EFFECT OF COMBINATION METFORMIN AND GLICLAZIDE ON CREATININE LEVEL IN PATIENTS SUFFERING FROM TYPE 2 DIABETES.

***A* Dissertation submitted to the Department of Pharmacy, East West University, as the partial fulfillment of the requirements for the degree of Master of Pharmacy.**

Supervised by

Dr. Sufia Islam

Professor

Department of Pharmacy

East West University

Submitted by

Fahmida Adib

ID: 2015-1-79-008

Spring-2016

Department of Pharmacy

East West University

DECLARATION BY THE CANDIDATE

I, Fahmida Adib (ID: 2015-3-79-008), hereby declare that this dissertation entitled **"Effect of combination metformin and gliclazide on creatinine level in patients suffering from type 2 diabetes."** submitted to the Department of Pharmacy, East West University, as the partial fulfillment of the requirement for the degree of Master of Pharmacy, is a genuine & authentic research work carried out by me under the guidance and supervision of Dr. Sufia Islam, Professor, Department of Pharmacy, East West University, Dhaka. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute or University for the award of any Degree or Diploma of Fellowship.

_____

Fahmida Adib
ID: 2015-1-79-008
Department of Pharmacy
East West University
Jahurul Islam city, Aftabnagar, Dhaka

CERTIFICATION BY THE SUPERVISOR

This is to certify that the desertion, entitled **"Effect of combination metformin and gliclazide on creatinine level in patients suffering from type 2 diabetes."** is a benefice research work done under my guidance and supervision by Fahmida Adib (ID: 2015-1-79-008), as the partial fulfillment of the requirement for the degree of Master of Pharmacy.

Dr. Sufia Islam
Professor
Department of Pharmacy
East West University
Jahurul Islam city, Aftabnagar, Dhaka

ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the entitled **"Effect of combination metformin and gliclazide on creatinine level in patients suffering from type 2 diabetes."** is a genuine research work carried out by Fahmida Adib (ID: 2015-1-79-008) under the supervision of Dr. Sufia Islam, Professor, Department of Pharmacy, East West University, Dhaka. I farther certify that no part of the thesis has been submitted for any other degree and all the resources of the information in this connection are duly acknowledged.

Dr. Shamsun Nahar Khan
Chairperson and Professor
Department of Pharmacy
East West University
Jahurul Islam city, Aftabnagar, Dhaka

ACKNOWLEDGEMENTS

At first, I would like to express my gratitude to Almighty God for giving me the strength and opportunity to complete my dissertation within the schedule time successfully.

I feel proud to express my deep sense of gratitude to my reverend teacher, guide and supervisor Dr. Sufia Islam, Professor , Department of Pharmacy, East West University, Dhaka, Bangladesh, for her day to day supervision, dexterous management, adept analysis, keen interest, optimistic counseling and unremitting backup.

I am very much pleased and thankful to, Dr. Shamsun Nahar Khan, Chairperson of the Department of Pharmacy and Professor, East West University, for her inspiration and guidance in my work. Moreover, I am grateful to my administration as they provide the facilities to use the laboratory for research work.

It is also great pleasure for me to offer my deepest indebtedness to all of my respected teachers & senior students of the Department of Pharmacy, East West University for extending their helping hands whenever needed.

My cordial thanks to my parents, brother, friends and to all my well-wishers for their wholehearted inspiration throughout the period of the research work.

Dedicated

to

My beloved parents and

Teachers

Table of Contents

List of Table

List of Figure

Abbreviation

- ACEIs : Angiotensin Converting Enzyme Inhibitors.
- ALT : Alanin Amino Transferase
- ARBs : Angiotensin Receptor Blockers
- AST : Aspartate Amino Transferase
- AUC : Alter the Overall Exposure
- CHF : Congestive Heart Failure
- CPK : Creatine Phosphokinase
- CRP : C-Reactive Protine
- CYP : Cyptochrome P
- DM : Diabetes Mellitus
- DPP-4 : Dipeptidyle Peptidase-4
- ED : Energy Dependent
- EMEA : European Medicines Energy
- ESRD : End-stage Renal Disease
- FDA : Food and Drug Administration
- GDM : Gestational Diabetes Mellitus
- GIP : Glucose-Dependent Insulinotropic Peptide
- GLP : Glucagone-like Peptide
- GLP-1 : Glucagone-like Peptide-1
- IDDM : Insulin-Dependent Diabetes Mellitus
- IDF : International Diabetic Federation
- LADA : Latent Autoimmune Diabetes of Adult
- MRDR : Malnutrition-related Diabetes Mellitus
- NPH : Neutral Protamine Hagedorn
- NIDDM : Non insulin-Dependent Diabetes Mellitus
- NYHA : New York Heart Association
- PEP : Prolyl Oligopeptidase

- PPARs : Peroxizome Proliferated Activated Receptors
- PPRE : Peroxizome Proliferator Responsive Elements
- RBCs : Red Blood Cells
- SU : Sulphonylurea

Abstract

Type 2 diabetes mellitus is one of the most common non communicable diseases worldwide. Diabetic nephropathy is a major complications in some patients with diabetes. Therefore, strict control of blood glucose level is essential to prevent or delay the onset of diabetic nephropathy. A number of antidiabetic medications are available in the market. However, only a few can be used safely in diabetic patients in chronic kidney disease. There may be a need for adjustment in dosing of the antidiabetic medications in such patients. Metformin has been recommended by the American Diabetes Association as the first line antidiabetic drug. . Monotherapy often fails to achieve the effective glycemic control for treating Type 2 diabetes. If adequate blood glucose control is not attained using a single oral agent, a combination of agent may result in better glycemic control. Better control of diabetes is essential for each of the patients to reduce the risk of diabetes related complications. This study was carried out to determine the combination effect of metformin and gliclazide on kidney function in type 2 diabetes patients. The other objective of the study was to assess whether the combination of metformin with gliclazide result in better glycemic control.This is a collaborative study between East West University(EWU) and Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). A total of200 patients were enrolled in BIRDEM hospital, Dhaka city, Bangladesh.Male and female patients aged between 40 and 65 years suffering from Type 2 diabetes were included in this study. The patients were treated with Metformin and Gliclazide; Metformin and Insulin and also other combination of oral antidiabetic drugs. Fasting glucose levels and creatinine levels were measured in Type 2 diabetes patients treated with different combinations of antidiabetic medications. The prescription of allpatients suffering from Type 2 diabetes mellitus were analyzed by using the Microsoft Excel and GraphPad Prism 6 software. The present study shows that the age (years)of patients treated with Metformin + Gliclazide and Metformin + Insulin was 46.64±7.393 and43.95±9.761(p = 0.2381) respectively. The fasting blood glucose (FBG) of the patients treated with Metformin and Gliclazide was 8.580±2.300 mmol/L and Metformine and Insulin was 10.20 ± 3.836 mmol/L. The difference was not statistically significant (p=0.0603).The creatinine level of Metformin and Gliclazide group was 1.919 ± 2.691 mg/dl and Metformin withInsulin was 0.9538±0.2943.There was no significant

difference between the groups.The age (years) of patients (46.64±7.393)treated with Metformin + Gliclazide and the age of patient (44.3±9.805) treated with other antidiabetic drugs was not significantly different (p=0.1644). The FBG of patients in Metformin + Gliclazide group was 8.58±2.300 mmol/L and other antidiabetic drugs group was 9.485±4.300 mmol/L; p=07773. The serum creatinine level of patients in Metformin + Gliclazide groupand other antidiabetic drugs group was 1.919±2.691 and 1.009±0.3210 respectively. There was no significant difference between the groups (p=0.6964).Metformin and Gliclazide is a good combination of drug for the adequate control of blood glucose level in Type 2 diabetes patients. This combination does not significantly elevate the creatinine level when compared to Metformin and Insulin combination.Further study is needed to determine the efficacy and safety of Metformin and Gliclazide combination inlarge group of patients with type 2 diabetes.

Keywords: Diabetes, Antidiabetic drugs, Insulin, Metformin, Gliclazide.

Chapter 1

Introduction

1.1Introduction

Diabetes mellitus is the important issue of chronic kidney disease (CKD) and a major public health issue in around the world**.** Inaddition to preventive measures such as lifestyle changes, effective and safe treatments are necessary to manage T2DM.Metformin has been recommended by the American Diabetes Associatioand is widely used as the first-line antidiabetic drug of choice. However, progression of the underlying pathogenetic factors despite metformin treatment in T2DM patients frequently requires additional glucose lowering drugs. Thus, the treatment of T2DM has moved towards combining metformin with other drugs with a different treatment criterion.

1.2 Diabetes mellitus:

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. More commonly referred to as "diabetes‖ a chronic disease associated with abnormally high levels of the sugar glucose in the blood.(WHO, 2014).

Diabetes is due to one of two mechanisms:

1. Inadequate production of insulin (which is made by the pancreas and lowers blood glucose), or
2. Inadequate sensitivity of cells to the action of insulin.

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular

disease, stroke, chronic, foot ulcers, and damage to the eyes. (International Diabetes Federation. 2006)

1.3 Types of Diabetes:

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced (Dorner *et al*., 1977).

There are three main types of diabetes mellitus:

 Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown. (WHO, 2013)

 Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop.This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise. (WHO, 2013)

 Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood-sugar level.(WHO, 2013)

Type 1 Diabetes:

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhansin the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T-cell-mediatedautoimmune attack leads to the loss of beta cells and thus insulin.(Rother,2007) It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children. (Rother *et al.*, 2007).

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.(WHO,1990) Still, type 1 diabetes can be

accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis, and sometimes with serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies. (Merck Publishing, 2010)These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes. (Dorner *et al*., 1977).

Type 2 diabetes:

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus.In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medicationsthat improve insulin sensitivity or reduce the liver's glucose production.Type 2 DM is due primarily to lifestyle factors and genetics.A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.(Williams textbook of endocrinology 12th ed) Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.Even those who are not obese often have a high waist–hip ratio.(Shoback *et al*.,2011).

Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.(American Diabetes Association,2014) The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.Eating lots of white ricealso may increase the risk of diabetes.A lack of exercise is believed to cause 7% of cases. (Davis, 2004).

Gestational diabetes

Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood sugar level. (WHO, 2013)Prevention and treatment involve a healthy diet, physical exercise, not using tobacco and being abnormal. Blood pressure control and proper foot care are also important for people with the disease. Type 1 DM must be managed with insulin injections. Type 2 DM may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby.Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnoseddiabetes exhibit high blood glucose (blood sugar) levels during pregnancy (especially during their third trimester).Gestational diabetes is caused when insulin receptors do not function properly. This is likely due to pregnancy-related factors such as the presence of human placental lactogen that interferes with susceptible insulin receptors. This in turn causes inappropriately elevated blood sugar levels.(International Diabetes Federation.2006).Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied. (Kitabchi *et al*.,2009).As with diabetes mellitus in pregnancy in general, babies born to mothers with untreated gestational diabetes are typically at increased risk of problems such as being large for gestational age (which may lead to delivery complications), low blood sugar, andjaundice. If untreated, it can also cause seizures or stillbirth. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decrease these risks. The food plan is often the first recommended target for strategic management of GDM.Women with unmanaged gestational diabetes are at increased risk of developing type 2 diabetes mellitus (or, very rarely, latent autoimmune diabetes or Type 1) after pregnancy, as well as having a higher incidence of pre-eclampsia and Caesarean section; their offspring are prone to developing childhood obesity, with type 2 diabetes later in life. Most women are able to manage their blood

glucose levels with a modified diet and the introduction of moderate exercise, but some require antidiabetic drugs, includinginsulin. (Kitabchi *et al*., 2009).

Other types

Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology. Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cellfunction. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to thepancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when

1.4 Pathophysiology

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, andgluconeogenesis, 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. (American Diabetes Association, 2014)

Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhansin 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). (Shoback *et al.*, 2011)

1.5 Epidemiology

As of 2013, 382 million people have diabetes worldwide. Type 2 makes up about 90% of the cases. This is equal to 8.3% of the adult population with equal rates in both women and men. In 2014, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.9 million deaths. The World Health Organization (WHO) estimated that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death. The discrepancy between the two estimates is due to the fact that cardiovascular diseases are often the cause of death for individuals with diabetes. More than 80% of diabetic deaths occur in low and middle-income countries. (International Diabetes Federation, 2014).

1.6 Sign and Symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). 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 dermatomes. (Cooke *et al.*, 2008).

1.7 History

Diabetes was one of the first diseases described, with an Egyptian manuscript from c.1500 BCE mentioning "too great emptying of the urine". The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine", noting the urine would attract ants. The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis. The disease was considered rare during the time of the Roman Empire, with Galen commenting he had only seen two cases during his career. This is possibly due the diet and life-style of the ancient people, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrhea urinosa). (Leonid, 2009)

The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation of diabetes with other diseases and he discussed differential diagnosis from the snakebite which also provokes excessive thirst. Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight. The term "mellitus" or "from honey" was added by the

Briton John Rolle in the late 1700s to separate the condition from diabetes insipid us, which is also associated with frequent urination. Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922. This was followed by the development of the long-acting insulin NPH in the 1940s.(Leonid, 2009).

1.8. Classification and Causes

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types". The "other specific types" are a collection of a few dozen individual causes. The term "diabetes", without qualification, usually refers to diabetes mellitus (Leonid *et a*l., 2009).

1.9 Treatment

For type 2 diabetic patients, several treatment options are available (Shoback *et al.*, 2011). While the major focus of diabetes treatment is glycaemic control, other strategies target coincident features of the disease such as insulin resistance or obesity. The current consensus treatment of type 2 diabetes follows a stepwise manner, starting with lifestyle interventions (e.g. diet and exercise) and pharmacotherapy with metformin. Eventually, combination therapy with lifestyle interventions, oral agents, and/or insulin is generally indicated for many type 2 diabetic patients. The success of the antidiabetic therapy is controlled by measuring blood glucose, as an index of acute glycaemia and HbA1c, i.e. glycosylated haemoglobin, as an index of chronic glycaemia. Lifestyle interventions to promote weight loss and increase exercise should, if possible, always be included in the treatment of diabetes. While weight loss can effectively ameliorate hyperglycaemia the long-term success of incorporating such intervention programs into the usual lifestyle and maintaining them is limited. For pharmacotherapy, several classes of antidiabetic medications are currently available, targeting different angles of the disease. Hepatic glucose production is decreased by metformin, resulting in decreased fasting glycaemia. Sulfonylureas and glinides act by enhancing insulin secretion. α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides, thereby lowering postprandial glucose levels.Glitazones increase the sensitivity of muscle, fat, and liver to insulin Finally, insulin is the oldest and most effective treatment for lowering glycaemia, and over time,

as β-cell function decreases, many diabetics require intensive insulin therapy. Metformin, sulfonylureas and glinides lower HbA1c by ~1.5%, more than the other oral antidiabetics, but not as much as insulin. Metformin is indicated at every stage of the disease .In the United Kingdom Prospective Diabetes Study it was shown not to affect body weight (Schulman *et al.*,2009).

These currently available therapies for type 2 diabetes have several disadvantages including increased risk of hypoglycaemia (sulphonylureas,insulin), gastrointestinal side effects (metformin, α-glucosidase inhibitors, amylin agonists), weight gain (sulphonylureas, glitazones, glinides, insulin), fluid retention and congestive heart failure (glitazones) (Diabetes Mellitus, Alvin C 18th ed), as well as myocardial infarction (rosiglitazone).One new approach yielding.Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce the liver's glucose production. Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders. Even those who are not obese often have a high waist–hip ratio. Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk. Eating lots of white rice appears to also play a role in increasing risk. A lack of exercise is believed to cause 7% of cases. (Schulman *et al.*, 2009).

1.10 Diagnosis

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). The rare disease diabetes insipidus has similar symptoms to diabetes mellitus, but without disturbances in the sugar metabolism (insipidusmeans "without taste" in Latin) and does not involve the same disease mechanisms. Diabetes is a part of the wider condition known as metabolic syndrome.(Schulman *et al*.,2009).

1.11 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 inwhole 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. (Harvard School of Public Health,2014)

1.12 Management

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 HbA1C 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 *(*Nathan *et al., 2005).*

Lifestyle of the patients suffering from Diabetes

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.(Adler , 2000).

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. (Cheng *et al.*, 2014).

Surgery

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 cutoffs 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. 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. (Polisena *et al.*, 2009)

1.13 Anti-Diabetic Drug

Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide andpramlintide, all are administered

orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type I, which must be injected. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. (Polisena *et al.*,2009)

Treatments include:

(1) agents that increase the amount of insulin secreted by the pancreas,

(2) Agents that increase the sensitivity of target organs to insulin, and

(3) Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Several groups of drugs, mostly given by mouth, are effective in Type II, often in combination.The therapeutic combination in Type II may include insulin, not necessarily because oral agents have failed completely, but in search of a desired combination of effects. The great advantage of injected insulin in Type II is that a well-educated patient can adjust the dose, or even take additional doses, when blood glucose levels measured by the patient, usually with a simple meter, as needed by the measured amount of sugar in the blood. (Polisena *et al*., 2009)

1.13.1 Type of anti-diabetic medication

A. Insulin

B. Sensitizers

C. Secretagogues

D. Alpha-glucosidase inhibitor

E. Peptide analogs

F. Glycosurics

A. Insulin

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research of other routes of administration is underway. In acute-care settings, insulin may also be given intravenously. In general, there are three types of insulin, characterized by the rate which they are metabolized by the body. They are rapid acting insulins, intermediate acting insulins and long acting insulins. (Powers in Harrison's Principles of Internal Medicine)

Examples of rapid acting insulins include

Examples of intermediate acting insulins include

Examples of long acting insulins include

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

B. Sensitizers

Insulin sensitizers address the core problem in Type II diabetes—insulin resistance.

Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery,including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, metformin, a biguanide, has become the most commonly used agent for type 2 diabetes in children and teenagers. Among common diabetic drugs, metformin is the only widely used oral drug that does not cause weight gain.

Typical reduction in glycated hemoglobin (A1C) values for metformin is 1.5–2.0%

Metformin is usually the first-line medication used for treatment of type 2 diabetes. In general, it is prescribed at initial diagnosis in conjunction with exercise and weight loss, as opposed to in the past, where it was prescribed after diet and exercise had failed. There is an immediate release as well as an extended-release formulation, typically reserved for patients experiencing GI side-effects. It is also available in combination with other oral diabetic medications.

Thiazolidinediones

Thiazolidinediones (TZDs), also known as "glitazones," bind to PPARγ, a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE). The PPREs influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.

Typical reductions in glycated hemoglobin (A1C) values are 1.5–2.0%. Some examples are:

2010,that it be suspended from the EU market due to elevated cardiovascular risks.

Multiple retrospective studies have resulted in a concern about rosiglitazone's safety, although it is established that the group, as a whole, has beneficial effects on diabetes.

The greatest concern is an increase in the number of severe cardiac events in patients taking it. The ADOPT study showed that initial therapy with drugs of this type may prevent the progression of disease, as did the DREAM trial. (Wood *et al.*, 2007)

Concerns about the safety of rosiglitazone arose when a retrospective meta-analysis was published in the New England Journal of Medicine. There have been a significant number of publications since then, and a Food and Drug Administration panel voted, with some controversy, 20:3 that available studies "supported a signal of harm," but voted 22:1 to keep the drug on the market. The meta-analysis was not supported by an interim analysis of the trial designed to evaluate the issue, and several other reports have failed to conclude the controversy. This weak evidence for adverse effects has reduced the use of rosiglitazone, despite its important and sustained effects on glycemic control. Safety studies are continuing. In contrast, at least one large prospective study, PROactive 05, has shown that pioglitazone may decrease the overall incidence of cardiac events in people with type 2 diabetes who have already had a heart attack. (Ajjan *et al.*, 2008).

C. Secretagogues

Secretagogues are drugs that increase insulin output from the pancreas. Sulfonylureas Sulfonylureas were the first widely used oral anti-hyperglycaemic medications. They are insulin secretagogues, triggering insulin release by inhibiting the KATP channel of the pancreatic beta cells. Eight types of these pills have been marketed in North America, but not all remain available. The "second-generation" drugs are now more commonly used. They are more effective than first-generation drugs and have fewer side-effects. All may cause weight gain. Sulfonylureas bind strongly to plasma proteins. Sulfonylureas are useful only in Type II diabetes, as they work by stimulating endogenous release of insulin. They work best with patients over 40 years old who have had diabetes mellitus for under ten years. They cannot be used with type I diabetes, or diabetes of pregnancy. They can be safely used with metformin or glitazones. The primary side-effect is hypoglycemia. Typical reductions in glycated hemoglobin (A1C) values for second-generation sulfonylureas are 1.0–2.0%. (Ajjan *et al.*, 2008).

D. Alpha-glucosidase inhibitor

Alpha-glucosidase inhibitors are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes.

Typical reductions in glycated hemoglobin (A1C) values are 0.5–1.0%.

These medications are rarely used in the United States because of the severity of their side-effects (flatulence and bloating). They are more commonly prescribed in Europe. (National Prescribing Service, 2010)

E. Peptide analogs

Injectable Incretin mimetics

Incretins are insulin secretagogues. The two main candidate molecules that fulfill criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide(glucose dependent insulinotropic peptide, GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Injectable Glucagon-like peptide analogs and agonists Glucagon-like peptide (GLP) agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half-life of only a few minutes, thus an analogue of GLP would not be practical.

1.14Gliclazide

Gliclazide is an oral hypoglycemic (anti-diabetic drug) and is classified as a sulfonylurea. Its classification has been ambiguous, as literature uses it as both a first-generation [1] and second-generation sulfonylurea. Gliclazide was shown to protect human pancreatic beta-cells from hyperglycemia-induced apoptosis. It was also shown to have an antiatherogenic effect (preventing accumulation of fat in arteries) in type 2 diabetes.

It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system. Gliclazide is used for control of hyperglycemia in gliclazide-responsive diabetes mellitus of stable, mild, non-ketosis prone, type 2 diabetes. It is used when diabetes cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate. National Kidney Foundation (2012 Update) claims that Gliclazide does not require dosage up titration even in end stage kidney disease.

Mechanism of action

Gliclazide selectively binds to sulfonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonylurea receptors (SUR-2A) in the heart.[8] This binding effectively closes the K+ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocytosis of insulin vesicles leading to insulin release.The mouse model of MODY diabetes suggested that the reduced gliclazide clearance stands behind their therapeutic success in human MODY patients, but Urbanova et al. found that human MODY patients respond differently and that there was no consistent decrease in gliclazide clearance in randomly selected HNF1A-MODY and HNF4A-MODY patients.(National Prescribing Service, 2010)

1.15 Metformin

Metformin, marketed under the trade nameGlucophage among others, is the first-line medication for the treatment of type 2 diabetes. This is particularly true in people who are overweight. It is also used in the treatment of polycystic ovary syndrome. Limited evidence suggests metformin may prevent the cardiovascular disease and cancer complications of diabetes. It is not associated with weight gain. It is taken by mouth.

Metformin is generally well tolerated. Common side effects include diarrhea, nausea, and abdominal pain. It has a low risk of developing low blood sugar. High blood lactic acid level is a concern if the drug is prescribed inappropriately and in overdose. It should not

be used in those with liver disease or kidney problems. While there is no clear harm if used during pregnancy, insulin is generally preferred for gestational diabetes. Metformin is in the biguanide class. It works by decreasing glucose production by the liver and increasing the insulin sensitivity of body tissues.

Metformin was discovered in 1922.[11] Study in humans began in 1950s by French physician Jean Sterne. It was introduced as a medication in France in 1957 and the United States in 1995. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic healthcare system. Metformin is believed to be the most widely used medication for diabetes which is taken by mouth. It is available as a generic medication.[3] The wholesale price in the developed world is between 0.21 and 5.55 USD per month as of 2014. In the United States, it costs 5 to 25 USD per month. (World Health Organization October 2013).

Mechanism of action

The exact mechanism of metformin is incompletely understood. The drug's main effect is to decrease hepatic glucose production. Metformin also increases insulin sensitivity, which increases peripheral glucose uptake.

Metformin decreases high blood sugar primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). The "average" person with type 2 diabetes has three times the normal rate of gluconeogenesis; metformin treatment reduces this by over one-third. The molecular mechanism of metformin is incompletely understood: inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on gut microbiota have been proposed as potential mechanisms.

Activation of AMPK, an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats, was required for metformin's inhibitory effect on the production of glucose by liver cells. Activation of AMPK was required for an increase in the expression of small heterodimer partner, which

in turn inhibited the expression of the hepatic gluconeogenic genes Phosphoenolpyruvate carboxykinase and glucose 6-phosphatase. Metformin is frequently used in research along with AICA ribonucleotide as an AMPK agonist. More recent studies using mouse models in which the genes for AM

PKα1 and α2 catalytic subunits (*Prkaa1/2*) or *LKB1*, an upstream kinase of AMPK, had been knocked out in hepatocytes, have raised doubts over the obligatory role of AMPK, since the effect of metformin was not abolished by loss of AMPK function. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, metformin increases the concentration of cytosolicadenosine monophosphate (AMP) (as opposed to a change in total AMP or total AMP/adenosine triphosphate). Increased cellular AMP has also been proposed to explain the inhibition of glucagon-induced increase in cAMP and activation of PKA.Metformin and other biguanides may antagonize the action of glucagon, thus reducing fasting glucose levels. Metformin also induces a profound shift in the faecal microbial community profile in diabetic mice and this may contribute to its mode of action possibly through an effect on glucagon-like peptide-1 secretion.

In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin-induced suppression of fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral use of glucose may be due to improved insulin binding to insulin receptors. The increase in insulin binding after metformin treatment has also been demonstrated in patients with NIDDM.

AMPK probably also plays a role in increased insulin as metformin administration increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose uptake. Some metabolic actions of metformin do appear to occur by AMPK-independent mechanisms; the metabolic actions of metformin in the heart muscle can occur independent of changes in AMPK activity and may be mediated by p38 MAPK- and PKC-dependent mechanisms.(Wood *et al.*, 2015)

Chapter 2

Objective

2.1 The objectives of the study are -

- To investigate the effect of metformin and gliclazide on creatinine level in type 2 diabetes patients.
- To assess the better glycemic control in Metformin and Gliclazide combination group for the treatment of Type 2 diabetes.

Chapter 3

Literature review

3.1 Literature review

Type 2 diabetes mellitus (T2DM) is a progressive condition requiring long-term treatment. Most patients with T2DM are unable to maintain normoglycemia using metformin alone; thus, combination therapy is a pivotal part of disease management. Addition of the dipeptidyl peptidase-4 inhibitor linagliptin, with its proven efficacy, low propensity for hypoglycemia, and weight neutrality, has been shown to improve glycemic control for patients who are not well controlled with metformin. As patients often have other comorbidities requiring pharmacotherapy, an increase in pill number, different prescribing frequencies, and timing of medications may adversely impact patients' adherence. Studies have shown that treatment nonadherence contributes to increased morbidity, mortality, and healthcare cost. In the United States, the single-pill combination (SPC) of linagliptin/metformin is available in three strengths approved for twice-daily administration: 2.5/500 mg, 2.5/850 mg, and 2.5/1000 mg. The SPC has the potential to reduce pill burden and simplify patients' treatment regimens, thereby promoting improved adherence and efficacy.(Haak *et al*., 2015)

Combinations of metformin-vidagliptin (MF-VG) and metfromin-glimepiride (MF-GP) in type 2 diabetes mellitus (T2DM) patients was investigated. A comparative randomized open-label trial was conducted on patients with uncomplicated T2DM, on treatment with MF for 4 months out of which on maximum tolerated dose of MF (1000-2500 mg/day) for 4 weeks, glycosylated Haemoglobin [HbA1c]) ≥6.5%, fasting blood glucose (FBG) ≥126 mg/dl and post prandial glucose (PPG) ≥200 mg/dl were included in the study. Patients were randomized to receive MF (500 mg BD) + VG (50 mg BD) or MF (500 mg BD) + GP (2 mg BD).(Gupta *et al*., 2015)

Evaluation the efficacy and safety of combinations of empagliflozin/linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. At week 24, reductions in HbA1c (mean baseline 7.90-8.02% [62.8-64.1 mmol/mol]) with empagliflozin/linagliptin were superior to those with empagliflozin or linagliptin alone as add-on to metformin; adjusted mean (SE) changes from baseline were -1.19% (0.06) (-13.1 mmol/mol [0.7]) with empagliflozin 25 mg/linagliptin 5 mg, -1.08% (0.06) (-11.8 mmol/mol [0.7]) with empagliflozin 10 mg/linagliptin 5 mg, -0.62% (0.06) (-6.8 mmol/mol [0.7]) with empagliflozin 25 mg, -0.66% (0.06) (-7.2 mmol/mol [0.7])

with empagliflozin 10 mg, and -0.70% (0.06) (-7.6 mmol/mol [0.7]) with linagliptin 5 mg (P < 0.001 for all comparisons). In these groups, respectively, 61.8, 57.8, 32.6, 28.0, and 36.1% of subjects with baseline HbA1c ≥7% (≥53 mmol/mol) had HbA1c <7% (<53 mmol/mol) at week 24. Efficacy was maintained at week 52. The proportion of subjects with adverse events (AEs) over 52 weeks was similar across treatment arms (68.6-73.0%), with no hypoglycemic AEs requiring assistance.(DeFronzo*et al*., 2015)

Some patients with type 2 diabetes mellitus (T2DM) receiving monotherapy with a sulfonylurea (SU) are unable to meet recommended glycemic targets over the long term and require additional pharmacologic agents to maintain glycemic control. The utility of adjunctive therapy with the dipeptidyl peptidase (DPP)-4 inhibitor linagliptin in patients with T2DM inadequately controlled with SU monotherapy. The efficacy and tolerability of linagliptin as add-on therapy in patients with inadequately controlled T2DM despite background therapy with SU.Mean baseline characteristics were similar in the linagliptin and placebo groups. Linagliptin treatment was associated with a placebo-corrected mean (95% CI) change in HbA(1c) from baseline (8.6%) to 18 weeks of -0.47% (-0.70 to -0.24; P < 0.0001). Patients in the linagliptin group were more likely compared with placebo to achieve the HbA(1c) target level of <7.0% after 18 weeks of treatment (15.2% vs 3.7%, respectively; odds ratio [OR] = 6.5; 95% CI, 1.7-24.8; P = 0.007). Similarly, patients in the linagliptin group were more likely to achieve an HbA(1c) reduction of ≥0.5% compared with those in the placebo group (57.6% vs 22.0%; OR = 5.1, 95% CI 2.7-9.6; P < 0.0001). The overall frequency of adverse events was similar between the linagliptin and placebo groups (42.2% vs 42.9%). The incidences of hypoglycemic events were not significantly different between the 2 groups (5.6% vs 4.8%), and none of the hypoglycemic episodes were assessed as severe by the investigator. The difference in the changes in mean body weight was not significant (+0.43 vs -0.01 kg; P = 0.12).

(Lewin*et al*., 2012)

Obtaining the suggested glycemic control is the most important achievement in order to prevent cardiovascular complications in patients with type 2 diabetes. Monotherapy often fails after a period of treatment, so that multiple drugs are needed to achieve effective glycemic control. A number of oral glucose lowering drugs is now available such as metformin, sulfonylureas, non-sulfonylureas secretagogues (metiglinides derivatives),

alpha-glucosidases inhibitors, and the newest agent: thiazolidinediones (TZD). The possible associations of oral glucose lowering drugs for optimal treatment of type 2 diabetes are briefly reviewed. In particular, the effects of different classes of drugs on cardiovascular risk factors (and particular hypertension and dyslipidemia) and well recognized cardiovascular disease markers in type 2 diabetes are analyzed: in this context TZD appear the more innovative drugs and have been shown to play a key role in the management of hypertension, dyslipidemia, inflammation and endothelial disfunction in diabetic patients. The possible adverse effects derived from the association of different drug classes are also considered.(Derosa*et al*., 2007)

The efficacy, safety and tolerability of linagliptin or placebo administered for 24 weeks in combination with pioglitazone in patients with type 2 diabetes mellitus (T2DM) exhibited insufficient glycemic control (HbA1c 7.5-11.0%).Patients were randomized to receive the initial combination of 30 mg pioglitazone plus 5 mg linagliptin (n = 259) or pioglitazone plus placebo (n = 130), all once daily. The primary endpoint was changed from baseline in HbA1c after 24 weeks of treatment, adjusted for baseline HbA1c and prior antidiabetic medication.

After 24 weeks of treatment, the adjusted mean change (±s.e.) in HbA1c with the initial combination of linagliptin plus pioglitazone was -1.06% (±0.06), compared with -0.56% (±0.09) for placebo plus pioglitazone. The difference in adjusted mean HbA1c in the linagliptin group compared with placebo was -0.51% (95% confidence interval [CI] -0.71, -0.30; $p < 0.0001$). Reductions in fasting plasma glucose (FPG) were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone; -1.8 and -1.0 mmol/l, respectively, equating to a treatment difference of -0.8 mmol/l (95% CI -1.2, -0.4; $p < 0.0001$). Patients taking linagliptin plus pioglitazone, compared with those receiving placebo plus pioglitazone, were more likely to achieve HbA1c of <7.0% (42.9 vs. 30.5%, respectively; $p = 0.0051$) and reduction in HbA1c of ≥0.5% (75.0 vs. 50.8%, respectively; $p < 0.0001$). β-cell function, exemplified by the ratio of relative change in adjusted mean HOMA-IR and disposition index, improved. The proportion of patients that experienced at least one adverse event was similar for both groups. Hypoglycaemic episodes (all mild) occurred in 1.2% of the linagliptin plus pioglitazone patients and none in the placebo plus pioglitazone group.(Gomis*et al*., 2011)

The objective of this study was to compare the effects of gliclazide/metformin on glycemic control in patients with Type 2 diabetes mellitus uncontrolled on monotherapy with sulfonylurea or metformin. This was a prospective, open-labeled, multicentric study over 12 weeks. Patients who were diagnosed of Type 2 diabetes and were uncontrolled on monotherapy with oral hypoglycemic agents, including gliclazide and metformin, characterized by HbA1c 7% or greater and 10% or less and fasting plasma glucose (FPG) 140 mg/dL or greater were enrolled in this study. The treatment regimen was started at 80 mg gliclazide plus 500 mg metformin once a day and was titrated to the next dose level depending on the clinician's judgment, not exceeding a total daily dose of 320 mg gliclazide and 2000 mg metformin. Changes from baseline HbA1c, FPG, and postprandial glucose were examined. After 12-weeks treatment, the gliclazide + metformin combination showed improvement in metabolic control as assessed by changes in HbA1c, FPG, and postprandial glucose. The primary efficacy parameter, HbA1c, was significantly reduced to 7.35 ± 1.10 at the end of treatment from the baseline value (8.51 ± 0.77) ($P < 0.001$). A total of 84.35% of patients showed a 0.5% or greater reduction in HbA1c and 37.39% of patients reported less than 7% HbA1c at the end of therapy. FPG and postprandial glucose were significantly reduced at the end of therapy as compared with baseline values ($P < 0.001$). Moreover, the lipid profile was also improved during the treatment period. The addition of gliclazide to metformin is an effective treatment for patients inadequately controlled on sulfonylurea or metformin alone. A combination of gliclazide with metformin achieves good glycemic control and improves lipid levels with better tolerability profile.(Pareek *et al*.,2010)

The effects of nateglinide plus metformin with gliclazide plus metformin on glycaemic control in patients with Type 2 diabetes was compared.

HbA1c was significantly ($P < 0.001$) decreased from baseline in both treatment groups (mean changes: nateglinide -0.41%, gliclazide -0.57%), but with no significant difference between treatments. Proportions of patients achieving a reduction of HbA1c >or= 0.5% or an end point HbA1c < 7% were also similar (nateglinide 58.1%, gliclazide 60.2%). Changes from baseline in FPG were similarly significant in both treatment groups (nateglinide -0.63, gliclazide -0.82 mmol/l). Reduction from baseline in maximum postprandial glucose excursion were significant in the nateglinide group only (nateglinide

-0.71, gliclazide -0.10 mmol/l; P = 0.037 for difference). Postprandial insulin levels were significantly higher with nateglinide compared with gliclazide. The overall rate of hypoglycaemia events was similar in the nateglinide group compared with the gliclazide group.(Risticet al.2006)

Patients with poorly controlled type 2 diabetes (HbA1c > or = 7.5% to < or =11.0%) received either pioglitazone 15 mg o.d. (titrated up to 45 mg; n = 317) or gliclazide 80 mg o.d. (titrated up to 320 mg; n = 313) and metformin at the pre-study dose were investigated. HbA1c, fasting plasma glucose (FPG), insulin, lipids and the urinary albumin/creatinine ratio were measured.

There were no significant differences in HbA1c (1% decrease in both groups) and FPG between groups. There was a decrease in fasting insulin in the pioglitazone group compared to an increase in the gliclazide group ($p < 0.001$). There were significantly greater improvements in triglycerides and HDL-cholesterol in the metformin plus pioglitazone group compared to the metformin plus gliclazide group ($p < 0.001$). Mean LDL-cholesterol decreased with metformin plus gliclazide and increased with metformin plus pioglitazone ($p < 0.001$); however, this increase was considerably less marked than that in HDL-cholesterol. The mean urinary albumin/creatinine ratio was reduced by 10% in the metformin plus pioglitazone group compared to an increase of 6% in the metformin plus gliclazide group ($p = 0.027$). The incidence of adverse events was comparable between groups and both combinations were well tolerated.(Matthews*et al*., 2005)

High blood glucose level, lipid profile disturbances and plasma homocysteine (Hcy) are important risk factors for cardiovascular diseases in patients with type 2 diabetes. This study was conducted to evaluate and compare effects of glimepiride/metformin combination versus gliclazide/metformin combination on cardiovascular risk factors in type-2 diabetes mellitus (T2DM) patients. One hundred and eighty T2DM patients were randomly allocated for treatment with placebo (control), metformin (500 mg twice daily), glimepiride (3mg once daily), gliclazide (80 mg once daily), metformin plus glimepiride or metformin plus gliclazide for 3 months. Plasma levels of glucose (PG), glycated hemoglobin (HbA1C), Hcy, vitamin B12, folic acid and lipid profile before treatment and 3 months post treatment were evaluated. Compared to metformin treated patients, glimepiride plus metformin induced significant reductions in: fasting plasma glucose,

postprandial PG level, HbA1C % and Hcy level. Conversely, plasma folic acid and vitamin B12 were significantly increased. The levels of total cholesterol and triglyceride were significantly decreased; low-density lipoprotein was markedly decreased, whereas high-density lipoprotein was significantly increased and hence risk ratio was significantly decreased. Similar results but with lower values were obtained using combination of metformin plus gliclazide on glycemic control only. Combination of glimepiride with metformin was superior to gliclazide plus metformin in alleviating the cardiovascular risk factors in type 2 diabetes mellitus patients.(Hassan*et al*.,2025)

Diabetes mellitus is a major public health problem globally and is associated with macro and microvascular problems. This is a leading cause of chronic kidney disease.

Metformin is the initial pharmacological agent for type 2 diabetes treatment. This drug acts mainly by decreasing hepatic glucose production, increasing peripheral glucose uptake, improving glucose tolerance and lowering fasting and postprandial plasma glucose. The prescription of metformin is contraindicated in DKD because it undergoes renal excretion and its most serious adverse effect is the development of lactic acidosis, although this is a very rare occurrence, with approximately 5 cases per 100,000 patient-years. A current United Kingdom (UK) guideline on the treatment of T2DM allows metformin use up to a GFR of 30 mL/min/1.73 m^2, with dose reduction advised at 45 mL/min/1.73 m^2. In the USA, metformin is contraindicated for men with serum creatinine ≥1.5 mg/dL and for women with serum creatinine ≥1.4 mg/dL. New evidence from the literature suggests that patients with mild-to-moderate DKD face more benefits than risks while using metformin.

Sulfonylureas (SUs) are drugs that stimulate endogenous insulin secretion by pancreatic β cells. These drugs may potentially cause hypoglycemia, especially in association with high doses; omission or reduction of carbohydrate intake; alcohol abuse; hepatic dysfunction; heart failure; malnutrition; advanced age; and interactions with certain drugs that displace SUs from their plasma protein-binding sites because one or more of their metabolites may accumulate, resulting in an increased risk of hypoglycemia. Several drugs are included in this class. Glipizide is metabolized by the liver into several inactive metabolites and its clearance and elimination half-life are not affected by a reduction in the estimated GFR (eGFR), so dose adjustments are not necessary in patients with CKD.

Therefore, glipizide is the SU of choice in patients with CKD. Glibenclamide and glyburide are each metabolized by the liver and are eliminated equally in the bile and urine. Hypoglycemic episodes may be severe in patients with renal failure, and the drugs are contraindicated from stage 3 of CKD (eGFR<60 mL/min). Meanwhile, glimepiride is metabolized by the liver into two main metabolites, one of which has hypoglycemic activity. In patients with renal impairment, these metabolites can accumulate. Nevertheless, glimepiride is associated with less hypoglycemia compared with glyburide, although its use should be avoided in patients with a GFR of <60 mL/min. Finally, gliclazide has inactive metabolites that are eliminated mainly in the urine (80%) and presents a lower risk of severe hypoglycemia than glibenclamide and glimepiride do. This drug can be considered in renal impairment if appropriate attention is paid to the dose. However, use should be avoided if the GFR falls to <40 mL/min. (Carolina*et al*., 2016)

Different combination of oral antidiabetic drugs are used to treat diabetes. In BIRDEM hospital patients are prescribed with different combination agents to treat Type 2 diabetes. To evaluate the safety of the combination agents on renal function, this study was carried out in 200 patients treated with combination antidiabetic drugs.

Chapter 4

Method and Materials

4.1Methods and Inclusion criteria of patients

Prescription was collected from Diabetic Books of the patients enrolled in angladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM). Two hundred patients with type 2 diabetes was included in this study. Their prescription was collected from outpatient department. The age of the patients was between 35 and 60 years.

Camera or Mobile phone camera was used to collect the data. Windows 2010(Microsoft Excel) andGraphPad Prism 6 were used to analyze the data.

4.2Sample characteristics

The sample was collected from the BIRDEM hospital, Shahabag, Dhaka from 15th March to 15th December 2016. All the prescriptions were collected retrospectively from the outpatients department.

4.3Exclusion criteria

- Age more than 70 years
- Type 1 diabetes patients
- Gestational diabetes patients

4.4Procedure

The study was performed by completing 3 stages of the procedure. In the beginning literature review was done from online literatures regarding diabetic treatment on prescription basis. The aim of the literature review was to observe the situations of prescribing combination and single anti diabetic drugs of 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 diabetic patients were collected from the prescription retrospectively from BIRDEM hospital Shahabag, Dhaka.

Chapter 5

Result

Table 1: Mean Fasting Blood Sugar (mmol/L) and Creatinine level (mg/dl) of Patients treated with combination metformin + gliclazide and other drugs

	Metformin+ Gliclazide	**Other Combination**	***P***
Age in years	**46.64±7.393**	**44.3±9.805**	**0.1644**
FBG (mmol/L)	**8.58 ± 2.300**	**9.485 ± 4.300**	**0.777**
Serum creatinine (mg/Dl)	**1.919 ± 2.691**	**1.009 ± 0.3210**	**0.696**

Table 1 shows mean value with SD of metformin with gliclazide and other antidiabetic drug.

The age (years) of patients of metformin + gliclazide group was 46.64±7.393 and other antidiabetic drugs group was 44.3±9.805. No significant difference was observed between the groups (p=0.1644). The FBG of patients treated with metformin + gliclazide was 8.58±2.300and other combination was 9.485±4.300. There was no significant difference between two groups (p=0.7773). The serum creatinine level of patients treated with metformin + gliclazide was 1.919±2.691and with other combination was 1.009±0.3210. There was no significant difference(p=0.6964)when compared between the groups.

Table 2: Mean Fasting Blood Sugar and Creatinine level of Patients treated with different combination of antidiabetic drugs

	Metformin HCl+Gliclazide	**Metformin HCl+Insulin**	***P***
Age in years	**46.64±7.393**	**43.95±9.761**	**0.2381**
FBG (mmol/L)	**8.58±2.300**	**10.2±3.836**	**0.0603**
Serum creatinine (mg/dL)	**1.919±2.691**	**0.9538±0.2943**	**0.4330**

Table 2showsthe Age of the patients, FBG (mmol/L) and serum creatinine level (Mean with SD) of metformin with gliclazide and metformin with insulin groups.The age of the patients treated with metformin and gliclazide combination was 46.64±7.393 and metformin and insulincombination was 43.95±9.761, there was no significant difference(*p*=0.2381).

The FBG 8.58±2.300 of patients treated with metformin + gliclazide was 8.58±2.300. The FBG of patient treated with metformin + insulin was 10.2±3.836. There was no significant difference (*p*=0.0603). The serum creatinine level was 1.919±2.691 mg/dL in patients treated with metformin + gliclazide and0.9538±0.2943 mg/dL in patients treated with metformin + insulin.There was no significant difference(*p*=0.4330) between two groups.

Fig 1: Mean age (years) of patients

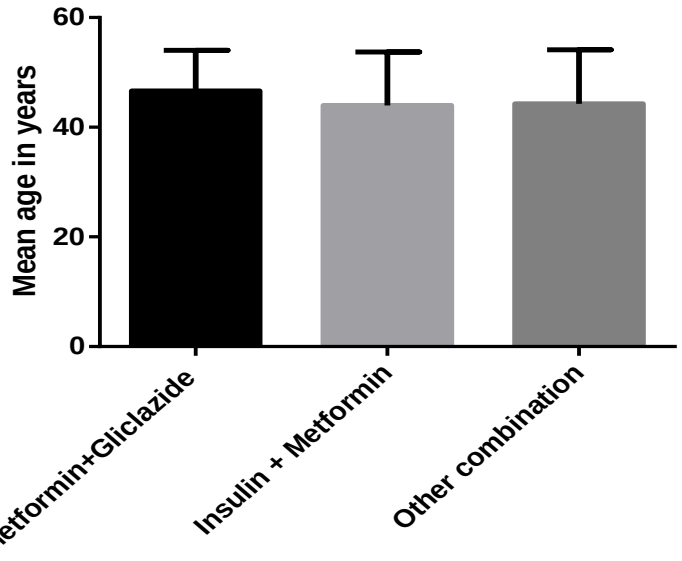


Figure 1 shows the mean age of the patients treated with metformin with gliclazide; metformin with insulin and other antidiabetic drugs.

The age (years)of patients of metformin + gliclazide group was 46.64±7.393 and metformin + insulingroup was 43.95±9.761 andthe antidiabetic drugs was 44.3±9.805.

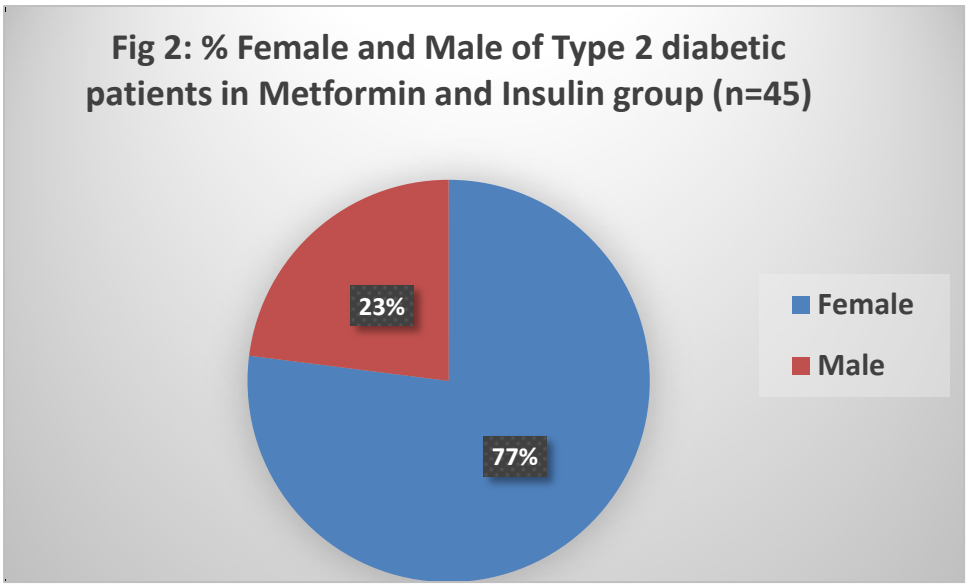
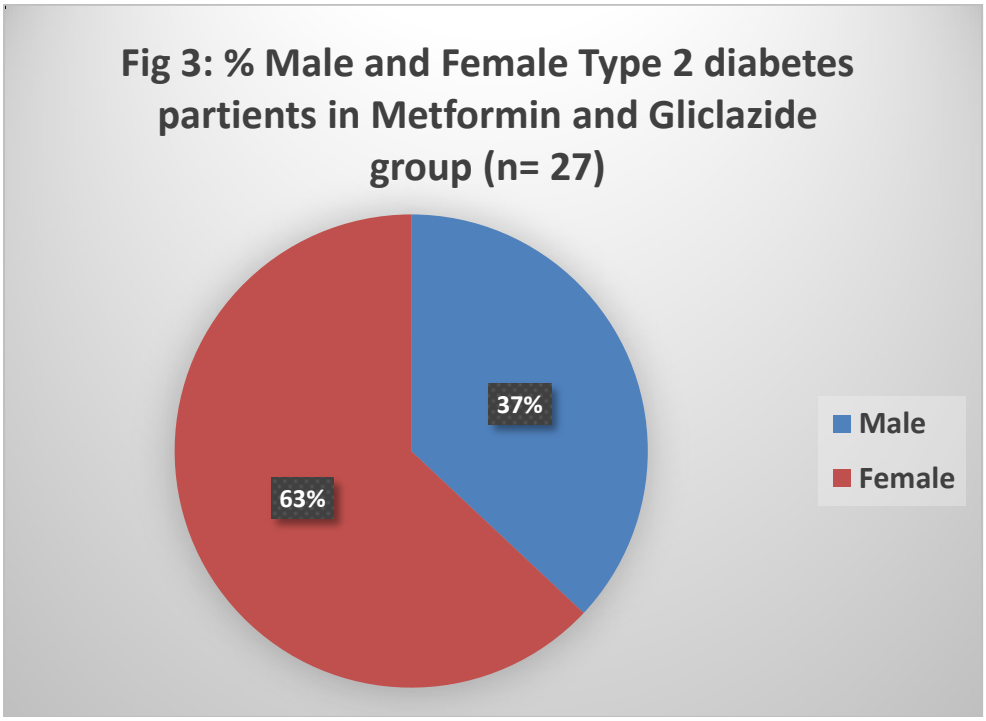
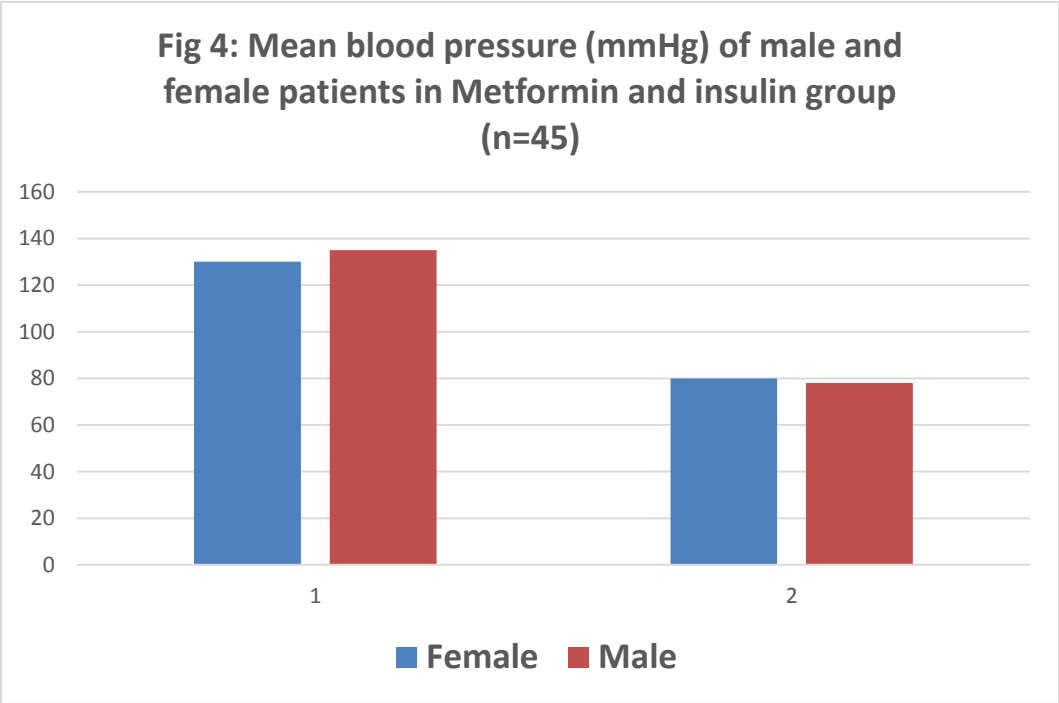


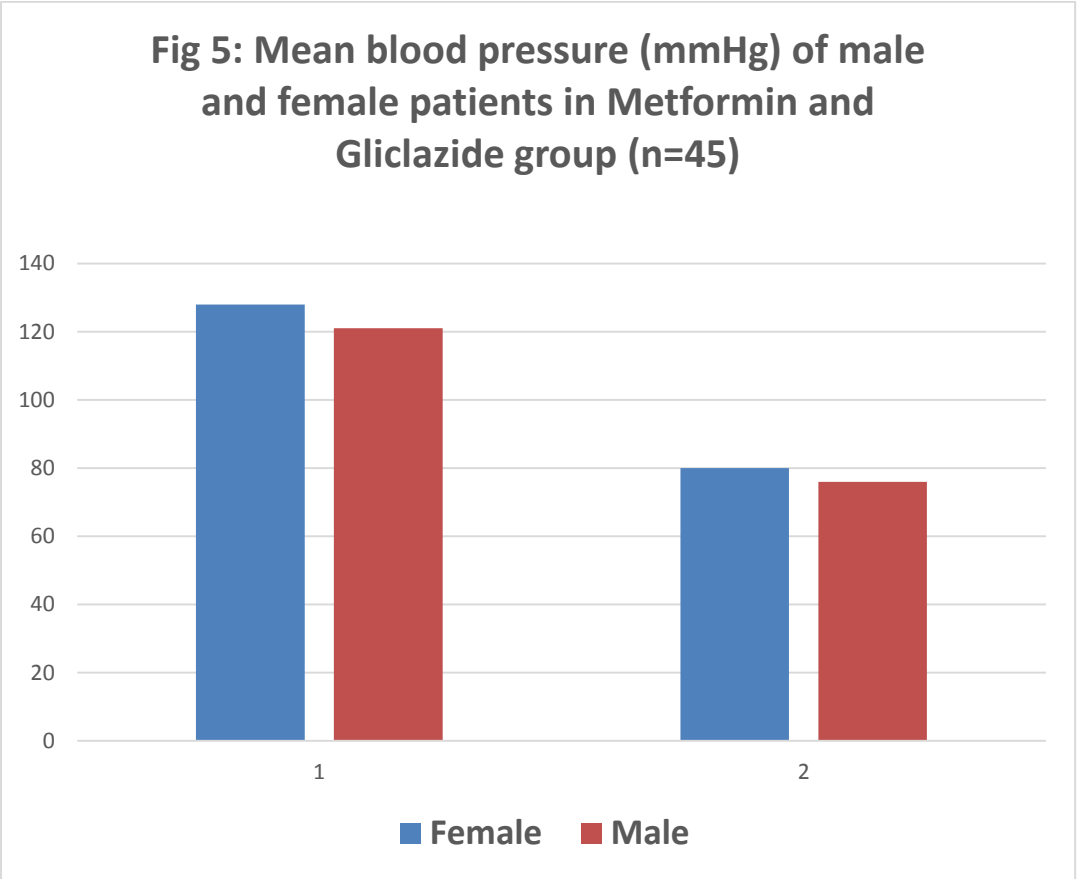
Fig 2 shows % distribution of male and female patients in metformin and insulin group. Twenty three percent patients are male and 77% female.



This figure (Fig 3) shows % distribution of male and female patients in metformin and gliclazide group. In this group 37% patients are male and 63% are female.



This figure (Fig 4) shows the mean blood pressure of male and female patients treated with metformin and insulin.The mean blood pressure of female was 130/80 mmHg and male was 135/78 mmHg.



This figure shows the mean blood pressure of male and female patients treated with metformin and gliclazide. The mean blood pressure of female was 128/80 mmHg and male was 121/76 mmHg.

Chapter 6

Discussion and Conclusion

6.1 Discussion and Conclusion

The present study was conducted to provide real-life data regarding the effect of metformin with gliclazide compared to other OADs in combination with metformin in the treatment of T2DM. Gliclazide is a free combination with metformin. About 200 patients with T2DM were enrolled into this study. The observation was on age,fasting blood glucose,serum creatinine level of patients taking metformin with gliclazide comparing with metformin with insulin and other antidiabetic drugs. There was no significant difference of FBG and Creatinine level between different combinations.

The effects of gliclazide/metformin on glycemic control in patients with Type 2 diabetes mellitus was evaluated. The treatment regimen was started at 80 mg gliclazide plus 500 mg metformin once a day and was titrated to the next dose level depending on the clinician's judgment, not exceeding a total daily dose of 320 mg gliclazide and 2000 mg metformin. Changes from baseline HbA1c, FPG, and postprandial glucose were examined. After 12-weeks treatment, the gliclazide + metformin combination showed improvement in metabolic control as assessed by changes in HbA1c, Fasting plasma glucose (FPG), and postprandial glucose. Moreover, the lipid profile was also improved during the treatment period. The addition of gliclazide to metformin is an effective treatment for patients inadequately controlled on sulfonylurea or metformin alone. A combination of gliclazide with metformin achieves good glycemic control and improves lipid levels with better tolerability profile. (Pareek et al.,2010). Our study also showed a better glycemic control in patients with Type 2 diabetes. Nephropathy screening in diabetes patients is recommended on an annual basis for patients suffering from Type 2 diabetes. This screening should start 5 years after the onset of diabetes. Because development of microvascular complication typically takes 5 years. For Type 2 diabetes patients screening of nephropathy should begin just after onset of diabetes. Because exact onset of diabetes is often unknown. Diabetes nephropathy can be detected by measuring on urine albumin or serum creatinine level. Diabetic nephropathy is a major complications in some patients with diabetes (Allison J. Hahr etal., 2015). Therefore, strict control of blood glucose level is essential to prevent or delay the onset of diabetic nephropathy. A number of antidiabetic medications are available in the market. However, only a few can be used safely in diabetic patients in chronic kidney disease. There may be

a need for adjustment in dosing of the antidiabetic medications in such patients. Our result showed that that creatinine level of Metformin and Gliclazide combination was not significantly different when compared with other combination drugs.

Metformin has been recommended by the American Diabetes Association as the first line antidiabetic drug. Monotherapy often fails to achieve the effective glycemic control for treating Type 2 diabetes. If adequate blood glucose control is not attained using a single oral agent, a combination of agent may result in better glycemic control. Better control of diabetes is essential for each of the patients to reduce the risk of diabetes related complications. In our study the fasting blood level of Type 2 diabetes was 8.58±2.300 mmol/L inMetformin and Gliclazide combination group. It shows that this combination effectively control the FBG in our study patients. The blood pressure of male and female diabetic patients in Metfomin and Gliclazide group is within the normal range.

The overall safety and efficacy of metformin in combination with gliclazide is same while comparing others combination like metformin with insulin or metformin with sitagliptin.There is no significant effect on serum creatinine level of patient taking metformin with gliclazide.

Therefore In conclusion, the work presented in this thesis contributes the information that metformin with gliclazide is an effective and well-tolerated treatment in type 2 diabetes treatment.

Chapter 7

Reference

References:

Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR (August 2000).

Ahmad S,Wang L, Ward PE,1992. Dipeptidyl(amino)peptidase IV and amino peptidase M metabolize circulating substance P in vivo. *J* Pharmacol Exp Ther;260:1257-61.
Ajjan,Grant,PJ (2008). "The cardiovascular safety of rosiglitazone".Expert opinion on drug safety 7 (4): 367–76.

Allison J. Hahr and Mark E, 2015. Management of diabetes mellitus in patients with chronic kidney disease. Molitch*Hahr and Molitch Clinical Diabetes and Endocrinology 1:2DOI 10.1186/s40842-015-0001-9

Amori RE, Lau J, Pittas AG,2007. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. *JAMA*;298:194-206.

Andrulionyte L, Zacharova J, Chiasson JL, Laakso M(2004). Common polymorphisms of the PPAR-gamma2 (Pro12Ala) and PGC-1alpha (Gly482Ser) genes are associated with the conversion from impaired glucose tolerance to type 2 diabetes in the STOP-NIDDM trial.

Barroso I,2005. Genetics of Type 2 diabetes. Diabet Med;22:517-35. (Accessed 27 june 2015)
Bergman AJ, Ader M,2000. Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab;11:351-6.

Bergman RN, Stevens C, Zhou Y, Yi B, Laethem M, De SM,*et a*,2006. Pharmacokinetic and pharmacodynamic properties of multiple oral doses of sitagliptin, a dipeptidyl peptidase-IV inhibitor: a double-blind, randomized, placebo-controlled study in healthy male volunteers. *Clin* Ther,28:55-72.

Bhattaram VA, Booth BP, Ramchandani RP, Beasley BN, Wang Y, Tandon V, *et al.* Impact of pharmacometrics on drug approval and labeling decisions: A survey of 42 new drug applications. *AAPS J* 2005;7(3):E503-12.

Boehringer Ingelheim. Investigator's Brochure Linagliptin. Biberach: Boehringer Ingelheim; 2008.

Bongers J, Lambros T, Ahmad M, Heimer EP,1992. Kinetics of dipeptidyl peptidase IV proteolysis of growth hormone-releasing factor and analogs. Biochim Biophys Acta;1122:147-53.

Carbone A, Gloghini A, Zagonel V, Aldinucci D, Gattei V, Degan M, *et al*,1995. The expression of CD26 and CD40 ligand is mutually exclusive in human T-cell n Callebaut C, Krust B, Jacotot E,
Hovanessian AG. T cell activation antigen, CD26, as a cofactor for entry of HIV in CD4+ cells. Science 1993 Dec;262:2045-50 on Hodgkin's lymphomas/leukemias. Blood;86:4617-26.

Carolina C R Betônico,Silvia M O Titan,Maria Lúcia C Correa-Giannella,MárciaNery, and MárciaQueiroz.(2016 Jan).Management of diabetes mellitus in individuals with chronic kidney disease: therapeutic perspectives and glycemic control.

Cheng J, Zhang W, Zhang X, Han F, Li X, He X, Li Q, Chen J (Mar 31, 2014). "Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality, Cardiovascular Deaths, and Cardiovascular Events in Patients With Diabetes Mellitus: A Meta-analysis.". *JAMA* internal medicine 174 (5):85 .

Cooke DW, Plotnick L (November 2008). "Type 1 diabetes mellitus in pediatrics". PediatrRev 29 (11): 374–84; quiz 385.

Cordero OJ, Ayude D, Nogueira M, Rodriguez-Berrocal FJ, de la Cadena MP,2000. Preoperative serum CD26 levels: diagnostic efficiency and predictive value for colorectal cancer. *Br J* Cancer 83:1139-46.
Cuchacovich M, Gatica H, Pizzo SV,2001, Gonzalez-Gronow M. Characterization of human serum dipeptidyl peptidase IV (CD26) and analysis of its autoantibodies in

patients with rheumatoid arthritis and other autoimmune diseases. Clin Exp Rheumatol;19:673-80.

Cukierman, T (8 Nov 2005). "Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies". Springer-Verlag.

Derosa G , Sibilla S.(2007 Oct) Optimizing combination treatment in the management of type 2 diabetesVasc Health Risk Manag.

Davis SN (2004). "The role of glimepiride in the effective management of Type 2 diabetes". *J*. Diabetes Complicat. 18 (6): 367–76.

Davis, Stephen N. (2005). "60. Insulin, oral hypoglycemic agents, and the pharmacology of the endocrine pancreas". In Brunton, Laurence L.; Lazo, John S.; Parker, Keith L.(eds.).

Goodman & Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-*Hill. p*. 1636.

Deacon CF,2005. What do we know about the secretion and degradation of incretin hormones? Regul Pept128:117-24.

DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD,2005. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformintreated patients with type 2 diabetes. Diabetes Care;28:1092-100.

De la Monte, SM (December 2014). "Type 3 diabetes is sporadic Alzheimer′s disease: mini-review.". European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology."Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism:(April 2010) *Merck Manual Professional"*. Merck Publishing.. Retrieved2010-07-30.
Diabetes Blue Circle Symbol"17 March 2006. International Diabetes Federation. Diabetes Fact sheet N°312". WHO. October 2013.

Diabetes Blue Circle Symbol"17 March.2014. International Diabetes Federation.

Dorner M, Pinget M, Brogard JM (May 1977). *"*Essential labile diabetes*"*. *MMW Munch Med Wochenschr (*in German).

Drucker DJ, Nauck MA,2006. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368:1696-705.

Dupre J, Ross SA, Watson D, Brown JC,1973. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin* Endocrinol Metab;37:826-8.

Matthias Blüher, Ira Kurz, Simone Dannenmaier, and Markus Dworak.(2015 sep). Efficacy and safety of vildagliptin in clinical practice-results of the PROVIL-study.

Eckhardt M, Langkopf E, Mark M, Tadayyon M, Thomas L, Nar H, *et al,*2007. 8-(3-(R)aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-4-methyl-quinazolin-2-ylmethyl)3,7-dihydropurine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes. *J* Med Chem;50:6450-3.

Eckhardt M, Hauel N, Himmelsbach F, Langkopf E, Nar H, Mark M, *et al,2008*. 3,5Dihydro-imidazo[4,5-d]pyridazin-4-ones: a class of potent DPP-4 inhibitors. *Bioorg* Med Chem Lett 18:3158-62.

Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes *(UKPDS 34),1998*. UK Prospective Diabetes Study *(UKPDS)* Group. *Lancet*;*352:854-65.*

Efendic S, Portwood N(2004). Overview of incretin hormones. Horm Metab Res ;36:742-6.

Elrick H, Stimmler L, Hlad CJ, Rai Y,1964. Plasma insulin response to oral and intravenous glucose administration. *J Clin* Endocrinol Metab;24:1076-82.

Farilla L, Hui H, Bertolotto C, Kang E, Bulotta A, Di MU, et al,2002. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. Endocrinology ;143:4397-408.

Ferrannini E(1998). Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus*:* problems and prospects.Endocr Rev*;19:477-90.*

Fukasawa KM, Fukasawa K, Sahara N, Harada M, Kondo Y, Nagatsu I,1981. Immunohistochemical localization of dipeptidyl aminopeptidase IV in rat kidney, liver, and salivary glands. *J* Histochem Cytochem;29:337-43.

Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al(2003). Follow-up report on the diagnosis of diabetes mellitus. Diabetes CarE;26:3160-7.

Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, et al(2008). Effects of intensive glucose lowering in type 2 diabetes. *N Engl J* Med ;358:2545-59.

Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA.(2011 Jul).Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study.

Gupta S, Khajuria V, Tandon VR, Mahajan A, Gillani ZH.(2015 Jul-Sep) Comparative evaluation of efficacy and safety of combination of metformin-vidagliptin versus metfromin-glimepiride in most frequently used doses in patients of type 2 diabetes mellitus with inadequately controlled metformin monotherapy-A randomised open label study.6(3):163-8

Haak T. (2015 Jan 4).Combination of Linagliptin and Metformin for the Treatment of Patients with Type 2Diabetes.

Hansen L, Deacon CF, Orskov C, Holst JJ, 1999. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. Endocrinology;140:5356-63.

Harris MI. Epidemiological correlates of NIDDM in Hispanics, whites, and blacks in the U.S,1991. population. Diabetes Care;14:639-48.

Hartel S, Gossrau R, Hanski C, Reutter W,1988. Dipeptidyl peptidase (DPP) IV in rat organs. Comparison of immunohistochemistry and activity histochemistry. Histochemistry;89:151-61.

Hassan MH, Abd-Allah GM.(2015 Sep). Effects of metformin plus gliclazide versus metformin plus glimepiride on cardiovascular risk factors in patients with type 2 diabetes mellitus.28(5):1723-30

Herrera C, Morimoto C, Blanco J, Mallol J, Arenzana F, Lluis C, *et al*,2001. Comodulation of CXCR4 and CD26 in human lymphocytes. *J* Biol Chem*;*276:19532-9.

Heise T, Graefe-Mody EU, Huttner S, Ring A, Trommeshauser D, Dugi KA. Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. Diabetes Obes Metab 2009;11:786-94 .

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA,2008. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*;359:1577-89.

Hong WJ, Petell JK, Swank D, Sanford J, Hixson DC, Doyle D,1989. Expression of dipeptidyl peptidase IV in rat tissues is mainly regulated at the mRNA levels. Exp Cell Res;182:256-66.

Hu EA, Pan A, Malik V, Sun Q (2012-03-15). "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". *BMJ* (Clinical research ed.) 344: e1454.

Huttner S, Graefe-Mody EU, Withopf B, Ring A, Dugi KA,2008. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of BI 1356, an inhibitor of dipeptidyl peptidase 4, in healthy male volunteers. *J Clin* Pharmacol 48:1171-8.

International Diabetes Federation. Diabetes Prevalence (document on the Internet). International Diabetes Federation (2009).Available from: http://www.idf.org/diabetes-prevalence.

Inzucchi SE,2002. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA;287:360-72.

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (*UKPDS* 33),. UK Prospective Diabetes Study (*UKPDS*) Group. *Lancet*;352:837-53.

Iwaki-Egawa S, Watanabe Y, Kikuya Y, Fujimoto Y,1998. Dipeptidyl peptidase IV from human serum: purification, characterization, and N-terminal amino acid sequence. *J* Biochem;124:428-33.

Kahn SE, Hull RL, Utzschneider KM(2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature *444:840-6.*

Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, *et al*,2005. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care;28:1083-91.

Kitabchi, AE; Umpierrez, GE; Miles, JM; Fisher, JN (Jul 2009)."Hyperglycemic crises in adult patients with diabetes.". Diabetes Care32 (7): 1335–43.(Accessed 24 September 2016)

Kim E. Barrett,(2012). Ganong's review of medical physiology. (24th ed.). New York: McGraw-Hill Medical.

Komatsu R, Matsuyama T, Namba M, Watanabe N, Itoh H, Kono N, 1989. Glucagonostatic and insulinotropic action of glucagonlike peptide I-(7-36)-amide. Diabetes . .(Accessed 13 june 2015)

Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes,1999. Diabetes 48:937-42.

Laios K, Karamanou M, Saridaki Z, Androutsos G (2012). "Aretaeus of Cappadocia and the first description of diabetes". Hormones 11 (1): 109–113.

Lambeir AM, Durinx C, Scharpe S, De M, I,2003. Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV. Crit Rev Clin Lab Sci 2003;40:209-94.

Lambert P, Bingley PJ (2002). "What is Type 1 Diabetes?". Medicine **30**: 1–5.

Leonid Poretsky, (2009). Principles of diabetes mellitus (2nd ed.). New York: Springer. P.

Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012)."Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". *The Lancet* 380 *(9838): 219–29.*

Lewin AJ, Arvay L, Liu D, Patel S, von Eynatten M, Woerle HJ.(2012 Sep).Efficacy and tolerability of linagliptin added to a sulfonylurea regimen in patients with inadequately controlled type 2 diabetes mellitus: an 18-week, multicenter,randomized, double-blind, placebo-controlled trial. Clin Ther. 2012 Sep.

Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, (1993). Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. *N Engl J* Med*;329:1988-92.*

Loster K, Zeilinger K, Schuppan D, Reutter W,1995. The cysteine-rich region of dipeptidyl peptidase IV (CD 26) is the collagen-binding site. Biochem Biophys Res Commun;217:341-8.

Lojda Z,1979. Studies on dipeptidyl (amino)peptidase IV (glycyl-proline naphthylamidase). II. Blood vessels. Histochemistry 1979;59:153-66.

Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010-03-23). "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". Circulation**121** (11): 1356–64. Marguet D, Baggio L, Kobayashi T, Bernard AM, Pierres M, Nielsen PF, 2000. Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. Proc Natl Acad Sci U S A;97:6874-9.

Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Schernthaner(G.2005 Mar-Apr). Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study.21(2):167-74.

Matthias Blüher, Ira Kurz, Simone Dannenmaier, and Markus Dworak.(2015 sep). Efficacy and safety of vildagliptin in clinical practice-results of the PROVIL-study.

Mentlein R, Gallwitz B, Schmidt WE,1993. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J* Biochem 1993;214:829-35.

Mentlein R, Dahms P, Grandt D, Kruger R. Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV. Regul Pept 1993;49:133-44.

Mentzel S, Dijkman HB, van Son JP, Koene RA, Assmann KJ,1996. Organ distribution of aminopeptidase A and dipeptidyl peptidase IV in normal mice. *J* Histochem Cytochem 44:445-61.

Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, et al,1992. Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. *N Engl J Med 1992;326:22-9.*

Mitani H, Takimoto M, Hughes TE, Kimura M,2002. Dipeptidyl peptidase IV inhibition improves impaired glucose tolerance in high-fat diet-fed rats: study using a Fischer 344 rat substrain deficient in its enzyme activity. *Jpn J* Pharmacol 2002;88:442-50.

Nagakura T, Yasuda N, Yamazaki K, Ikuta H, Yoshikawa S, Asano O, 2001. Improved glucose tolerance via enhanced glucose-dependent insulin secretion in dipeptidyl peptidase IV-deficient Fischer rats. Biochem Biophys Res Commun. .

Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, et al(2003). Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*;348:2294-303.

Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al(2005). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* ;353:2643-53.

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al,(2008). Medical Management of Hyperglycemia in Type 2 Diabetes: a Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care;32:193203.

Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, et al(1968). Incretin effects of increasing glucose loads in man calculated from venous insulin and Cpeptide responses. *J Clin* Endocrinol Metab,63:492-8.

Nauck M, Stockmann F, Ebert R, Creutzfeldt W,1986. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia,29:46-52.

Nissen SE, Wolski K,2007. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J* Med.356:2457-71.

O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW (29 January 2013). "2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American

College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.".Circulation **127** (4): e362–425.

Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al(1995). Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract;28:103-17.

Orskov C, Holst JJ, Nielsen OV,1988. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. Endocrinology;123:2009-13(Accessed 11 june 2015). Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al*(2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J* Med;358:2560-72.

Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al(1995). Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract;28:103-17.

Orskov C, Holst JJ, Nielsen OV,1988. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. Endocrinology;123:2009-13.

Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, *et al*(2008). Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J* Med;358:2560-72.

Perfetti R, Zhou J, Doyle ME, Egan JM,2000. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. Endocrinology ;141:4600-5.

Picot,J; Jones, J; Colquitt, JL; Gospodarevskaya, E; Loveman, E; Baxter, L; Clegg, AJ (September 2009). "The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation". Health Cash, *Jill* .

Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, (2007). Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care;30:137483.

Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K (2009). "Home telehealth for diabetes management: a systematic review and meta-analysis". Diabetes Obes Metab 11 (10): 913–30.

Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL,2008. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev CD006739.

Rippe, edited by Richard S. Irwin, James M. (2010). Manual of intensive care medicine (5th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 549. *ISBN* 9780781799928.

Risérus U, Willett WC, Hu FB (January 2009). "Dietary fats and prevention of type 2 diabetes". Progress in Lipid Research ***48*** *(1): 44–51*.

Ristic S, Collober-Maugeais C, Pecher E, Cressier F.(2006 Jul). Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with Type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone.23(7):757-6.

Robert K. Murray (2012). Harper's illustrated biochemistry (29th ed.). New York: McGraw-Hill Medical.

Ross SA, Dupre J,1978. Effects of ingestion of triglyceride or galactose on secretion of gastric inhibitory polypeptide and on responses to intravenous glucose in normal and diabetic subjects. Diabetes;27:327-33.

Rother KI (April 2007). "Diabetes treatment—bridging the divide". The New England Journal of Medicine **356** (15): 1499–501.

RSSDI textbook of diabetes mellitus. (Rev. 2nd ed.). New Delhi: Jaypee Brothers Medical Publishers. 2012. p. 235. *ISBN* 9789350254899.

Samara E, Granneman R. Role of population pharmacokinetics in drug development. A pharmaceutical industry perspective. *Clin* Pharmacokinet 1997;32:294312.

Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J (2010). "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies". *The Lancet* 375 (9733): 2215–22.

Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J,

Pareek A[1], Chandurkar N, Zawar S, Agrawal N. (2010 Nov-Dec). Evaluation of efficacy and tolerability of gliclazide and metformin combination: a multicentric study in patients with type 2 diabetes mellitus uncontrolled on monotherapy with sulfonylurea or metformin.

Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I (February 2010). "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials".The *Lancet* 375 (9716): *735–42.*

Schulman, AP; del Genio, F; Sinha, N; Rubino, F (September–October 2009). "Metabolic" surgery for treatment of type 2 diabetes mellitus". Endocrine practice,official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists15 (6): 624–31 .

Shi, Yuankai; Hu, Frank B (7 June 2014). "The global implications of diabetes and cancer". The *Lancet* **383** (9933): 1947–8. *doi:*10.1016/S0140-6736(14)60886-2.*PMID* 24910221.

Shoback, edited by David G. Gardner, Dolores (2011). Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical.

Singh S, Loke YK, Furberg CD,2007. Thiazolidinediones and heart failure: a teleoanalysis. Diabetes Care;30:2148-53.

Stoffers DA, Kieffer TJ, Hussain MA, Drucker DJ, Bonner-Weir S, Habener JF,2000. Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. Diabetes ;49:741-8.

Thomas L, Eckhardt M, Langkopf E, Tadayyon M, Himmelsbach F, Mark M2008.(R)8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazoli n-2ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a novel xanthine-based dipeptidyl peptidase 4 inhibitor, has a superior potency and longer duration of action compared with other dipeptidyl peptidase-4 inhibitors. *J* Pharmacol Exp Ther 2008;325:175-82.

Thomas L, Tadayyon M, Mark M,2008 . Chronic Treatment with the Dipeptidyl Peptidase-4 Inhibitor (R)-8-(3-Amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4methyl-quinazoli n-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356) Increases Basal Glucagon-Like Peptide-1 and Improves Glycemic Control in Diabetic Rodent Models. *J* Pharmacol Exp Ther;328:556-63.

Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al,2001. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin* Endocrinol Metab;86:3717-23.

Trumper A, Trumper K, Trusheim H, Arnold R, Goke B, Horsch D,2001. Glucosedependent insulinotropic polypeptide is a growth factor for beta (INS-1) cells by pleiotropic signaling. Mol Endocrinol;15:1559-70.

Trumper A, Trumper K, Horsch D,2002. Mechanisms of mitogenic and anti-apoptotic signaling by glucose-dependent insulinotropic polypeptide in beta(INS-1)-cells. *J* Endocrinol;174:233-46.

Tsuji E, Misumi Y, Fujiwara T, Takami N, Ogata S, Ikehara Y,1992. An active-site mutation (Gly633-->Arg) of dipeptidyl peptidase IV causes its retention and rapiddegradation in the endoplasmic reticulum. Biochemistry;31:11921-7.

United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study (UKPDS),1995.Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years.

Valenzuela A, Blanco J, Callebaut C, Jacotot E, Lluis C, Hovanessian AG, *et al*,1997. Adenosine deaminase binding to human CD26 is inhibited by HIV-1 envelope glycoprotein gp120 and viral particles. *J* Immunol 158:3721-9.

Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van WC,2005. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev;(2):CD003639.

Verstovsek S, Cabanillas F, Dang NH,2000. CD26 in T-cell lymphomas: a potential clinical role? Oncology (Williston Park);14(6 Suppl 2):17-23.

Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F (December 2012). "Seizures and type 1 diabetes mellitus: current state of knowledge". European journal of endocrinology 167(6): 749–58.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V; et al. (Dec 15, 2012). "Years lived with disability (YLDs) for

1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study.

Watanabe Y, Kojima T, Fujimoto Y,1987. Deficiency of membrane-bound dipeptidyl aminopeptidase IV in a certain rat strain. Experientia;43:400-1. (Accessed 1 October 2015)

Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ,1993. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. Dig Dis Sci;38:665-73.

Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA. Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulindependent) diabetic patients. *J Clin* Endocrinol Metab 1996;81:327-32.

Wild S, Roglic G, Green A, Sicree R, King H(2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030.Diabetes Care ;27:104753(Accessed 29 August 2015)

Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J (Dec 12, 2007). Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA:* the Journal of the American Medical Association 298 (22): 2654–64. Available From: https://en.wikipedia.org/wiki/Diabetes-mellitus.

Wolf M, Albrecht S, Marki C,2008. Proteolytic processing of chemokines: implications in physiological and pathological conditions. Int *J* Biochem Cell Biol ;40:1185-98.

Wood, Shelley (2007-07-31).FDA Advisory Panels Acknowledge Signal of Risk With Rosiglitazone, but Stop Short of Recommending Its Withdrawal. Heartwire. Retrieved 2007-09-21. Available From: https://en.wikipedia.org/wiki/Anti-diabetic medication.

World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications,(1999): Report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. *Geneva:* World Health Organization.

World Health Organization (1999). Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications (PDF).Available From: https://en.wikipedia.org/wiki/Diabetes-mellitus.

World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia(2006): Report of a WHO/IDF consultation. *Geneva*: World Health Organization.

World Health Organization (2006), *Geneva*. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation (PDF.

World Health Organization International Working Group for Drug Statistics Methodology (August 27, 2008). ATC/DDD Classification (FINAL): New ATC 5th level codes. WHO Collaborating Centre for Drug Statistics Methodology.

World Health Organization(October 2013).Diabetes Fact sheet N°312. Retrieved 25 March 2014. Available From: https://en.wikipedia.org/wiki/Diabetes-mellitus.

World Health Organization (2014). Diabetes Programme. Retrieved 22 April 2014. Available From: https://en.wikipedia.org/wiki/Diabetes-mellitus.

Xu G, Stoffers DA, Habener JF, Bonner-Weir S,1999. Exendin-4 stimulates both betacell replication and neogenesis, resulting in increased beta-cell mass and improved glucose tolerance in diabetic rats.Diabetes;48:2270-6.

Yalow RS, Berson SA (July 1960). Immunoassay of endogenous plasma insulin in man. The Journal of Clinical Investigation 39 (7): 1157–75. Available From: https://en.wikipedia.org/wiki/History-of-diabetes.

Yki-Jarvinen H,1997.Acute and chronic effects of hyperglycaemia on glucose metabolism: implications for the development of new therapies. Diabet Med;14 Suppl 3:S32-S37.

Yki-Jarvinen H,2004. Thiazolidinediones. *N Engl J* Med;351:1106-18.

Zander M, Madsbad S, Madsen JL, Holst JJ,2002. Effect of 6-week course of glucagonlike peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet;*359:824-30.