East West University

Effect of Metformin with & without Vildagliptin on renal function in type 2 diabetes patients enrolled in BIRDEM Hospital

A Project report submitted to the Department of Pharmacy in partial fulfillment for the requirements of the degree of Master of Pharmacy (M.Phrm)

Submitted By

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Submitted To

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Dedicated To

My Family, Friends and Teachers

DECLARATION BY THE CANDIDATE

I, Priyata Dey (ID # 2015–1–79–006), hereby declare that, the Project entitled “Effect of Metformin with & without Vildagliptin on renal function in type 2 diabetes patients enrolled in BIRDEM Hospital” has been submitted by me to the Department of Pharmacy, East West University, Aftabnagar, Dhaka, Bangladesh in the partial fulfillment of the requirement for the award of the Degree of Master of Pharmacy (M.Phrm).It is a record of original Project work carried out by me during 2015 – 2016, under the supervision and guidance of Dr. Sufia Islam, Professor, Department of Pharmacy, East West University, Aftabnagar, Dhaka, Bangladesh, and it has not formed the basis for the award of any other Degree/Diploma/Fellowship or other similar title to any candidate of any University.

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CERTIFICATION BY THE PROJECT SUPERVISOR

This is to certify that, the dissertation, entitled **"**Effect of Metformin with & without Vildagliptin on renal function in type 2 diabetes patients enrolled in BIRDEM Hospital**"** is a research work done, under our guidance and supervision, by Priyata Dey(ID : 2015-1-79-006), in partial fulfillment of the requirement for the degree of Master of Pharmacy. We further certify that, all the sources of information and laboratory facilities availed in this connection are duly acknowledged.

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ENDORSEMENT BY THE CHAIRPERSON

This is to certify that, the dissertation, entitled **"**Effect of Metformin with & without Vildagliptin on renal function in type 2 diabetes patients enrolled in BIRDEM Hospital**"** is a research work done by Priyata Dey(ID: 2010-3-70-042) in partial fulfillment of the requirements for the degree of Master of Pharmacy, under the guidance of Dr. Sufia Islam, Professor, Department of pharmacy, East West University, Dhaka, Bangladesh. We further certify that, all the sources of information and laboratory facilities availed in this connection are duly acknowledged.

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Abbreviation

1. ACEIs - Angiotensin Converting Enzyme Inhibitors.
2. ALT - Alanin Amino Transferase
3. ARBs - Angiotensin Receptor Blockers
4. AST - Aspartate Amino Transferase
5. AUC - Alter the Overall Exposure
6. CHF - Congestive Heart Failure
7. CPK - Creatine Phosphokinase
8. CRP - C-Reactive Protine
9. CYP - Cyptochrome P
10. DM - Diabetes Mellitus
11. DPP-4 - Dipeptidyle Peptidase-4
12. ED - Energy Dependent
13. EMEA - European Medicines Energy
14. ESRD - End-stage Renal Disease
15. FDA - Food and Drug Administration
16. GDM - Gestational Diabetes Mellitus
17. GIP - Glucose-Dependent Insulinotropic Peptide
18. GLP - Glucagone-like Peptide
19. GLP-1 - Glucagone-like Peptide-1

20. IDDM - Insulin-Dependent Diabetes Mellitus

21. IDF - International Diabetic Federation

22. LADA - Latent Autoimmune Diabetes of Adult

23. MRDR Malnutrition-related Diabetes Mellitus

24. NPH - Neutral Protamine Hagedorn

25. NIDDM – Non insulin-Dependent Diabetes Mellitus

26. NYHA - New York Heart Association

27. PEP - Prolyl Oligopeptidase

28. PPARs - Peroxizome Proliferated Activated Receptors

29. PPRE- Peroxizome Proliferator Responsive Elements

30. RBCs - Red Blood Cells

31. SAR - Structure Activity Relationship

32. TZDs - Thiazolidinediones

Abstract

Diabetes Mellitus is one of the major causes of renal impairment and a major public health problem globally. Diabetes is associated with microvascular complications that also includes nephropathy. Diabetes nephropathy is the leading cause of renal failure in such patients. Diabetes Mellitus is one of the major causes of renal impairment and a major public health problem globally. Adequate glycemic control is essential to prevent or delay the onset of diabetic nephropathy. There are availability of antidiabetic medications in the market. However, only a few can be used safely in patients suffering from both diabetes and chronic kidney disease. Metformin has been recommended as the first line antidiabetic drug recommended by the American Diabetes Association. If a single agent is failed to achieve adequate glucose control, a combination oral antidiabetics may result in better glycemic control in patients with Type 2 diabetes. This study was designed to assess the efficacy and safety of metformin without vildagliptine (M without V)) and metformin with vildagliptine (M with V)in type 2 diabetic patients on blood glucose and renal function. During eight months study period, 600 prescription (Diabetic Books prescription and new patients initial form prescription) of patients suffering from diabetes mellitus were analyzed from BIRDEM, Shahabag, Dhaka, Bangladesh. Patients suffering from Type 2 diabetes, male or female, age ≥22 years were included in the study. The patients were prescribed Metformin with and without vildagliptin and also other combination drugs for the treatment of diabetes. The present study shows that the fasting blood glucose of the patients of M without V was 8.838 ± 2.145 mmol/L and M with V was 9.231 ± 3.475 mmol/L. The difference was not statistically significant (p=0.8504). The blood glucose level after 2 hours breakfast (ABF) was 12.81 ± 2.942 mmol/L in M without V group and 12.02 ± 4.315 mmol/L in M with V group (p=0.022). The creatinine value of M without V group was 1.075 ± 0.92 mg/dl and M with V was 1.011±0.246. The difference between the group is not statistically significant (p=0.507). Metformin with and without Vildagliptin effectively control fasting blood glucose level in type 2 diabetes patients. The blood glucose level after 2 hour breakfast is better controlled by Metformin with Vildagliptin. Metformin with and without Vildagliptin has no significant effect on creatinine level. Further study is needed with a large sample size to determine the efficacy and safety of combination Metformin and Vildagliptin in type 2 diabetes patients.

Keywords: Diabetes, Antidiabetic drugs, Insulin, Metformin HCL, Vildagliptin, Sitagliptin, Linagliptin.

Contents

Chapter 1

Introduction

1.1Diabetes mellitus

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of different organs, especially eyes, kidneys, nerves, heart, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the beta cells of the pancreas with consequent insulin deficiency to abnormalities those results in resistance to insulin action(American Diabetes Association, 2012).

Diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia. Symptoms of marked hyperglycemia include polyurea, polydipsia, weight loss, sometimes with poly polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia (American Diabetes Association, 2014).

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type 1 and type 2 DM was clearly made. Type 2 DM was first described as a component of metabolic syndrome in 1988. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 DM results from interaction between genetic, environmental and behavioral risk factors (Bastaki,2005).

People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa(Bastaki,2005).

- Diabetes is a chronic condition associated with abnormally high levels of sugar (glucose) in the blood.
- Insulin produced by the pancreas lowers blood glucose.
- Absence or insufficient production of insulin causes diabetes.
- The two types of diabetes are referred to as type 1 and type 2. Former names for these conditions were insulin-dependent and non-insulin-dependent diabetes, or juvenile onset and adult onset diabetes.
- Symptoms of diabetes include increased urine output, thirst, hunger, and fatigue.
- Diabetes is diagnosed by blood sugar (glucose) testing.
- The major complications of diabetes are both acute and chronic.
    - **Acute complications:** dangerously elevated blood sugar (hyperglycemia), abnormally low blood sugar (hypoglycemia) due to diabetes medications may occur
    - **Chronic complications:** disease of the blood vessels (both small and large) which can damage the feet, eyes, kidneys, nerves, and heart may occur

Diabetes treatment depends on the type and severity of the diabetes. Type 1 diabetes is treated with insulin, exercise, and a diabetic diet. Type 2 diabetes is first treated with weight reduction, a diabetic diet, and exercise. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, insulin medications and other inject able medications are considered(Mikhail, 2008).

1.2 Adverse effects of diabetes

Over time, diabetes can lead to blindness, kidney failure, and nerve damage. These types of damage are the result of damage to small vessels, referred to as microvascular disease. Diabetes is also an important factor in accelerating the hardening and narrowing of the arteries (atherosclerosis), leading to strokes, coronary heart disease, and other large blood vessel diseases. This is referred to as macrovascular disease. Diabetes affects approximately 26 million people in the United States, while another 79 million gave prediabetes. In addition, an estimated additional 7 million people in the United States have diabetes and don't even know it.

From an economic perspective, the total annual cost of diabetes in 2011 was estimated to be 174 billion dollars in the United States. This included 116 billion in direct medical costs (healthcare costs) for people with diabetes and another 58 billion in other costs due to disability,

premature death, or work loss. Medical expenses for people with diabetes ate over two times higher than those for people who do not have diabetes. Remember, these numbers reflect only the population in the United States. Globally, the statistics are staggering.

Diabetes was the 7th leading cause of death in the United States listed on death certificates in 2007 (Stöppler, 2014).

In 1985, the best data available suggested that 30 million people had diabetes worldwide. Fast-forward 15 years and the numbers were revised to just over 150 million. Today, less than 10 years on, the new figures – launched at the 20th World Diabetes Congress in Montreal, Canada – put the number closer to 300 million, with more than half aged between 20 and 60.

Professor Jean Claude Mbanya, President of the International Diabetes Federation, voiced concern: “The data from the latest edition of the IDF Diabetes Atlas show that the epidemic is out of control. We are losing ground in the struggle to contain diabetes. No country is immune.”

Type 1 diabetes cannot be prevented. It is an autoimmune disease in which the body destroys its own insulin-producing cells. People with type 1 diabetes require daily injections of insulin to survive. The majority of all diabetes is type 2 diabetes (85%-95%), which in many cases can be prevented. People with type 2 diabetes cannot use the insulin they produce effectively, but can often manage their condition through exercise and diet, although many go on to require medication, including insulin, to properly control blood glucose levels. It is estimated 60% or more of type 2 diabetes could be prevented.

Both type 1 and type 2 diabetes represent a serious health threat. Diabetes claims four million lives every year and is a leading cause of blindness, kidney failure, heart attack, stroke and amputation(World Health Organization, 2006).

1.3Classification of diabetes mellitus

1.3.1 Type 1 diabetes mellitus

The type 1 diabetes is selective B-cell destruction and severe or absolute insulin deficiency. Administration of insulin is essential in patients with type 1 diabetes. Type 1 diabetes is further subdivided into immune and idiopathic causes. The immune form is the most common form of

type 1 diabetes. Although most patients are younger than 30 years of age at the time of diagnosis, the onset can occur at any age. Type 1 diabetes is found in all ethnic groups, but the highest incidence is in people from northern Europe and from Sardinia. Susceptibility appears to involve a multifactorial genetic linkage but only 10-15% of patients have a positive family history(Kahn *et al.*,2007).

1.3.2 Type 2 diabetes mellitus

Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a *relative* deficiency in insulin secretion. A given individual may have more resistance or more B-cell deficiency, and the abnormalities may be mild or severe. Although insulin is produced by the B cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL). Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control the blood glucose. It is likely that 10-20% of individuals in whom type 2 diabetes was initially diagnosed actually has both type 1 and type 2 or a slowly progressing type 1, and ultimately will require full insulin replacement. Although persons with type 2 diabetes ordinarily do not develop ketosis, ketoacidosis may occur as the result of stress such as infection or use of medication that enhances resistance, e.g. corticosteroids. Dehydration in untreated and poorly controlled individuals with type 2 diabetes can lead to a life-threatening condition called nonketotichyperosmolar coma. In this condition, the blood glucose may rise to 6-20 times the normal range and an altered mental state develops or the person loses consciousness. Urgent medical care and rehydration is required (Pickup, 1997).

1.3.3 Other diabetes mellitus

This type designation refers to multiple other specific causes of elevated blood glucose: non pancreatic diseases, drug therapy etc (Katzung*et al.*,2012).

1.3.4 Gestational diabetes

Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy. Gestational diabetes is diagnosed in approximately 4% of all

pregnancies in the USA. During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. Risk assessment for diabetes is suggested starting at the first prenatal visit. High-risk women should be screened immediately. Screening may be deferred in lower-risk women until the 24th to 28th week of gestation (Creighton, 1993).

1.4 Etiology of Type 1 diabetes

Type 1 diabetes is also known as childhood diabetes, insulin dependent diabetes mellitus, or juvenile diabetes. This is a type of diabetes mellitus that occurs due to the autoimmune destruction of the insulin producing beta cells of the pancreas. The exact etiology of diabetes mellitus of this kind is not fully understood. It is said that immunological factors, along with genetic and environmental factors are the cause behind childhood diabetes symptoms. This is in fact a polygenic disease, that is, many different genes contribute to its expression. The etiology of diabetes can also include strong environmental factors, as it has been seen that this strongly influences the expression of type 1 diabetes (Davis, 2006).

1.5 Etiology of Type 2 diabetes

Diabetes mellitus that affects people in adulthood is known as type 2 diabetes, or non-insulin dependent diabetes or adult onset diabetes. This is a disorder that is characterized by high levels of glucose in the blood that occurs due to an increase in the resistance of the body to insulin. There are many factors that can lead to diabetes mellitus, or at least that can exacerbate this type of diabetes. These factors include obesity (around 55 percent of type 2 diabetes patients are obese at diagnosis), high blood pressure, elevated cholesterol along with hyperlipidemia and with the condition often termed metabolic syndrome. Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis and the use of certain drugs. Additional factors found to increase the risk of type 2 diabetes include aging and a diet that is high in fats along with a sedentary lifestyle (Khardori,2014).

1.6 Symptoms of diabetes

Though diabetes can produce a number of symptoms, many of its early signs can look quite similar to the symptoms of certain other health conditions. This can make it difficult to recognize this condition. But it is important to identify and treat it early, as untreated diabetes can lead to some serious health complications. Knowledge about the symptoms of this condition is immensely important for preventing such complications.

- The early symptoms of untreated diabetes are related to elevated blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine can cause increased urine output and lead to dehydration. Dehydration causes increased thirst and water consumption.
- The inability of insulin to perform normally has effects on protein, fat and carbohydrate metabolism. Insulin is an anabolic hormone, that is, one that encourages storage of fat and protein.
- A relative or absolute insulin deficiency eventually leads to weight loss despite an increase in appetite.
- Some untreated diabetes patients also complain of fatigue, nausea and vomiting.
- Patients with diabetes are prone to developing infections of the bladder, skin, and vaginal areas.
- Fluctuations in blood glucose levels can lead to blurred vision. Extremely elevated glucose levels can lead to lethargy and coma.

  - **Excessive Thirst and Urination**: Excessive thirst and urination are considered as some of the most common symptoms. Both men and women can experience frequent urination or 'polyuria' and excessive thirst or 'polydipsia'. Frequent urination is caused by a high level of glucose, which adversely affects the filtering capacity of the kidneys. The kidneys start to draw more water from blood, as a result of which the affected person experiences an increase in the frequency of urination. Frequent urination causes the loss of excess fluid from the body or dehydration, which manifests in increased thirst.
  - **Unusual Weight Loss and Fatigue**: Unexplained weight loss can result due to the fact that the body cells fail to absorb and utilize glucose from the bloodstream effectively. The cells of the body need glucose to produce energy and so, an inability to absorb glucose can also result in unusual fatigue.

- **Increase in Appetite**: Diabetic patients experience constant hunger or an increase in appetite, if the body produces a high level of insulin in an attempt to bring down the level of blood sugar. Presence of a high level of insulin in the body can increase hunger, for which some diabetic patients can start eating more. An increase in appetite can sometimes result in weight gain. However, some of the affected individuals could lose weight in spite of eating more than usual.
- **Nerve Damage**: Nerves, especially the nerves of the peripheral nervous system can be damaged by consistently high levels of glucose. This is termed as diabetic neuropathy. Damage to the peripheral nervous system can manifest in tingling and numbness in legs, feet, hands and the fingers and toes.
- **Recurrent Infection and Slow Healing of Wounds:** A high level of blood sugar can also slow down the healing of wounds. Along with this, some men can get recurrent infections. These two are considered as the warning signs of a high level of blood sugar.
- **Vision Changes:** Blurred vision or vision changes can be a common complaint among individuals with high blood sugar level. When the level of blood sugar is consistently high, sugar can accumulate in the lens of the eye and damage the blood vessels of the retina. This condition is known as diabetic retinopathy, which if left untreated can lead to blindness.
- **Erectile Dysfunction**: Diabetes and a high level of blood glucose can slowly damage the nerves and the blood vessels of the penis. This eventually can lead to erectile dysfunction.
- **Other Symptoms**: Apart from the above mentioned symptoms, a few additional symptoms can be observed in some individuals. These symptoms include dry mouth, headaches, swollen, red and tender gums and development of dark skin patches on the neck (Bora,2012).

Mechanism of insulin release in normal pancreatic beta cells — insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose. Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and

gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is 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 is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, 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 be excreted in the urine (glycosuria). 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 be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). (King*et al*,2004*)*

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)
- Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)
- Glycated hemoglobin (HbA_{1C}) ≥ 48 mmol/mol (≥ 6.5 DCCT %).

A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus.Per the World Health Organization people with fasting glucose levels from 6.1 to 6.9 mmol/l (110 to 125 mg/dl) are considered to have impaired fasting glucose. people with plasma glucose at or above 7.8 mmol/l (140 mg/dl), but not over 11.1 mmol/l (200 mg/dl), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease. The American Diabetes Association since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/l (100 to 125 mg/dl).Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause. The rare disease diabetes insipidus has similar symptoms to diabetes mellitus, but without disturbances in the sugar metabolism (*insipidus* means "without taste" in Latin) and does not involve the same disease mechanisms. Diabetes is a part of the wider condition known as metabolic syndrome. (Bartoli*et al,*2011)

1.7 Risk factors of diabetes

- **Obesity:** Obesity is the major type 2 diabetes risk, with millions of people throughout the world facing obesity. Almost a quarter of adults in the UK are recorded as being obese. Furthermore, the numbers continue to climb, both amongst adults and children. The number of children being diagnosed with type 2 diabetes caused by obesity is climbing everywhere. In the UK, about one in three children are classed as obese.
- **Lack of exercise & sedentary way of life:** Living a sedentary lifestyle without sufficient exercise is seriously damaging to health. Being inactive often leads to being overweight, which can lead to pre-diabetes and type 2 diabetes.
- **Unhealthy Eating Habits:** Unhealthy eating contributes largely to obesity. Too much fat, not enough fiber, and too many simple carbohydrates all contribute to a diagnosis of diabetes. Eating right is can turn the diagnosis around and reverse or prevent Type 2.

- **Family History and Genetics:** It appears that people who have family members who have been diagnosed with type 2 diabetes are at a greater risk for developing it themselves. African Americans, Hispanic-Americans and Native Americans all have a higher than normal rate of type 2 diabetes. Having a genetic disposition towards type 2 is not a guarantee of a diagnosis however. Lifestyle plays an important part in determining who gets diabetes**.**
- **High Blood Pressure and High Cholesterol:** Both of these bodily forces are risks for many diseases, one of which is type 2 diabetes.
- **History of Gestational Diabetes:** Gestational diabetes affects about 4% of all pregnant women. It begins when hormones from the placenta make the mother insulin resistant. Many women who have gestational diabetes develop type 2 diabetes years later. Their babies are also at some risk for developing diabetes later in life.
- **Increased Age:** It's a sad but true fact. The older we get, the greater our risk of type 2 diabetes. Even if an elderly person is thin, they still may be predisposed to getting diabetes. Scientists theorize that the pancreas ages right along with us, and doesn't pump insulin as efficiently as it did when we were younger. Also, as our cells age, they become more resistant to insulin as well (Manzella, 2014).

1.8 Chronic complications of diabetes

These diabetes complications are related to blood vessel diseases and are generally classified into small vessel disease, such as those involving the eyes, kidneys and nerves (microvascular disease), and large vessel disease involving the heart and blood vessels (macrovascular disease). Diabetes accelerates hardening of the arteries (atherosclerosis) of the larger blood vessels, leading to coronary heart disease (angina or heart attack), strokes, and pain in the lower extremities because of lack of blood supply (claudication) (Tonna, 2001).

1.8.1 Eye complications

The major eye complication of diabetes is called diabetic retinopathy. Diabetic retinopathy occurs in patients who have had diabetes for at least five years. Diseased small blood vessels in the back of the eye cause the leakage of protein and blood in the retina. Disease in these

blood vessels also causes the formation of small aneurysms (microaneurysms), and new but brittle blood vessels (neovascularization). Spontaneous bleeding from the new and brittle blood vessels can lead to retinal scarring and retinal detachment, thus impairing vision.

To treat diabetic retinopathy a laser is used to destroy and prevent the recurrence of the development of these small aneurysms and brittle blood vessels. Approximately 50% of patients with diabetes will develop some degree of diabetic retinopathy after 10 years of diabetes, and 80% of diabetics have retinopathy after 15 years of the disease. Poor control of blood sugar and blood pressure further aggravates eye disease in diabetes.

Cataracts and glaucoma are also more common among diabetics. It is also important to note that since the lens of the eye lets water through, if blood sugar concentrations vary a lot, the lens of the eye will shrink and swell with fluid accordingly. As a result, blurry vision is very common in poorly controlled diabetes. Patients are usually discouraged from getting a new eyeglass prescription until their blood sugar is controlled. This allows for a more accurate assessment of what kind of glasses prescription is required (Stöppler, 2014).

1.8.2 Kidney damage

Kidney damage from diabetes is called diabetic nephropathy. The onset of kidney disease and its progression is extremely variable. Initially, diseased small blood vessels in the kidneys cause the leakage of protein in the urine. Later on, the kidneys lose their ability to cleanse and filter blood. The accumulation of toxic waste products in the blood leads to the need for dialysis. Dialysis involves using a machine that serves the function of the kidney by filtering and cleaning the blood. In patients who do not want to undergo chronic dialysis, kidney transplantation can be considered.

The progression of nephropathy in patients can be significantly slowed by controlling high blood pressure, and by aggressively treating high blood sugar levels. Angiotensin converting enzyme inhibitors (ACE inhibitors) orangiotensin receptor blockers (ARBs) used in treating high blood pressure may also benefit kidney disease in diabetic patients (Stöppler,2014).

1.8.3 Nerve damage

Nerve damage from diabetes is called diabetic neuropathy and is also caused by disease of small blood vessels. In essence, the blood flow to the nerves is limited, leaving the nerves without blood flow, and they get damaged or die as a result (a term known as ischemia). Symptoms of diabetic nerve damage include numbness, burning, and aching of the feet and lower extremities. When the nerve disease causes a complete loss of sensation in the feet, patients may not be aware of injuries to the feet, and fail to properly protect them. Shoes or other protection should be worn as much as possible. Seemingly minor skin injuries should be attended to promptly to avoid serious infections. Because of poor blood circulation, diabetic foot injuries may not heal. Sometimes, minor foot injuries can lead to serious infection, ulcers, and even gangrene, necessitating surgical amputation of toes, feet, and other infected parts.

Diabetic nerve damage can affect the nerves that are important for penile erection, causing erectile dysfunction (ED, impotence). Erectile dysfunction can also be caused by poor blood flow to the penis from diabetic blood vessel disease.

Diabetic neuropathy can also affect nerves to the stomach and intestines, causing nausea, weight loss, diarrhea, and other symptoms of gastroparesis (delayed emptying of food contents from the stomach into the intestines, due to ineffective contraction of the stomach muscles).

The pain of diabetic nerve damage may respond to traditional treatments with certain medications such as gabapentin (Neurontin), henytoin (Dilantin), and arbamazepine (Tegretol) that are traditionally used in the treatment of seizure disorders. mitriptyline (Elavil, Endep) and desipramine (Norpraminine) are medications that are traditionally used for depression. While many of these medications are not indicated specifically for the treatment of diabetes related nerve pain, they are used by physicians commonly.

The pain of diabetic nerve damage may also improve with better blood sugar control, though unfortunately blood glucose control and the course of neuropathy do not always go hand in hand. Newer medications for nerve pain include Pregabalin (Lyrica) and duloxetine (Cymbalta) (Stöppler, 2014).

1.9 Acute complications of diabetes

1. Severely elevated blood sugar levels due to an actual lack of insulin or a relative deficiency of insulin.
2. Abnormally low blood sugar levels due to too much insulin or other glucose-lowering medications.

1.9.1 Acute complications of type 2 diabetes

In patients with type 2 diabetes, stress, infection, and medications (such as corticosteroids) can also lead to severely elevated blood sugar levels. Accompanied by dehydration, severe blood sugar elevation in patients with type 2 diabetes can lead to an increase in blood osmolality (hyperosmolar state). This condition can worsen and lead to coma (hyperosmolar coma). A hyperosmolar coma usually occurs in elderly patients with type 2 diabetes. Like diabetic ketoacidosis, a hyperosmolar coma is a medical emergency. Immediate treatment with intravenous fluid and insulin is important in reversing the hyperosmolar state. Unlike patients with type 1 diabetes, patients with type 2 diabetes do not generally develop ketoacidosis solely on the basis of their diabetes. Since in general, type 2 diabetes occurs in an older population, concomitant medical conditions are more likely to be present, and these patients may actually be sicker overall. The complication and death rates from hyperosmolar coma is thus higher than in DKA.

Hypoglycemia means abnormally low blood sugar (glucose). In patients with diabetes, the most common cause of low blood sugar is excessive use of insulin or other glucose-lowering medications, to lower the blood sugar level in diabetic patients in the presence of a delayed or absent meal. When low blood sugar levels occur because of too much insulin, it is called an insulin reaction. Sometimes, low blood sugar can be the result of an insufficient caloric intake or sudden excessive physical exertion (Ralph,1999).

Blood glucose is essential for the proper functioning of brain cells. Therefore, low blood sugar can lead to central nervous system symptoms such as:

- dizziness
- confusion
- weakness and

- tremors

The actual level of blood sugar at which these symptoms occur varies with each person, but usually it occurs when blood sugars are less than 65 mg/dl. Untreated, severely low blood sugar levels can lead to coma, seizures, and, in the worst case scenario, irreversible brain death. At this point, the brain is suffering from a lack of sugar, and this usually occurs somewhere around levels of <40 mg/dl.

The treatment of low blood sugar consists of administering a quickly absorbed glucose source. These include glucose containing drinks, such as orange juice, soft drinks (not sugar-free), or glucose tablets in doses of 15-20 grams at a time (for example, the equivalent of half a glass of juice). Even cake frosting applied inside the cheeks can work in a pinch if patient cooperation is difficult. If the individual becomes unconscious, glucagon can be given by intramuscular injection.

Glucagon is a hormone that causes the release of glucose from the liver (for example, it promotes gluconeogenesis). Glucagon can be lifesaving and every patient with diabetes who has a history of hypoglycemia (particularly those on insulin) should have a glucagon kit. Families and friends of those with diabetes need to be taught how to administer glucagon, since obviously the patients will not be able to do it themselves in an emergency situation. Another lifesaving device that should be mentioned is very simple; a medic alert bracelet should be worn by all patients with diabetes (Stöppler,2014).

1.10 Acute symptoms of type 1diabetes

Insulin is vital to patients with type 1 diabetes - they cannot live without a source of exogenous insulin. Without insulin, patients with type 1 diabetes develop severely elevated blood sugar levels. This leads to increased urine glucose, which in turn leads to excessive loss of fluid and electrolytes in the urine. Lack of insulin also causes the inability to store fat and protein along with breakdown of existing fat and protein stores. This dysregulation, results in the process of ketosis and the release of ketones into the blood. Ketones turn the blood acidic, a condition called diabetic ketoacidosis (DKA). Symptoms of diabetic ketoacidosis include nausea, vomiting, and abdominal pain. Without prompt medical treatment, patients with diabetic ketoacidosis can rapidly go into shock, coma, and even death.

Diabetic ketoacidosis can be caused by infections, stress, or trauma all which may increase insulin requirements. In addition, missing doses of insulin is also an obvious risk factor for developing diabetic ketoacidosis. Urgent treatment of diabetic ketoacidosis involves the intravenous administration of fluid, electrolytes, and insulin, usually in a hospital intensive care unit. Dehydration can be very severe, and it is not unusual to need to replace 6-7 liters of fluid when a person presents in diabetic ketoacidosis. Antibiotics are given for infections. With treatment, abnormal blood sugar levels, ketone production, acidosis, and dehydration can be reversed rapidly, and patients can recover remarkably well(Bora, 2012).

1.11 Effects of type 2 diabetes in patients:

Type 2 diabetes affects all parts of the body. It can cause serious, potentially life-threatening complications. These include:

- **Atherosclerosis** — Atherosclerosis is fat buildup in the artery walls. This can impair blood flow to the all the organs. The heart, brain and legs are most often affected.
- **Retinopathy** — Tiny blood vessels at the back of the eye become damaged by high blood sugar. Caught early, retinopathy damage can be minimized by tightly controlling blood sugar and using laser therapy. Untreated retinopathy can lead to blindness.
- **Neuropathy** — This is nerve damage. The most common type is peripheral neuropathy. The nerves to the legs are damaged first, causing pain and numbness in the feet. This can advance to cause symptoms in the legs and hands. Damage to the nerves that control digestion, sexual function and urination can also occur.
- **Foot problems** — Sores and blisters on the feet occur for two reasons:
    - If peripheral neuropathy causes numbness, the person will not feel irritation in the foot. The skin can break down and form an ulcer.
    - Blood circulation can be poor, leading to slow healing. Left untreated, a simple sore can become infected and very large.
- **Nephropathy** — Damage to the kidneys. This is more likely if blood sugars remain elevated and high blood pressure is not treated aggressively (American Diabetes Association, 2012).

Mechanism of insulin release in normal pancreatic beta cells — insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing

absorbable glucose.Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus.The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is 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 is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, 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 be excreted in the urine (glycosuria). 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 be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). (King*et al*,2004*)*

1.12 Prevention

There is no known preventive measure for type 1 diabetes.Type 2 diabetes can often be prevented by a person being a normal body weight, physical exercise, and following a healthful diet.Dietary changes known to be effective in helping to prevent diabetes include a diet rich in whole grains and fiber, and choosing good fats, such as polyunsaturated fats found in nuts, vegetable oils, and fish.Limiting sugary beverages and eating less red meat and other sources

of saturated fat can also help in the prevention of diabetes. Active smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well. (Balion *et al,*2008*)*

1.13Management

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations.Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications (insulin in the case of type 1 diabetes; oral medications, as well as possibly insulin, in type 2 diabetes).Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels.The goal of treatment is an HbA_{1C} level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise.Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal, however. (Urban *et al,*2009*)*

1.14 Lifestyle

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure. (Chiarelli *et al,*2012)

1.15 Medications

Medications used to treat diabetes do so by lowering blood sugar levels. There are a number of different classes of anti-diabetic medications. Some are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists. Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs.Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality.It works by decreasing the liver's production of glucose.Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type II DM. These include agents that increase insulin release, agents that decrease absorption of sugar from the intestines, and agents that make the body more sensitive to insulin.When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications.Doses of insulin are then increased to effect.Since cardiovascular disease is a serious complication associated with diabetes, some recommend blood pressure levels below 120/80 mmHg; however, evidence only supports less than or equal to somewhere between 140/90 mmHg to 160/100 mmHg. Amongst medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with DM while the similar medications angiotensin receptor blockers (ARBs) do not. Aspirin is also recommended for patient with cardiovascular problems, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes. (Kirkman *et al,*2010)

1.16Surgery

A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation.Weight loss surgery in those with obesity and type two diabetes is often an effective measure.Many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased.There however is some

short-term mortality risk of less than 1% from the surgery.The body mass index cut offs for when surgery is appropriate are not yet clear.It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control. (Zimmet *et al,*2012*)*

1.17 Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care in a team approach. Home telehealth support can be an effective management technique. (Brandenburg *et al,*2007*)*

1.18 Diabetes diagnosis

Doctor will perform tests to confirm if one has diabetes. These tests are used for diagnosis:

The fasting blood glucose (sugar) test is the preferred way to diagnose diabetes. It is easy to perform and convenient. After the person has fasted overnight (at least 8 hours), a single sample of blood is drawn and sent to the laboratory for analysis. This can also be done accurately in a doctor's office using a glucose meter (Akram, 2013).

Table -1:WHO diabetes diagnostic criteria (World Health Organization,2006)

WHO diabetes diagnostic criteria				
Condition	2 hour glucose	Fasting glucose	HbA_{1c}	
Unit	mmol/l(mg/dl)	mmol/l(mg/dl)	mmol/mol	DCCT %
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) &<7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

- Normal fasting plasma glucose levels are less than 100 milligrams per deciliter (mg/dl).
- Fasting plasma glucose levels of more than 126 mg/dl on two or more tests on different days indicate diabetes.
- A random blood glucose test can also be used to diagnose diabetes. A blood glucose level of 200 mg/dl or higher indicates diabetes.

When fasting blood glucose stays above 100mg/dl, but in the range of 100-126mg/dl, this is known as impaired fasting glucose (IFG). While patients with IFG do not have the diagnosis of diabetes, this condition carries with it its own risks and concerns, and is addressed elsewhere.

- A fasting plasma glucose test measures your blood glucose after you have gone at least 8 hours without eating. This test is used to detect diabetes or pre-diabetes.
- An oral glucose tolerance test measures your blood glucose after you have gone at least 8 hours without eating and 2 hours after you drink a glucose-containing beverage. This test can be used to diagnose diabetes or pre-diabetes.
- In a random plasma glucose test, your doctor checks your blood glucose without regard to when you ate your last meal. This test, along with an assessment of symptoms, is used to diagnose diabetes but not pre-diabetes.

Positive test results are confirmed by your doctor, by repeating the fasting plasma glucose test or the oral glucose tolerance test on a different day (Sarwar*et al.*,2010).

1.18.1 Fasting plasma glucose (FPG) test:

Because of ease of use, acceptability to patients and lower cost, the FPG is the preferred diagnostic test. Fasting is defined as no caloric intake for at least 8 hours.

- If your fasting glucose level is 100 to 125 mg/dL, you have a form of pre-diabetes called impaired fasting glucose (IFG), meaning that you are somewhat more likely to develop type 2 diabetes but do not have it yet.
- A level of 126 mg/dL or above, confirmed by repeating the test on another day, means that you have diabetes (Rother, 2007).

1.18.2 Oral glucose tolerance test (OGTT)

Though not routinely used anymore, the oral glucose tolerance test (OGTT)is a gold standard for making the diagnosis of type 2 diabetes. It is still commonly used for diagnosing gestational diabetes and in conditions of pre-diabetes, such as polycystic ovary syndrome. With an oral glucose tolerance test, the person fasts overnight (at least eight but not more than 16 hours). Then first, the fasting plasma glucose is tested. After this test, the person receives 75 grams of glucose. There are several methods employed by obstetricians to do this test, but the one

described here is standard. Usually, the glucose is in a sweet-tasting liquid that the person drinks. Blood samples are taken at specific intervals to measure the blood glucose(Krentz and Friedmann,2006).

For the test to give reliable results:

- The person must be in good health (not have any other illnesses, not even a cold).
- The person should be normally active (not lying down, for example, as an inpatient in a hospital), and
- The person should not be taking medicines that could affect the blood glucose.
- The morning of the test, the person should not smoke or drink coffee.

The classic oral glucose tolerance test measures blood glucose levels five times over a period of three hours. Some physicians simply get a baseline blood sample followed by a sample two hours after drinking the glucose solution. In a person without diabetes, the glucose levels rise and then fall quickly. In someone with diabetes, glucose levels rise higher than normal and fail to come back down as fast.

People with glucose levels between normal and diabetic have impaired glucose tolerance (IGT). People with impaired glucose tolerance do not have diabetes, but are at high risk for progressing to diabetes. Each year, 1% to 5% of people whose test results show impaired glucose tolerance actually eventually develop diabetes. Weight loss and exercise may help people with impaired glucose tolerance return their glucose levels to normal. In addition, some physicians advocate the use of medications, such as metformin (Glucophage), to help prevent/delay the onset of overt diabetes.

Research has shown that impaired glucose tolerance itself may be a risk factor for the development of heart disease. In the medical community, most physicians are now understanding that impaired glucose tolerance is not simply a precursor of diabetes, but is its own clinical disease entity that requires treatment and monitoring (Bartoli*et al.*,2011).

1.18.3 Evaluating the results of the oral glucose tolerance test

Glucose tolerance tests may lead to one of the following diagnoses:

- **Normal response:** A person is said to have a normal response when the 2-hour glucose level is less than 140 mg/dl, and all values between 0 and 2 hours are less than 200 mg/dl.
- **Impaired glucose tolerance:** A person is said to have impaired glucose tolerance when the fasting plasma glucose is less than 126 mg/dl and the 2-hour glucose level is between 140 and 199 mg/dl.
- **Diabetes:** A person has diabetes when two diagnostic tests done on different days show that the blood glucose level is high.
- **Gestational diabetes:** A pregnant woman has gestational diabetes when she has any two of the following :a fasting plasma glucose of 92 mg/dl or more, a 1-hour glucose level of 180 mg/dl or more, or a 2-hour glucose level of 153 mg/dl, or more (Satyanarayana&Chakrapani,2006).

1.18.4 Random plasma glucose test

A random blood glucose level of 200 mg/dL or more, plus presence of the following symptoms, can mean that you have diabetes:

- increased urination
- increased thirst
- unexplained weight loss

Other diabetes symptoms include fatigue, blurred vision, increased hunger, and sores that do not heal. Your doctor will check your blood glucose level on another day using the FPG or the OGTT to confirm the diagnosis (Bartoli *et al.*,2011).

1.19 Non-pharmacologic treatment of diabetes

These strategies are the key to diabetes prevention:

- **Food**: What and how much you eat will affect your blood sugar level. Blood sugar is typically highest one to two hours after a meal.
- **Physical activity**: Physical activity moves sugar from your blood into your cells. The more active you are, the lower your blood sugar level.
- **Medication:** Any medications you take may affect your blood sugar level, sometimes requiring changes in your diabetes treatment plan.

- **Illness:** During a cold or other illness, your body will produce hormones that raise your blood sugar level.
- **Alcohol**: Alcohol and the substances you use to make mixed drinks can cause either high or low blood sugar, depending on how much you drink and whether you eat at the same time.
- **Stress**: The hormones your body may produce in response to prolonged stress may prevent insulin from working properly (Kumar*et al*.,2011).

1.20 Pharmacologic treatment of diabetes

1.20.1 Treatment of type 1 diabetes

Type 1 diabetes is treated with insulin.

Insulin was purified and crystallized by Abel within a few years of its discover. Sanger established the amino acid sequence of insulin in 1960, the protein was synthesized in 1963, and Hodgkin and coworkers elucidated insulin's three-dimensional structure in 1972. Insulin was the hormone for which Yalow and Berson first developed the radioimmunoassay (Kahn and Roth, 2004).

Insulin is a small protein with a molecular weight in humans of 5808. It contains 51 amino acids arranged in two chains (A and B) linked by disulfide bridges; there are species differences in the amino acids of both chains. Proinsulin, a long single-chain protein molecule, is processed within the Golgi apparatus and packaged into granules, where it is hydrolyzed into insulin (Rotella*et al.*, 2007).

Insulin has several broad actions including:

- It causes the cells in the liver, muscle, and fat tissue to take up glucose from blood and convert it to glycogen that can be stored in the liver and muscles.
- Insulin also prevents the utilization of fat as an energy source. In absence of insulin or in conditions where insulin is low glucose is not taken up by body cells, and the body begins to use fat as an energy source.

- Insulin also controls other body systems and regulates the amino acid uptake by body cells.
- It has several other anabolic effects throughout the body as well.

1.20.2 Treatment of type 2 diabetes

Type 2 diabetes is treated first with weight reduction, a diabetic diet, and exercise. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, treatment with insulin is considered(Bolen *et al.*, 2007).

Table 2: Current therapeutic agents for type 2 diabetes

Drug class	Molecular target	Site(s) of action	Adverse events
Insulin	Insulin receptor	Liver, muscle, fat	Hypoglycaemia, weight gain
Sulphonylureas (e.g. glibenclamide) plus nateglinide and repaglinide	SU receptor/ K^+ ATP channel	Pancreatic β-cell	Hypoglycaemia, weight gain
Metformin — biguanides	Unknown	Liver (muscle)	Gastrointestinal disturbances, lactic acidosis
Acarbose	α-glucosidase	Intestine	Gastrointestinal disturbances
Pioglitazone, rosiglitazone (thiazolidinediones)	$PPAR_\gamma$	Fat, muscle, liver	Weight gain, oedema, anaemia

1.21 Older classifications and medicines of diabetes drugs

- **Sulfonylureas:** These medications are the oldest of the oral diabetes drugs, and until 1995 they were the only drugs available for managing type 2 diabetes. Sulfonylureas stimulate the pancreas to release more insulin into the blood stream. Hypoglycemia can be a side effect of these drugs.
- **Biguanides**: These lower the production of glucose that is made in the liver. It also makes the body more sensitive to insulin. Cholesterol levels may be lowered as well. For example, Metformin.
- **Alpha-Glucosidase Inhibitors**: These delay the conversion of carbohydrates into glucose during digestion. This prevents blood glucose levels from peaking too high. For example, acarbose, miglitol.
- **Thiazolidinediones**: Sensitizes muscle and fat cells to accept insulin more easily. For example, Rosiglitazone, Pioglitazone.
- **Meglitinides:** These stimulate insulin production when there is glucose present in the blood. If blood sugar is low, the drug does not work as well. For example, repaglinide (Manzella, 2014).

Table 3: Dosing adjustments by CKD Stage for drugs used to treat hyperglycemia

Class	Drug	Dosing Recommendation CKD Stages 3, 4, or Kidney Transplant	Dosing Recommendation Dialysis
First-generation sulfonylureas	Acetohexamide	Avoid	Avoid
	Chlorpropamide	Reduce dose by 50% when GFR <70 and ≥50 mL/min/1.73 m^2 Avoid when GFR <50 mL/min/1.73 m^2	Avoid
	Tolazamide	Avoid	Avoid
	Tolbutamide	Avoid	Avoid
Second-generation sulfonylureas	Glipizide	Preferred sulfonylurea No dose adjustment necessary	Preferred sulfonylurea No dose adjustment necessary
	Gliclazide	Preferred sulfonylurea No dose adjustment necessary Not available in US	Preferred sulfonylurea No dose adjustment necessary Not available in US
	Glyburide	Avoid	Avoid
	Glimepiride	Initiate at low dose, 1 mg daily	Avoid
Alpha-glucosidase inhibitors	Acarbose	Not recommended in patients with SCr >2 mg/dL	Avoid
	Miglitol	Not recommended in patients with SCr >2 mg/dL	Avoid
Biguanides	Metformin	Contraindicated with kidney dysfunction defined as SCr ≥1.5 mg/dL in men or ≥1.4 mg/dL in women	Avoid
Meglitinides	Repaglinide	No dose adjustment necessary	No dose adjustment necessary
	Nateglinide	Initiate at low dose, 60 mg before each meal	Avoid
Thiazolidinediones	Pioglitazone	No dose adjustment necessary	No dose adjustment necessary
	Rosiglitazone	No dose adjustment necessary	No dose adjustment necessary
Incretin mimetic	Exenatide	No dose adjustment necessary	No dose adjustment necessary
Amylin analog	Pramlintide	No dose adjustment necessary for GFR 20-50 mL/min/1.73 m^2	No data available
DPP-4 inhibitor	Sitagliptin	Reduce dose by 50% (50mg/day) when GFR < 50 and ≥ 30 mL/min/1.73 m^2 and by 75% (25 mg/day) when GFR < 30 mL/min/1.73 m^2	Reduce dose by 75% (25 mg/day)

1.22 New classifications and medicines

- **DPP-4 Inhibitors:** These drugs block an enzyme (DPP-4) that normally deactivates a protein (GLP-1) that keeps insulin circulating in the blood. Slowing the deactivation process helps reduce sugar production, lowering blood glucose levels (Palalau*et al.*,2009).

- **Incretin Mimetics**: These mimic the action of incretin hormones which help the body make more insulin. They also slow the rate of digestion so that glucose enters the blood more slowly.
- **Byetta (exenatide)**: Byetta is an injectable medication that is used in combination with other oral diabetes medications. It is not an insulin and it does not take the place of insulin. It is used for type 2 diabetes only and cannot be given with insulin. Byetta comes in a pre-filled injector pen. The dose is 5 mcg. to start, twice a day within 60 minutes prior to your morning and evening meals. Your doctor may increase the dose to 10 mcg. based on your results.
- **Anti hyperglycemic Synthetic Analogs**: These are medications that are created as synthetic versions of human substances, in this case a human hormone called amylin, which is used by the pancreas to lower blood glucose levels.
- **Symlin (pramlintide acetate):**Symlin is an injectable medication which is used with insulin for tighter blood glucose control. Symlin can increase the risk of severe hypoglycemia, therefore patients who are put on Symlin are selected carefully and monitored closely by their healthcare providers (Manzella,2010).

1.23 Types of Insulin for diabetes treatment

There are many forms of insulin to treat diabetes. They are classified by how fast they start to work and how long their effects last.

The types of insulin include:

- Rapid-acting
- Short-acting
- Intermediate-acting
- Long-acting
- Pre-mixed

The following chart lists the types of injectable insulin with details about onset (the length of time before insulin reaches the bloodstream and begins to lower blood sugar), peak (the time period when the insulin is the most effective in lowering blood sugar) and duration (how long insulin continues to lower blood sugar). These three factors may vary, depending on your body's

response. The final column provides some insight into the "coverage" provided by the different insulin types in relation to mealtime (Dansinger, 2013).

1.24 Vildagliptin

Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Vildagliptin inhibits the inactivation of and by DPP-4, allowing GLP-1 and GIP to potentiate the secretion of insulin in the beta cells and suppress glucagon release by the alpha cells of the islets of Langerhans in the pancreas.

Vildagliptin has been shown to reduce hyperglycemia in type 2 diabetes mellitus.Vildagliptin acts primarily by inhibiting DPP-4, the enzyme responsible for the degradation of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). 9 The administration of vildagliptin results in a rapid and complete inhibition of DPP-4 activity resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 and GIP. By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with vildagliptin 50-100 mg daily in patients with type 2 diabetes significantly improved markers of beta cell function including HOMA-β (Homeostasis Model Assessment–β), proinsulin to insulin ratio and measures of beta cell responsiveness from the frequently-sampled meal tolerance test. In non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels. By increasing endogenous GLP-1 levels, vildagliptin also enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia. The known effect of increased GLP-1 levels delaying gastric emptying is not observed with vildagliptintreatment(Hughes *et al,* 2007).

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1.25 Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia or increased weight gain. Metformin may exert its glucose-lowering effect via three mechanisms: - by reduction of hepatic glucose production through inhibition of gluconeogenesis and glycogenolysis; - in muscle, by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation; - by delaying intestinal glucose absorption. Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4). In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces serum levels of total cholesterol, LDL cholesterol and triglycerides. The prospective randomised UKPDS (UK Prospective Diabetes Study) study has established the longterm benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed: - a significant reduction in the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034; - a significant reduction in the absolute risk of diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017; - a significant reduction in the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patientyears (p=0.021); - a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years (p=0) (Manzella, 2014).

1.26 Serum Creatinine

Creatinine is a chemical waste molecule that is generated from muscle metabolism.Creatinine is produced from creatine, a molecule of major importance for energy production in muscles.Approximately 2% of the body's creatine is converted to creatinine every day.Creatinine is transported through the bloodstream to the kidneys. The kidneys filter out most of the creatinine and dispose of it in the urine.Because the muscle mass in the body is relatively constant from day to day, the creatinine production normally remains essentially unchanged on a daily basis.

The kidneys maintain the blood creatinine in a normal range. Creatinine has been found to be a fairly reliable indicator of kidney function. Elevated creatinine level signifies impaired kidney function.

As the kidneys become impaired for any reason, the creatinine level in the blood will rise due to poor clearance of creatinine by the kidneys. Abnormally high levels of creatinine thus warn of possible malfunction or failure of the kidneys. It is for this reason that standard blood tests routinely check the amount of creatinine in the blood.

A more precise measure of the kidney function can be estimated by calculating how much creatinine is cleared from the body by the kidneys. This is referred to as creatinine clearance and it estimates the rate of filtration by kidneys (glomerular filtration rate, or GFR). The creatinine clearance can be measured in two ways. It can be calculated (estimated) by a formula using serum (blood) creatinine level, patient's weight, and age. The formula is 140 minus the patient's age in years times their weight in kilograms (times 0.85 for women), divided by 72 times the serum creatinine level in mg/dL. Creatinine clearance can also be more directly measured by collecting a 24-hour urine sample and then drawing a blood sample. The creatinine levels in both urine and blood are determined and compared. Normal creatinine clearance for healthy women is 88-128 mL/min. and 97 to 137 mL/min. in males (normal levels may vary slightly between labs).

Blood urea nitrogen (BUN) level is another indicator of kidney function. Urea is also a metabolic byproduct which can build up if kidney function is impaired. The BUN-to-creatinine ratio generally provides more precise information about kidney function and its possible underlying cause compared with creatinine level alone. BUN also increases with dehydration(Ji*et al.*, 2013).

1.27 LITERATURE REVIEW

Lindström stated that there are different treatment options available fortype 2 diabetes mellitus (T2DM), but long-term glucose control remains unsatisfactory in patients with Type 2 diabetes. The authors reviewed some literature on randomized controlled trials. Vildagliptin is a highly selective DDP-4 inhibitor, but evidence support its use in combination with metformin is not convincing (Jaana,2002).

M Epstein,J R Sowers stated that Type 2 diabetes mellitus (T2DM) is an increasingly health problem worldwide . Unsatisfactory blood glucose control may result in the development of chronic complications in diabetic patients, including heart disease, stroke, amputation, blindness, nephropathy and peripheral neuropathy . With increasing disease duration, the treatment intensity for T2DM needs to be enhanced. The conventional stepwise escalation of therapy starts from lifestyle modification, followed by single OHA at increasing dosage, simultaneous use of multiple OHAs, and finally insulin. Dipeptidyl peptidase-4 (DDP-4) inhibitors are a relative new class of agents that indirectly increases insulin secretion and suppresses hepatic glucose production .DPP-4 inhibitors target a different set of physiological and molecular targets than metformin: increasing insulin sensitivity via stimulating GLP-1 secretion and reducing endogenous hepatic glucose production (Epstein & Sowers,2001).

Juarez R Braga stated that the single-tablet combination of vildagliptin and metformin addresses key defects of type 2 diabetes for improved glycemic control. By inhibiting the dipeptidyl peptidase-4 (DPP-4) enzyme, vildagliptin raises the levels of the active incretin hormones, glucagonlike peptide 1 and glucose-dependent insulinotropic peptide. This leads to increased synthesis and release of insulin from the pancreatic beta cells and decreased release of glucagon from the pancreatic alpha cells. In clinical trials, the overall incidence of any adverse event was similar in patients randomized to vildagliptin plus metformin and placebo plus metformin. Available data support the use of vildagliptin in combination with metformin as a

promising second-line treatment for the management of type 2 diabetes and this is reflected in the latest UK National Institute for Health and Clinical Excellence draft guideline for consultation on new agents for blood glucose control in type 2 diabetes (Braga,2008).

Giugliano D**,** Ceriello A**,** PaolissoGstated that long-term high-fat diet consumption is known to cause obesity, insulin resistance, and cardiac dysfunction .and have been shown to increase the risk of having ischemic heart disease . While revascularization is the goal of myocardial ischemia treatment, reperfusion therapy is known to induce reperfusion injury and lead to greater myocardial damage. This adverse effect has been shown to be even more severe in obese insulin resistance, resulting in increased infarct size and increased myocardial susceptibility to ischemia-reperfusion (I/R) injury. I/R injury has been shown to associate with fatal cardiac arrhythmias . Cardiac mitochondrial damage has been implicated as one of the major factors responsible for myocardial cell death from I/R injury . Several lines of evidence showed that increased intracellular and mitochondrial calcium accumulation can trigger cell apoptosis , . Previous studies also demonstrated that decreased Connexin 43 (Cx43), the principal gap junction protein, is found in acute myocardial infarction(Giuglianо*et al*.,1995).

Shelley C. Springerstated that type 2 diabetes mellitus (T2DM) is pathophysiologically characterized by a combination of insulin resistance and beta-cell dysfunction. Consequently, a proper treatment of such a disease should target both of these defects. Dipeptidyl peptidase-4 (DPP-4) inhibitors are among the most recent additions to the therapeutic options for T2DM and are able to increase circulating levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thus stimulating glucose-dependent insulin secretion.This paper provides an overview of the clinical results of combination therapy with metformin and the DPP-4 inhibitor vildagliptin in T2DM patients.Vildagliptin–metformin single-tablet combination is indicated for the treatment of T2DM patients not achieving a sufficient glycemic control at their maximally tolerated dose of metformin. Results from clinical trials provide evidence of vildagliptin efficacy administered in addition to metformin, as either first- or second-line treatment. (Springer *et al*.,2013).

Juarez R Braga stated that vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. To compare the efficacy and safety of vildagliptin and metformin initial combination therapy with individual monotherapies in treatment-naive patients with type 2 diabetes mellitus (T2DM).This was a 24-week, randomized, double-blind, active-controlled study. Treatment-

naive patients with T2DM who had a glycated hemoglobin (HbA_{1c}) of 7.5–11% (N = 1179) were randomized equally to receive vildagliptin plus high-dose metformin combination therapy (50 mg + 1000 mg twice daily), vildagliptin plus low-dose metformin combination therapy (50 mg + 500 mg twice daily), vildagliptin monotherapy (50 mg twice daily) or high-dose metformin monotherapy (1000 mg twice daily). The primary objective was to demonstrate that HbA_{1c} reduction from baseline with either combination therapy is superior to both monotherapy at the week 24 endpoint. Patients who failed glycaemic-screening criteria [HbA_{1c} >11% or fasting plasma glucose (FPG) >15 mmol/l (270 mg/dl)] could enter a 24-week, single-arm substudy. These patients (N = 94) received open-label vildagliptin plus high-dose metformin combination therapy (100 mg + 1000 mg twice daily)(Braga *et al*.,2013).

T. Kue Youngstated that from comparable baseline values (8.6–8.7%), HbA_{1c} decreased in all four treatment groups, to the greatest extent with vildagliptin plus high-dose metformin combination therapy. Mean (SE) HbA_{1c} change from baseline was −1.8% (0.06%), −1.6% (0.06%), −1.1% (0.06%) and −1.4% (0.06%) with vildagliptin plus high-dose metformin combination therapy, vildagliptin plus low-dose metformin combination therapy, and vildagliptin and metformin monotherapies respectively. The between-group difference was superior with vildagliptin plus high-dose metformin combination therapy ($p < 0.001$ vs. both monotherapies) and vildagliptin plus low-dose metformin combination therapy ($p < 0.001$ and $p = 0.004$, vs. vildagliptin and metformin monotherapies, respectively. The potential dose-sparing effect of adding vildagliptin to low-dose metformin in preference to the up-titration of metformin may allow patients to achieve equivalent or superior HbA_{1c} lowering without the GI tolerability issues associated with higher doses of metformin(Young *et al*.,2000).

Paquot N.stated that vildagliptin (Galvus) and fixed combination vildagliptine-metformin (Eucreas) in the treatment of type 2 diabetes. Vildagliptin (Galvus) is a selective inhibitor of dipeptidylpeptidase-4, an enzyme involved in the metabolism of glucagon-like peptide-1 (GLP-1) secreted by L cells of the intestine. It potentiates the insulin secretory response (incretin effect reference) by enhancing the endogenous post-prandial response of GLP-1 (incretin enhancer) in a glucose-dependent manner. Vildagliptin is indicated in the treatment of type 2 diabetes. It improves blood glucose control (HbA1c) in patients treated by diet alone, metformin, sulfonylurea, glitazone or insulin. Therapy can be administered separately

or by using a fixed combination vildagliptin-metformin (Eucreas), which should improve drug compliance(Paquot N.2004)

Matthews DRstated that, a randomized double-blind trialDurability of good glycaemic control (HbA1c) is of importance as it can be the foundation for delaying diabetic complications. It has been hypothesized that early initiation of treatment with the combination of oral anti-diabetes agents with complementary mechanisms of action can increase the durability of glycaemic control compared with metformin monotherapy followed by a stepwise addition of oral agents. Dipeptidyl peptidase-4 inhibitors are good candidates for early use as they are efficacious in combination with metformin, show weight neutrality and a low risk of hypoglycaemia. It is the first study to investigate the long-term clinical benefits of early combination treatment vs. the standard-of-care metforminmonotherapy with a second agent added by threshold criteria (Matthews DR,2011).

BramlageP.stated that vildagliptin , a DPP-4 inhibitor for the twice-daily treatment of type 2 diabetes mellitus with or without metformin.Dipeptidyl peptidase-4 inhibitors increase circulating levels of glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide regulating glucose-dependent insulin secretion. In addition, GLP-1 suppresses glucagon secretion, delays gastric emptying and increases satiety. The combination of vildagliptin with the biguanide metformin is of particular interest because of its complementary mode of action, addressing insulin resistance, alpha- and beta cell function in the islet of the pancreas. There is increasing evidence that compared with sulfonylureas, vildagliptin has favorable effects on pancreatic alpha- and beta-cell function. Vildagliptin in combination with metformin, improve glycemic control with a favorable safety and tolerability profile, making it an attractive therapeutic option in patients where metformin monotherapy alone is not sufficient(BramlageP,2008).

Viana Rstated that, Cost-effectiveness of metformin plus vildagliptin compared with metformin plus sulphonylurea for the treatment of patients with type 2 diabetes mellitus: a Portuguese healthcare system perspective.To evaluate the cost-effectiveness of vildagliptin plus metformin vs generic sulphonylurea plus metformin in patients with type 2 diabetes mellitus, not controlled with metformin, from a Portuguese healthcare system perspective. . Baseline patient characteristics and clinical variables were derived from a Portuguese epidemiological study. Cost estimates were based on direct medical costs only.The

model excluded several diabetes-related morbidities, such as peripheral neuropathy and ulceration, and did not model second events. Patients were presumed to enter the model with no diabetes-related complications.Treatment with metformin plus vildagliptin compared with metformin plus sulphonylurea is expected to result in a lower incidence of diabetes-related AEs and to be a cost-effective treatment strategy(Viana R,2003)

Zhao ZG stated that the aim of the present study was to assess the efficacy and safety of vildagliptin plus metformin combination therapy in patients with type II diabetes mellitus. Type II diabetic patients with poor glycemic control following at least three months of metformin treatment were selected and randomized into two groups. Vildagliptin or placebo was administered with metformin. Body weight, fasting blood glucose (FBG), postprandial glucose (PPG), glycated hemoglobin (HbA1c), blood lipid and hepatorenal function levels were analyzed in the patients prior to and 24-weeks after the trial. FBG, PPG and HbA1c levels of the patients in the vildagliptin group significantly decreased following the trial, whereas no statistically significant differences were observed in the various indicators of the placebo group prior to and following the trial.Therefore, vildagliptinplus metformin combination therapy effectively reduced FBG, PPG and HbA1c levels in patients with no risk of weight gain or hepatorenal dysfunction (Zhao ZG,2009).

Hong Mei stated Combined Vildagliptin and Metformin Exert Better Cardioprotection than Monotherapy against Ischemia-Reperfusion Injury in Obese-Insulin Resistant Rats.Obese-insulin resistance caused by long-term high-fat diet (HFD) consumption is associated with left ventricular (LV) dysfunction and increased risk of myocardial infarction. Metformin and vildagliptin have been shown to exert cardioprotective effects. However, the effect of these drugs on the hearts under obese-insulin resistance with ischemia-reperfusion (I/R) injury is unclear. We hypothesized that combined vildagliptin and metformin provide better protective effects against I/R injury than monotherapy in obese-insulin resistant rats.Although both vildagliptin and metformin improved insulin resistance and attenuate myocardial injury caused by I/R, combined drugs provided better outcomes than single therapy by reducing arrhythmia score and mortality rate (Hong Mei ,2014).

Dr A.A.S. Alwan stated that combination treatment in the management of type 2 diabetes: focus on vildagliptin and metformin as a single tablet. Vildagliptin is a potent and selective inhibitor of

dipeptidyl peptidase-IV (DPP-4), orally active, that improves glycemic control in patients with type 2 diabetes (T2DM) primarily by enhancing pancreatic (α and β) islet function. Thus vildagliptin has been shown both to improve insulin secretion and to suppress the inappropriate glucagon secretion seen in patients with T2DM. Vildagliptin reduces HbA_{1c} when given as monotherapy, without weight gain and with minimal hypoglycemia, or in combination with the most commonly prescribed classes of oral hypoglycemic drugs. Metformin, a sulfonylurea, a thiazolidinedione, or insulin. Metformin, with a different mode of action not addressing β-cell dysfunction, has been used for about 50 years and still represents the universal first line therapy of all guidelines. Therefore, by specifically combining these agents in a single tablet, there is considerable potential to achieve better blood glucose control and to improve compliance to therapy (Alwan1995)

Ceriello A**,** stated that the combination of vildagliptin and metformin, two oral anti-diabetic agents with complementary mechanisms of action, provides superior efficacy and allows more patients to reach their glycemic targets compared to continuing metformin monotherapy, without increasing the risk of hypoglycemia, without exposing to weight gain and without altering common cardiovascular risk factors (hypertension and lipid profile). In addition, this combination has demonstrated favorable effects on pancreatic α- and β-cells. The availability of vildagliptin and metformin in a single tablet (Eucreas®) further enhances convenience and likely adherence to treatment. This new fixed-combination of vildagliptin and metformin could thus take a promising place in therapy and become the preferred combination with metformin in these mildly hyperglycemic patients and in older and more fragile individuals (Ceriello,2014)

Chapter 2

Objective

2.1 Objective:

The main objective of the study was to compare the efficacy and safety of metformin combination (metformin+vildagliptine) and metformine single regime in type 2 diabetes patient on blood glucose concentration test and renal function test.

2.2 Specific Objective:

In this research, fasting blood glucose concentration test and renal function test (serum creatinine) were performed to compare the safety and efficacy between metformin combination(metformin+vildagliptine)and metformine single drug.

Chapter 3

Methods and Materials

Methods and Materials

3.1 Research Design

The study was a descriptive study; in which 600 outcome patients (Age between 15 to 75 years) prescription with diabetes were taken. Treatment information were collected retrospectively from patients diabetic books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.)

3.2 Materials and Methods

Prescription was collected from Diabetic Books of the patients enrolled in Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). Their prescription was collected from outpatient department.
Camera or Mobile phone camera was used to collect the data. Windows 2010 (Microsoft Excel) and GraphPad Prism 6 were used to analyze the data.

3.3 Sample characteristics

The sample was collected from the Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) HospitalShahabag, Dhaka from 18th February 2016 to 18th October 2016. All the prescription were collected retrospectively from the patients' prescription.

3.4 Inclusion criteria

The following was included-

1. Type 2 diabetes, male or female, age ≥18 years

2. Currently under one of the following treatments for diabetes: OAD only, OAD combined with insulin, or OAD combined with GLP-1 receptor agonists
3. At least one outpatient medical record for diabetes
4. Live in local area for at least 6 consecutive months
5. For community hospitals, a patient must have HbA1c examination from the same community hospital where he/she is recruited, and did not visit referral hospital in the last 3 months
6. The first 7 patients who visit the investigator each day will be eligible

3.5 Exclusion criteria

1. Secondary diabetes
2. Lifestyle intervention only
3. Insulin only
4. Inpatients
5. Type 1 diabetes
6. Pregnant, breast-feeding women
7. Mental incapacity or other reasons precluding adequate understanding or cooperation in the study

3.6 Sampling technique

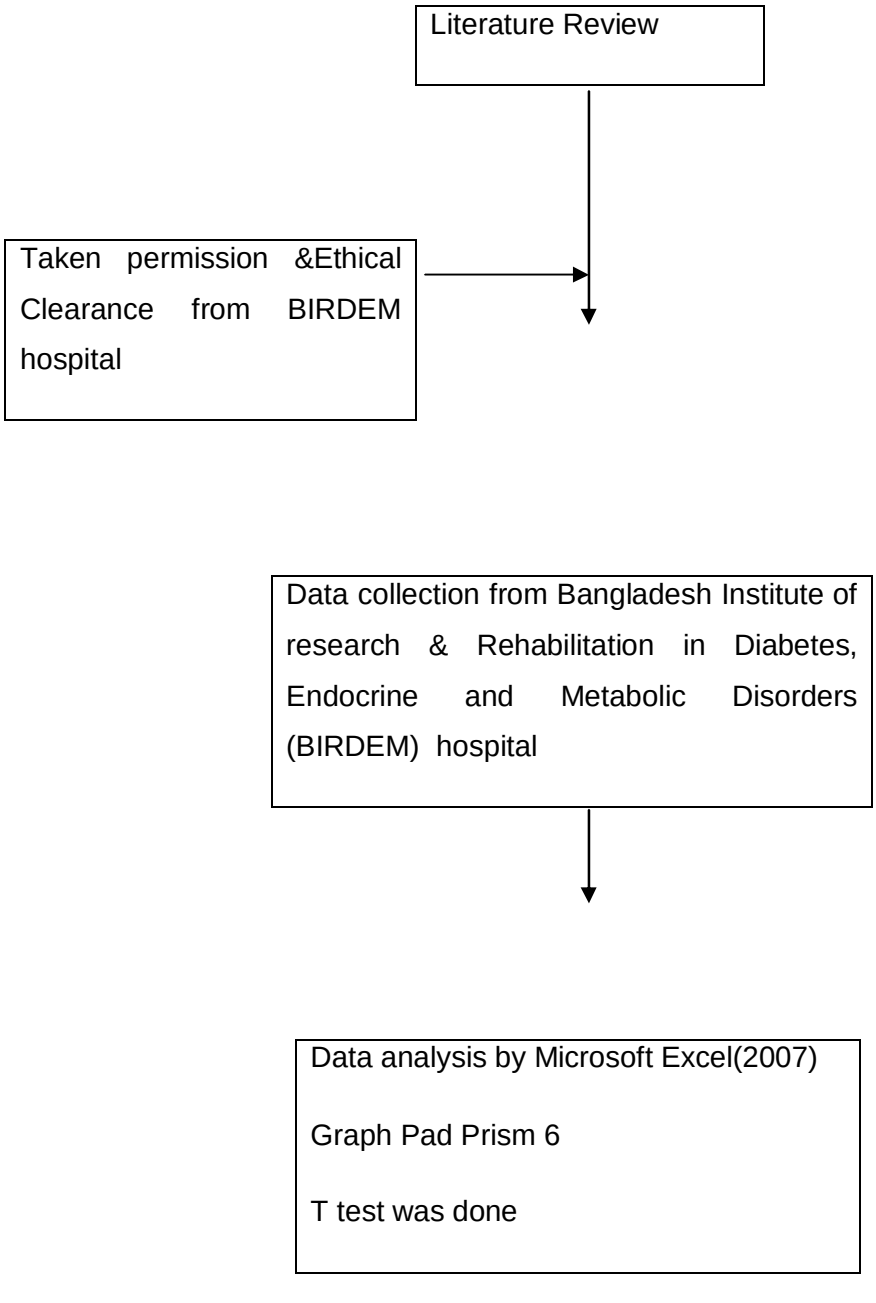
In this study random sampling was followed.

3.7 Study period

The duration of the study was about four months that started from 18th February 2016 to 18th October 2016.

3.8 Data analysis

The study was performed by completing 3 stages of the procedure. In the beginning literature review was done from 60 online literatures regarding diabetic treatment on prescription basis. The aim of the literature review was to observe the situations of the prescription of outcome diabetic patients. Followed by the literature review data collection step was executed by collecting data with the help of diabetic treatment on prescription basis. Data regarding treatment given to the outpatient diabetic patients were collected by survey retrospectively from patients' diabetic prescriptions ofBangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders(BIRDEM) HospitalShahabag, Dhaka. Data collection periods wereFebruary 18th 2016 to 18th December 2016. After collecting, all the data were checked and analyzed with the help of Microsoft Excel 2007 and Graph pad prism 6.

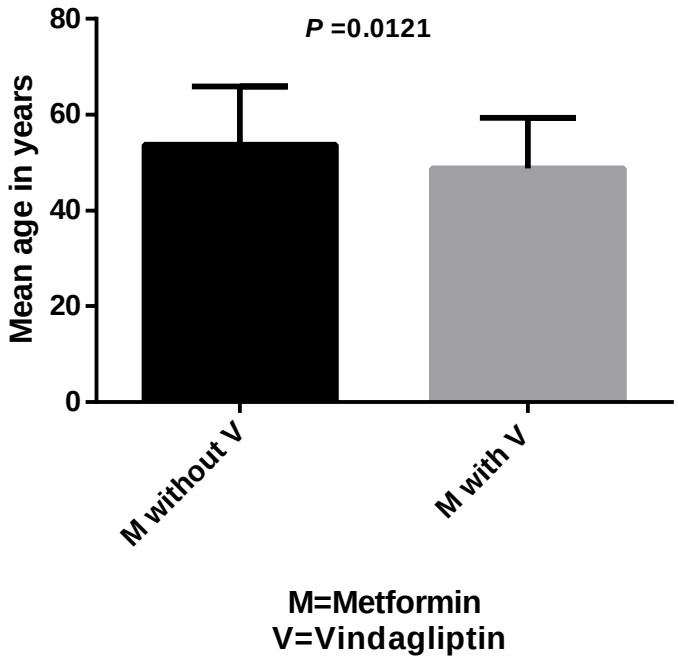

Literature Review
Taken permission &Ethical Clearance from BIRDEM hospital
Data collection from Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) hospital
Data analysis by Microsoft Excel(2007)
Graph Pad Prism 6
T test was done

Chapter 4

Results

4.1 Mean age of the patients suffering from Type 2 diabetes

Fig 1: Mean age (years) of Type 2 diabetes patients of different treatment group (n=100)



M=Metformin
V=Vindagliptin

This Figure shows that the mean age of the patient of M without V group was 53.71±12.12 and M with V was 48.79±10.51 respectively. The difference between the group is statistically significant (p=0.0121).

4.2 Mean weight of the patients suffering from Type 2 diabetes

Fig 2: Mean weight (Kg) of the patients treated with different oral antidiabetic drugs (n=100)

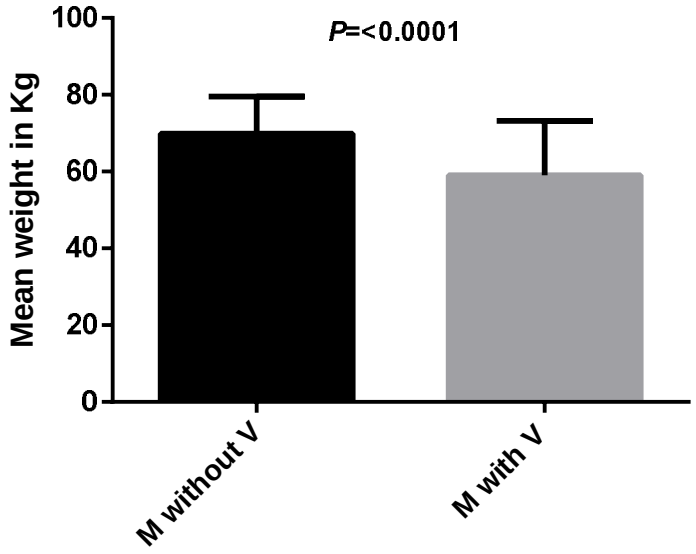
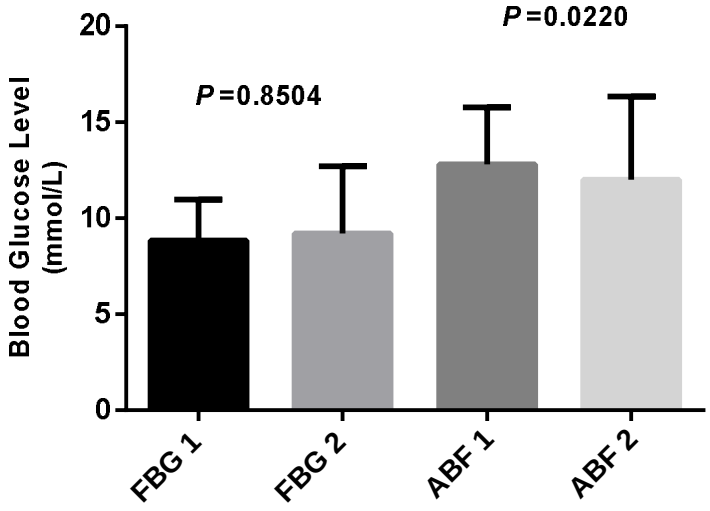


Figure 2 shows that the mean weight of M without V group was 69.95±9.633and M with V was 59.01±14.24 respectively. The difference between the group is statistically significant (p<0.0001).

4.3 Mean blood glucose level before and after breakfast of the patients suffering from Type 2 diabetes

Fig 3: Blood glucose level before and after breakfast when treated with Metformin with and without Vildagliptin

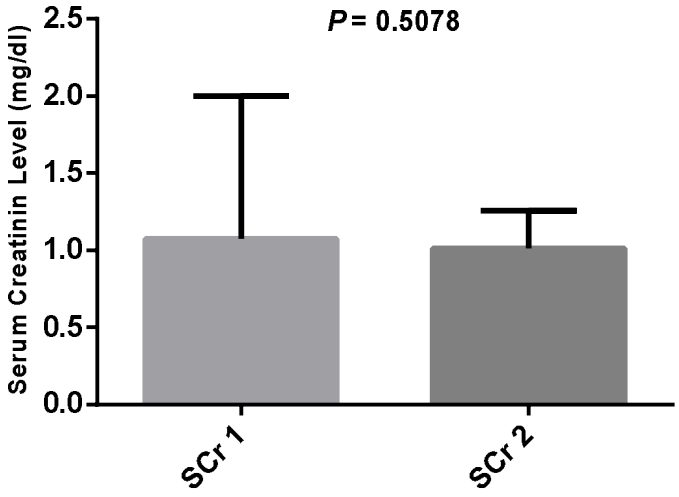


FBG1= Metformin without Vindagliptin before breakfast
FBG2=Metformin with Vindagliptin before breakfast
ABF1= Metformin without Vindagliptin after breakfast
ABF2= Metformin with Vindagliptin after breakfast

The above Figure shows that the fasting blood glucose of the patients of M without V was 8.838 ± 2.145 mmol/L and M with V was 9.231 ± 3.475 mmol/L. The difference was not statistically significant (p=0.8504).The blood glucose level after 2 hours breakfast (ABF) was 12.81 ± 2.942 mmol/L in M without V group and 12.02 ± 4.315 mmol/L in M with V group (p=0.022).

4.5 Mean Serum Creatinine suffering from Type 2 diabetes

Fig 4: Mean serum creatinine level of the patients treated with different oral antidiabetic drug (n=100)



SCr 1 = Serum Creatinine in Metformin without Vindagliptin group

SCr 2 =Serum Creatinine in Metformin with Vindagliptin group

This Figure shows that the creatinine value of M without V group was 1.075 ± 0.92 mg/dl and M with V was 1.011±0.246. The difference between the group is not statistically significant (p=0.507).

Chapter 5

Discussion& Conclusion

Discussion and Conclusion

This study was designed to observe the effect of the new antidiabetic drugs prescribing practice in diabetic hospital in our country on renal function. During eight months study period, 600 prescription(Diabetic Books prescription and new patients initial form prescription) of patients suffering fromType 2 diabetes mellitus were registered. This is a collaborative study between East West University (EWU) and Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM),Shahabag, Dhaka, Bangladesh.This research was carried out to investigate the effect of different combination drugs on renal function in patients suffering from Type 2 diabetes. In this study the combination drugs include metformin with and without vildagliptin and other types of oral antidiabetic drugs.

Diabetes Mellitus is one of the major cause of renal impairment and a major public health problem globally. Metformin has been recommended as the first line antidiabetic drug recommended by the American Diabetes Association. If a single agent is failed to achieve adequate glucose control, a combination oral antidiabetics may result in better glycemic control in patients with Type 2 diabetes. In the present study the patients were prescribed Metformin with and without vildagliptin (M with or without V) and also other combination drugs for the treatment of diabetes. The present study shows that the fasting blood glucose of the patients of M without V was 8.838 ± 2.145 mmol/L and M with V was 9.231 ± 3.475 mmol/L. The difference was not statistically significant (p=0.8504). The blood glucose level after 2 hours breakfast (ABF) was 12.81 ± 2.942 mmol/L in M without V group and 12.02 ± 4.315 mmol/L in M with V group (p=0.022). The creatinine value of M without V group was 1.075 ± 0.92 mg/dl and M with V was 1.011±0.246 respectively. The difference between the group is not statistically significant (p=0.507). Metformin with and without Vildagliptin effectively control fasting blood glucose level in type 2 diabetes patients. The blood glucose level after 2 hour breakfast is better controlled by Metformin with Vildagliptin. Metformin with and without Vildagliptin has no significant effect on creatinine level.Metformin vildagliptin combination is prescribed in small number of patients in our country.So, this result supports the need of updating the vildagliptin and other new antidiabetic drugs with modern evidence based effective drugs.

In addition to the Type 2 diabetes patients suffer from many macrovascular and microvascular diseases like Hypertension, Dyslipidemia, coronary heart disease, neuropathy, nephropathy. It has been shown that most of the diabetic patients specially suffer from hypertension and

dyslipidemia. A survey was conducted almost 240,000 patients throughout the China demonstrated that, overall, patients with T2DM do not meet the treatment guideline set by the American Diabetes Association (ADA). More specifically, less than one third of individuals with type 2 diabetes using OADs, either alone or in combination with insulin or GLP-1 receptor agonists, achieved glycemic control as defined by HbA1c <7.0%. Our analysis did not include patients treated with diet and lifestyle interventions alone or insulin without oral agents. Glycemic control appeared to be greater among individuals treated with only OADs compared to those receiving more intensive therapy with OADs in combination with insulin (Bartoli*et al,*2011).

Our study shows fasting blood glucose and serum creatinine level are not significantly different between two groups (M+V and M without V). It has been shown from other literatures that vildagliptin still seems to be not well accepted by most of the physicians. Furthermore, multicenter research with a large sample is still needed to consolidate the observation of this study. Diabetes is a major non communicable disease, ranking as a leading cause of death and disability worldwide. Despite heavy burden, currently there are no epidemiologic studies in Bangladesh that investigate prevalence of diabetes and risk factors using nationally representative data.

This study discussed about Diabetes patients, their current condition about FBG and creatinine, and treatment. The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly among Bangladeshi adults, and limited data are available on T2DM management and the status of glycemic control in Bangladesh. Now a days diabetes is well known diseases in all parts of the world. As of 2014, an estimated 387 million people have diabetes worldwide, with type 2 DM making up about 90% of the cases. Diabetes at least doubles a person's risk of death. The number of people with diabetes is expected to rise to 592 million by 2035.The global economic cost of diabetes in 2014 was estimated to be $612 billion USD. In the United States, diabetes cost $245 billion in 2012. *(*World Health Organization*,* 2014)

Our study was a descriptive study; in which initially 600patients aged between 15 and 75 years prescription with diabetes were taken. Treatment information were collected retrospectively from patients' diabetic books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.)HospitalShahabag, Dhaka.In this study it was found that, symptoms of untreated diabetes is weight loss. Symptoms may develop rapidly (weeks or months) in type 1 DM, while

they usually develop much more slowly and may be subtle or absent in type 2 DM.Several other signs and symptoms can mark the onset of diabetes, although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.(WHO,2013).

Future study may include other sing and symptoms. This study discovered that most commonly prescribed drugs were insulin, metformin,vildagliptin and other supportive drugs. Insulin takes one third share of total drugs in case of treatment of diabetes.(Dry et al , 2009). We have seen in our study that oral antidiabetic drug can manage the blood sugar level in Type 2 diabetes mellitus.

A better glycemic control in patients with Type 2 diabetes was shown with different treatments in our study. Screening of nephropathy is recommended on an annual basis for patients suffering from Type 2 diabetes. This is because diabetes is associated with microvascular complications which also includes nephropathy. Diabetes Mellitus is one of the major causes of renal impairment and also is the leading cause of renal failure. This is a major public health problem worldwide. Therefore, adequate control of blood glucose level is critical to prevent or delay the onset of microvascular disease like, diabetes nephropathy.Metformin with and without Vildagliptin effectively control fasting blood glucose level in type 2 diabetes patients. In our study we have seen that the blood glucose level after 2 hour breakfast is better controlled by Metformin with Vildagliptin. Metformin with and without Vildagliptin has no significant effect on creatinine level.Further study is needed with a large sample size to determine the efficacy and safety of combination Metformin and Vildagliptin in type 2 diabetes patients.

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