 and Vijan 2010)

The World Health Organization definition of diabetes (both type 1 and type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either (WHO 2011) :

I.8. Risk Factors for diabetes:

- Physical inactivity
- 1st degree relative with diabetes
- High risk ethnic groups(African-AmerLatino,Asian- Amer, Pacific Islanders)
- Women who delivered a baby >9lbs +GDM
- Hypertension
- HDL<35 or Trigs >250
- Women with PCOS
- IGT or IFG on previous testing
- Hx CVD
- Severe obesity or acanthosis nigricans

I.9 Specific Goals and Measures:

For most chronic diseases, including diabetes, the most efficient improvement strategy is to focus on a limited number of specific improvement goals. These may be based on observed gaps in care, potential clinical impact, cost considerations or other criteria. In type 2 diabetes, focusing on **glycemic control, lipid control and blood pressure control** is a strategy that has been shown to be effective in preventing up to 53% of heart attacks and strokes, the leading drivers of excess mortality and costs in adults with diabetes (Gaede et al. 2003).

Good management of type 2 diabetes with pharmacologic and non-pharmacologic therapies is important and includes patient education, evaluation, and self-management, for microvascular and macro vascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.

Non pharmacologic therapy as seen in pre diabetic cases includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. (Vos et al. 2012)

I.9.1 Glycemic management:

I.9.1.1. Oral euglycemic drugs

- **Biguanides**

  In patients with type 2 diabetes, diet and physical activity are essential first line therapies, and many groups now recommend initiating metformin at diagnosis.

  Pharmacologic intervention should be considered at diagnosis for patients with type 2 diabetes. Metformin should be prescribed as the first line agent unless there are contradictions to its use. (Note that Metformin should be stopped at the time an iodinated

contrast agent is administered. Resume metformin after 48 hours if serum creatinine level is stable.) The choice of subsequent agents remains controversial (Boussageon et al. 2011). Sulfonylureas should be considered as a second-line agent. Weight-neutral medications have clinical appeal, but no outcomes data to support their use over any other medication. In general, if the patient has not achieved glycemic goal after four weeks of therapy at a maximal dose of an oral agent, the therapy should be considered inadequate. Insulin is the only anti-diabetic medication (besides metformin) with well documented clinical outcome data (Cukierman et al. 2005).

It typically reduces A_{1C} by 1-1.5% (Washington et al. 2010). Metformin is usually the first-line medication used for treatment of type 2 diabetes. In general, it is prescribed at initial diagnosis in conjunction with exercise and weight loss, as opposed to in the past, where it was prescribed after diet and exercise had failed. There is an immediate release as well as an extended-release formulation, typically reserved for patients experiencing GIT side-effects. It is also available in combination with other oral diabetic medications (Eurich et al. 2007).

Metformin has several characteristics that may provide secondary benefit:

- When used as a single agent, it rarely causes hypoglycemia and it does not cause weight gain.
- It appears to have favorable effects on lipid profiles and is associated with slightly lower cardiovascular mortality compared to sulfonylureas or insulin (Lambert and Bingley 2002).However, metformin has negative side effects and should not be used with some patients.
- Nausea and diarrhea are seen in up to 30% of patients; GI side effects are dose related. Metformin XR formulation may decrease diarrhea compared to the immediate release.
- Metformin should be avoided in patients with reduced creatinine clearance or who are at risk for the rare complication of lactic acidosis (e.g., patients with cirrhosis or severe CHF).
- It should be withheld in clinical settings such as IV contrast administration, surgery, or dehydration.

When initiating metformin, start with 500 mg daily with food, then increase the dose by 500 mg per week to 2000 mg per day as 2 or 3 divided doses as tolerated. Metformin therapy should be considered inadequate if the patient has not achieved his or her

glycemic goal after four weeks of therapy at a maximum dose. Even after instituting pharmacologic therapy, careful attention should still be given to diet and physical activity. In patients who are either not candidates for metformin therapy or have failed to achieve glycemic goals on maximal tolerated metformin dose, a second agent should be added. Options include sulfonylureas, non-sulfonylurea secretagogues, DPP4 inhibitors, alpha-glucosidase inhibitors and injectable medications. The choice of a second agent should be tailored to the individual patient, taking into consideration a variety of factors including BMI, renal function, medical problem list and patient preferences.(Diabetes Care" 2010"ADA).

- **Alphaglucosidase**

Alpha-glucosidase inhibitors like miglitol , acarbose and voglibose are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity.

These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes. Typical reductions in glycated hemoglobin (A_{1C}) values are 0.5–1.0%. These medications are rarely used in the United States because of the severity of their side-effects (flatulence and bloating). They are more commonly prescribed in Europe. They do have the potential to cause weight loss by lowering the amount of sugar metabolized (Krentz, et al. 2005).

I.9.1.2. Oral hypoglycemic secretagogues

- **Sulfonylureas**

Sulfonylureas: lower serum glucose by increasing insulin secretion, in a glucose-independent manner (Reis and Velho 2002). While sulfonylureas were traditionally used as first line agents in type 2 diabetes, they should now be considered a second tier choice. Compared to metformin, sulfonylureas have equivalent but less favorable effects on weight and increased risk of hypoglycemia. Additionally, weak evidence indicates that patients treated with sulfonylureas have higher cardiovascular mortality compared to patients treated with metformin (Lambert and Bingley 2002). Glyburide, glipizide and glimeperide all have comparable efficacy at HbA_{1c} reduction. In terms of clinical

response, the sulfonylureas, on average, lower Hb_{A1c} by 1–2% (Nathan et al. 2006). For patients with any renal impairment, glipizide is preferred.

As insulin secretagogues, the pharmacodynamics effects of sulfonylureas are dependent on functioning β cells; thus, they are typically used earlier in the course of the disease process. In later stages of the disease, when β-cell dysfunction becomes most prevalent, sulfonylurea efficacy may decline and may necessitate an increase in drug dosage or the switch to other non-insulin secretagogue therapy.

More recently, studies in isolated rodent and human islets showed that sulfonylureas induce β-cell apoptosis (Aquilante 2010) As such, concern has been raised as to whether sulfonylureas may exacerbate the pathogenesis of Type 2 diabetes.

Severe hypoglycemia can occur in patients with significant renal impairment.

Patients typically treated with a second-generation sulfonylurea starting at a low dose. Dose increments may be made every two weeks. If the patient has not achieved glycemic goal after four weeks of therapy at a maximal sulfonylurea dose, sulfonylurea therapy should be considered inadequate (Lambert et al. 2002).

- **Non-sulfonylureas (meglitinides)**

Non-sulfonylurea insulin secretogogues: as meglitinides (repaglinide , nateglinide), these medications also lower serum glucose by increasing insulin secretion. They are often used in the place of sulfonylureas in sulfonylurea -allergic patients or when their shorter half-life and frequent dosing might reduce the risk of hypoglycemia in the event of skipped or delayed meals. Effects on weight and hypoglycemia risk are comparable to sulfonylureas. . Typical reductions in glycated hemoglobin (HbA_{1C}) values are 0.5–1.0%.

I.9.1.3. Thiazolidinedione

Thiazolidinediones (TZD): also known as "glitazones" reduce insulin resistance and lower blood glucose levels by improving sensitivity to insulin in muscle and adipose tissue. They reduce both glucose and insulin levels and do not cause hypoglycemia when used as single agents (or in combination with metformin). These medications are very effective at lowering HbA_{1c} (1.5–2.0%). however due to their side effect profile, they should be considered third tier agents. TZDs are associated with significant weight gain. The FDA has issued a box warning for both available TZDs due to an increased risk of congestive heart failure (CHF), therefore these drugs should be avoided in patients with CHF. Both TZDs are associated with fluid retention and peripheral edema, which occur in at least 15% of patients. TZDs are

strongly associated with increased fracture risk in post-menopausal women. TZDs may worsen diabetic macular edema. Renal dosage adjustment is not necessary; Pioglitazone has been associated with an increased risk of bladder cancer. (Aquilante 2010). Some examples are: rosiglitazone (Avandia) that it be suspended from the EU market due to elevated cardiovascular risks (National Institute for Health and Clinical Excellence. London 2008) , pioglitazone (Actos), and troglitazone (Rezulin) which used in 1990s, withdrawn due to hepatitis and liver damage risk. (Hinterthuer and Adam 2008).

I.9.1.4. Peptideanaloge

- **injectable incretin mimetics**

Incretins are naturally occurring insulin secretagogues which increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, before blood glucose levels become elevated. They also slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying and may directly reduce food intake. As expected, they also inhibit glucagon release from the alpha cells of the Islets of Langerhans.

The two main candidate molecules that fulfill criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (glucose-dependent insulinotropic peptide, GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) (Amori et al. 2007).

- **injectable glucagon-like peptide analog**

Glucagon-like peptide (GLP) agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half-life of only a few minutes, thus an analogue of GLP would not be practical (Briones and Bajaj 2006). Exenatide (also Exendin-4, marketed as Byetta) is the first GLP-1 agonist approved for the treatment of type 2 diabetes.

Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life. Typical reductions in HbA_{1C} values are 0.5–1.0%. These agents may also cause a decrease in gastric motility, responsible for the common side effect of nausea, and is probably the mechanism by which weight loss occurs (Cvetković and Plosker 2007).

- **Gastric inhibitory peptide analog**
- **Dipeptidyl peptidase**

Dipeptidyl peptidase-4 (DPP-4) inhibitors: Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion and suppress glucagon. These incretin hormones are rapidly degraded by DPP-4. DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin , linagliptin, alogliptin and septagliptin), enhance the effect of these incretin hormones by inhibiting DPP-4. The first di peptidyl peptidase 4 (DPP-4) inhibitor sitagliptin was approved in 2006 as treatment for diabetes concurrently with lifestyle changes. A combined product of sitagliptin and Glucophage approved by the U.S. Food and Drug Administration in 2007 (FDA 2008). The second DPP-4 inhibitor, saxagliptin, was approved in the U.S. It was approved both as mono therapy as well as in combination with metformin, sulfonylurea, or thiazolidinedione (Ripsin et al. (2009). The use of a DPP-4 inhibitor called vildagliptin was approved in Europe and Latin America also as a combination with metformin, sulfonylurea, or thiazolidinedione. Two other DPP-4 inhibitors are also available (linagliptin and alogliptin). A DPP-4 inhibitor may be used as mono therapy in the event of intolerance to metformin and is a useful second tier agent for use in combination therapy (DPP-4 inhibitors are not associated with weight gain. When used as mono therapy, hypoglycemia is rare with these agents. Data on the effects of these drugs on lipid profiles or cardiovascular outcomes is limited. Dosage adjustments are required for renal insufficiency with Sitagliptin and Saxagliptin but not with Linagliptin. DPP-4 inhibitors lowered hemoglobin HbA_{1C} values by 0.74%, comparable to other antidiabetic drugs (Amori et al 2007).

Combination oral therapy: Each class of oral agents works by a different mechanism and they may be combined to achieve optimal glucose control. The obvious exceptions are sulfonylureas and non-sulfonylurea insulin secretagogues, which should not be combined. Typically, patients with type 2 diabetes are started on metformin, with a second agent or third agent added as needed. In general, the addition of an oral agent will reduce HbA_{1c} by an additional 1.0%. Tablets combining two classes of oral agents are now available. Combinations offer less dosing flexibility but cost is not necessarily greater compared to single-agent tablets.

Incretin mimetic agents, Exenatide (Byetta), Exenatide Liraglutide (Victoza), and Extended-Release Exenatide (Bydureon) are approved for type 2 diabetes. They are typically used with metformin or other oral agents. They enhance insulin release in presence of hyperglycemia, slow gastric emptying and suppress appetite, which can lead to weight loss in overweight individuals. Hypoglycemia is rare when these agents are used as a single agent or in

combination therapy with metformin. Data are limited regarding cardiovascular outcomes in relation to these drugs, though favorable effects on lipid profiles have been suggested, the most common side effects are nausea and vomiting. The FDA warns that exenatide may be associated with an increased risk for pancreatitis and subsequent acute renal failure (Arguedas et al.2013). If pancreatitis is suspected, exenatide should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology for the pancreatitis is identified. Exenatide should not be used in those with GFR<30. It should be used cautiously in those with GFR between 30 and 50, with careful monitoring of renal function and GI side effects.

Combination of oral/injectable therapy: Patients with type 2 diabetes who do not have adequate glucose control on oral agents will need to start an injectable agent or insulin therapy. DPP-4 inhibitors should not be combined with incretin mimetics such as exenatide or liraglutide. If insulin is initiated, most experts would agree that metformin should be continued. However, other hypoglycemic agents are usually discontinued. Arguments can be made for continuing other hypoglycemic agents in combination with insulin; however, no consensus exists as to what combinations should be used.

The addition of bedtime NPH remains a traditional approach. However, therapy with once daily Lantus has become increasingly popular due to its lack of an insulin peak and its 24-hour duration of action. Therapy may be intensified as needed with twice daily split/mixed insulin, or a basal/bolus insulin approach as needed to achieve glycemic goals.

- **glycosuric**

  Sodium glucose co transporter 2 inhibitors (SGLT-2 inhibitors) (Canagliflozin, Dapagliflozin) block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine. This causes both mild weight loss, and a mild reduction in blood sugar levels with little risk of hypoglycaemia. Urinary tract infection is a common side effect (Merck Veterinary Manual. 2005. Retrieved 2011).

I.9.1.5. Insulin

Adequate control is defined as an HbA_{1C} level less than 7 percent for most people; insulin may be recommended early if the HbA_{1C} remains elevated despite lifestyle changes and oral drugs, especially if the HbA_{1C} is higher than 8.5 percent**.** Type 2 diabetes typically progresses over time, causing the body to produce less insulin and resist the action of insulin that is produced. In addition, it can be difficult for some people to follow the recommended diet, exercise, or treatment plan.

Other people will need to add insulin because their blood sugar levels are not controlled. Using a combination of treatments (oral medication plus insulin) generally means that the person can

take a lower dose of insulin, compared to if insulin treatment is used alone. There may also be a reduced risk of weight gain if combination therapy is used. Insulin usually given once per day, either in the morning or at bedtime. Small insulin doses generally recommended when treatment first begins; the dose is adjusted over days, weeks, and months, once the body's response to insulin treatment is known.

To determine how and when to adjust the dose, the blood sugar level should be measured every morning before eating. If the value is consistently higher than 130 mg/dL (7.2 mmol/L), the clinician may recommend increasing the insulin dose. Insulin alon**e** Current recommendations are for most people with type 2 diabetes to be treated with metformin plus another medication such as insulin, as necessary.

However, for a variety of reasons, some people are treated only with insulin. People taking insulin alone often require two injections of intermediate-acting insulin or one injection of long-acting insulin per day. If a long-acting insulin or a twice daily injection of intermediate-acting insulin is not adequate to control blood sugar levels, a more intensive insulin treatment regimen may be recommended **(**Turner 2005).

A further danger of insulin treatment is that while diabetic microangiopathy is usually explained as the result of hyperglycemia, studies in rats indicate that the higher than normal level of insulin injected to control the hyperglycemia may itself promote small blood vessel disease (Kanasaki et al. 2013).

While there is no clear evidence that controlling hyperglycemia reduces diabetic macrovascular and cardiovascular disease, there are indications that intensive efforts to normalize blood glucose levels may worsen cardiovascular and cause diabetic mortality (Pignone et al. 2010).

Rapid-acting insulin, begins to work about 15 minutes after injection, peaks in about 1 hour, and continues to work for 2 to 4 hours. Types: Insulin glulisine (Apidra), insulin lispro (Humalog), and insulin aspart (NovoLog)

- **Regular or Short-acting insulin** usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from 2 to 3 hours after injection, and is effective for approximately 3 to 6 hours. Types: Humulin R, Novolin R, are used in conjunction with meals or to treat acute episodes of hyperglycemia. Since the onset and duration of rapid-acting insulin are more physiologic than Regular insulin, some practitioners prefer their use. However, in type 2 patients, Regular insulin is an appropriate choice and is less expensive.
- **Intermediate-acting insulin** generally reaches the bloodstream about 2 to 4 hours after

injection, peaks 4 to 12 hours later, and is effective for about 12 to 18 hours. Types: NPH (Humulin N, Novolin N). are typically given twice daily. A morning dose provides for daytime basal insulin requirements, and the post-lunchtime peak of action may reduce the need for short-acting insulin at lunch time. An evening dose, often given at bedtime, is titrated to fasting blood glucoses, to avoid nocturnal hypoglycemia.

- **Long-acting insulin** reaches the bloodstream several hours after injection and tends to lower glucose levels fairly evenly over a 24-hour period. Types: Insulin detemir (Levemir) and insulin glargine (Lantus). It can be used as a basal" insulin in both type 1 and type 2 diabetes. It is frequently prescribed at a starting dose of 20 units at bedtime and titrated by 2 to 4 units every 2-3 days for fasting blood sugar > 130 mg/dl.
- Mixtures of NPH and short acting insulin are available in many forms. The two mixtures most frequently used are 75/25 NPH/lispro (Humalog mix) and 70/30 NPH/aspart (Novolog mix). Twice daily injections (before breakfast and supper) of these mixtures may provide good control for patients with type 2 diabetes. However, their use is rarely successful in patients with type 1 diabetes.

Premixed insulin can be helpful for people who have trouble drawing up insulin out of two bottles and reading the correct directions and dosages. It is also useful for those who have poor eyesight or dexterity and is convenient for people whose diabetes has been stabilized on this combination.

Symlin is not a type of insulin but an amylinomimetic agent approved as adjunct therapy in patients with type 1 and type 2 diabetes who use meal time insulin, but who are not achieving optimal control. Symlin is used at mealtimes to augment the effects of insulin on glycemic control. This can cause hypoglycemia which can occur within 3 hours after a symlin injection. Symlin and insulin should never be mixed in the same syringe. Symlin can also suppress appetite and lead to weight loss. Nausea is the most common side effect but improves with time in most patients.

I.10 Development of dipeptidyl peptidase-4 inhibitors:

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are enzyme inhibitors that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4) and are a potent treatment for type 2 diabetes. Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretin that play an important role in insulin secretion and blood glucose control regulation (Green et al. 2006). Type 2 diabetes is a chronic metabolic disease that can be caused by pancreas β-cell dysfunction, deficiency in insulin secretion, insulin resistance and/or increased hepatic glucose production. It is one of the fastest growing health concerns in the world. Current treatments are often inefficient at sustaining glycemic control and may cause undesirable side effects, such as weight gain and episodes of hypoglycemia. Therefore, new and more effective drugs have been developed with DPP-4 inhibitors playing a significant role (Sebokova et al. 2006).

DPP-4: The protein encoded by the DPP4 gene is an antigenic enzyme expressed on the surface of most cell types and is associated with immune regulation, signal transduction and apoptosis. It is an intrinsic membrane glycoprotein and a serine exo peptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides.

It is a rather indiscriminate enzyme for which a diverse range of substrates are known. (Chen X 2006) the substrates of CD26/DPPIV are proline (or alanine)-containing peptides and include growth factors, chemokines, neuropeptides, and vasoactive peptides.

DPP4 is related to attractin, FAP, DPP8 and DPP9, it plays a major role in glucose metabolism. It is responsible for the degradation of incretin such as GLP-1(Barnett 2006). Furthermore, it appears to work as a suppressor in the development of cancer and tumours. (Pro and Dang 2004).

CD26/DPPIV plays an important role in tumor biology, and is useful as a marker for various cancers, with its levels either on the cell surface or in the serum increased in some neoplasms and decreased in others(Havre et al. 2008).

Since the discovery of DPP-4 in 1967, it has been a popular subject of research (Gallwitz 2007). Inhibitors of DPP-4 have long been sought as tools to elucidate the functional significance of the enzyme. The first inhibitors were characterized in the late 1980s and 1990s. It should be noted that the inhibitors fall into two main classes, those that interact covalently with DPP-4 and those that do not.

I.10a: DPP-4 mechanism:

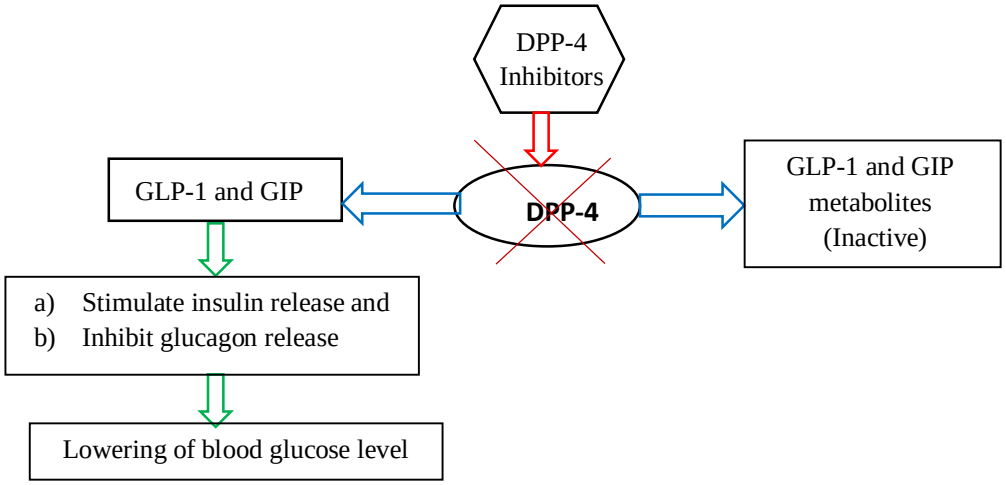


Figure I.1: DPP-4 inhibitors inhibit DPP-4 and thus prolong the duration of GLP-1 and GIP activity, resulting in lower blood glucose level (Gallwitz 2007)

During a meal the incretinglucagon-like peptide 1 (GLP-1) and glucose-dependent gastric inhibitory polypeptide (GIP) are released from the small intestine into the vasculature. The hormones regulate insulin secretion in a glucose-dependent manner. GLP-1 has many roles in the human body; it stimulates insulin biosynthesis, inhibits glucagon secretion, slows gastric emptying, reduces appetite and stimulates regeneration of islet β-cells. GIP and GLP-1 have extremely short plasma half-lives due to a very rapid inactivation. The enzyme responsible for the metabolism is DPP-4. Inhibition of DPP-4 leads to potentiation of endogenous GIP and GLP-1 and hence improves treatment of type 2 diabetes (Figure 1)(Gallwitz 2007).

I.10b: \DPP-4 distribution and function

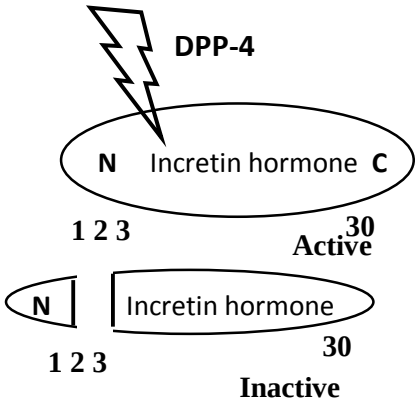


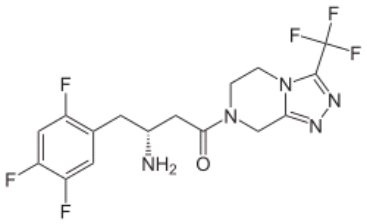
Figure I.2: DPP-4 cleaves two amino acids from the N-terminal end of peptides, such as GLP-1.(Iskandar and Richard 2007).

I.11 Sitagliptin:

Sitagliptin (INN; previously identified as **MK-0431** and marketed as the phosphate salt under the trade name **Januvia**) is an oral anti-hyperglycemic (anti diabetic drug) of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. It was developed, and is marketed, by Merck & Co. This enzyme-inhibiting drug is used either alone or in combination with other oral antihyperglycemic agents (such as metformin or a thiazolidinedione) for treatment of diabetes mellitus type 2 (Behme et al. 2003). The benefit of this medicine is its fewer side effects (e.g., less hypoglycemia, less weight gain) in the control of blood glucose values. While safety is its advantage, efficacy is often challenged as it is often recommended to be combined with other agents such as metformin. The 100 mg once daily dose gave the same results as 50 mgs twice daily (Hanefeld et al. 2007).

Systematic (IUPAC) name:(*R*)-4-oxo-4-[3-(trifluoromethyl)-5, 6-dihydro [1, 2,4] triazolo [4,3-*a*] pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine

Figure I.3: Chemical structure of sitagliptin



Sitagliptin (Januvia) has a novel structure with β-amino amide derivatives (Figure 3). Since sitagliptin has shown excellent selectivity and in vivo efficacy it urged researches to inspect the new structure of DPP-4 inhibitors with appended β-amino acid moiety. Further studies are being developed to optimize these compounds for the treatment of diabetes (Karagiannis, et al. 2012).Crystallographic structure of sitagliptin along with molecular modeling has been used to continue the search for structurally diverse inhibitors. A new potent, selective and orally bioavailable DPP-4 inhibitor was discovered by replacing the central cyclo hexylamine in sitagliptin with 3-aminopiperidine. A 2-pyridyl substitution was the initial SAR breakthrough since that group plays a significant role in potency and selectivity for DPP-4 (McIntosh et al. 2005).

It has been shown with an X-raycrystallography how sitagliptin binds to the DPP-4 complex,(McIntosh et al. 2005).

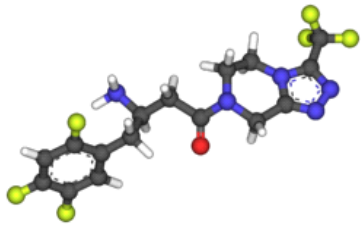


Figure I.4: The structure of sitagliptin

I.11.a Pharmacokinetic data of sitagliptin:

Steady state plasma concentrations were reached on day 3, Sitagliptin is eliminated renally, with a terminal half live of 11.8–14.4 hours,(Miller et al. 2006) there does not seem to be a clinically meaningful effect of age, gender or obesity on the pharmacokinetics of sitagliptin (Bergman et al.2005).

Table I.5: pharmacokinetic data of sitagliptin.

Pharmacokinetic data	
Routes	Oral
Bioavailability	87%
Protein binding	38%
Metabolism	Hepatic (CYP3A4- and CYP2C8-mediated)
Half-life	8 to 14 h
Excretion	Renal (80%)

Iskandar; 2007.

I.11b: Mechanism of action:

Sitagliptin works to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretinGLP-1 and GIP, gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the alpha cells of the pancreas. This drives blood glucose levels towards normal. As the blood glucose level approaches normal, the amounts of insulin released and glucagon suppressed diminishes, thus tending to prevent an "overshoot" and subsequent low blood sugar (hypoglycemia) which is seen with some other oral hypoglycemic agents. Sitagliptin has been shown to lower HbA_{1c} level by about 0.7% points versus placebo. It is slightly less effective than metformin when used as a mono therapy. It does not cause weight gain and has less hypoglycemia compared to sulfonylureas. Sitagliptin is recommended as a second line drug (in combination with other drugs) after the combination of diet/exercise and metformin fails

I.11c: Adverse effects

In clinical trials, adverse effects were as common with sitagliptin (whether used alone or with metformin or pioglitazone) as they were with placebo, except for extremely rare nausea and common cold-like symptoms, including photosensitivity. There is no significant difference in the occurrence of hypoglycemia between placebo and sitagliptin (Wu S et al. 2014).

There have been several post marketing reports of pancreatitis (some fatal) in people treated with sitagliptin and other DPP-4 inhibitors, and the U.S. package insert carries a warning to this effect, (Gooßen, and Gräber 2012). although the causal link between sitagliptin and pancreatitis has not yet been fully substantiated (McIntosh et al. 2005). One study with lab rats published 2009 concluded that some possible risks of pancreatitis, or pancreatic cancer from sitagliptin may be reduced when it is used with metformin. However, while DDP-4 inhibitors show an increase in such risk factors, as of 2009, there is no reported increase in pancreatic cancer in individuals taking DDP-4 inhibitors (Wu S et al. 2014).

The existence of rare case reports of renal failure and hypersensitivity reactions is noted in the United States prescribing information, but a causative role for sitagliptin has not been establish (Lusten and Harry 2013).

Sitagliptin was approved by the U.S. Food and Drug Administration (FDA), on October 17, 2006.Sitagliptin became the first DPP-4 inhibitor that got FDA approval for the treatment of type 2 diabetes(Gallwitz 2007). In addition, is marketed in the US as **Januvia** by Merck & Co. on April 2, 2007, the FDA approved an oral combination of sitagliptin and metformin marketed in the US as Janumet. On October 7, 2011, the FDA approved an oral combination of sitagliptin and simvastatin marketed in the US as Juvisync (Aleksey 2009) Marketed in Pakistan with brand name Trevia (Sitagliptin) & Treviamet (Sitagliptin + Metformin) by Getz Pharma. In India, Glenmark Pharmaceuticals launched a similar molecule in the name of ZITA & ZITAMET.

I.12 Complications of diabetes mellitus:

The **complications of diabetes mellitus** are far less common and less severe in people who have well-controlled blood sugar levels (Nathan et al. 2005).

Wider health problems accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.

I.12.1. Acute complication:

I.12.1a Diabetic ketoacidosis:

Diabetic ketoacidosis (DKA) is an acute and dangerous complication that is always a medical emergency and requires prompt medical attention. Diabetic ketoacidosis occurs in 4.6–8.0 per 1000 people with type1diabetes annually (Kitabchi et al. 2006). Low insulin levels cause the liver to turn fatty acid to ketone for fuel (i.e., ketosis); ketone bodies are intermediate substrates in that metabolic sequence. This is normal when periodic, but can become a serious problem if sustained. Elevated levels of ketone bodies in the blood decrease the blood's pH, leading to DKA.

DKA is common in type 1 diabetes as this form of diabetes is associated with an absolute lack of insulin production by the islets of Langerhans. In type 2 diabetes, insulin production is present but is insufficient to meet the body's requirements because of end-organ insulin resistance. Usually, these amounts of insulin are sufficient to suppress ketogenesis. If DKA occurs in someone with type 2 diabetes, their condition is called "ketosis-prone type 2 diabetes", (Umpierrez et al. 2006). The exact mechanism, for this phenomenon is unclear, but there is an evidence, of both impaired insulin secretion and insulin action (Kitabchi et al. 2009). Once the condition has been treated, insulin production resumes, and often the patient may be able to resume diet or tablet treatment as normally recommended in type 2 diabetes (Kitabchi et al. 2009).

Cerebral edema, which is the most dangerous DKA complication, is probably the result of a number of factors. Some authorities suggest that, it is the result from over vigorous fluid replacement, but the complication may develop before treatment has been commenced(Glaser 2006). It is more likely in those with more severe DKA,and in the first episode of DKA (Dunger 2004). Likely factors in the development of cerebral edema are dehydration, acidosis and low carbon dioxide levels; in addition, the increased level of inflammation and coagulation may, together with these factors, lead to decreased blood flow to parts of the brain, which then swells up once fluid replacement has been commenced (Glaser 2006). The swelling of brain tissue leads to raised intracranial pressure ultimately leading to death (Brown 2004).

Investigations: Diabetic ketoacidosis may be diagnosed when the combination of hyperglycemia (high blood sugars), ketones in the blood or on urinalysis and acidosis are demonstrated. Arterial blood gas measurement is usually performed to demonstrate the acidosis; this requires taking a blood sample from an artery. Subsequent measurements (to ensure treatment is effective), may be taken from a normal blood test taken from a vein, as there is little difference between the arterial and the venous pH (NHS Diabetes Retrieved 2012).

In addition to the above, blood samples are usually taken to measure urea and creatinine (measures of kidney function, which may be impaired in DKA as a result of dehydration) and electrolytes. Furthermore, markers of infection (complete blood count, C-reactive protein) and acute pancreatitis (amylase and lipase) may be measured. Given the need to exclude infection, chest radiography and urinalysis are usually performed. (kitabchi et al. 2009).

If cerebral edema is suspected because of confusion, recurrent vomiting or other symptoms, computed tomography may be performed to assess its severity and to exclude other causes such as stroke.(Brown 2004).

Management: The main aims in the treatment of diabetic ketoacidosis are replacing the lost fluids and electrolytes while suppressing the high blood sugars and ketone production with insulin. (NHS Diabetes. Retrieved 2012).

I.12.1b: Cerebral edema:

Cerebral edema, it may lead to coma, which necessitates admission to intensive care, artificial ventilation, and close observation. The administration of fluids is slowed. The ideal treatment of cerebral edema in DKA is not established, but intravenous mannitol and hypertonic saline (3%) are used—as in some other forms of cerebral edem to reduce the swelling(Dunger et al. 2004).

I.12.1c Hyperglycemia hyperosmolar state:

Hyperosmolar non ketotic state (HNS) is an acute complication (predominantly seen in type 2 DM**)** sharing many symptoms with DKA, but an entirely different origin, ketone bodies, organic molecules that are the underlying driver for DKA but are usually not detectable in HHS**.** and different treatment.A person with very high (usually considered to be above 300 mg/dl (16 mmol/L)) blood glucose levels, water is osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine. This results in loss of water and an increase in blood osmolarity. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels, combined with the loss of water, will eventually lead to dehydration. Electrolyte imbalances are also common and are always dangerous. Urgent treatment is necessary, commonly beginning with fluid volume replacement. Lethargy may ultimately progress to a coma (Tintinalli et al. 2004).

Diagnosis: The major differential diagnosis is diabetic ketoacidosis (DKA). In contrast to DKA, serum glucose levels in HHS are extremely high, usually greater than 40-50 mmol/L, but an anion-

gap metabolic acidosis is absent or mild. Altered mental status is also more common in HHS than DKA. Although traditionally DKA has been associated with Type I Diabetes, whereas HHS has been associated with Type II, HHS can be seen in patients of both types.

Management:

- **Intravenous fluids:**
- **Electrolyte replacement:**
- **Insulin:**

I.12.1d. Hypoglycemia:

Hypoglycemia, (low blood glucose), is an acute complication of several diabetes treatments. It is rare otherwise, either in diabetic or non-diabetic patients (Cryer et al. 2001).

The patient may become agitated, sweaty, weak, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilized panic. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death. In patients with diabetes, this may be caused by several factors, such as too much or incorrectly, timed insulin, too much exercise (exercise decreases insulin requirements) or not enough food (specifically glucose containing carbohydrates) the variety of interactions makes cause (Cryer et al. 2009).

In most cases, hypoglycemia is treated with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with effects largely opposite to those of insulin).

In hospitals, intravenous dextrose is often used (American Diabetes Association". 2012).

I.12.1e Diabetic coma:

Diabetic coma is a reversible form of coma(Richard et al. 2008) found in people with diabetes mellitus. It is a medical emergency.

Three different types of diabetic coma are identified:

- Severe diabetic hypoglycemia
- Diabetic ketoacidosis advanced enough to result in unconsciousness from a combination of severe hyperglycemia, dehydration and shock, and exhaustion
- Hyperosmolar nonketotic coma in which extreme hyperglycemia and dehydration alone are sufficient to cause unconsciousness.

Treatment depends upon the underlying cause:

I.12.1f. Respiratory infections:

I.12.1g. Periodontal disease:

I.12.2. Chronic complications:

Mechanisms of chronic complications: Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin. They then form more surface glycoproteinsthan normal, and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under "microvascular disease" (due to damage to small blood vessels) and "macrovascular disease" (due to damage to the arteries)(Pittenger et al. 1993).

However, some research challenges the theory of hyperglycemia as the cause of diabetic complications. The fact that 40% of diabetics who carefully control their blood sugar nevertheless develop neuropathy, and that some of those with good blood sugar control still develop nephropathy (Rich 2006) requires explanation. It has been discovered that the serum of diabetics with neuropathy is toxic to nerves even if its blood sugar content is normal (Rich 2006). Recent research suggests that in type 1 diabetics, the continuing autoimmune disease, which initially destroyed the beta cells of the pancreas, may also cause retinopathy, neuropathy and nephropathy (Stoner 2005).

One researcher has even suggested that retinopathy may be better treated by drugs to suppress the abnormal immune system of diabetics than by blood sugar control (Adams 2008). Non-diabetic offspring of type 2 diabetics have been found to have increased arterial stiffness and neuropathy despite normal blood glucose levels, (Foss et al. 2001) and elevated enzyme levels associated with diabetic renal disease have been found in non-diabetic first-degree relatives of diabetics.(Ban et al. 2008). Even rapid tightening of blood glucose levels has been shown to worsen rather than improve diabetic complications, though it has usually been held that complications would improve over time with more normal blood sugar, provided this could be maintained (Taubes 2008).

However, one study continued for 41 months found that, the initial worsening of complications from improved glucose control was not followed by the expected improvement in the complications.(Brinchmann-Hansen et al. 1988). In a systematic review with meta-analysis including 6 randomized controlled trials involving 27,654 patients, tight blood glucose control

reduces the risk for some macro-vascular and microvascular events, without effect on all-cause mortality and cardiovascular mortality, (Buehler et al. 2013). In terms of pathophysiology, studies show that the two main types of DM (DM1 and DM2) cause a change in balancing of metabolites such as carbohydrates, lipids and blood coagulation factors, (Mard-Soltani et al. 2011) and subsequently bring about complications like microvascular and cardiovascular complications.

I.12.2.1: Types of chronic complications:

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

- **Cardiovascular disease**:
- **Kidney disease (diabetic nephropathy)**.
- **Nerve disease (diabetic neuropathy)**.
- **Eye disease (diabetic retinopathy)**.
- **Diabetic encephalopathy**
- **Macrovascular disease**: leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor:
    - Coronary artery disease, leading to angina or myocardial infarction (heart attack)
    - Diabetic myonecrosis ('muscle wasting')
    - Peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.(Scott 2013).
    - Stroke (mainly the ischemic type)

In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults, anddiabetic nephropathy is the main illness requiring renal dialysis in the United States.(Mailloux 2007).

Aim of study:

- To investigate the effects and side effects of sitagliptin in type 2 diabetic patients.

- To elucidate the efficacy of sitagliptin, in reducing all diabetic parameters, (fasting blood sugar, post-prandial blood sugar and glycosylated hemoglobin).

- Compare these findings with other group, receiving metformin

CHAPTER-II

PATIENT AND METHOD

II.1. study design.

This study designed as unicenter study and it was conducted at Benghazi Diabetic Center (BDC). The protocol of this study was designed as prospective study and was approved by the local research committee of Faculty of Medicine, University of Benghazi. Type 2 DM patients were included in our study.

II.2: patients:

Seventy-five Libyan type 2 DM patients were included in the study.A thirty sitagliptin (17 female &13 male), and forty-five metformin group (26 female &19 male). They were known diabetic on oral anti-diabetic, mainly metformin, their FBS>150mg% and glycosylated hemoglobin ≥7%.

The patients were interviewed for their free from concomitant disease as hypertension before their participation in the study.

II.2.1. Exclusion criteria include:

Type I diabetes, pregnancy, breast feeding, acute MI, CHF, renal disease, liver disease, patient taking lipid lowering agent, and any other drug elevate blood sugar.

The patient groups were divided to two groups:

- Sitagliptin group: this group consist of 30 patients they were on metformin and other oral anti-diabetic, their FBS> 150mg%, and their glycosylated haemoglobin ≥ 7%. They receive 100mg once a day sitagliptin in addition to metformin 850mg once and they stop other anti-diabetic medications.
- Metformin group: this group consists of 45 patients; they were on metformin and other oral anti-diabetic, their FBS> 150mg%, and their glycosylated hemoglobin≥7%.they increase dose of metformin to become 850mg twice a day and they stop other anti-diabetic medications.

II.3 data collection:

Duration of the study was 3 months; in the first visit, we collect the following data:

Patient name, gender, age, duration of diabetes, history of diabetic complication should be excluded and drug history, especially anti-lipid.

All patients were subjected to the following investigations:

- Fasting plasma glucose.
- 2hr postprandial plasma glucose.
- Glycated hemoglobin (HbA_{1c}%).
- Lipid profile: (total cholesterol (TC), Triglyceride (TG), High densitylipoprotein (HDL), Low density lipoprotein (LDL).
- Liver function tests (Alanine aminotransferase, Aspartate aminotransferase, alkaline phosphatase)
- Renal function tests (Urea, creatinine).

All these investigations were performed at the biochemistry laboratory of BDC. All patients were reviewed after 2 weeks, here we repeat FBS and PPBS measurement, every 2 weeks and all investigations were repeated after three months, at the end of the study.

II.4.Materials and Instruments.

II.4.a. Materials.

The following chemicals were used during the experments.

- Glucose kits manufactured by Beckman company (USA).
- Cholesterol kits manufactured by Analyticon Biotechnologies AG company (Germany).
- HDL kits manufactured by Analyticon Biotechnologies AG company (Germany).
- Alanine aminotransferase kits manufactured by Analyticon Biotechnologies AG company (Germany).
- Aspartate aminotransferase kits manufactured by Analyticon Biotechnologies AG Company (Germany).
- Triglyceride kits manufactured by Biomaghreb Company (Tunisia).
- Alkaline phosphatase kits manufactured by Fabricate company (Brasil).
- HbA_{1c} kits manufactured by Boditech Med company (Korea).
- Urea kits manufactured by Beckman company (USA)..
- Creatinine kits manufactured by Beckman Company (USA).

II.4.b. Instruments.

- Glucose analyzer manufactured by Speedstat™ company (Austria).
- Cholesterol, triglyceride, HDL, ALT and AST analyzer manufactured by ChemWell company (USA).
- HbA_{1c} analyzer manufactured by i-CHROMA™ company (China).

- Urea and Creatinine analyzer manufactured byBeckman company (USA).
- Centrifuge manufactured by Rotofix 32A company (UK).
- Spectrophotometer manufactured by Photometer 5010 company (Germany).

II.5. Methods.

II.5.1.Glucose test:

The blood glucose level was determined using glucoxidase method . Glucose is determined after enzymatic oxidation in the presence of glucose oxidase. The hydrogen peroxide formed reacts, under catalytic action of peroxidase, with sodium phenolate and 4-aminoantipyrine to form a red-violet quinoeimine dye as indicator (Borel 1953).

II.5.2.HbA_{1c} test:

Is an immunoassay system for quantitative measurement of Hemoglobin A_{1c} in human blood with i-Chroma Reader. Glycated protien is formed post-translaionally through the slow, non-enzymatic reaction between glucose and amino groups on protiens.

i-Chroma HbA_{1c} is based on the fluorescence immunoassay technology, specifically the competition immune-detection method. Whole blood is added to the mixture of hemolysis buffer and detection buffer, which results in hemolysis buffer, which results in hemolysis of red blood cells.

The mixture containing HbA_{1c} from the hemolyzed red blood cells and fluorescence-labeled HbA_{1c} peptides from detection buffer is loaded onto the sample well of the cartidge. The mixture then migrates through the nitrocellualar matrix of the test strip by capillary action. HbA_{1c} from the blood competes with fluorescence-labelled HbA_{1c} peptides for binding sites on HbA_{1c} antibodies fixed on the nitrocellualar matrix. As a result, the higher concentration of the HbA_{1c} produces a lower fluorescence signal from HbA_{1c}-peptides.

The signal is interpreted and the result displayed on i-Chroma reader in units of percentage (Goldstein 1986).

II.5.3. Cholesterol test:

Enzymatic colorimetric in vitro test for the quantitative determination of cholesterol in human serum and plasma was used.

Cholesterol is determined enzymatically using cholesterolesterase and cholesterol oxidase.Cholesterol esters are cleaved by the action of cholesterol esterase to yield free cholesterol

and fatty acids.

$$\text{Cholesterol ester + H2O} \xrightarrow{\text{cholestrol estrase}} \text{Cholesterol + fatty acids.}$$

Cholesterol converted by oxygen with the aid of cholesterol oxidase to clolesten-3-one and hydrogen peroxide.

$$\text{Cholestrol} + \text{O}_2 \xrightarrow{\text{cholestrol oxidase}} \text{Cholesten} - 3 - \text{one} + \text{H2O2}$$

$$2\text{H}_2\text{O}_2 + \text{Phenol} + \text{4Aminoantipyrine} \xrightarrow{\text{peroxidas}} \text{Quinineimine dye} + 4\,\text{H}_2\text{O}$$

The created hydrogen peroxide forms a red dyestuff by reacting with 4-aminoantipyrine and phenol under the catalytic action of peroxidase. The color intensity is directly proportional to the concentration of cholesterol and can be determined photometrically (Bennett ST et al. 1992).

II.5.4 Triglycerides test:

The triglycerides are enzymatically hydrolyzed to glycerol according to the following reactions:

$$Triglycerides \xrightarrow{lipoprotien\ lipase} Glycerol + Fatty\ acids$$

$$Glycerol + ATP \xrightarrow{Glycerolkinase\ Mg++} Glycerol - 3 - phosphate + ADP$$

$$\text{Glycerol} - 3 - \text{p} + \text{O}_2 \xrightarrow{\text{3.GlycerolphosphateOxidase}} \text{Dihydroacetone} - \text{p} + \text{H}_2O_2.$$

$$\text{H}_2O_2 + 4 - \text{aminophenazone} + \text{p} - \text{cholorophenol} \xrightarrow{\text{peroxidase}} \text{H}_2\text{O} + \text{Quinonimine}$$

Then measured photometrically at 505 nm wavelength (Fossati 1982).

II.5.5. High density lipoprotien(HDL) test :

The chylomicrons, very low-densitylipoprotein (VLDL) and low-densitylipoproteins (LDL) are precipitated by addition phosphotungestic acid and magnesium chloride. After centrifugation, the supernant fluid contains the HDL fraction. Their cholesterol content is determined enzymatically (Assmann 2001).

II.5.6. Low density lipoprotein (LDL) test:

Fried Ewald equation is a mathematical formula to calculate the concentration of LDL in the bloodstream .This equation calculates the concentration of LDL based upon the presence of total cholesterol, HDL and triglyceride levels (Lindsey et al, 2004).

LDL= Total cholesterol – [HDL + (Triglyceride/5)].

II.5.7.Alanine aminotransferase (ALT):

It was previously known as Glutamic pyruvate transaminase (GPT). Alanine aminotransferase belongs to the group of transaminases, which catalyze the convertion of amino acids to the corresponding α-keto acids via transfer of amino groups.

This was determined according to the method recommended by International Federation of Clinical Chemistry, (IFCC, 1977) (Bergmeyer et al. 1986).

Principle:

The method enables the kinetic determination of alanine aminotransferase activity associated with an indicative reaction, which produces reduced NAD. This determination was also performed in human serum, using phosphate buffer 80 mM, pH 7.4, according to the following reactions:

$$\text{Oxoglutamate} + \text{L} - \text{Alanine} \xrightarrow{\textbf{ALT}} \text{Glutamate} + \text{Oxaloacetae}$$

$$\text{Pyrivate} + \text{NADH} + H^{+} \xrightarrow{LDH} \text{L} - \text{lactate} + NAD^{+}$$

The rate of NADH consumption was measured at 340 nm, and was directly proportional to the ALT activity in the sample.

LDH: (Lactate dehydrogenase)

II.5.8. Aspartate aminotransferase (AST):

It was previously known as called Glutamic oxaloacetate transaminase (GOT). This was determined according to the method recommended by International Federation of Clinical Chemistry (IFCC, 1977) (Bergmeyer et al. 1986)

Principle:

The method enables the kinetic determination of aspartate aminotransferase activity associated with an indicative reaction which produces reduced NAD. This determination was also performed in human serum, using phosphate buffer (80 mM pH 7.4), according to the following reactions:

$$\text{Oxoglutamate} + \text{L} - \text{Aspartate} \xrightarrow{\textbf{GOT}} \text{Glutamate} + \text{Oxaloacetae}$$

NADH

$$\text{Oxaloacetae} + \text{NADH} + H^+ \rightarrow \text{Malate} + NAD^+$$

The rate of NADH consumption was measured at 340 nm, and was directly proportion to the GOT activity in the sample.

GOT: (Glutamte oxaloacetate transaminase).

MDH: (malate dehydrogense).

II.5.9. Alkaline phaphatase :

Optimized method used is based on German society of clinical chemistry and scandinavian society of clinical chemistry recommendation.

In alkaline solution, ALP catalyses the hydrolysis of p-nitrophenyl phosphate into p-nitrophenol and phosphate.

The rate of formation of p-nitrophenol, proportional to the ALP activity, is measured at 405 nm (Burtis et al. 1999).

II.5.10.Urea test:

The buffered urase catalyzes the convertion of the non ionic urea to ionic ammonium bicarbonate. A conductivity electrode is used to measure the rate of increase conductivity, which is directly proportional to the original concentration of urea in the sample .The rate is then converted and displayed as mg blood urea nitrogen per dL (Chin et al. 1961).

II.5.11.Creatinine test:

When a sample is injected into the alkaline picrate reagent, creatinine from the sample combines with picric acid to form a red colored complex. The developed red dye color that measured spectrophotometrically at 520 nm is proportional to the creatinine concentration in the samples.

The proportionality of the rate of color formation is only valid for a small time interval before pseudo-creatinine substances add to the total color formation (Heingard 1973).

II.6. Statistical analysis:

The results were expressed:

- Graphically by bar chart.
- Statistically by student paired t-test.

The P value < 0.05 was considered statistically significant; the data was handled and analyzed by statistical package for social science (SPSS version 21).

CHAPTER-III

RESULTS

III-1 Background Characteristics of the studied population

Table III-1 Background Characteristics of the studied population

	Sitagliptin	metformin
No. of patient(total)	30	45
No. of female	17	25
No. of male	13	20
Mean of age	52	58
Mean diabetic mellitus duration(years)	8.2	12
Mean fasting plasma glucose value(base line reading)	221	172
Mean post-prandial plasma glucose value(base line reading)	303	255
Mean glycosylated haemoglobin value(base line reading)	9.7	9.02
Mean cholesterol value (base line reading)	179.7	222.7
Mean triglyceride value(base line reading)	201.4	289.5
Mean VLDL value(base line reading)	33.38	33.54
Mean LDL value((base line reading)	113.05	123
Mean HDL value((base line reading)	33.3	41.8
Mean alkaline phosphatase value((base line reading)	87.8	80.4
Mean AST value((base line reading)	26	15.4
Mean ALT value((base line reading)	33.6	23.4
Mean creatinine value((base line reading)	0.75	0.87
Mean urea value((base line reading)	22	25

III-2-a Effect of Sitagliptin 100mg tablet per day, on lipid profile.

As shown in figure 1, the effect of 100mg sitagliptin on lipid profile after 12 weeks of treatment showed non-significant decrease in (cholesterol, TAG, and LDL, and non-significant increase in HDL, which is known as beneficial lipid. Our results showed a significant decrease in the VLDL ($P<0.037$), while decline in other parameters were not significant.

III-2-b Effect of Metformin Tab. (850mg) Twice per Day on lipid profile.

As seen in figure 2, the administration of metformin (850 mg twice daily) on lipid profile for 12 weeks of treatment showed non-significant decrease on TAG, LDL, and VLDL level however a significant increase in the level of HDL was observed ($p< 0.014$).

III-2-cComparison between the effects of sitagliptin (100mg tablet per day) with that of the metformin tablet (850mg twice daily) on lipid profile:

As previously mentioned in sections III-1-a and III-1-b, both metformin and sitagliptin non-significantly reduce the levels of cholesterol, TAG and LDL. While a significant increase in the level of HDL was observed with Metformin, and significant reduction in the VLDL was observed with sitagliptin.

When compare metformin and sitagliptin both produce larger increase in the levels of HDL. However, the difference between the two drugs did not reach statistical significance.

Table III.2. Comparison of effect of sitagliptin with Metformin on lipid profile.

	Sitagliptin group	**Metformin group**	**p- value**
Δ Triglycerides (mg/dl)	-66	-152.9	0.39
Δ LDL (mg/dl)	-2.7	-11.2	0.77
Δ HDL (mg/dl)	+16.7	+4.3	0.13
Δ VLDL (mg/dl)	-6.6	-14.3	0.42

III-3-a- Effect of sitagliptin 100mg on liver function parameters (LF).

Data presented in figure 3, and 3a, show that daily administration of sitagliptin (100mg), has no effect on liver function.

III-3-b Effect of metformin on liver function (LF).

As indicated in fig. 4, the administration of 850 mg of metformin twice daily for 12 weeks has no significant effect on AST, ALT, and ALK, and also bilirubin as shown in figure 4 a.

III-4-a Effect of sitagliptin (100 mg/day) on renal function (RF):

As presented in figure 5, sitagliptin has no significant effect on renal function.

III-4-b Effect of metformin (850 mg twice daily) on renal function test (RF).

As indicated in Figure 6, metformin 850mg twice daily significantly increases the level of urea ($p<0.05$). However, no significant changes were observed on creatinine level.

III-5-a Effect of sitagliptin 100mg on FBS in diabetic patient after two weeks of treatment

The result in fig.7, showed that after two weeks of treatment with 100 mg sitagliptin, FBS was significantly decreased($p<0.001$), from 221 ±8 mg/dL to 142 ± 5 mg/dL.

III-5-b Effect of Metformin 850mg on FBS in diabetic patient after 2 weeks of treatment

As shown in figure 8**,** two weeks treatment with 850 mg of metformin twice daily, produces a significant decline in FBS ($p<0.001$) from 173±5.7 mg/dL to 141±4.47 mg/dL.

III-5-c Comparison between the effect of sitagliptin (100mg/day)and effect of metformin (850mg twice daily) on FBS in diabetic patient after 2 weeks of treatment.

As seen in table 3, in the sitagliptin group FBS decreased by 35.7% while in the metformin group FBS decreased by 18.5% only.

III-5-d Effect of 12 weeks of treatment with sitagliptin(100mg) or metformin (850mg twice daily) on FBS in diabetic patient-aged groups

Data presented in fig.9, showed that sitagliptin significantly lower ($p<0.001$) the level of FBS in the (25-49) years old group from 211±8 to131± 4 mg /dl. These figures in the (50-74) years old group were significantly decline ($p<0.05$) from 249±10 to 166±5 mg/dl.

As presented in fig.10, metformin significantly lower ($p<0.001$) the level of FBS in the (25-49) years old group from 175± 11.1 to 135± 5.4mg /dl.

Data in the same figure also showed that the level of FBS in the (50-75)

years old group was significantly declined($p<0.008$) from 172±6.9 to 141± 5.3 mg /dl., due to two weeks of administration of metformin.

Results in table 4, showed that, the level of decrease in FBS due to treatment with sitagliptin or metformin was 37.9% and 22.9% respectively in the (25-49) years old group.In the (50-75) year aged patients, the percentage of decline in FBS due to treatment with sitagliptin and metformin were 33.3% and 18% respectively.

III-6- Effect of two weeks treatment with sitagliptin (100mg/day)or metformin (850mg twice daily) on postprandial blood sugar(PPBS) of diabetic patients.

As indicated in figure 11**,** the PPBS was significantly decreased ($p< 0.01$),in sitagliptin treated group as compared to pre-treated one i.e. in the pre-treated group the PPBS was 303mg/dl± 9.1& after treatment with sitagliptin, it decreases to 195mg/dl± 6.9.

The level of PPBS was significantly lowered ($p<0.05$), from 255±9mg /dl in the pre-treated group to 214± 8.4 mg/dl upon treatment with metformin. Data in table 5, Showed that the decline in PPBS due to treatment with sitagliptin was stronger (35.6%), as compared to that observed with metformin (16%).

III-7: Effect of 2 weeks of treatment with sitagliptin (100mg/day)or metformin(850mg twice daily) on postprandial blood sugar(PPBS) in diabetic patients with different ages:

The effect of sitagliptin or metformin on PPBS in different age groups were investigated, as presented in fig. 12, the level of PPBS in the patients of (25- 49) years old, pre and after sitagliptin administration was significantly decreased ($p<0.001$) from 297 ±10.8 to 191±8.1 mg/dl respectively.

In (50-74) years aged patients this level was also significantly changed ($p<0.005$) from pre (315± 16.9 mg/dl) to post treatment (204±13.4 mg/dl) upon treatment with sitagliptin.

With regard to the effect of metformin on the PPBS levels in different ages, and as presented in figure13, it is quite clear that metformin administration, significantly lowered ($p < 0.01$) the PPBS from 243 ±16.3 to 202 ± 14.56 mg/dl in (25-49 year) age group. While PPBS, decrease from 257 ± 5.2 to 217 ± 9.7 in the (50- 74) years old patients.

As shown in table 6, the decline in PPBS in the (25-49 years old patients was 35.7% and 16.9% due to sitagliptin &metformin respectively. However, in (50- 74) years old patients, this decline was 35.2%&16% respectively due to the same treatment.

III-8 Effect of 12 weeks of treatment with sitagliptin (100mg daily) or metformin (850mg/twice daily) on glycosylated haemoglobin (HbA_{1c}) in diabetic patient:

Figure 14, showed that in all patients, sitagliptin significantly reduces HbA_{1c} ($p<0.01$) from 9.7% ±0.206 to 7.4% ±0.208.

In addition, metformin significantly reduces HbA_{1c} ($p < 0.01$) from 9± 0.24% to 7.7 ± 0.19%.

As presented in table 7, the percentage of decline in HbA_{1c} due to sitagliptin was 23.7% whereas in case of metformin it was 14%.

III-9 Effect of 12 weeks of treatment with sitagliptin (100mg daily) or metformin (850mg/twice daily) on glycosylated haemoglobin (HbA_{1c}) in diabetic patient of different ages:

Results in fig.15, showed that sitagliptin significantly decreases ($p<0.001$) the level of HbA_{1c} from 9.7%±0.5 to 7.3%± 0.41 in the (25- 49) years old patient group.

The level of HbA_{1c}in the (50- 74) years old patients, pre and post sitagliptin administration was

significantly decrease ($p<0.008$), from 9.9%±1.13 (pre) to 7.9% ±0.7 (post treatment).

Results in fig. 16, showed, that, the level of HbA_{1c} was significantly decreased due to treatment with metformin in the (25-49) years old from 8.7% ±0.78 in pre-treatment, to 7.1% ±0.26 in post treated group, however in the (50-74) years old patients, metformin showed a significant decrease in the level of HbA_{1c} from 9% ± 0.25 pre-treatment, to 7.8% ± 0.22-post treatment.

The degree of decline in the HbA_{1c} in groups of different ages was indicated in table 8, in the (25-49) years old diabetic patients, the decline in HbA_{1c} in sitagliptin & metformin was 24.7% &18% respectively, whereas in the (50- 74) years old patients, these figures in the sitagliptin & metformin were 21% and 13% respectively.

III-10: Effect of sitagliptin or metformin, on FBS in different diabetes mellitus duration-time suffering groups.

Results in fig. 17, showed that sitagliptin significantly lowered ($p< 0.05$) the level of FBS in the group of patients suffering from diabetes less than 10 years (from 215±8.6 -- to 139±5.7 mg/dl) and in (10-24) years diabetic suffering group(from 241±15.6 to 150±10.6 mg/dl) respectively

As presented in fig.18, the level of FBS in patients suffering from diabetes less than 10 years was significantly decreases ($p<0.01$) due to metformin (from 162±10 to133± 8.4 mg/dl) and in the (10-24) years suffering patients (from 182±11 to 144± 8.6 mg/dl) respectively ($P<0.01$)

The degree decline in FBS (table 9), in group that less than 10 years suffering from diabetes on sitagliptin or metformin was 35% and 18% respectively.

Whereas in the group suffering between 10- 24 years of diabetes, they were 38% and 21% respectively.

III-11: Effect of sitagliptin or metformin on post-prandial blood sugar (PPBS) in, different diabetic mellitus duration suffering groups:

In patients with diabetes duration less than 10 years, (fig.19), sitagliptin reduced PPBS from 292±14.4 to 195±8.1 mg/dL and this reduction was statistically significant ($p< 0.001$)), however in patients with duration of (10-24) years, PPBS was significantly reduced ($p <0.01$) with the same treatment from 331 ±19.7 to 195±14.2 mg/dl.

As shown in figure 20, metformin reduces PPBS from 238 ± 11.1 to 197±9.3 mg/dl in the less than 10 years suffering diabetic patients, this reduction in PPBS was statistically significant ($p<0.04$). The PPBS in patient with duration of (10-24) years was significantly reduced ($p< 0.01$)

with the same treatment (from 267 ± 13.1to 227± 12.5 mg/dl).

As mentioned in table 10, the PPBS in the group of patients that are less than 10 years with diabetes was decline by 33% and 17% with sitagliptin or metformin respectively. The decline was significantly different ($p<0.01$). However decline in PPBS in (10-24) years suffering patients, it was also significantly reduced ($p<0.01$). This Percentage of decline in PPBS was 41% and 15% in sitagliptin or metformin treated groups respectively.

III-12 Effect of sitagliptin (100mgdaily) or metformin (850mg/day) on glycosylated HB (HbA_{1c}) in different diabetic mellitus duration suffering groups.

With regard to effect of sitagliptin on glycosylated HbA_{1c} in different diabetic duration, results in figure 21, indicated that in

Patients with diabetes less than 10 years, sitagliptin significantly reduced ($p<0.001$) HbA_{1C} from 9.6% ± 0.23 to 7.5% ± 0.27 where as it reduces this parameters in (10- 24) years suffering from diabetes from 10% ± 0.43 to 7.3% ± 0.29 ($p<0.01$).

On the other hand and as shown in fig. 22, metformin significantly reduces the HbA_{1c} in the less than 10 years, suffering patients from 8.1%± 0.36 to 7.3%± 0.25 ($p<0.01$).

In case of (10 – 24) years suffering patients, HbA_{1c} significantly was reduced from 9.5% ± 0.41 to 7.9% ± 0.32 ($p < 0.05$).

The percentage of decline in HbA_{1c} in the group of less than 10 years with diabetes treated with metformin was 10% and with sitagliptin, was 22% as shown in table 11.

However, this decline in the (10-24) years suffering patients was 17% for metformin and 27% for sitagliptin.

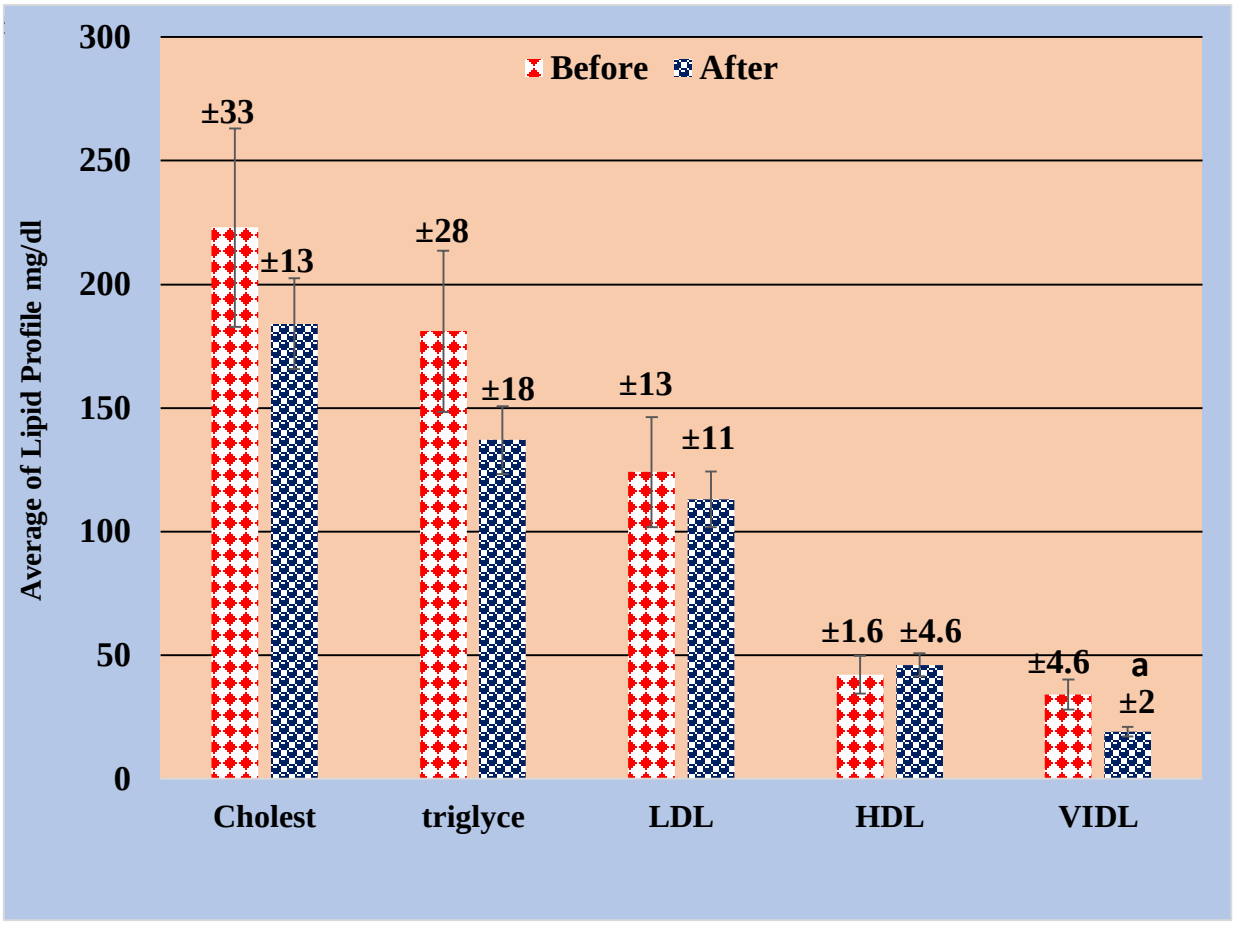


Figure 1: Effect of sitagliptin 100mg tablet, on lipid profile (cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol and VLDL) after 12 weeks of treatment.(Average lipid profile is expressed as mg/dl and each value presents the mean±SEM)

a- Significantly different from pretreatment$(p < 0.037)$.

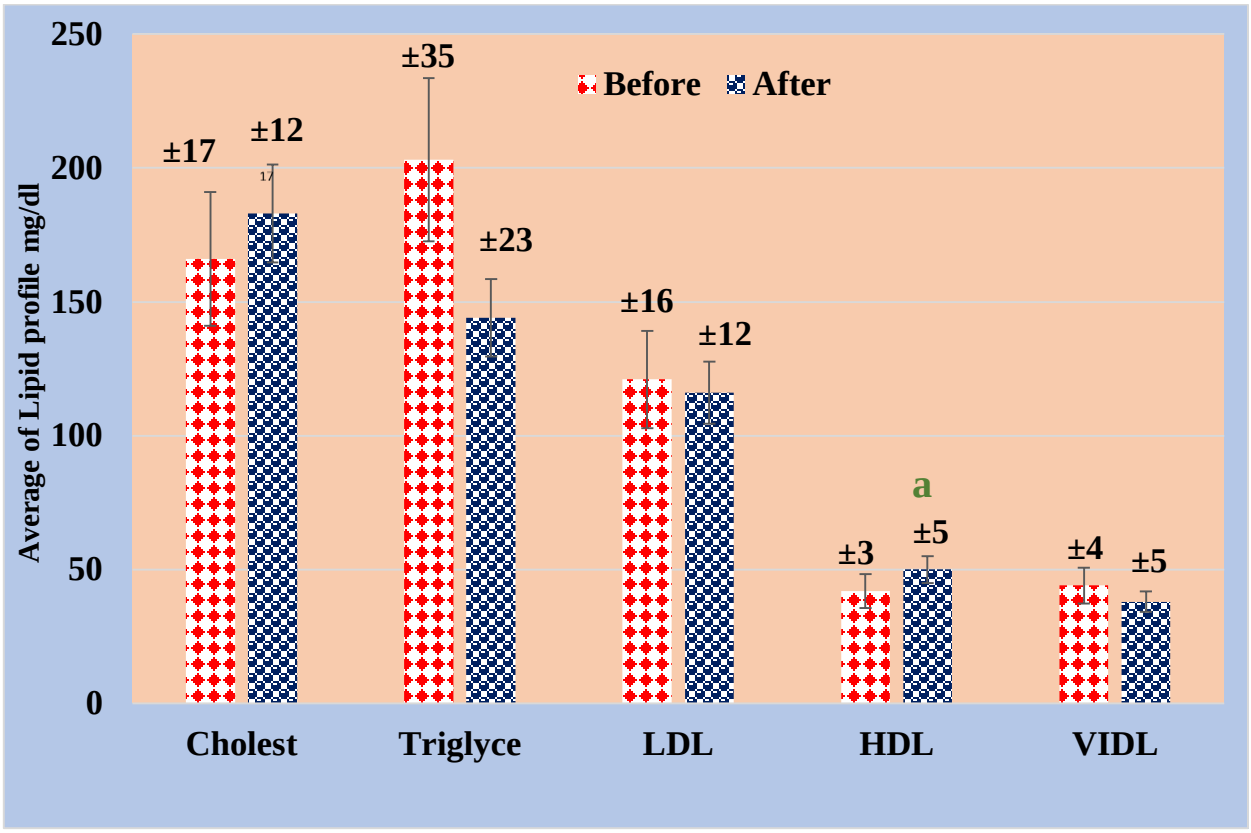


Figure 2: Effect of metformin (850mg twice a day) on lipid profile

a. Significantly different from pretreatment$(p < 0.014)$.

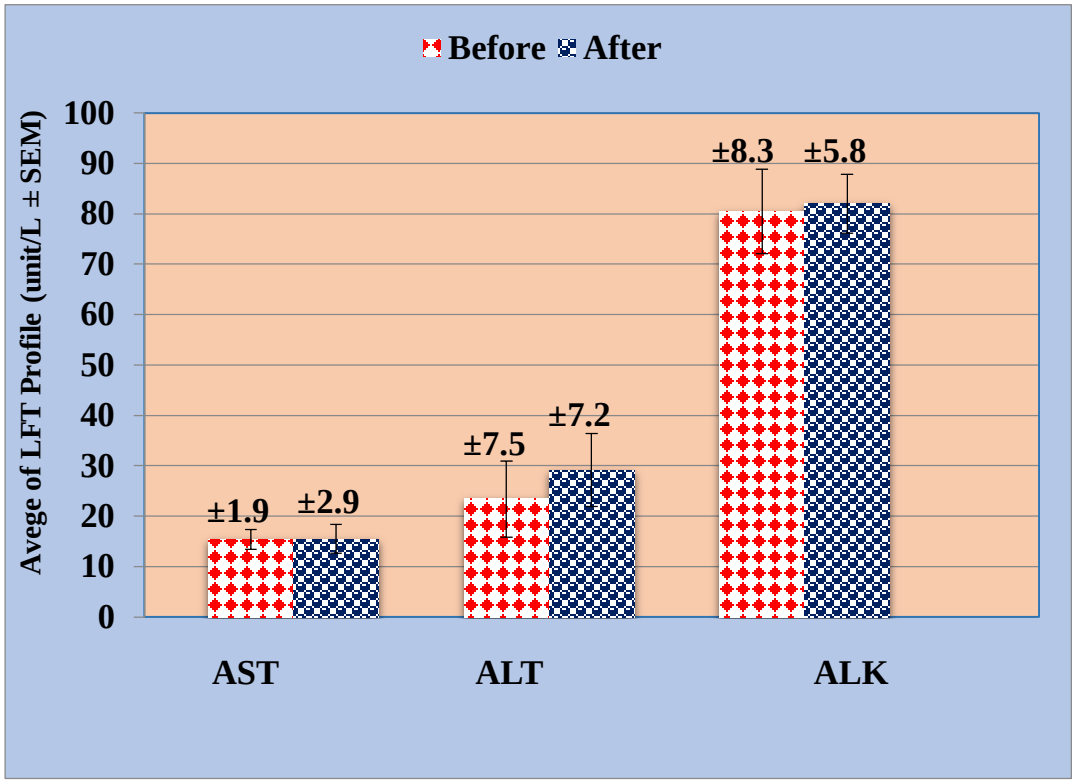


Figure 3: changes in LFT parameters after administration of 100mg sitagliptin a day for 12 weeks.

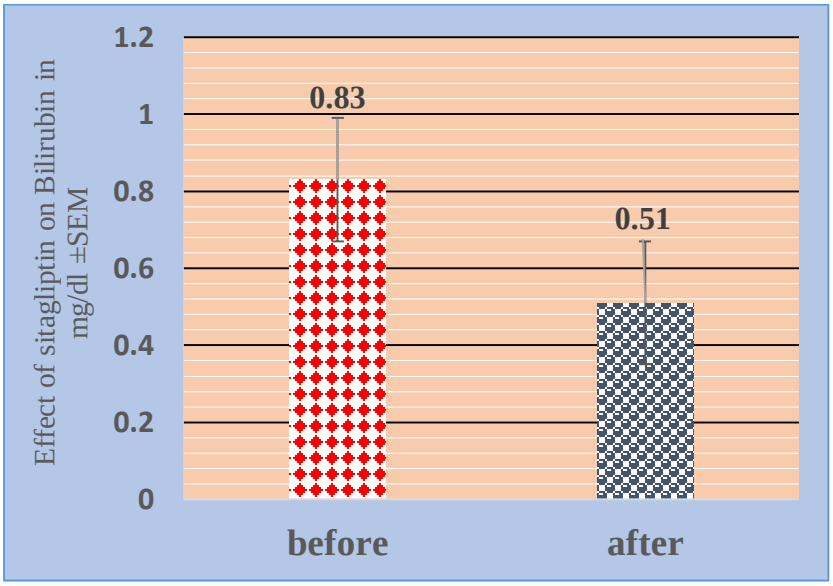


Figure 3a: Effect of Sitagliptin 100mg on Bilirubin.

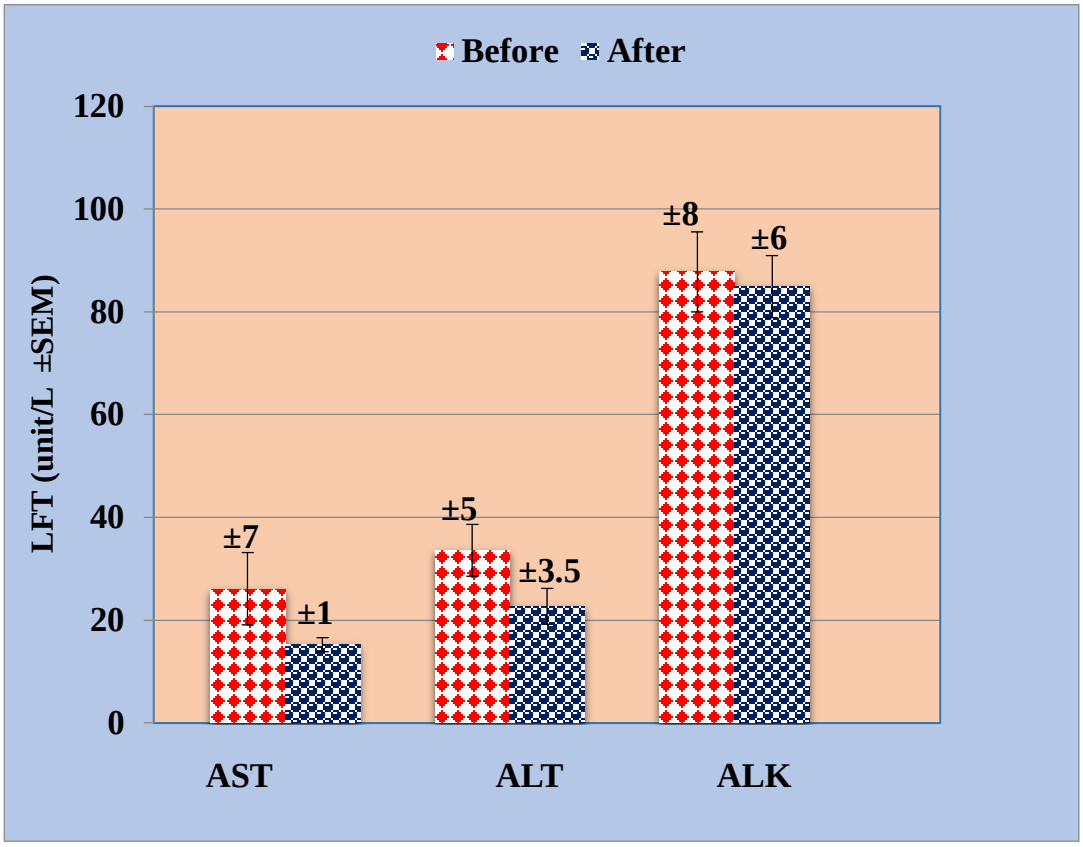


Figure 4: Effect of metformin 850mg on LFT (liver function test)

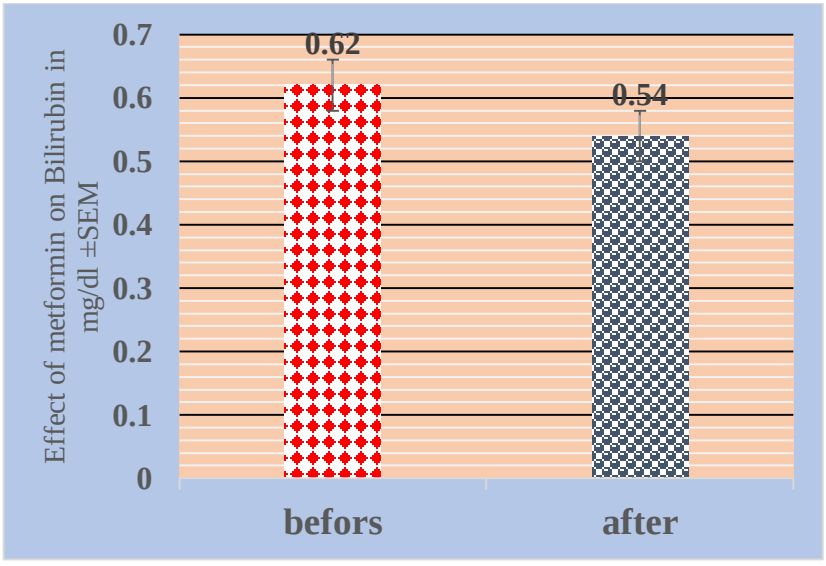


Figure 4a: Effect of metformin 850mg on Bilirubin.

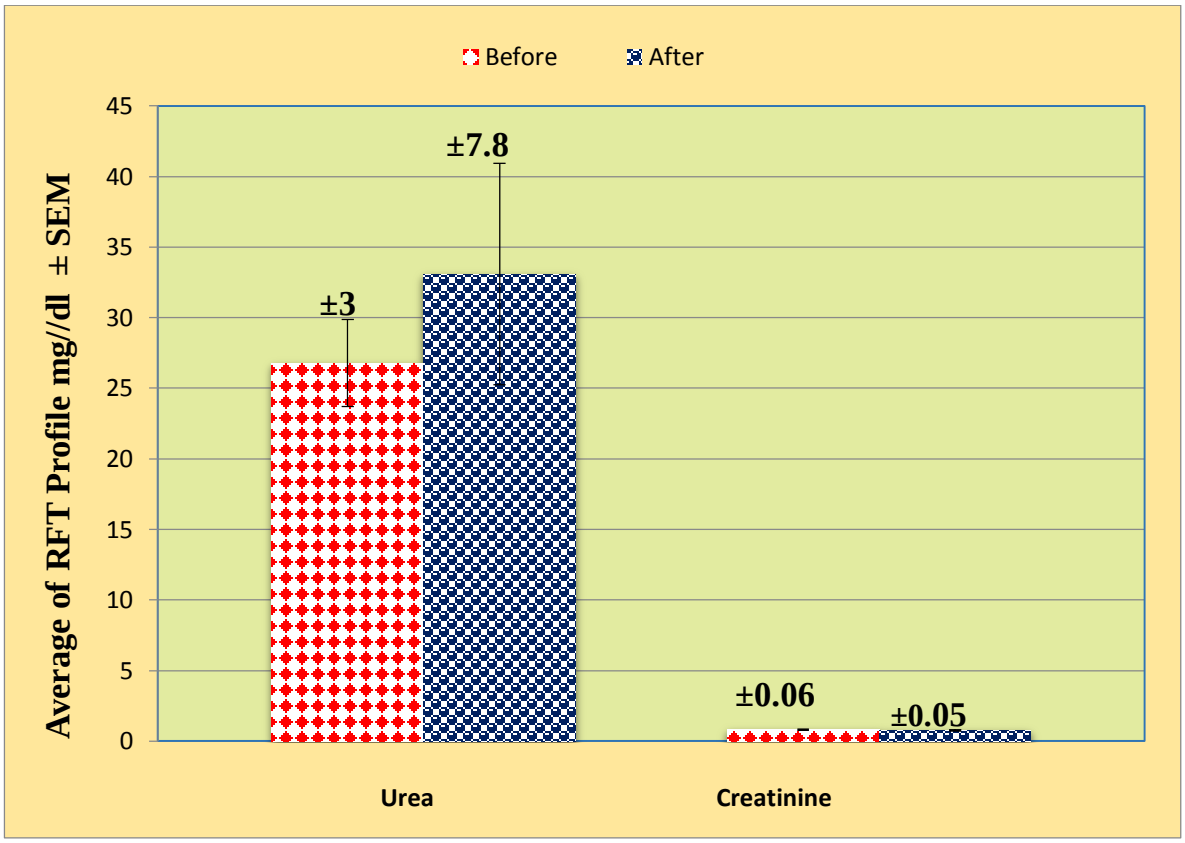


Figure 5: Effect of sitagliptin (100 mg tablet /daily) on renal function parameters.

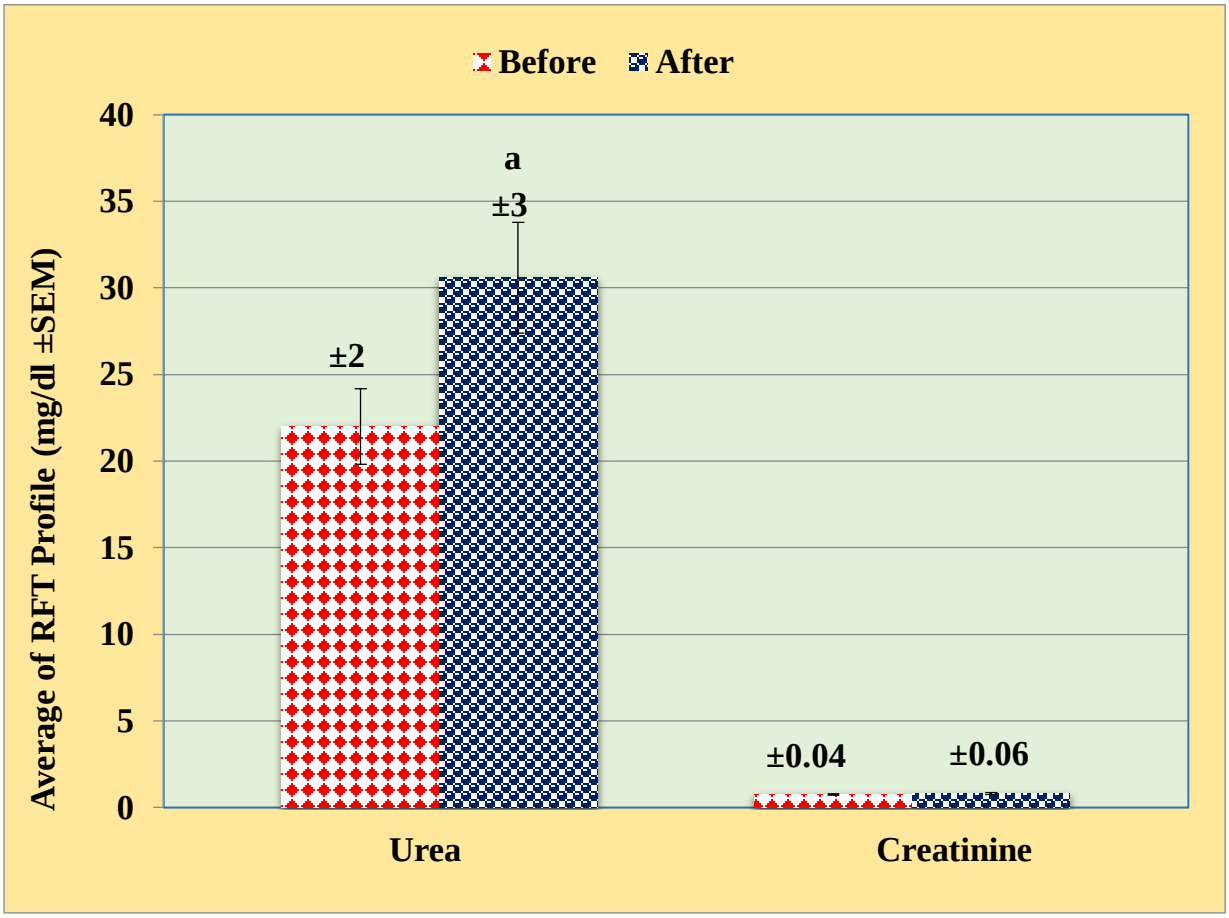


Figure 6: The effect of metformin (850mg/twice daily) on the parameters of renalfunction.

a- Significantly different from pre-treatment$(p < 0.05)$.

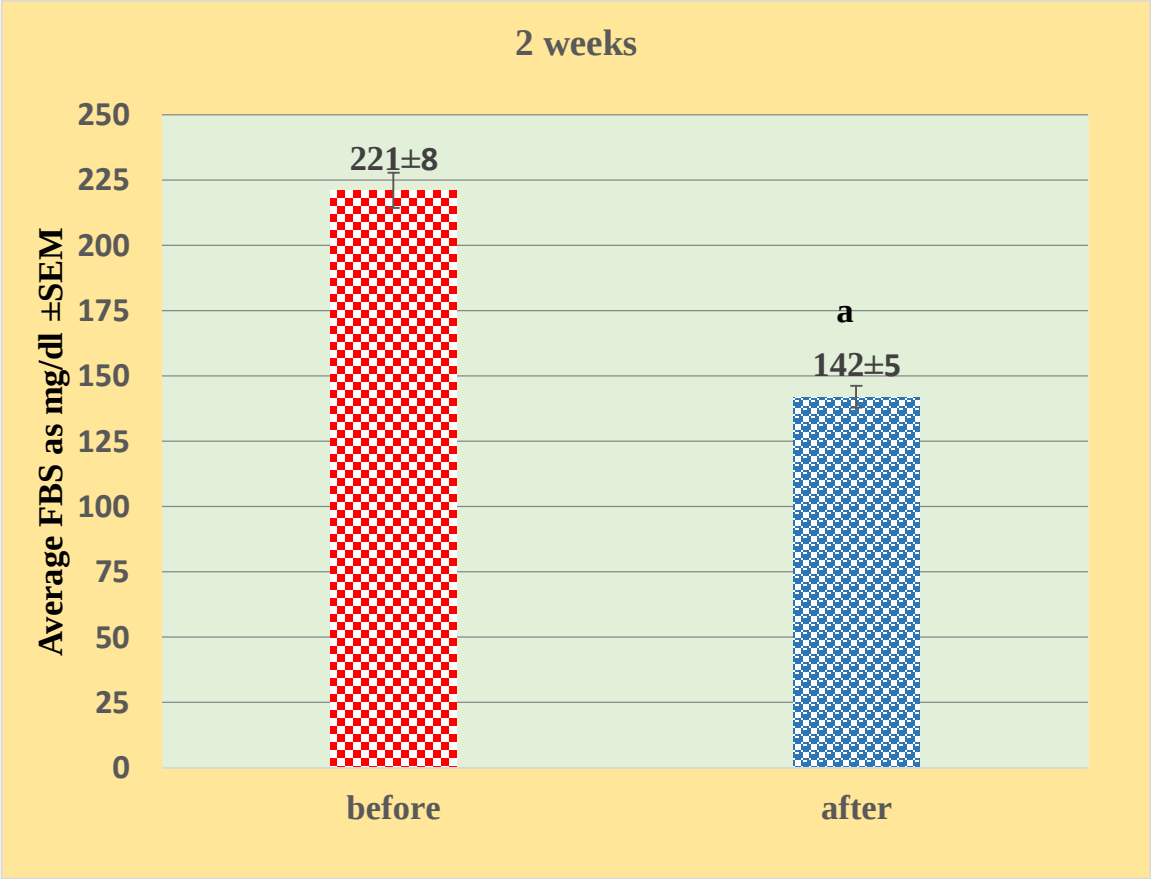


Figure 7: Effect of sitagliptin 100mg on FBS in diabetic patient after two weeks of treatment.

a- Significantly different from pre-treatment$(p < 0.001)$.

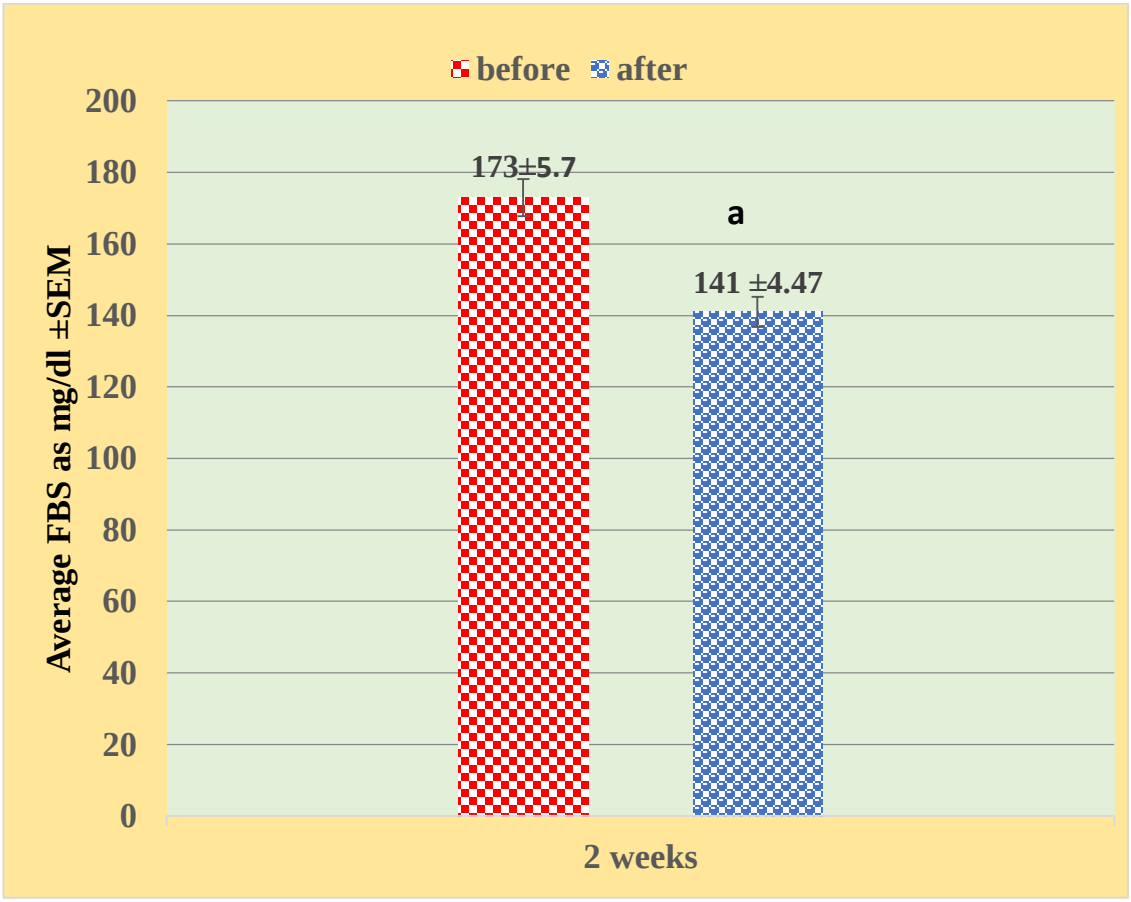


Figure 8: Effect of Metformin 850mg on FBS in diabetic patients after two weeks of treatment.

a. Significantly different from pre-treatment$(p < 0.001)$.

Table 3: Percentage of decline in FBS after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily).

	Sitagliptin (100 mg daily)	Metformin (850 mg twice daily)
Percentage of decline in FBS	**35.7 %**	**18.5 %**

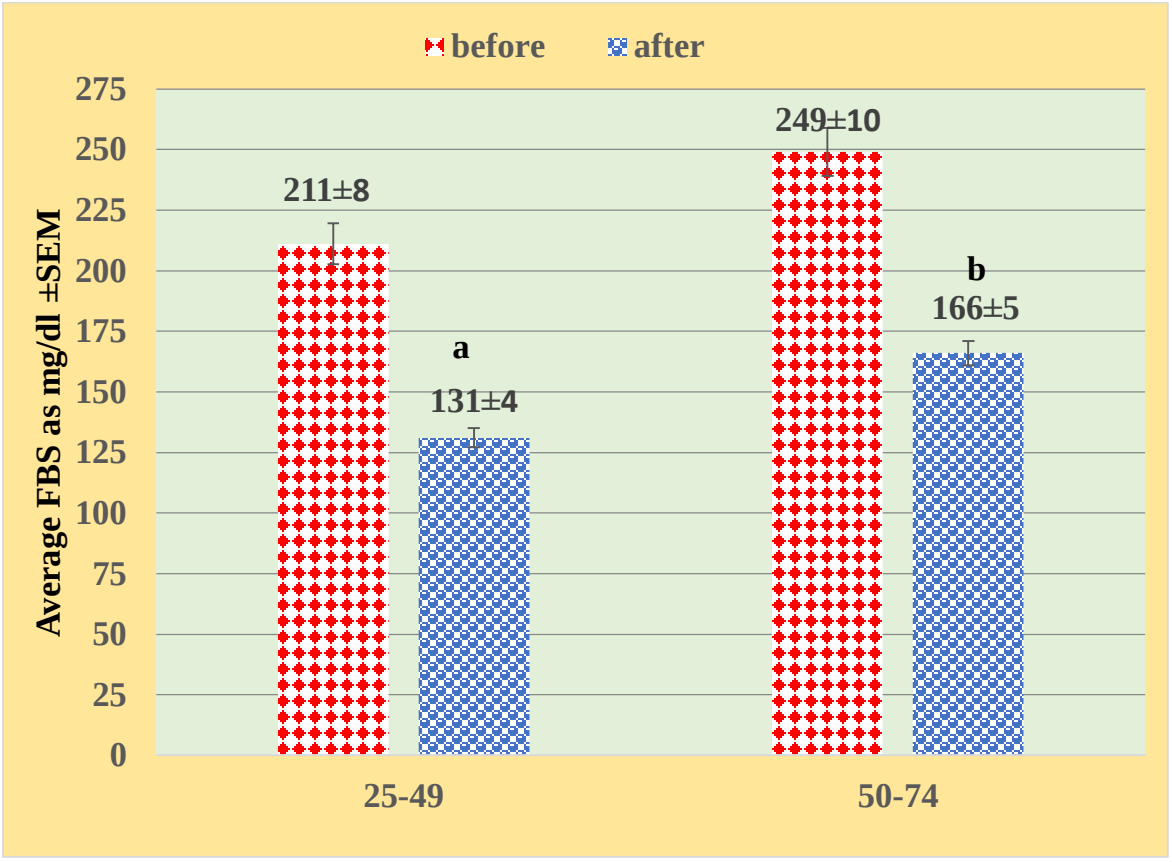


Figure 9: Effect of Sitagliptin (100mg daily) on FBS in diabetic patients after two weeks of treatment according to age group.

a. Significantly different from pre-treatment group$(p < 0.001)$.
b. Significantly different from pre-treatment group $(p < 0.05)$

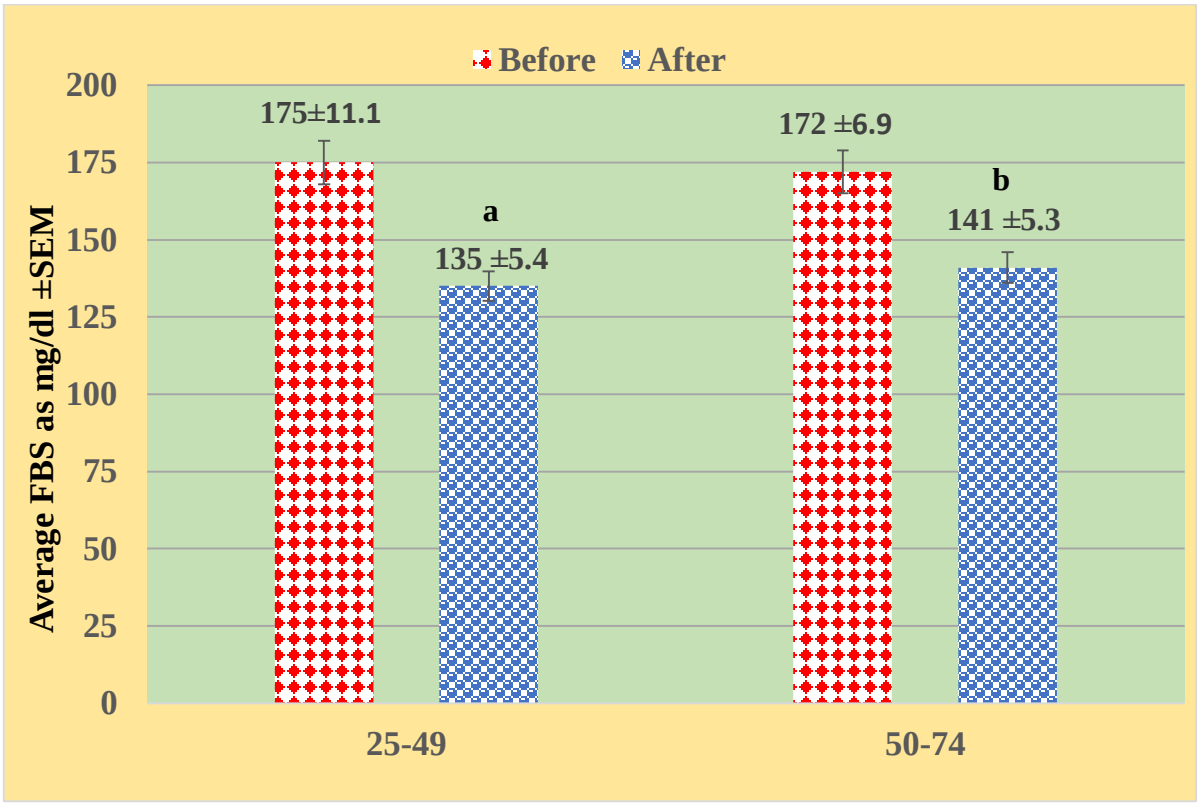


Figure 10: Effect of Metformin (850mg twice a day) on FBS in diabetic patients after two weeks of treatment according to age group.

a. Significantly different from pre-treatment group($p < 0.001$)
b. Significantly different from pre-treatment group ($p < 0.008$)

Table 4: Percentage of decline in FBS after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily), according to age according to age group.

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Age (years)	**25 - 49**	**50 - 74**	**25 - 49**	**50 - 74**
Percentage of decline in FBS	**37.9 %**	**33.3 %**	**22.9 %**	**18 %**

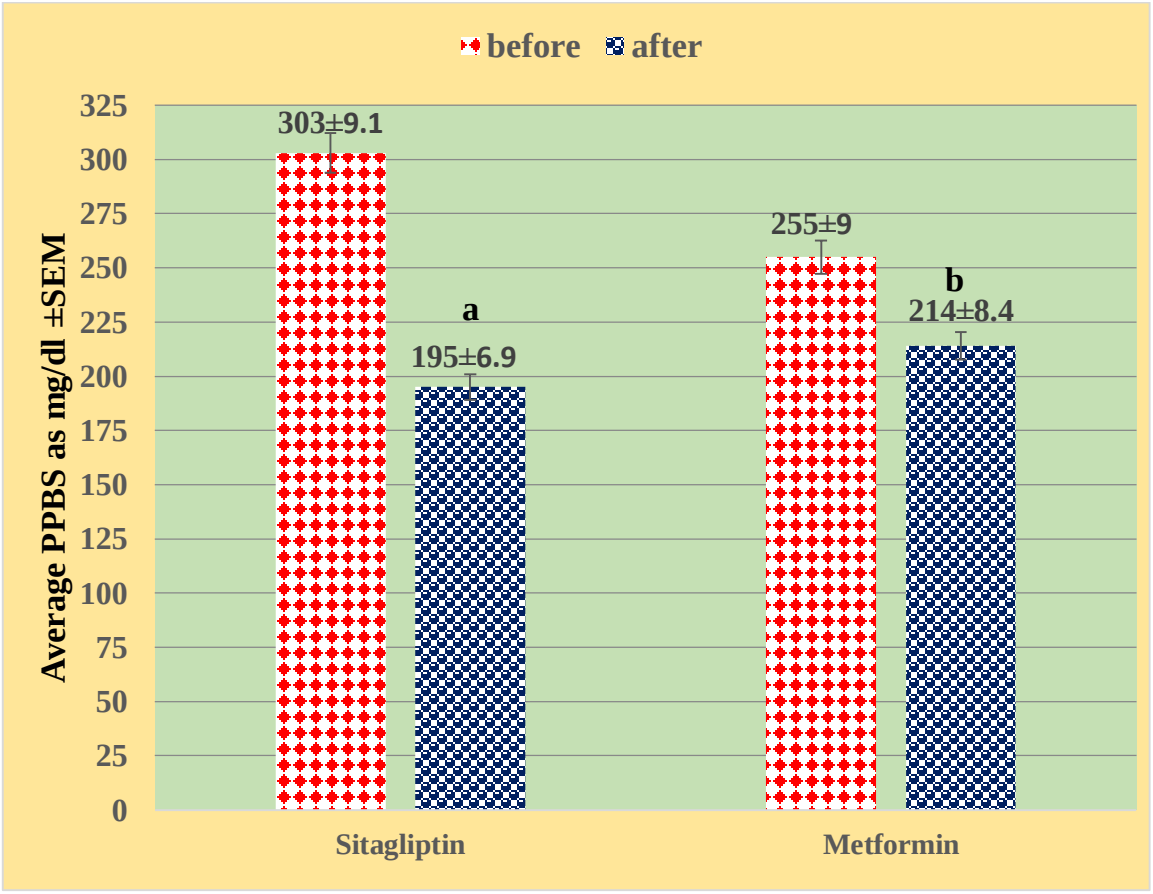


Figure 11: Effect of sitagliptin 100mg and metformin 850mg twice a day on PPBS in diabetic patient after two weeks of treatment.

a. Significantly different from pre-treatment$(p < 0.01)$.
b. Significantly different from pre-treatment$(p < 0.05)$.

Table 5: Percentage of decline in PPBS after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily).

	Sitagliptin (100 mg daily)	Metformin (850 mg twice daily)
Percentage of decline in PPBS	**35.6 %**	**16 %**

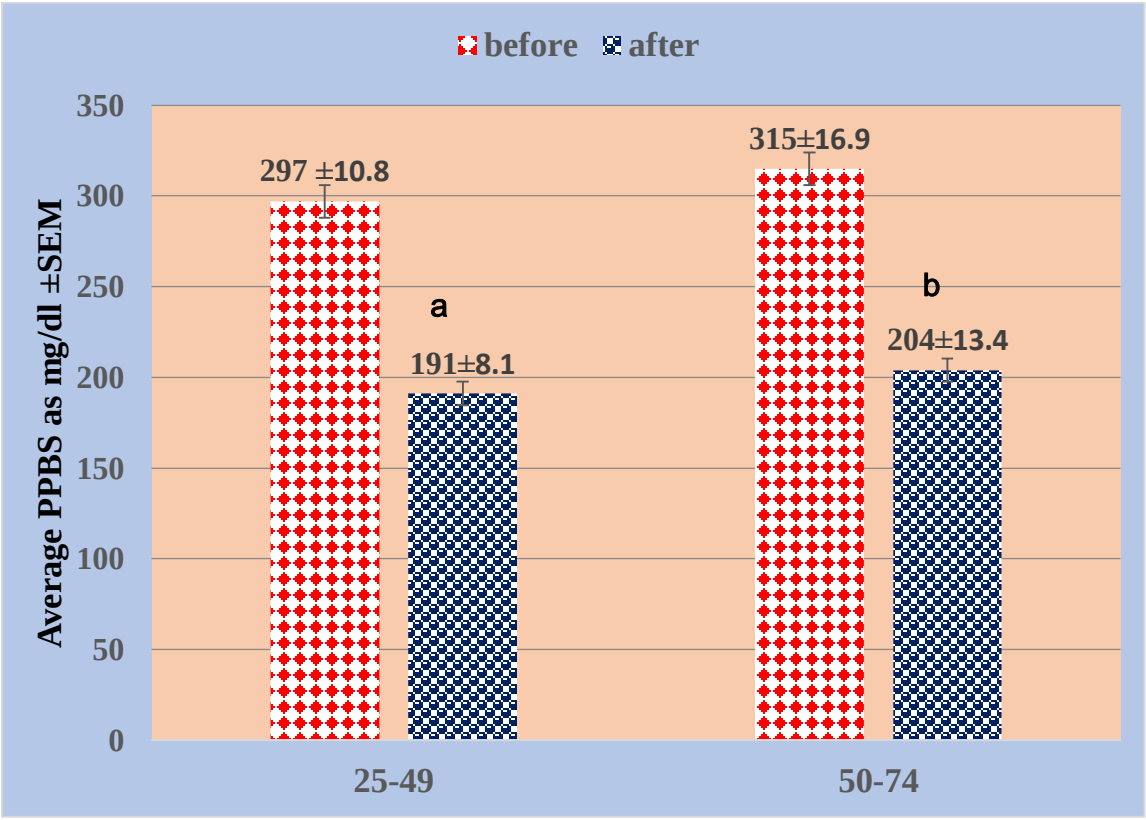


Figure 12: Effect of Sitagliptin 100mg on PPBS in diabetic patients after two weeks of treatment according to age group.

a. Significantly differentfrom pre-treatment$(p < 0.001)$.
b. Significantly different from pre-treatment$(p < 0.005)$.

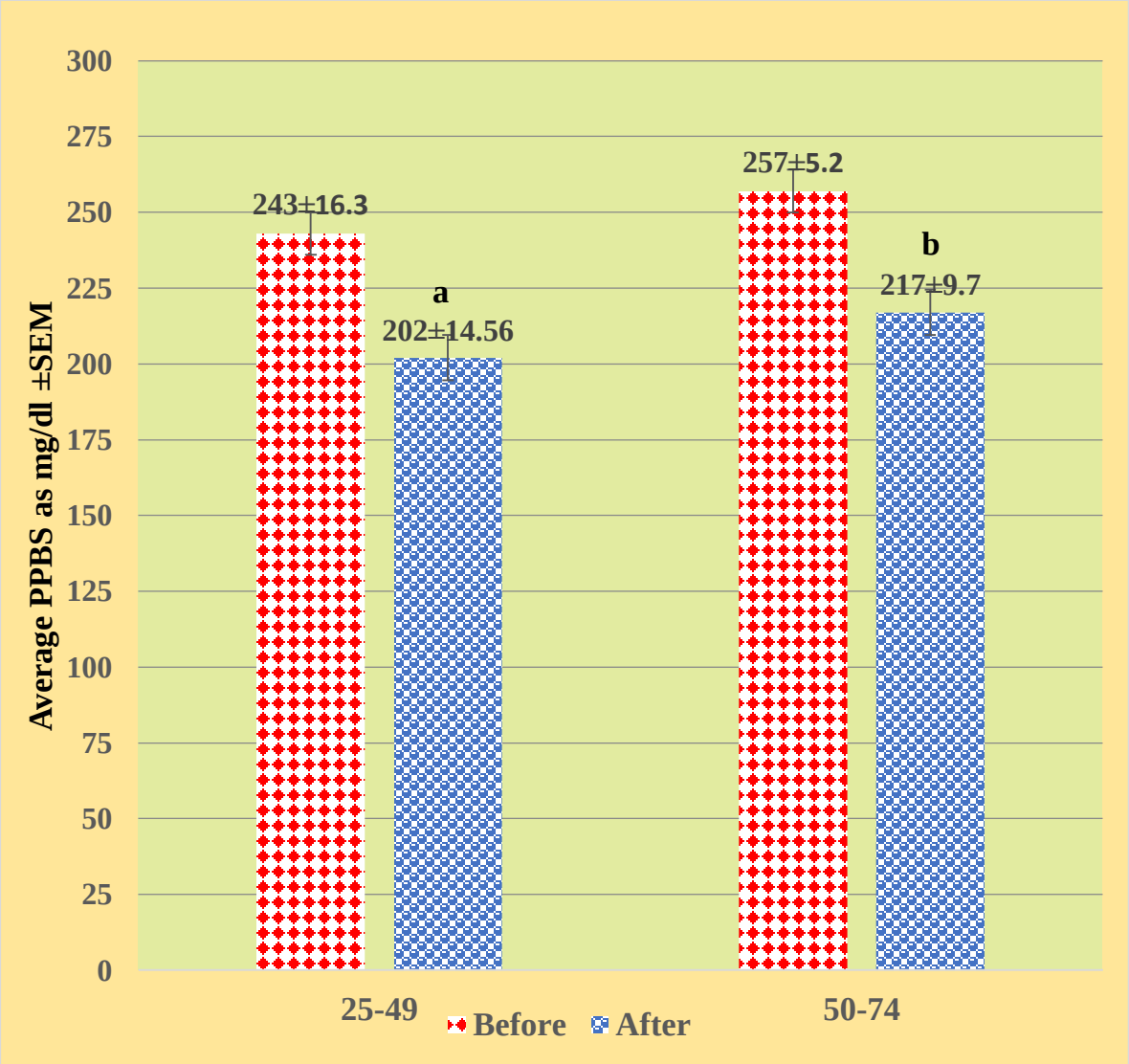


Figure 13: Effect of Metformin 850mg twice a day on PPBS in diabetic patients after two weeks of treatment according to age group.

a. Significantly lower than pre-treatment$(p < 0.01)$
b. Significantly lower than pre-treatment$(p < 0.05)$.

Table 6: Percentage of decline in PPBS after administration of Sitagliptin (100 mg daily) metformin (850 mg twice daily), according to age group.

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Age (Years)	**25 - 49**	**50 - 74**	**25 - 49**	**50 - 74**
Percentage of decline in PPBS	**35.7 %**	**35.2 %**	**16.9 %**	**16 %**

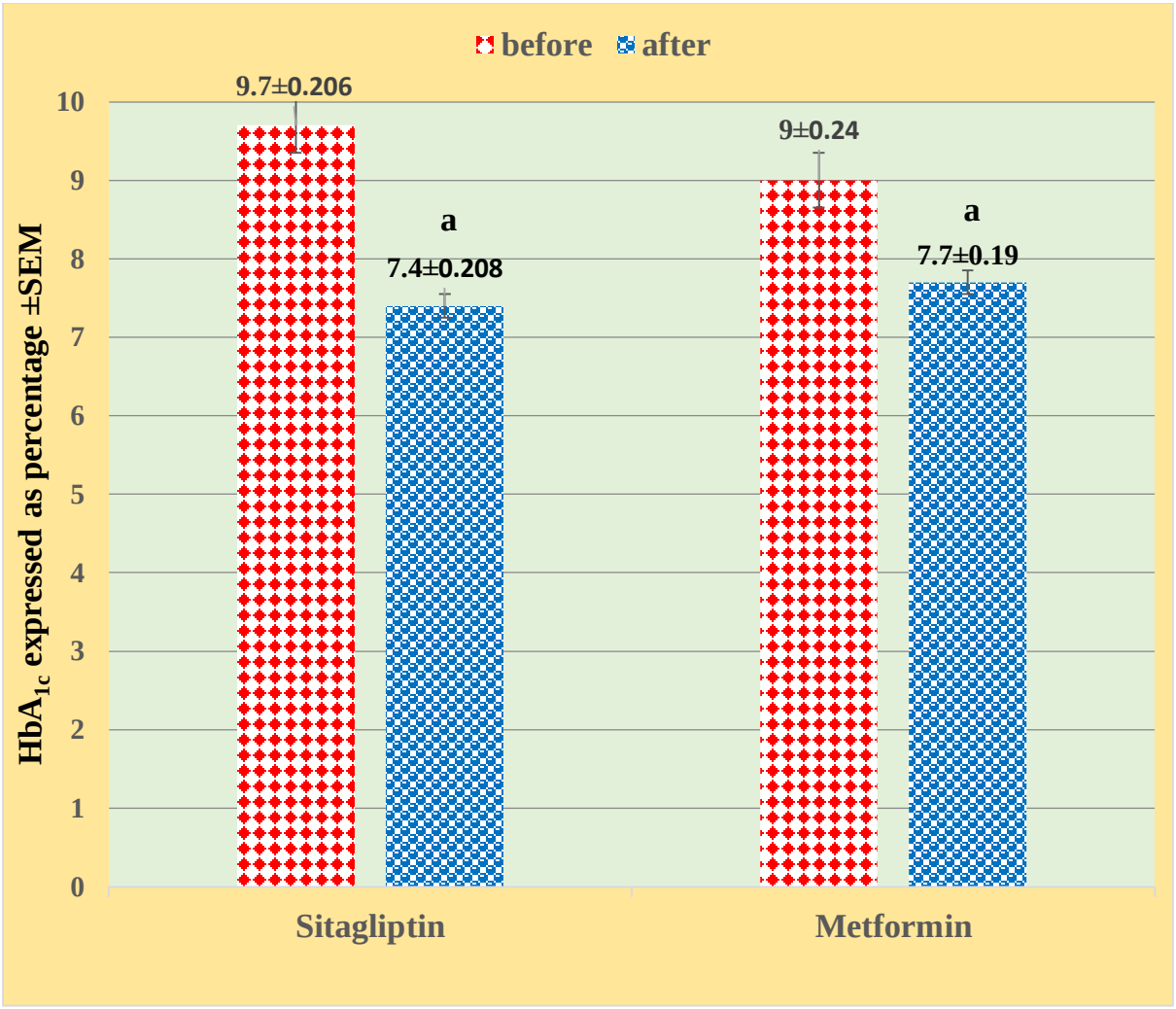


Figure 14: Effect of sitagliptin 100mg and metformin 850mg twice a day on HbA_{1c} in diabetic patient after 12 weeks of treatment.

a- Significantly lower than pre-treatment$(p < 0.01)$.

Table 7: Percentage of decline in HbA_{1c} after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily).

	Sitagliptin (100 mg daily)	Metformin (850 mg twice daily)
Percentage of decline in HbA_{1c}	**23.7 %**	**14 %**

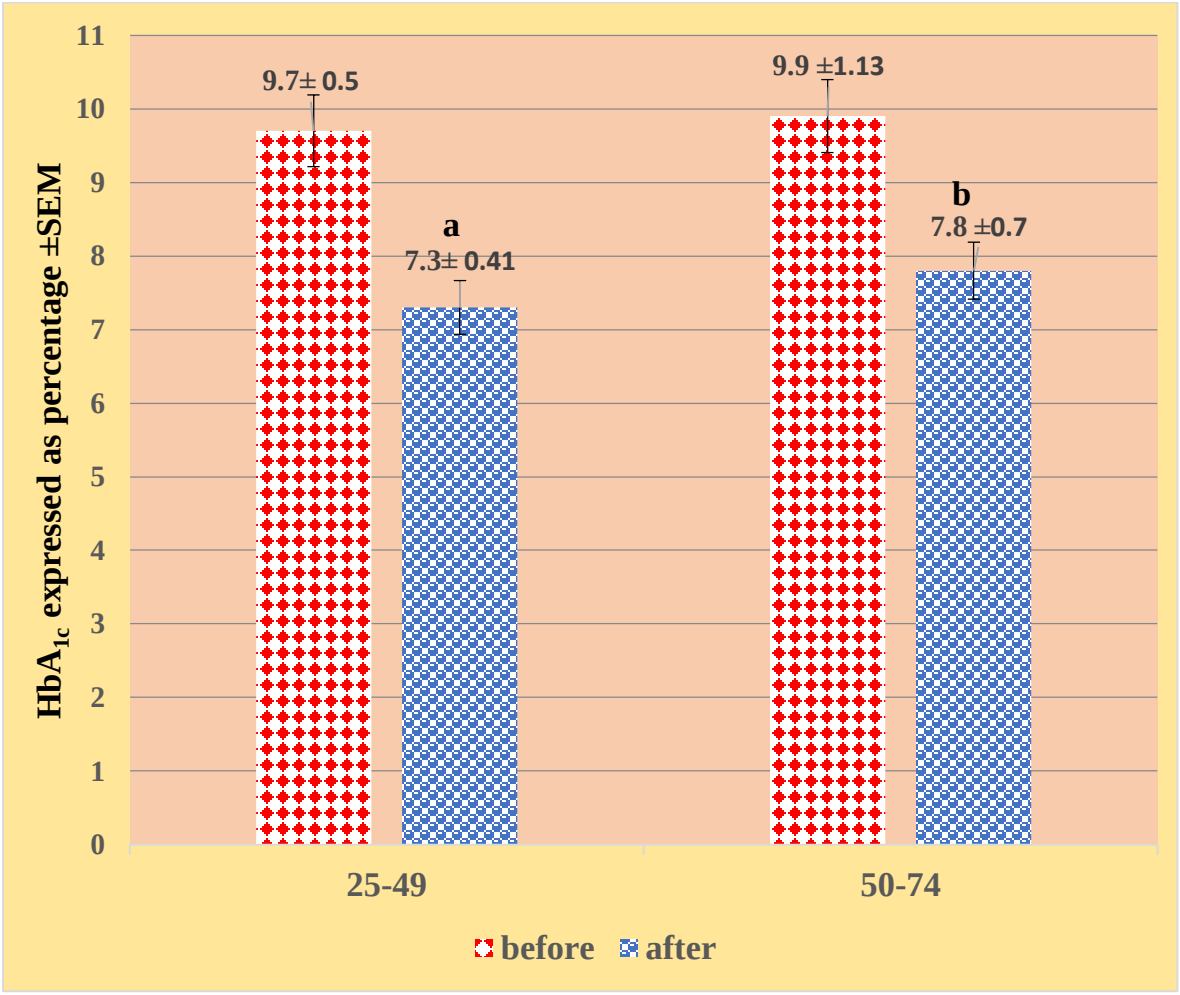


Figure 15: Effect of Sitagliptin 100mg on HbA_{1c} in diabetic patients after 12 weeks of treatment according to age group.

a- Significantly different from pre-treatment$(p < 0.001)$.
b- Significantly different from pre-treatment$(p < 0.008)$.

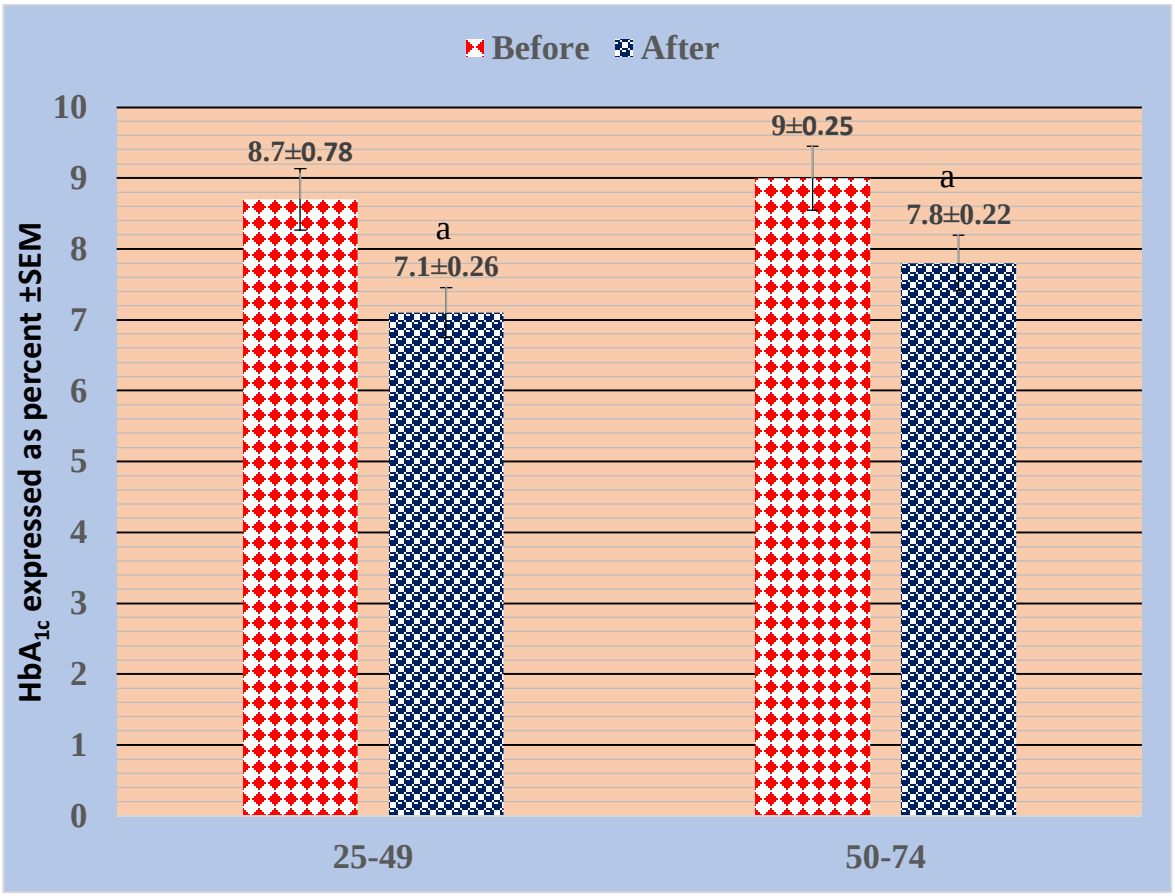


Figure 16: Effect of Metformin (850mg twice a day) on HbA_{1c} in diabetic patients after 12 weeks of treatment according to age group.

a- Significantly different from pre-treatment$(p < 0.05)$

Table 8: Percentage of decline in HbA_{1c} after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily) according to age group.

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Age (Years)	**25-49**	**50-74**	**25-49**	**50-74**
Percentage of decline in HbA_{1c}	**24.7 %**	**21%**	**18 %**	**13 %**

Figure 17: Effects of 100 mg/day of sitagliptin on FBS after 2 weeks in different diabetic mellitus duration groups.

a- Significantly different from pre-treatment$(p < 0.05)$.

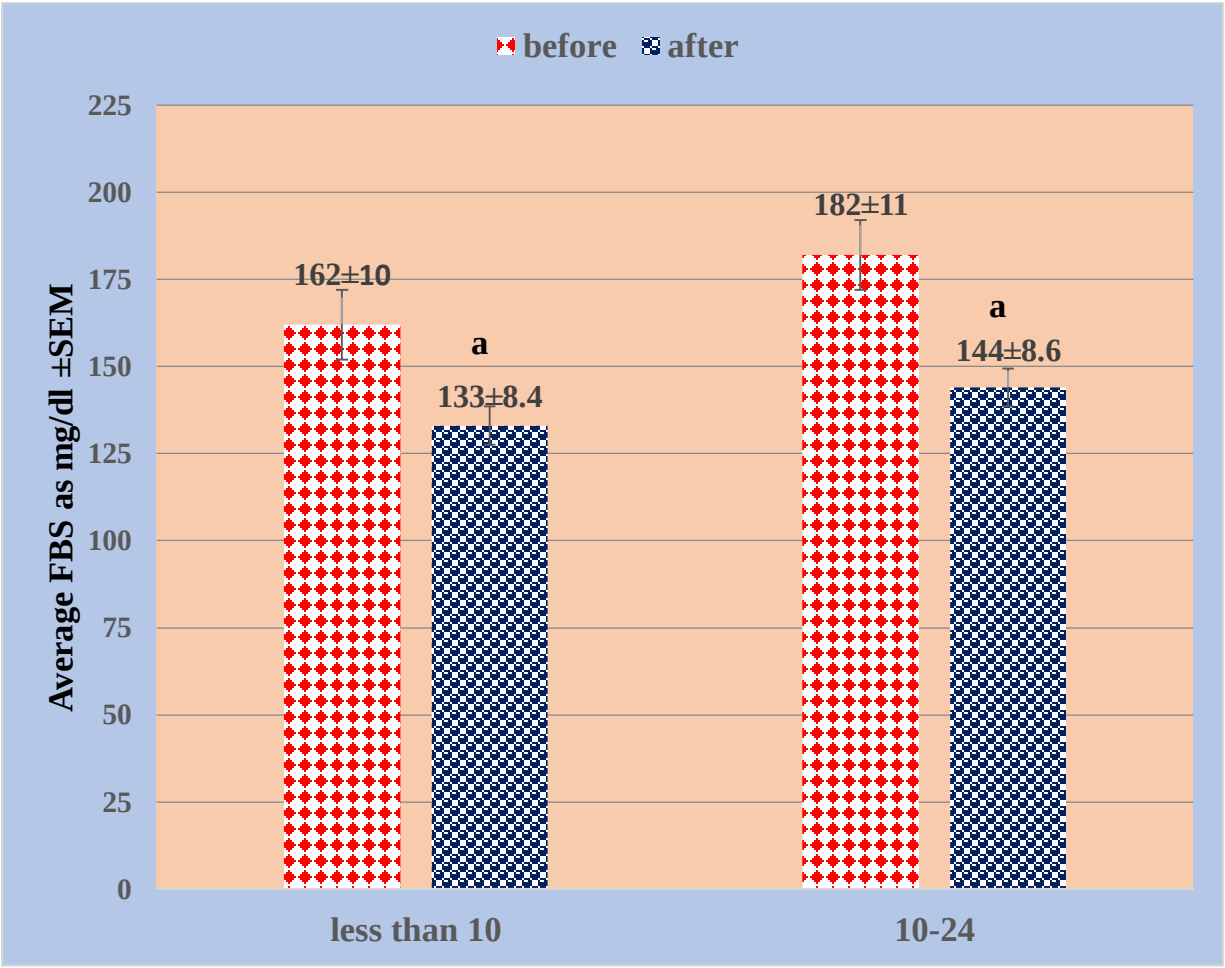


Figure 18: Effects of 850 mg of metformin twice daily twice a day on FBS after 2 weeks in different diabetic mellitus duration groups.

a- Significantly different from pre-treatment$(p < 0.01)$.

Table 9: Percentage of decline in FBS after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily) according to diabetic mellitus duration groups.

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Duration (Years)	**< 10**	**10 - 24**	**< 10**	**10 - 24**
Percentage of decline in FBS	**35%**	**38%**	**18%**	**21%**

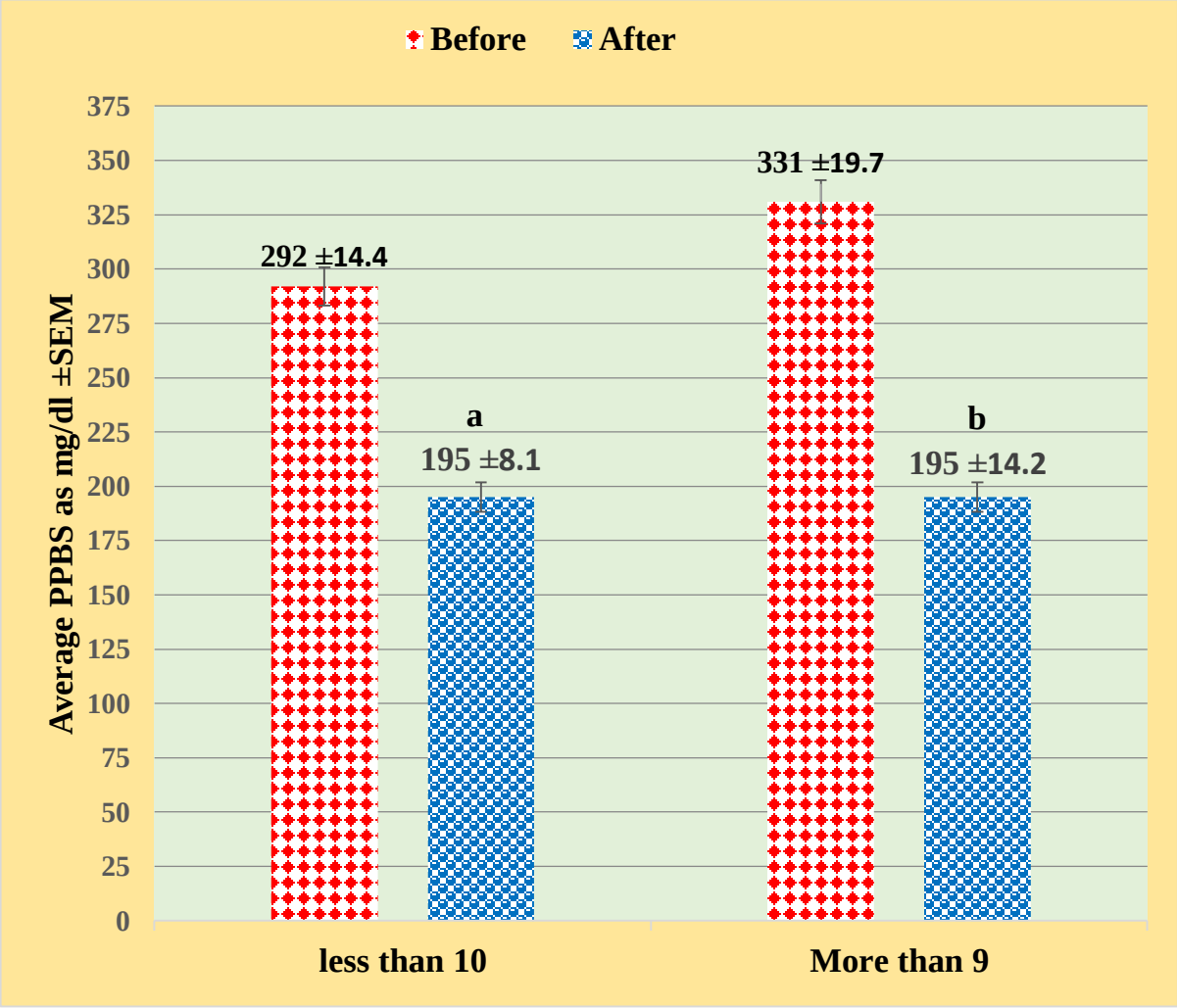


Figure 19: Effects of 100 mg sitagliptin on PPBS after 2 weeks in different diabetic mellitus duration groups.

a- Significantly different from pre-treatment($p < 0.001$).
b- Significantly different from pre-treatment($p < 0.01$).

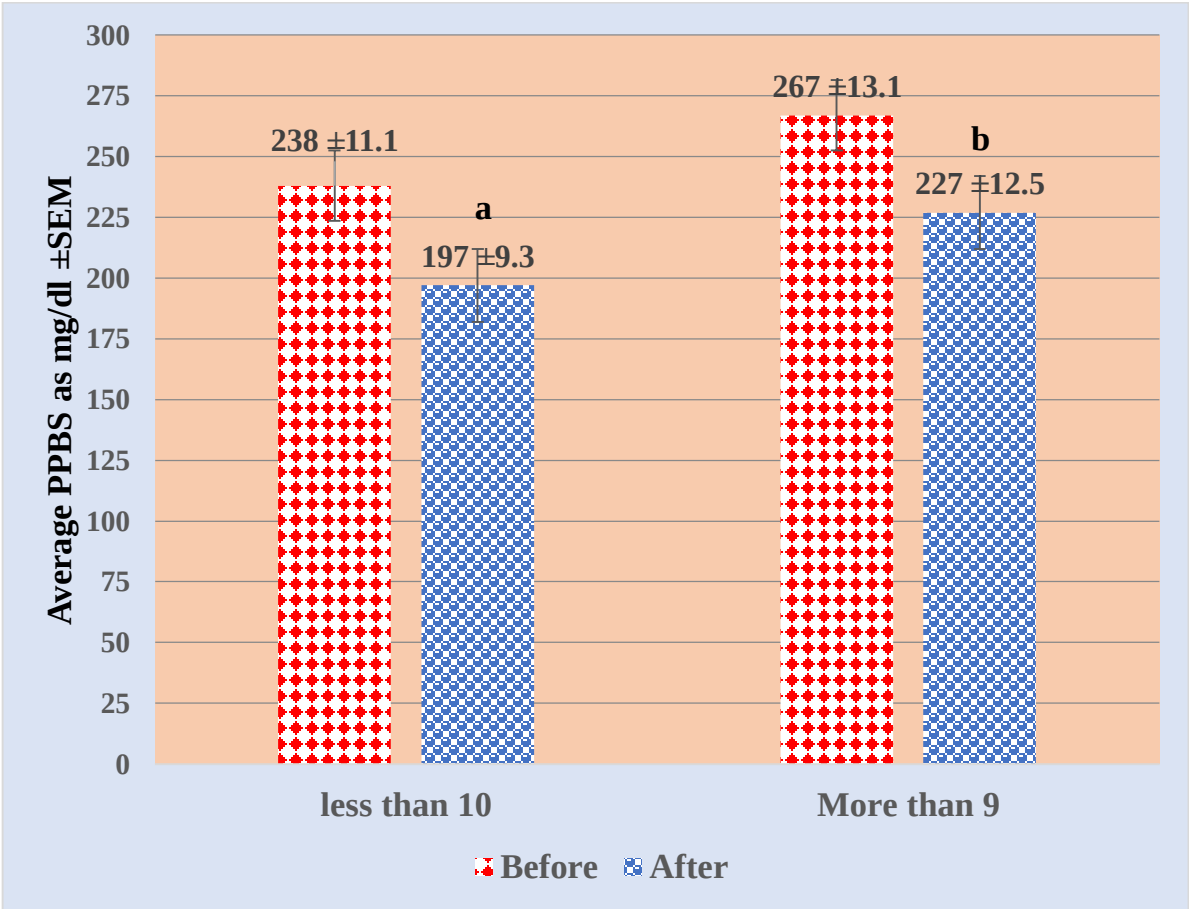


Figure 20: Effects of 850 mg metformin twice a day on PPBS after 2 weeks in different diabetic mellitus duration groups.

a- Significantly different from pre-treatment$(p < 0.04)$.
b- Significantly different from pre-treatment$(p < 0.01)$.

Table 10: Percentage of decline in PPBS after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily)according to duration of diabetic mellitus.

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Duration (Years)	**< 10**	**10 - 24**	**< 10**	**10 - 24**
Percentage of decline in PPBS	**33%**	**41%**	**17%**	**15%**

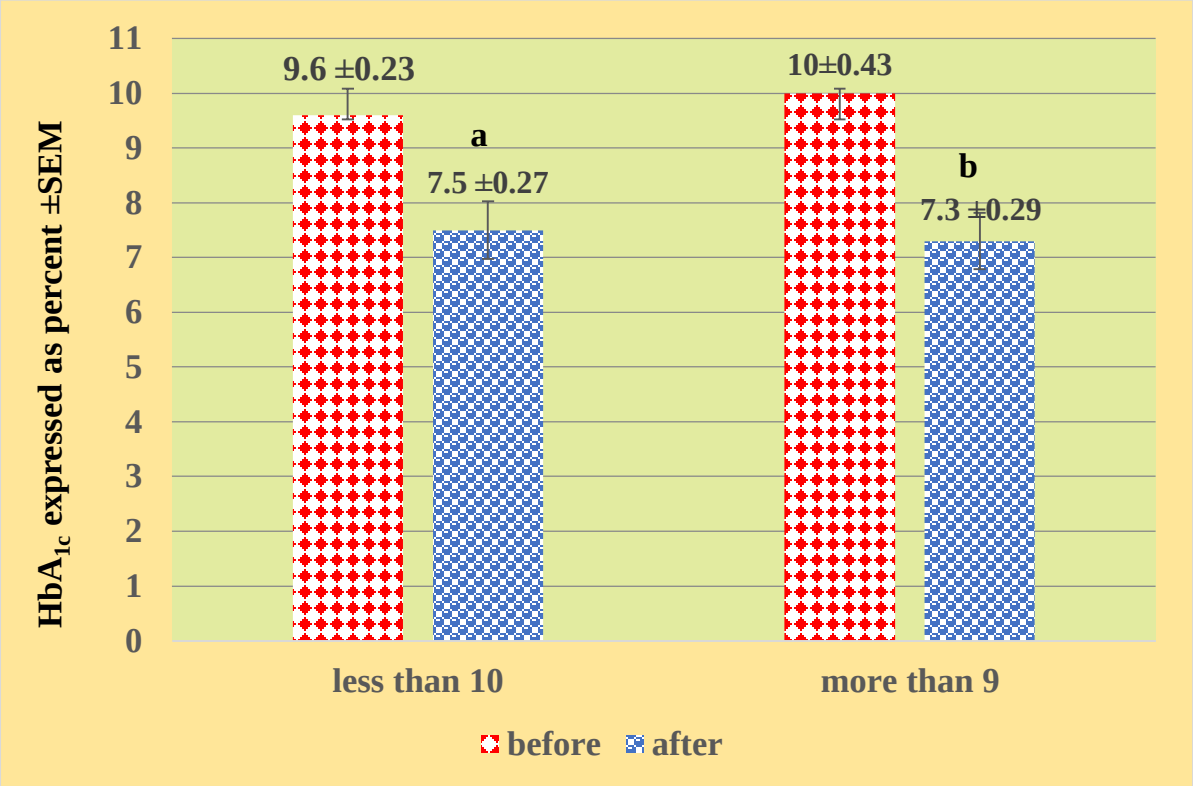


Figure 21: effects of 100 mg of sitagliptin on HbA_{1c} after 12 weeks in different diabetic groups.

a- Significantly different from pre-treatment $(p < 0.001)$
b- Significantly different from pre-treatment $(p < 0.01)$

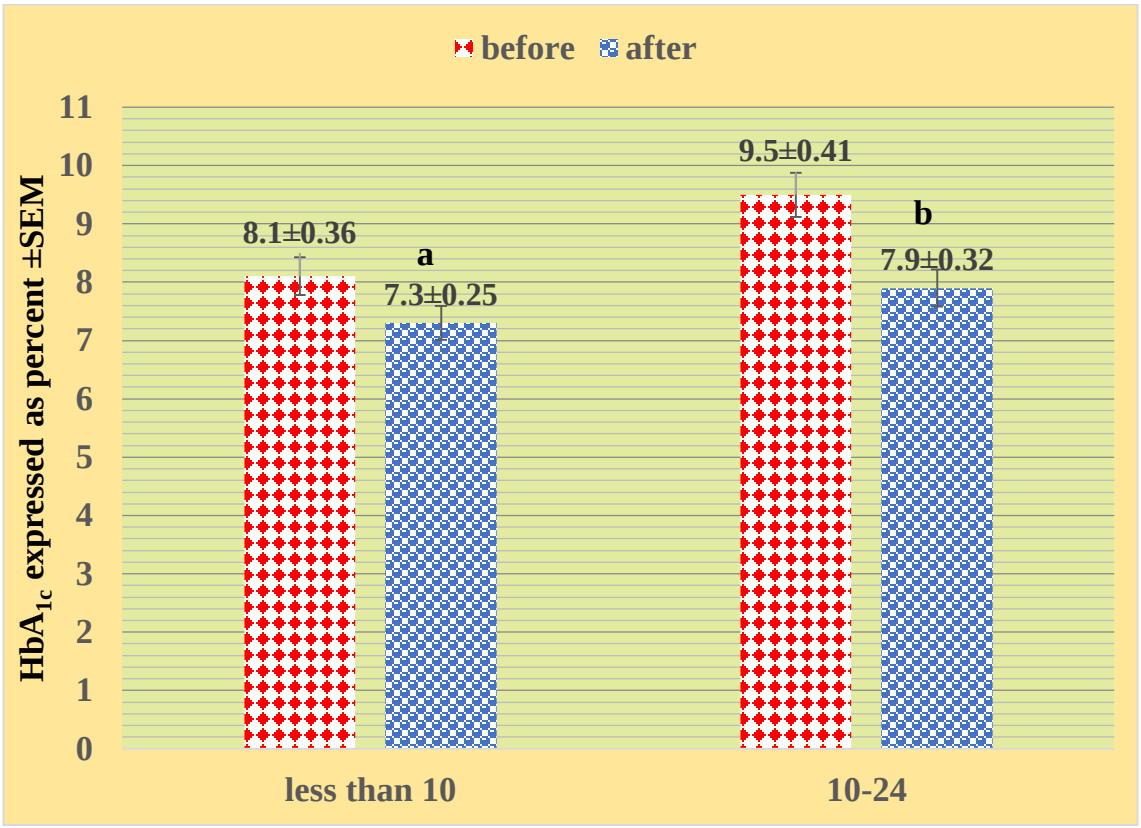


Figure 22: Effects of 850 mg metformin twice a day on HbA_{1c} after 12 weeks in different diabetic mellitus duration groups.

a- Significantly different from pre-treatment$(p < 0.01)$.
b- Significantly different from pre-treatment$(p < 0.05)$.

Table 11: Percentage of decline in HbA_{1c} after administration of Sitagliptin (100 mg daily) or metformin (850 mg twice daily) according to diabetic mellitus duration groups

	Sitagliptin (100 mg daily)		Metformin (850 mg twice daily)	
Duration (Years)	**< 10**	**10 - 24**	**< 10**	**10 - 24**
Percentage of decline in HbA_{1c}	**22%**	**27%**	**10%**	**17%**

Chapter-IV
Discussion and conclusion

Type 2 diabetes mellitus is a common chronic disease that causes significant morbidity and mortality worldwide. The primary goal of treatment is to target glycemic control by maintaining the glycosylated haemoglobin level near 6-7% without predisposing patients to hypoglycaemia. Diabetes results from a combination of increased hepatic glucose production, decreased insulin secretion from beta cells, and insulin resistance in the peripheral tissues. Currently available anti-diabetic agents work by different mechanisms to lower blood glucose levels. Unfortunately, each of them has its tolerability and safety concerns that limit its use and dose titration. Sitagliptin is the first anti-diabetic agent from the class of dipeptidyl peptidase-4 enzyme inhibitors. It increases the amount of circulating incretin, which stimulates insulin secretion and inhibits glucose production. The US Food and Drug Administration (FDA) approved Sitagliptin for use with diet and exercise to improve glycaemic control in adult patients with type 2 diabetes. In 2005 and 2006, the US Food and drug administration reviewed the abstracts published by the American Diabetes Association on the new drug sitagliptin, and selected information produced by the drug manufacturer (ADA, 2006). In conclusion, this drug can be used alone or in combination with metformin or a thiazolidinedione (pioglitazone or rosiglitazone) when treatment with either drug alone provides inadequate glucose control. The usual adult dose is 100 mg once daily. A dose of 25-50 mg once daily is recommended for patients with moderate-to-severe renal impairment (Choy M, Lam S, 2013).

In current study, which lasted 3 months, we investigated the effect and safety of sitagliptin when added to ongoing metformin therapy (where metformin alone was ineffective to control hyperglycemia). A hundred milligrams of sitagliptin were given once a day after lunch time, and the group of patients receiving this combination was referred to as sitagliptin group (consisting of 30 patients). The results obtained for this group were compared to another group referred to as the metformin group (consisting of 45 patients). In the metformin group, the selected patients were on metformin and their diabetes was uncontrolled using metformin dose of 500 mg twice a day, accordingly, the dose of metformin was increased to 850mg twice a day.

Sitagliptin, a highly selective DPP-4 inhibitor, is given orally once a day. It was evaluated in this study, as an add-on therapy, or as an initial therapy given in combination with metformin. It was shown to provide effective fasting and postprandial glycaemic control in a wide range of patients with type 2 diabetes. In addition, Sung-Chen Liu et al, (2013) reported that sitagliptin improved glycosylated haemoglobin. In the clinical trials they conducted they showed that sitagliptin was generally well tolerated with a low risk of hypoglycaemia or gastrointestinal adverse experiences, and had a neutral effect on body weight (Rosenstock et al. 2006).

Sitagliptin is usually prescribed for patients who are already on metformin and sulphonylurea, or as monotherapy, this means that sitagliptin can be initiated alone or when the older groups of antidiabetes medications failed to produce adequate glycemic control (VanDeKoppel, 2008).

Future clinical studies are required and should evaluate whether this class of agents has the potential to delay progression and/or prevent type 2diabetes.

With regard to the effect of sitagliptin on lipid profile, following taking sitagliptin 100mg tablet once a day by our patients, there was decline in all lipid parameters (cholesterol, LDL, TAG, VLDL) , while there was increase in HDL, which is a beneficial lipid. When the level of significance was applied, we found that the differences in laboratory finding before and after treatment were statistically insignificant except for VLDL. Insulin resistance is the basis for the development of type 2 diabetes. As a consequence of the onset of insulin resistance, hepatic production of very-low-density lipoprotein (VLDL) increases through an increase of free fatty acids and hyperglycemia due to ineffective hyperinsulinemia. In addition, insulin-dependent lipoprotein lipase activity decreases and the apoCIII content of VLDL increases. Furthermore, catabolism of VLDL is decreased and this leads to high levels of both VLDL and remnant lipoprotein (Yoshino et al. 1988)

Increased remnant lipoproteins, in patients with type 2 diabetes mellitus has attracted attention as one of the risk factors for the development of atherosclerosis. The total apoB-100 level gives the total number of lipoprotein particles in LDL + intermediate-density lipoprotein (IDL) + VLDL, This cholesterol values represented in these fraction equates the total cholesterol (TC) minus HDL cholesterol (HDL-C); thus, LDL + IDL + VLDL + CM remnant cholesterol is called non-HDL cholesterol (non-HDL-C). Some investigators suggest that the non-HDL-C, a marker for all apoB-containing lipoproteins, better represents “atherogenic lipoprotein” than does LDL cholesterol (LDL-C), Havel et al, (1995) and Garg et al. (1990).

Continuous treatment of healthy subjects with GLP-1 has been reported to contribute to lowering serum triglyceride (TG) levels before and after meals (Meier et al, 2006).

Regarding the mechanisms by which GLP-1 inhibits postprandial hyperlipidemia, reduced TG absorption due to slowing of gastric emptying and inhibition of lipolysis by high insulin secretion is thought to reduce CM levels. The results of recent studies suggest that GLP-1 signalling decreases the levels of TGs, cholesterol and apoB48 produced by the small intestine. Accordingly, GLP-1 is considered to decrease intrinsic VLDL production and increase CM clearance (Hsieh, J. et al, 2010; Nogueiras, R. et al, 2009).

Sitagliptin is a new medication that improves glycemic control by selectively inhibiting DPP-4, which is the enzyme responsible for inactivating GLP-1 and GIP, thus stimulating insulin secretion by promoting the activity of these incretins to suppress excessive glucagon secretion (Drucker, D.J. 2003).

Sitagliptin is expected to contribute to better glycemic control as a drug with a new mechanism of action and a low incidence of adverse events. Nonclinical (animal) studies conducted overseas have shown that inhibition of DPP-4 increases the GLP-1 level and thus affects the secretion of cholesterol and apoB by the small intestine (Hsieh et al. 2010)

It has also been found in clinical studies that inhibition of DPP-4 leads to a decrease of the elevated postprandial levels of TGs, CMs and apoB48 in patients with type 2 diabetes (Matikainen N, et al, and 2006; Kubota A, et al, 2012).

However, it is unclear what effects the usual clinical dose of sitagliptin might have on lipid metabolism. Generally, there is no agreement about the changes of lipid parameters after administration of sitagliptin, although decreases of TC, TG and non-HDL-C have been reported in clinical studies (Takihata M,et al, 2013; Tremblay, et al, 2001).

As discussed in a study done by Shigematsu (2014) among the lipid parameters, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) showed significant decreases.

In another study by Kutoh and Yamashita (2012), sitagliptin group, high triglyceride (TG) and free fatty acid (FFA) levels significantly decreased. Moreover, the study carried out by Derosa and Dario (2012) showed positive effects of sitagliptin on lipid profile in particular, sitagliptin decreased TC by −13.3%, LDL-C by −20.4%, and TAG by −32.3%, and on the contrary increased HDL-C by + 13.6%. Sitagliptin proved to be effective in improving lipid profile.

In another study in agreement with our results, no changes in serum total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein were reported following Sitagliptin treatment (Hsieh et al. 2014).

Results from a different study suggested that sitagliptin caused a significant decrease of TC, LDL-C and non-HDL-C, particularly in patients with high baseline TG levels and those using strong statins (Shigematsu et al, 2014).

Most likely sitagliptin acts by increasing incretin hormone levels, reducing circulating plasma FFA concentrations and improving insulin sensitivity and β-cell function (Perusicová J.Vnitr Lek. 2007).

In case of metformin patients' group, after 12 weeks of treatment with 850mg metformin twice a day, we noticed decline in TAG, LDL and VLDL, and an increase in HDL. When student paired-T test was applied to the results a significant increase for HDL in metformin patients' group were found. In case of metformin, Wulffele et al. (2004) demonstrated that metformin reduced the level of TC (total cholesterol). While Robinson et al, (1998) demonstrated declines in TC and TAG following the use of metformin. Metformin seems to reduce plasma total and LDL cholesterol significantly compared with control treatment by a glycaemia-lowering independent mechanism. These latter effects on lipid profile are, however, limited and not expected to result in major reductions in cardiovascular event end-points (Wulffelé et al, 2004).

Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities; the most common abnormalities seen are in ALT levels, in which mild chronic elevations of transaminases often reflect underlying insulin resistance. Elevation of transaminases within three times the upper limits of normal is not a contraindication for starting oral antidiabetic or lipid-modifying therapy. In contrast, antidiabetic agents have generally been shown to decrease alanine aminotransferase levels as tighter blood glucose levels are achieved (Elizabeth , 2005).

Liver function tests (LFTs) are commonly used in clinical practice to screen for liver disease, monitor the progression of known disease, and monitor the effects of potentially hepatotoxic drugs. In our study we measured the effects of each drug (sitagliptin and metformin), on liver parameters. The most common LFTs include the serum aminotransferases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in addition to alkaline phosphatase (AP), and bilirubin. In our study we found no changes in liver enzymes after using 100mg sitagliptin daily tablets for 12 weeks. The results published by Fukuhara and Hyogo, (2014) are in agreement with our study.

In case of metformin patients' there is insignificant changes in liver parameters except for bilirubin. Salpeter and Greyber study in 2010 reported no effect on liver enzymes, and they were in agreement with our study findings.

When we studied the effect of sitagliptin on kidneys, our study revealed insignificant changes in renal parameters in sitagliptin group, this is in agreement with study done by Wilding, (2012).

Since most DPP-4 inhibitors are eliminated by the kidney, a dose reduction is required for patients with moderate to severe renal impairment.

Giorda et al. (2014) conducted a systematic review on the pharmacokinetics, safety, and efficacy of DPP-4 inhibitors in patients with both T2DM and renal impairment, and suggested that DDP-4 inhibitors could be appropriate drugs for patients with renal impairment.

In another study, Pendergrass (2012) reported an increased incidence of ARF in diabetic versus non-diabetic patients but no association between use of sitagliptin and ARF. Because of the limitations of the observational analysis, they could not exclude the possibility of a very small increased risk.

If people with type 2 diabetes have impaired renal function, their kidneys do not filter the blood as efficiently as people with normal kidney function. These patients can pose a management problem because some diabetes treatments are either unsuitable for them, or the dosage must be adjusted dependent upon renal function.

The sitagliptin license extension means that patients with advanced renal impairment, stages 4 and 5 CKD can now be controlled with a simple dosage adjustment, For patients with mild renal impairment no dose adjustment is required, which is a real practical benefit (Haluzík, 2013).

In our study, we measured FBG after using sitagliptin, 100mg once a day for two weeks, FBS declined from 221± 8 mg/dl to 142 ± 5 mg/dl, (36% reduction).

GLP-1 improves glucose homeostasis via additional actions on both glucose sensors, inhibition of gastric emptying, food intake and glucagon secretion (Drucker, 2003). As such, GLP-1 administration potently stimulates insulin secretion and reduces blood glucose level in human subjects with type 2 diabetes (Klonoff DC,et al,2008).

Dipeptidyl peptidase IV (DPP-IV) is the enzyme responsible for the degradation of endogenous GLP-1 and GIP, rapidly cleaving and inactivating GLP-1 and GIP into inactive metabolite (Lambeir et al,2003).

Hence, recent glucose-lowering strategic approach is to enhance active incretin hormone levels and activity through the development of selective DPP-IV inhibitor (Holst et al. 2003). The approach in both preclinical animal models of type 2 diabetes and in clinical studies of patients with type 2 diabetes had shown to increase levels of intact GLP-1 and GIP, ultimately leading to meaningful improvements in overall glucose homeostasis (Ristic et al. 2005; Mari et al. 2005).

In case of metformin group, we use 850mg twice a day of metformin for two weeks, FBG declined from 173± 6 to 141± 4 mg/dl, (around 18.5%). The fluctuation of the metabolite cortisol indicated that the neuroendocrine system was involved in the anti-diabetic effect of metformin. Actually,

we found that metformin induced AMPK/liver X receptor α (LXRα) phosphorylation, followed by pro-opiomelanocortin (POMC) suppression in rat pituitary cells. We confirmed this result by administering metformin in an animal study. Given that cortisol stimulates gluconeogenesis, we propose the anti-hyperglycemic effect of metformin is attributed to reduced POMC/adrenocorticotropic hormone (ACTH)/cortisol levels following AMPK/LXRα phosphorylation in the pituitaries.

Metformin is frequently prescribed for type 2 diabetes and has many advantages including neutral weight effect and no hypoglycemic effect (UK Prospective Diabetes Study (UKPDS) Group, 1998).

Metformin exerts its antihyperglycemic action primarily by inhibiting hepatic gluconeogenesis and by increasing the action of insulin in certain target organs such as muscle and adipose tissue (Moreno-Navarrete et al. 2011).

Additionally, metformin is progressively used in polycystic ovary syndrome (PCOS) and many studies suggest that metformin could affect pituitary gonadotropin-secreting cells. However, the underlying mechanism by which metformin regulates blood glucose levels and/or affects pituitary function remains unknown.

It is well known that the pleiotropic actions of metformin are associated with AMP-activated protein kinase (AMPK) (Zhou et al. 2001).

The pituitary-mediated actions of metformin were elucidated in PCOS and diabetes. In particular, Tosca L, et al. (2011) reported that metformin-induced AMPK activation could exert its action in pituitary cells. Recent studies showed that orally dosed metformin rapidly crosses the blood-brain-barrier (BBB) and accumulates in the pituitary gland and hypothalamus of rats. However, the anti-hyperglycaemic mechanism of metformin, associated with the neuroendocrine system still not fully understood.

In a study by Hanefeld and Caria, (2006), sitagliptin tablet (100mg) daily conducted to see changes in FBS, declines of about 33% - 36% were found, while metformin decreased FBS by 16% - 19%. Reported changes by this study are in agreement with our results i.e. declines in values in our study were within the same range.

Sitagliptin and metformin effect on PPBS showed that after three months of treatment sitagliptin decreased PPBS by about 108mg/dl (35.6%), while metformin decreased PPBS by about 41mg/dl (around 16%). Therefore, our study emphasizes the strong effect of sitagliptin on PPBS.

In a study done by Charbonnel, et al (2006) it was shown that PPBS levels decreased by approximately 47 to 50 mg per dL (2.6 to 2.8 mmol/L).

Other study showed that the reduction in 2-hour postprandial blood sugar from baseline was significantly ($P<0.001$) greater with sitagliptin 100 mg/dL (–2.7 mmol/L [–48.9 mg/dL]) (Aschner P, et al. 2006).

In a different study Nonaka, et al. (2008) reported that Sitagliptin not only reduced the HbA1c levels but also improved the fasting and postprandial blood glucose. It reduced HbA1c about 2.6%, while metformin, in same age group decreased HbA1c by about 2%.

In our study sitagliptin lowered glycosylated haemoglobin levels by 2.3% in sitagliptin patients' group, while metformin decreased glycosylated haemoglobin by 1.3% in metformin patients' group.

HbA1C levels decreased by an average of 0.8 percent in patients with a baseline A1C of 8.1 percent using sitagliptin (Aschner P, Kipnes MS, Lunceford JK, et al, 2006).

In patients with moderately uncontrolled diabetes (HbA1c baseline of less than 8 percent but at least 7 percent) sitagliptin decreased the A1C level by 0.6 percent; in patients with a higher HbA1c baseline (9 percent or greater) it decreased the A1C level by 1.5 percent (Merck & Co., Inc. Accessed July 3, 2007).

Adding sitagliptin to either metformin or pioglitazone (Actos) can decrease the A1C level by an additional 0.7 percent (Charbonnel et al. 2006).

Zerilli and Pyon, (2007) conducted a study in which they supported our observation concerning the reduction in glycosylated haemoglobin (HbA1c), i.e., with 100 mg of sitagliptin reduction ranged from approximately 0.5% to 0.7%. In combination trials, adding metformin to sitagliptin, HbA1c was reduced by approximately 0.7%.

Overall, sitagliptin provides a treatment option for patients with type 2 diabetes as a mono therapy, or as an adjunct therapy to metformin or a thiazolidinedione when patients achieve inadequate glycaemic control.

In a 24-week clinical trial, Sung-Chen Liu et al, (2013) showed a decline in HbA1c of about 0.5 - 0.8% using sitagliptin, hence it was shown to be non-inferior to metformin. Patients with more severe base line hyperglycaemia (A1C $\geq$ 9%) had the largest reductions with co administration of sitagliptin and metformin. This observation in the randomized cohort was re inforced by the large reduction of 2.9% from base line observed in the open- label cohort. The

marked reduction observed in A1C with coadminstration corresponded with the substantial improvements in both FBS and PPBS. (Barry J. Goldstein, Mark N. Feinglos, et al, 2013).

Sitagliptin, added to previously taken anti- diabetic agents, proved to be effective in improving glycaemic profile, reducing HbA_{1c} by 1.5% (Derosa and Dario, 2012).

. In a trial using sitagliptin as monotherapy for diabetic inadequately controlled by diet and exercise, a daily dose of 100 mg of sitagliptin reduced HBA1c by 1.0% compared to placebo (Mohan et al. 2009).

Aschner et al. (2010) studied the effect of sitagliptin as mono therapy in type II diabetics, they found that 100 and 200 mg Sitagliptin produced significant reductions in A1C (-0.79 and -0.94%, respectively. Patients with baseline A1C $\geq$ 9% had greater reductions in A1C with sitagliptin 100 and 200 mg (-1.52 and -1.50%, respectively) higher than those with A1c baseline of < 8% (-0.57 and -0.65%) $\geq$ 8 to < 9.0% (-0.80 and -1.13%, respectively, and reduction in fasting blood sugar (-1.0 mmol/l [-17.1 mg/dl] and -1.2 mmol/l [-21.3 mg/dl], respectively).

In this 24-week study, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of beta-cell function, and was well tolerated in patients with type 2 diabetes.

In addition to dividing patients according to ages, we divided our patients to groups according to duration of diabetes, and studied the changes in of FBS, PPBS, and glycosylated haemoglobin in each of them.

In those who are diabetic, for less than 10 years duration, they were young (less than 40 years old) in case of sitagliptin patients' group and around age of 60s in case of metformin patients' group. In these groups FBS declined after use of sitagliptin from 220mg% to 140mg%, around 36%, In case of our study metformin changed FBS from 160mg% to 135mg% about 25mg% only in same group, a decline by 15.6%. In the same group the effect of sitagliptin is double that of metformin, these percentage of decline located in the range given by Hanefeld et al. (2006) demonstrate range of decline in FBS between (33% - 36%) while metformin decreased FBS by (16% - 19%).

In case of the second group (10 – 24 years diabetes) sitagliptin changed FBS from 250mg% to 150mg%, hence there is good drop of about 100mg% (declined by 66.7%), while in case of metformin FBS changed from 190mg% to about 140mg% (about 50mg% drop). Therefore, it decreased by 26.3%, less than half the effect of sitagliptin. There is more effect of sitagliptin in lowering of FBS in comparison to metformin effect in different groups.

The effect of each of these drugs on glycosylated HB (HBA1c) in different diabetes mellitus duration groups varies such that in first group, sitagliptin patients' group, for those who were diabetic for less than 10 years HbA1c changed from 9.9 % to 7.5 % (around 2.4%), while for metformin patients' group HbA1c changed from 8.1 % to 7.3 % (around 0.8%).

In second sitagliptin patients' group, those who were diabetic for more than 9 years, HbA1c change from 10% to 7.3% (around 2.7%), while for metformin patients' group HbA1c changed from 9.5% to 7.9% (around 1.6%).

The sitagliptin treatment lowered HBA1c by 0.89% compared to placebo in one study done by (Hermansen K, Kipnes M, Luo E, et al 2007).

In another study by Goldstein et al. (2007), following the use of 100 mg sitagliptin glycosylated hemoglobin was reduced by 1.9%.

In sitagliptin patients' group (<10 years diabetes duration), PPBS change from 292 mg % to 195 mg %, it decreased by 33%. Whereas in case of metformin (<10 years diabetes duration) PPBS changed from 238 mg% to197mg%, it declined by 17%.

In the second group with diabetes duration of more than 9 years and treated with sitagliptin, PPBS changed from 331 mg % to 195 mg %.it declined by 41%. While in corresponding metformin group, PPBS changed from 267 mg % to 227 mg %, it dropped 15% only, hence in two situations there is same findings, a greater decrease in postprandial glucose due to effect of sitagliptin.

Aschner and Kipnes (2006) studied the effect of sitagliptin as mono therapy in type II diabetics, in a meal tolerance test, sitagliptin 100 and 200 mg significantly decreased 2-h postprandial glucose (PPG) (placebo-subtracted PPG -2.6 mmol/l [-46.7 mg/dl] and -3.0 mmol/l [-54.1 mg/dl], respectively). Results were not significantly different between different sitagliptin doses.

Sitagliptin has been shown to be effective and well-tolerated in various treatment regimens and may be considered for both initial therapy and as add-on therapy for patients with type 2 diabetes.

CONCLUSION

From this study, we may conclude the following:

I. Sitagliptin improves clinical outcomes in type 2 diabetic patients, with undetectable side effects.

II. Sitagliptin improves FBS, PPBS and glycosylated haemoglobin, and when compare it is effect to that of metformin, it was twice that of metformin.

III. Glycaemic control after use of sitagliptin, appear within two weeks.

IV. Use of sitagliptin in addition to other oral anti-diabetic, delay onset to start insulin treatment, and reduce dose of other anti-diabetic treatment.

V. Use of sitagliptin in diabetic patients with liver diseases is safe because sitagliptin has no effect on LFT

VI. DPP-4 inhibitors are effective at lowering HbA_{1c} in T2DM patients with moderate to severe renal impairment. DPP-4 inhibitors also have a potential advantage in lowering the risk of adverse events. Regarding the low quality of the evidence according to GRADE, additional well-designed randomized trials that focus on the safety and efficacy of DPP-4 inhibitors in various CKD stages are needed urgently.

VII. Sitagliptin has no effect on RFT, but should be used with precaution in patients with renal impairment

VIII. Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant females with type 2 diabetes, with modest efficacy and a favorable weight-change profile. Careful post marketing surveillance for adverse effects, especially among the DPP4 inhibitors, and continued evaluation in longer-term studies and in clinical practice are required to determine the role of this new class among current pharmacotherapies for type 2 diabetes

الخلاصـــــــــة

دراســة مقارنــة عن السيتــاقليبتين والميتفورمين لعــلاج مــرضى الســكــري مــن النــوع الثــاني

يعتبــر مــرض الســكري من الامراض المــزمنة الأكثر شيوعاً في العالم خاصة النوع الثاني والبحوث جارية ومستمرة لإيجاد الدواء الأكثر فاعلية والاقل اعراض جانبية والأقل تكلفة

وقد تم خلال هذه الدراسة بيان فاعلية كل دواء في تنظيم معدلات السكر والتراكمي ووظائف الكبد والكلى ومعدلات الدهون و مع إجراء المقارنة بين النتائج المتحصل عليها لكلا الدوائين تبين أن السيتاقليبتين أكثر فاعلية في خفض مستوى السكر والتراكمي في الدم مع ثبات وظائف الكبد والكلى والدهــون فــي الجسم.

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ABSTRACT

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to absolute or relative deficiency of insulin. This can arise in many different ways. Lack of insulin, whether absolute or relative affects the metabolism of carbohydrate, protein, fat, water and electrolytes. Death may result from acute metabolic decompensation while long-standing metabolic derangement is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, those of the vascular system being particularly susceptible. These changes lead in turn to the development of well-defined clinical entities, the so-called "complication of diabetes" which most characteristically affect the eye, the kidney and the nervous system.

DYSLIPIDEMIA is common feature in diabetic patients and considered responsible largely for cardio vascular related morbidity and mortality.

This study aimed to evaluate glycaemic and lipid control in type ii diabetic patients, by using two types of drugs, biguanide (metformin) andDPP-4 inhibitors (sitagliptin).

In this study, we investigate the effect of sitagliptin and metformin on lopid profile, liver function, renal function, FBG and HbAc1 in diabetic patients. Our data showed that sitagliptin and metformin non significantly decreases lipid profile.

Data also indicated that sitagliptin has no effect on liver function nor kidney function.

Both sitagliptin and metformin decrease the FBG level and HbAC1 level but the effect of sitagliptin is more pronounced than metformin